FIFTY YEARS IN CHEMICAL DRUG RESEARCH

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The presented review is a survey of the efforts of the author and his team (3rd Department of organic synthesis at the Research Institute for Pharmacy and Biochemistry in Prague) during the last fifty years to synthesize pharmacologically active original compounds and to develop – with the help of colleagues in all of the necessary biological lines – therapeutically useful drugs. The approach used consisted mostly in manipulations with structures of the known active molecules and in the screening of compounds originating from systematic chemical processing (functionalization) of some neglected pharmacophores (or carrier systems). The work included very diversified types of organic compounds in which the presence of amino group was mostly the common denominator. From the pharmacological point of view, the work was concentrated to agents acting at the vegetative and central nervous system. In addition to finding some interesting and unexpected types of organic reactions and to contributing to the knowledge of structure – activity relationships in some structural fields, the result of the work were twenty six original drugs which found practical use and the place on the pharmaceutical market, further twenty three original substances reaching the stage of clinical trials, and finally seventeen compounds which were the object of detailed preclinical tests but were dropped on the basis of various reasons. The most important results were the antihistamine agents **208**, **213**, **632** (R = 2-CH_3) and **903** (R = H), two spasmolytic sulfonium salts (**260**, **264**), the antidepressant prothiadene (**632**, R = H) which found a practically worldwide use, and the neuroleptic agents **737** (R = 8-Cl), **756** (R = 8-SCH_3), **771**, and finally **755** (R = 3-F-8-$CH(CH_3)_2$), being not yet marketed.

1 INTRODUCTION

My first contact with chemical drug research goes back to the end of 1939 when – after the forced closure of the Czech universities – I found refuge in the pharmaceutical laboratory od Dr Z. Klan in Prague. It was the period of the antibacterial sulfonamides and so the first task was to help under the guidance of Mr Antonín Pártl to solve the problem of an alternative synthesis of sulfacetamide (**1**). We started from di(4-nitrophenyl) disulfide and wanted to proceed via N-acetyl-4-nitrobenzenesulfonamide. The work did not lead to a practical synthesis of **1**; nevertheless this experience transformed me to an embryo of a drug chemist. After two years intermission (work in the analytical laboratory of a cement factory), I gladly joined again Mr A. Pártl who became in the meantime technical director of a more important pharmaceutical factory REMED in Prague. As a personal technician-chemist of Mr Pártl, I carried out syntheses of samples of various substances which could be of interest for the company. In 1944 I elaborated a modified synthesis of sulfaguanidine (**2**) (ref.[3]) which was manufactured for some time under the name of Enterina® (cf. ref.[4]). The first original contribution was the synthesis of an antispasmodic derivative of benzilic acid (will be described at the appropriate place), marketed for some time as Prospasmin® (ref.[1]).

This introduction should not be a biographical treatise but at least a sketch in this line is necessary. After the war, I finished the studies in chemistry at the Technical University in Prague (1946) and spent six months of the year 1947 in the laboratory of Prof. Vlado Prelog at the Federal Technical University in Zurich. From 1951 to 1986 I headed a department of organic synthesis of the newly established Research Institute for Pharmacy and Biochemistry in Prague which was the central research institute of the Czechoslovak pharmaceutical industry (SPOFA). In this position, I formulated most of the research projects, followed the daily progress of the experiments and summarized the results in the form of publications and patent applications. All of my co-workers, who carried out the experiments, sometimes on the basis of their own synthetic concepts, are named (mostly repeatedly) in the list of references. The most important of them, who were connected with our team for decades or for the time of their whole professional career, have to be mentioned here: Jiří Jílek, Miroslav Rajšner, Karel Šindelář, Zdeněk Vejdělek, Vladimír Valenta, and Zdeněk Polívka. Only for several years with us but important in some lines were the following: Miloš Borovička (antihistaminics, ganglionic blockers), Ludvík Novák (antihistaminics, reserpoids), Edita Adlerová (antispasmodics), Věra Seidlová (antidepressants), Otto Exner (sulfonium salts), Jiří Pliml (pyridine derivatives), Vladimír Hach (local anaesthetics), Ivan Ernest and Ivo Jirkovský (reserpoids), Karel Pelz and Václav Bártl (neuroleptics). Very helpful technicians for long years with us were Josef Pomykáček, Zdeněk Šedivý, Marta Hrubantová, Marie Vlková, František Mikšík, and Luboš Tůma.

The work of the team consisted in the synthesis of series of new compounds, their proper characterization (in the first years only the usual physical constants and analyses and then increasing use of spectral characterization starting with UV and IR and since 1965 MS, ^{1}H NMR and more recently ^{13}C NMR (important co-operation with E. Knobloch, B. Kakáč, E. Svátek, M. Ryska, J. Holubek, and M. Buděšínský)). Chromatographic methods were commonly used for the characterization (paper chromatography, TLC, GC) and especially for separation of mixtures (column chromatography). Identification of unexpected products or of minor by-products became inseparable constituent of the work – even when the goal was the preparation of identified compounds for pharmacological testing. The laboratory techniques in organic chemistry were too important for the work which brought me to contributing to monographical treatises in this line[78,96,189].

The topic of the work was the chemistry of drugs in general. The Czech literature after the war in this area was completely lacking; the gap was filled at least partly by a monograph on synthetic drugs written together with the late Dr Zdeněk Buděšínský[89,158]. The strategy of designing new structures of potential drugs used mainly two approaches: (i) Manipulation with structures of known active compounds (natural products, active compounds discovered here or by others) by modifications according to the lines exemplified in ref.[38]. Serendipity and systematic pharmacological screening played an important role and led in one case to the discovery of our own prototype[212,219,357]. The result was a good basis for systematic research work lasting for fifteen years. (ii) Use of some cyclic (mostly bicyclic and tricyclic systems) as pharmacophores or carrier systems, their functionalization in various positions, especially by introducing amino groups, carboxyl, hydroxyl or thiol groups and by their further derivatization by aminoalkylation to obtain aminoalkylamino, aminoalkoxycarbonyl, aminoalkoxy and aminoalkylthio side-chains. Also the C-aminoalkylation by the Grignard reaction or by the direct attack at activated carbon atoms played a role. The balance between the lipophilic and hydrophilic parts of the designed molecules was considered in the stage of project formulations. Many partial rules governing relations between structure and activity (SAR) were found and discussed. Some structural fields of activities were more or less defined. On the other hand, I preserved for the whole time of my activity scepticism towards formulation of too general SAR rules and towards the use of QSAR for predicting new active structures.

Most of the compounds described in this review were the object of experimental work of cooperating pharmacological and in selected cases also toxicological, pharmacokinetic, metabolic, general screening and clinical teams. More interesting biological findings are mentioned in this review because the aim of the work was to find biologically active and possibly practically useful compounds. The names of the respective coworkers in these lines appear in parts A and B of references. The most important of them, however, have to be given at this place already: Jiří Křeček, Václav Jelínek, Zdeněk Votava, Václav Trčka, Jiřina Metyšová, Jan Metyš, František Hradil, Marie Bartošová, Vladislav Wildt, Martin Valchář, Milena Queisnerová, Zdeněk Franc and Oldřich Vinař.

The years 1946 - 1960 were devoted mainly to searching after new drugs influencing the vegetative nervous system: histamine H_1-antagonists and antispasmodics (for reviews cf. refs[2,57,139]; the chemistry of antihistamine drugs and the histamine group was described in a monograph[102]) were followed by ganglionic blocking agents and peripheral myorelaxants. There were three parallel episodes: (i) search after peripheral vasodilatory pyridines - mainly derivatives of nicotinic acid and 3-pyridyl carbinol, (ii) synthetic experiments in the field of estrogenic hormones, and (iii) search after antihypertensive drugs initiated by the discovery of reserpine and by its total synthesis[563,564]. Since 1960 the research interest shifted into the field of psychotropic agents (mainly antidepressants and neuroleptics) as a natural continuation of the antihistamine chemistry. This topic remained then for thirty years the main object of my interest. The contributions of the Prague team were repeatedly reviewed[218,260,261,295,343,491]. For psychopharmacological conferences I prepared general reviews on the progress in this field (chemistry and pharmacology); a part of these reviews was published: refs[259,270,294,296,311,371,398,466].

For describing in a condensed form the work done by our team the choice of a system was an important task. Three possibilities were considered to this end: (i) chronological system, (ii) system according to the pharmacological profiles, and finally (iii) the chemical system. Because this article is published in a chemical journal, the chemical system was selected. It was the most complicated one for the preparation of the manuscript but it has the advantage of bringing together chemically related compounds irrespective of the chronology of their origin and of their pharmacological character. The hierarchy of the system used is the conventional one: starting from aliphatic compounds it continues via the alicyclic, aromatic, araliphatic, condensed aromatic to heterocyclic compounds. The only exception made related to 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl and sometimes 1-piperazinyl compounds in which these groups mimic the dimethylamino or diethylamino groups and, therefore, are classified as being aliphatic instead of heterocyclic.

Most of the final products determinated for pharmacological evaluation were amines which were tested in the form of their salts (hydrochlorides, maleates, succinates, methanesulfonates etc.).These salts were in many cases the crystalline forms of the products but they will mostly not be mentioned in the following text. References related to the known starting materials will not be given in this survey; they are available in the original papers.

For the interesting compounds which were the object of preclinical or clinical research or which reached the stage of practical use in therapy, several types of short names are used in the text: (i) our own generic names which are preferred and are used without any special designation, (ii) international nonproprietary generic names which are designed with (INN), (iii) trade names which are designed with ®, (iv) other generic names which are designed by their origin.

2 ALIPHATIC COMPOUNDS

Reaction of sodium ethoxide with 2-(1-piperidinyl)ethyl chloride in ethanol[10] afforded the ether **3**. Treatment of hexanol with powdered sodium in boiling xylene and the following treatment with 2-(1-piperidinyl)ethyl chloride afforded the ether **4** (ref.[15]). This compound (**4**) was transformed via the methiodide to the quaternary ammonium hydroxide which was decomposed by heating to 150°C; hexanol, N-methylpiperidine and acetylene were identified as products. Reduction of ketones with lithium aluminium hydride(cf.[47]) and reaction of aldehydes with alkylmagnesium halides gave eight butylalkylmethanols and reactions of ketones, esters and diethyl carbonate with alkylmagnesium bromides gave eight butyldialkylmethanols. These alcohols were transformed by treatment with sodium amide and 2-dimethylaminoethyl chloride to the corresponding ethers **5** and **6** (ref.[59]). They were prepared as the aliphatic analogues of the antihistamine drug diphenhydramine (cf. formula **164**). The most active members of the series were **5** ($R = C_5H_{11}$) and **6** ($R^1 = C_4H_9$, $R^2 = CH_3$) attaining in vitro 15 % of the diphenhydramine activity.

Reaction of the sodium salt of 2-(1-piperidinyl)ethanethiol with hexyl bromide[15] in ethanol gave the sulfide **7**. As possible intermediates for the synthesis of 2-aminoethanethiols, the dithiocarbonates **8** and **9** were prepared by reactions of potassium ethyl xanthate with 2-diethylaminoethyl chloride and 2-(1-piperidinyl)ethyl chloride in boiling ethanol[15].

Pentamethonium bromide (**10**) (ref.[565]) and azamethonium bromide (**11**) (ref.[566]) are bisquaternary ammonium salts possessing the properties of ganglionic blocking agents and finding use in the treatment of some forms of hypertension.

Manipulation with their structures resulted first[80] in the series of three disulfonium iodides **12** (n = 3, 4, 5). The synthesis in the series started by reactions of dihaloalkanes with sodium methanethiolate giving the sulfides **13** (n = 2 – 5). Treatment with methyl iodide led in the case of the first member of the series only to the monosulfonium iodide **14**, whereas the higher members gave the disulfonium iodides **12**. Unexpectedly[567] compounds **12** were only poor ganglionic blockers and had hypotensive action of short duration but **14** proved a hypotensive activity near to that of **10**. Reaction of 2-(methylthio)ethanethiol with 2-(methylthio)ethyl chloride afforded the trisulfide **15** which was transformed by treatment with methyl iodide to the disulfonium iodide **16**, considered to be an analogue of **11** (ref.[80], cf. also ref.[73]).

Introduction of the sulfur atom into the central position of the pentamethonium bromide (**10**) chain resulted in a further series of bisquaternary ammonium salts[88]. They were prepared by reactions of the sodium salts of the thiols RCH_2CH_2SH with the chlorides RCH_2CH_2Cl (R = dimethylamino, diethylamino, 1-piperidinyl, 4-morpholinyl) and by the following reaction of the diamino sulfides **17** with methyl or ethyl iodide. These products proved significant ganglionic blocking and hypotensive activity and the most active **18** (thiamethonium iodide) (refs[567,568]) was selected for preclinical and clinical trials. These proved the utility of **18** in regulated hypotension in various indications[569-573]. Under the trade name Thiamethon® it was marketed in Czechoslovakia by SPOFA for at least twenty five years (since 1963).

Compound **19**, a homologue of **10**, known as decamethonium bromide (also iodide) (refs[574,575]) is a prototype of peripheral myorelaxants, the so-called leptocurares which produce muscular relaxation by selective depression of central polysynaptic pathways (cause a depolarization on the neuro-muscular junctions) (ref.[576]).

Another compound of this type which found practical use in anaesthesia during operative manipulations, is suxamethonium iodide (or chloride) (**20**) (ref.[577]). Our first approach to analogues of **19** (ref.[85]) resulted in the series of nine bis-, tris- and tetrakis-quaternary ammonium compounds **21** (n = 2 - 6), **22**, **23**, and **24** ($R = CH_3$ or C_2H_5). The synthesis of **21** – **23** started by reactions of alkanediols $HO(CH_2)_nOH$ (n

= 2 – 6), N-methyldiethanolamine and triethanolamine with 2-diethylaminoethyl chloride in the presence of sodium amide and proceeded by the following treatment of the products with ethyl iodide. Compounds **24** were obtained by reaction of sodium 2-(dimethylamino)ethanethiolate with 1,4-diiodobutane and by the following addition of methyl and ethyl iodide. The best ratio of myorelaxant activity (head-drop test in rabbits) were shown by **21** (n = 2) and **23** (refs[165,578]) which, however, were not better than **19**.

Two types of sulfonium analogues of **19** were prepared[86]. Reaction of sodium 2-(methylthio)ethoxide with pentamethylene dibromide and the following addition of methyl iodide afforded **25**. Reactions of sodium 2-(methylthio)ethanethiolate with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-diiodobutane, and 1,5-dibromopentane and the usual treatment with methyl iodide gave **26** (n = 2 – 5). The activity of these compounds was less interesting[165,578]. The synthesis of **20** by transesterification reaction from diethyl succinate and 2-dimethylaminoethanol and by the following addition of methyl iodide was modified[86] and this ultrashort-acting myorelaxant was introduced by SPOFA on the market as Succinylcholinjodid® (refs[579,580]). Four new analogues of **20** were prepared[86]: The first of them was succinylthiocholine iodide (**27**), obtained by reaction of succinyl chloride with 2-(dimethylamino)ethanethiol and subsequent treatment with methyl iodide. A further compound was succinylsulfocholine iodide (**28**), prepared by reaction of succinyl chloride with 2-(methylthio)ethanol and by treatment with methyl iodide. The third was succinylthiosulfocholine iodide (**29**) obtained by reaction of sodium 2-(methylthio)ethanethiolate with succinyl chloride and by the following treatment with methyl iodide. The analogue of **28** with reversed elements of carboxyl (**30**) resulted from the reaction of ethane-1,2-diol with 3-(methylthio)propionyl chloride in pyridine and by subsequent reaction with methyl iodide. Compounds **27** – **30** did not reveal in the hands of our colleagues[165,578] any considerable activity. On the other hand, the Italian authors[581,582] described three years after our publication[86] compound **28** as a myorelaxant of the leptocurare type of high activity in the head-drop test in rabbits.

Choline and its esters are simple aliphatic compounds playing important role in physiological processes and possessing significant pharmacodynamic activities[583]; acetylcholine salts are the prototypes of cholinergic parasympathomimetics. We also were partly involved in investigating this structural field of activity. Reaction of N-butyl-N-methyl-2-aminoethanol with methyl iodide gave the choline iodide homologue **31** (ref.[544]). Similar reaction of 2-(methylthio)ethanol gave sulfocholine iodide (**32**) (ref.[124], cf. also ref.[584]) which was necessary as a potential metabolite of our antispasmodic hexadiphensulfonium iodide (cf. **260**). 2-(Methylthio)ethanethiol was transformed to the sodium salt which was reacted with acetyl chloride and the product was treated with methyl iodide giving acetylthiosulfocholine iodide (**33**) which was found to have only 1 % of the spasmogenic effect of acetylcholine chloride on the isolated rat ileum[79]. Methyl 3-(methylthio)propionate was prepared from sodium methanethiolate and methyl 3-chloropropionate[136], and transformed by the following treatment with methyl iodide to **34**, the RC-analogue (reversed carboxyl analogue) of acetylsulfocholine iodide. This compound proved a very high parasympathomimetic activity and was clinically tested as carbmethosulfonium iodide. The rather limited clinical usefulness of parasympathomimetics prevented its marketing. The next higher homologue **35** was prepared similarly from ethyl 3-chloropropionate[129]. Reaction of ethyl 2-(methylthio)acetate with methyl iodide proceeded as transalkylation[129] and the only isolated product was trimethylsulfonium iodide. Acylation of 2-dimethylaminoethanol with 2,2-dimethylpropanoyl, heptanoyl, octanoyl, decanoyl, and hexadecanoyl chloride afforded the esters **36** and **37** (n = 5, 6, 8, 14) designed as possible cerebral stimulators[548]; their testing was problematic (**37** (n = 5) showed some central stimulating effect in mice – increase of motility).

2-Propylpentanoic acid (valproic acid) (**38a**) in the form of salts and its amide **38b** (valpromide) are aliphatic anticonvulsants[585,586] which are used in the treatment of some forms of epileptic seizures, and **38b** also as a prophylactic in the maniodepressive illness[587]. Our team was involved in the synthesis of thia analogues of these agents[558]. Alkylation of diethyl 2-(methylthio)ethylmalonate with ethyl bromide and propyl bromide, the following alkaline hydrolysis and decarboxylation afforded the acids **39a** ($R^1 = C_2H_5, C_3H_7$). Via acid chlorides they were transformed to the amides **39b** ($R^1 = C_2H_5, C_3H_7$). These acids and amides were found ineffective as anticonvulsants in the electroshock test in mice. Alkylation of 3-thiapentanenitrile with propyl bromide in the presence of aqueous sodium hydroxide and benzyltriethylammonium chloride gave 2-propyl-3-thiapentanenitrile which was hydrolyzed with hydrochloric acid in boiling dioxane to **40a**, transformed via acid chloride to **40b**. These two compounds, being per se ineffective as anticonvulsants, significantly potentiate the anticonvulsant action of diazepam. Reaction of valproic acid chloride with ethyl N-(2-hydroxyethyl)carbamate afforded **41**, another potential anticonvulsant[558].

3 ALICYCLIC COMPOUNDS

Cyclohexanol treated with powdered sodium in boiling xylene and then with 2-(1-piperidinyl)ethyl chloride afforded the ether **42** as a model compound in the synthesis of potential antihistaminics[15]. 2-Methylcyclohexanone, 2,2-dimethylcyclohexanone, 2,2,6-trimethylcyclohexanone and 2,2,6,6-tetramethylcyclohexanone were processed by a series of reactions (reduction of oximes, reactions with methylmagnesium iodide, dehydration and Ritter reaction, N-formylation and reduction of the formamides, and finally methylation of the primary amines with formaldehyde and formic acid) to give the series of thirty two cyclohexylamines out of which the secondary and tertiary amines polymethylated in the vicinity of the amino group showed a high degree of ganglionic blocking and hypotensive activity[144,568]. The most active compound penhexamine (**43**) underwent preclinical study[588] and successful clinical trial. For SAR study, compound **43** brought a proof of correctness of the hypothesis that the norbornane skeleton, appearing in the molecule of the ganglionic blocking and hypotensive agents mecamylamine (cf. **61**) and dimecamine (cf. **63**), is not indispensable: a sterically hindered methylamino or dimethylamino group on an alicyclic or even aliphatic (cf. penbutamine, refs[589,590]) skeleton is the indispensary condition. 1,2,2-Trimethylcyclopentanol was processed by the Ritter reaction (potassium cyanide in a mixture of acetic and sulfuric acid), the obtained formamido derivative was hydrolyzed to the primary amine which was N-methylated by the Eschweiler – Clarke method and gave **44** (penpentamine) (ref.[213]). This compound proved in clinical tests[591] the best properties as an antihypertensive agent in comparison with the other sterically hindered amines of this type.

Until 1970 (+)-tubocurarine chloride was considered to be a macrocyclic bisquaternary ammonium salt (in 1970 this view was revised[592] and it was proven that the alkaloid is a monoquaternary salt) which led us to design **45** as the most simple macrocyclic model of the alkaloid[117]. The synthesis of **45** started from cyclooctadecane-1,10-dione obtained from sebacic acid chloride which was cyclized by using the Blomquist' s cyclization of bifunctional ketenes. The dioxime of the diketone was reduced with sodium in ethanol to 1,10-diaminocyclooctadecane giving **45** directly by treatment with methyl iodide in a methanolic potassium hydroxide solution. From the pharmacological point of view, **45** (cyclomethonium iodide) is a very interesting substance[165,593-595]. In the head-drop test in rabbits, **45** is more active than tubocurarine chloride and **19**; it is a short-acting substance belonging to a mixed type of relaxants. It was clinically tested but not recommended for practical use. Several months after publishing our paper[117], Lüttringhaus et al.[596,597] published two papers concerning the synthesis of **45** by a different procedure; their pharmacological data[598] were similar to ours but neither in Germany **45** did find practical use.

In 1959 - 1963 there was a great interest in variously substituted hydrazines as monoamine oxidase inhibitors and as an alternative in the pharmacotherapy of mental depression[599]. Our team was also to some extent involved in this field and it was in the first time the series of cycloalkyl hydrazines which seemed to be neglected. Our attempts to prepare the basic members of the series[252] by reduction of hydrazones of cyclopentanone, cyclohexanone and cycloheptanone with lithium aluminium hydride or sodium borohydride were unsuccessful. Only N,N'-dicycloheptylhydrazine (**46**) could be prepared by reduction of cycloheptanone azine with lithium aluminium hydride. An alternative synthetic approach was successful: reactions of benzhydrazide with the mentioned cycloalkanones gave the N-benzoylhydrazones which were hydrogenated on platinum catalyst in acetic acid to N-benzoyl-N'-cycloalkylhydrazines. Hydrolysis with boiling 6M-HCl afforded the cycloalkylhydrazines **47** (n = 1 – 3).

Betanidine (**48**) was described[600] as a representative of the group of adrenergic neuron blocking agents and antihypertensive drugs. Compound **49** was designed as an alicyclic analogue of **48** and synthesized[327] from 1-methylcyclohexylamine via **50** and **51**. Compound **49** was found to be rather toxic but in general it possessed the pharmacodynamic profile of guanethidine, the prototype of this series.

Reactions of cyclopentylacetyl, cycloheptylacetyl and 1-cyclopentylhexanoyl chloride with 2-dimethylaminoethanol gave the esters **52** – **54**; **53** was found to antagonize the halothan-induced amnesia in rats and **54** is an anticholinergic antispasmodic agent[548].

1-Cyclohexylcyclohexene was subjected to the Ritter reaction with potassium cyanide in a mixture of sulfuric and acetic acid; the formamide **55** obtained was hydrolyzed to **56** which was methylated by the Eschweiler – Clarke method. The resulting sterically hindered tertiary amine **57** was tested as a potential ganglionic blocking agent with negative results[213]. Spiro[5.6]dodecan-7-one (**58**) was transformed by treatment with methylmagnesium iodide and the following dehydration by heating with iodine to spiro[5.6]dodec-7(8)-ene which was subjected to the Ritter reaction followed by reduction with lithium aluminium hydride. Structures **59** and **60**, which were assigned to the last two products, are in agreement with analyses and the IR spectra (the only available data at the time of the experimental work). Because of the possibility of skeletal rearrangements, these structures cannot be considered proven[213]. The final product was inactive as a ganglionic blocking agent.

The impetus to search after ganglioplegic antihypertensives in the series of secondary and tertiary amines was the discovery of the 2-amino-2,3,3-trimethylnorbornane derivative mecamylamine (**61**) (refs[601,602]). Our work[135] included the synthesis of **61** as a necessary standard but proceeded further by Eschweiler – Clarke methylation of **61** and **62** to the dimethylamino analogue **63** (dimecamine). Reaction of **61** with glutaric acid chloride and the following reduction gave **64** whose methiodide combines the structural elements of pentamethonium iodide (the bromide, cf. **10**) and mecamylamine; nevertheless it was found inactive. On the other hand, dimecamine (**63**) in the form of the hydrobromide was found to be more active as a ganglionic blocking and hypotensive agent[603,604] than **61**. After pharmacokinetic[605] and clinical pharmacology[606] studies it was clinically tested with very good results in patients with hypertension[607-612]. An analytical method for its differentiation from mecamylamine (**61**) was elaborated[613] and the introduction of **63** on the market (Dimecamin ®) was announced[614].

4 AROMATIC COMPOUNDS

4.1 Aryl Ethers, Sulfides, Amines Etc.

The Williamson reaction of the sodium salts of phenol and thymol with aminoalkyl chlorides afforded ethers **65** – **69** (refs[10,14,44,239]) as model compounds in the antihistamine field. The methiodide of **66** was transformed to the ammonium hydroxide, heating of which produced phenyl vinyl ether and N-methylpiperidine[15]. The effort to increase the low antihistamine activity of **65** led to the synthesis of di- and tri(2-diethylaminoethyl) ethers of catechol, resorcinol, hydroquinone, pyrogallol, and phloroglucinol[10]; their antihistamine activity was negligible; the pyrogallol ether **70**, however, proved important. Its quaternary salt **71** (gallamine triethiodide) was described by Bovet[615] as an outstanding peripheral myorelaxant. Our team[115,165] investigated and improved the synthesis of **70** and **71** and our priority with the base **70** (ref.[10]) enabled the manufacture and marketing of **71** in Czechoslovakia (Parexyl®, Remyolan®, ref.[616]). A complexometric determination of **71** was developed[617,618], the drug was included into the Czechoslovak Pharmacopeia[619] and its clinical testing confirmed its usefulness as a myorelaxant of medium duration of action in a large variety of surgical procedures[620,621].

Alkyl aryl ethers with the dimethylsulfonium cationic head in the alkyl residue were prepared as potential antihistaminics[41] and peripheral myorelaxants[86]. The ethers **72** and **73** (R^1 = CH_3, C_2H_5) were prepared[415] as analogues of the selective 5-hydroxytryptamine uptake inhibitor and antidepressant fluoxetine (**74**) (ref.[622]). Ethers **72** were obtained by reactions of potassium salts of the 2-alkoxyphenols with 3-dimethylamino-2-methylpropyl chloride in the presence of potassium iodide. Partial demethylation to **73** proceeded by treatment with ethyl chloroformate and the following alkaline hydrolysis. In the behavioural tests in animals, **72** and **73** proved inactive. Ethers **75** (X = O, S, NH) and their diethylamino, piperidino and morpholino analogues[20] were obtained by the Williamson reaction from the corresponding phenols. Only the sulfide **75** (X = S) had a rather high antihistamine activity but did not attain the activity of phenyltoloxamine (**75**, X = CH_2) (ref.[623]).The *p*-isomers of compounds **75** are inactive[20]. Attempts to prepare the bis(2-dimethylaminoethyl) ester of 4-chlorophenoxymalonic acid either by direct esterification with 2-dimethylaminoethanol or from the diethyl ester by ester exchange reaction[548] were unsuccessful; in both cases only **76** was obtained which is the known cerebral stimulant meclofenoxate[624].

Ammonolysis and aminolysis of methyl 3,4,5-trimethoxyphenoxyacetate led to a series of amides[358] out of which **77** (trimethophenoxamide) displayed antiarrhythmic activity comparable with that of procainamide. After a detailed pharmacological and pharmacokinetic investigation[625], **77** was tested clinically[628]; it proved active only in some types of cardiac rhythm disorders and caused hypotension as a side effect - for these reasons it was dropped. Similar amides of 3,4,5-trichlorophenoxyacetic, 2,4,6-trimethylphenoxyacetic and 4-bromo-3,5-dimethoxyphenoxyacetic acid[449] displayed only weak and structurally nonspecific actions (local anaesthetic, hypotensive, peripheral vasodilating).

Reaction of the sodium salt of thiophenol with 2-(1-piperidinyl)ethyl chloride gave the sulfide **78**. Its methiodide was transformed to the quaternary ammonium hydroxide giving on heating phenyl vinyl sulfide and 1-methylpiperidine[15]. 2-(Methylthio)ethyl phenyl sulfide added only one molecule of methyl iodide[51] and gave the monosulfonium salt **79**. 4-Nitrothiophenol (sodium salt) reacted with 2-dimethylaminoethyl chloride and the nitro group was reduced with iron and hydrochloric acid; the resulting amino sulfide afforded by treatment with methyl iodide **80**. 4-Nitrophenyl 2-chloroethyl sulfone was reacted with diethylamine, the nitro group was similarly reduced and addition of methyl iodide gave **81**; these compounds were prepared as potential ganglionic blocking agents[142]

Thiophenol and sixteen derivatives reacted with chloroacetonitrile and the products were transformed by treatment with hydroxylamine to a series of 2-(arylthio)acetamidoximes (**82**). In the case of 4-chloro-3-fluorothiophenol, the reaction with chloroacetonitrile led to an unexpected product identified as **83**. One member of the series of **82** (R = 3-OCH_3) displayed antireserpine activity in the test of ptosis in mice and in the test of reserpine-induced ulcer formation in rats and may thus be considered a potential antidepressant[406]. 4-Toluenesulfonamide and 4-toluenesulfonanilide were treated with sodium methoxide in methanol or with sodium amide in toluene and then with 2-dimethylaminoethyl chloride and 2-diethylaminoethyl chloride. The final treatment with methyl iodide gave **84** - **86** which proved only very weak ganglionoc blocking agents[142].

The high degree of local anaesthetic activity of lidocaine (**87**) (ref.[627]) led us to manipulation with its structure. Whereas the isomer **88** (ref.[66]) did not prove interesting, the known but neglected methylhomologue **89** (mesocaine), prepared by Hach in our team[628], showed very favourable properties[629-631] and after extensive clinical trials in most different indications[632-642] was introduced by SPOFA (Mesocain ®) on the market.

2,4-Dimethylchloroacetanilide treated with sodium methanethiolate gave the corresponding sulfide which reacted with methyl iodide without complications and gave the sulfonium salt **90** (ref.[109]). On the other hand the ring unsubstituted (methylthio)acetanilide reacted with methyl iodide under transalkylation and the product was identified as the molecular complex of **91** with trimethylsulfonium iodide[129]. N-Ethylaniline and diphenylamine were treated with 3-chloropropionyl chloride, the products reacted with sodium methanethiolate and then with methyl iodide giving sulfonium salts **92** and

93. The latter (**93**) displayed in vitro extremely high antispasmodic activity of the anticholinergic type (phenamsulfonium iodide) (ref.[129]).

A limited interest was devoted to the biphenyl derivatives. The ether **94** was prepared as a lower homologue of the atypical antidepressant and cerebral activator bifemelane (**97**) (refs[643,644]). It was obtained via the 4-bromobutoxy analogue and was found to have the profile of a thymoleptic agent: antireserpine activity in two tests and potentiation of yohimbine toxicity in rodents[527]. Addition of 2-hydroxybiphenyl to acrylonitrile gave **95** which could not be directly hydrolyzed to **96** (cleavage of acrylonitrile). For converting **95** to **96** it was necessary to proceed via the O-ethyl imidate hydrochloride and the ethyl ester of **96**. The acid **96** displayed higher analgetic potency than ibuprofen[527]. In the search after new ß-adrenergic blocking agents, compound **98** was prepared from 4-hydroxybiphenyl and epichlorohydrine and the following reaction with isopropylamine[245]. Compound **99** was prepared as a potential local anaesthetic from 2-aminobiphenyl by reaction with chloroacetyl chloride and by the following treatment with diethylamine[66].

4.2 ARYLALKYL DERIVATIVES

4.2.1 *Monoarylalkyl Derivatives*

The aralkyl ethers **100** and **101** were synthesized by the Williamson reaction as model compounds in the antihistamine field[10,15]. The methiodide of **101** was transformed to the quaternary base which decomposed on heating to benzyl alcohol, acetylene and 1-methylpiperidine[15]. The same **102** was obtained on the one hand from 2-diethylaminocyclohexanol, and from 2-diethylaminocyclohexyl chloride on the other[44]; it is assumed to have the *trans*-configuration. Ethers **103** and **104** were prepared similarly like **72** and **73** as potential antidepressants[415] but proved in vivo inactive.

Reaction of sodium benzyl mercaptide with 2-(1-piperidinyl)ethyl chloride afforded **105** whose methiodide was transformed to the quaternary base; its decomposition by heating resulted in benzyl vinyl sulfide[15]. Hydrochlorides of benzylamine, benzyldimethylamine, dibenzylamine, and tribenzylamine were tested with negative results for antihistamine activity within a trial to verify a hypothesis on the mechanism of action of antihistaminic aralkylamines[81]. N,N-Bis(2-chloroethyl)benzylamine reacted with dimethylamine in methanol in the autoclave and gave the monoquaternary piperazine **106** as the only product[98]. Reactions of 2-(benzylthio)benzyl chloride with secondary amines afforded six benzylamines out of which **107** is active in two antireserpine tests, potentiates the toxicity of yohimbine, has high affinity to imipramine as well as desipramine binding sites in the rat brain and strongly inhibits the re-uptake of 5-hydroxytryptamine as well as of noradrenaline in the rat brain structures and appears thus to be a promising potential antidepressant[534]. Even higher activity in the mentioned lines is displayed by moxifetin (**108**), the synthesis of which was described[532,562a] by several routes from 2-(3-methoxyphenylthio)benzoic acid together with thirty one analogues. Even after the correction of the statement of selectivity of the moxifetin action (it was found that **108** is also a strong inhibitor of noradrenaline re-uptake in the brain[645]), the compound remains an interesting antidepressant candidate and is being prepared in the form of the hydrogen maleate by preclinical tests to clinical trials. Its crystal and molecular structure was determined by the X-ray analysis[646]. Biochemical pharmacology[647,648], animal pharmacology[649], pharmacokinetics[650,651] and metabolism[652-654] were described. Its chiral homologue **109** was synthesized, resolved in the stage of the methoxy precursor but some stereoselectivity of action was found only in the line of inhibition of noradrenaline re-uptake[532].

Substitution reactions of 1,4-bis(chloromethyl)-2,3,5,6-tetrachlorobenzene with amines afforded ten diamines of the type **110** (ref.[319]); compounds **110** displayed some central stimulant activity. The benzylaniline derivative **111** (phenbenzamine, Antergan ®) was the first antihistamine agent which was practically used in the treatment of allergic diseases[655]. Our team prepared the piperidine and morpholine analogues of **111** by reactions of benzylaniline with 2-(1-piperidinyl)ethyl chloride and 2-(4-morpholinyl)ethyl chloride in the presence of sodium amide in benzene[23], out of which **112** showed 20% of the activity of **111** in vitro. The similarly prepared oxygen analogue **113** of **111** proved inactive[48]. The sulfonium analogue **114** showed 10% of the activity of **111** in vitro[51]. 1-Phenylalkanols were transformed to 1-phenylalkyl chlorides which were reacted with N-(2-dimethylaminoethyl)aniline in the presence of sodium amide. Out of the obtained α-alkyl homologues of **111**, the ethyl compound (**115**, $n = 1$)displayed the full activity of **111** in vitro[63]. Combination of α-methylation with benzyl p-substitution in the molecule of **111**, represented by **116** ($R = CH_3$, F, Cl, Br), resulted in the almost complete disappearance of the antihistamine[178] activity.

The sulfonium salt of the N-benzylpropionanilide series **117** (benzamsulfonium iodide) proved a very strong anticholinergic antispasmodic[129] like **93**, which was considered for clinical testing. Both compounds (**93**, **117**) were dropped because at the same time even more active ones became available (cf. **260**). A combination of molecules of the antihistaminic phenbenzamine (**111**) and the local anaesthetic procaine (**118**) (ref.[656]), represented by **119**, destroyed the antihistamine activity[35] (cf. also refs[7,27]). In the series of the sulfonium analogues of local anaesthetics[109], the ester **120** was found to display the full local anaesthetic activity of **118**. The reserpine model **121** was prepared by hydrogenation of hordenine and by the following acylation with 3,4,5-trimethoxybenzoyl chloride[127]; it was devoid of hypotensive activity. Aminoalkyl esters **122**, derived from 2-phenoxybenzoic, 2-phenylthiobenzoic[33], and 2-(phenylthiomethyl)benzoic acid[222] were prepared either from the acid chlorides or from the sodium salts of the acids; they have low antispasmodic activity and hypotensive effects of short duration. In the series of syringic acid derivatives[484], the amide **123** displayed some anticonvulsant activity. Our homologue 124 of the antiemetic trimethobenzamide[657] showed only hypotensive effects of short duration[484]. 4-Ethoxybenzamidines 125, prepared as potential antihistaminics[13] from 4-ethoxybenzonitrile via the O-ethyl imidate hydrochloride, were devoid of the expected type of activity.

Bis(2-phenylethyl) sulfide was cleaved during reaction with methyl iodide and under transalkylation dimethyl-2-phenylethylsulfonium iodide was formed[75]. A modified synthesis of the dopamine analogue 2-(3-fluoro-4-hydroxyphenyl)ethylamine was carried out[498] (cf. also ref.[658]) and found inactive as a dopaminergic compound. The diphenhydramine (cf. 164) isomer 126 was prepared from 1-phenyl-2-dimethylaminoethanol by treatment with benzyl chloride in the presence of sodium amide[68]. A similar reaction in the presence of sodium carbonate at 160°C led to hydramine cleavage[659] combined with N-benzylation under the formation of N,N-dimethylbenzylamine and acetophenone. Compound 126 was practically devoid of antihistamine activity. A clinical paper[660] on the high ganglionic blocking activity of phenyldimethonium (127) induced us to elaborate its synthesis from phenylacetonitrile via 2-(4-aminophenyl)ethylamine[98] (cf. also ref.[661]). The activity of 127 was confirmed by Trčka[567]. The synthesis of 128 as a potential myorelaxant was carried out[117] starting from (4-hydroxyphenyl)acetonitrile and proceeding via 2-(4-(2-dimethylaminoethoxy)phenyl)ethylamine; the product was found less active than 71. The amines 129, potential antidepressants[534], were prepared from 2-(phenylthio)benzaldehyde by reaction with nitromethane, by the folllowing reduction with lithium aluminium hydride and by N-methylation. The O-(aminoalkyl)oximes 130 and 131 were synthesized[545] by O-aminoalkylation of 4-(isopropylthio)acetophenone oxime as analogues of the serotonergic antidepressant fluvoxamine[662]. Our compound 130 displayed significant antireserpine activity and potentiated the yohimbine toxicity in rodents; it thus behaved like an antidepressant. The ester 132, obtained from sodium phenylacetate and 2-(methylthio)ethyl chloride, gave the methiodide by reaction with methyl iodide in low yield[129]. The ester 132 was also obtained by reaction of sodium 2-phenyl-2-(1-hydroxycyclohexyl)acetate with 2-(methylthio)ethyl chloride (the thermic cleavage of the said hydroxy acid to phenylacetic acid and cyclohexanone was known). The esters 133 did not reveal in the screening any appreciable activity[222]. ((2-Phenylthio)phenyl)acetonitrile was used to prepare the amidoxime 134 and several amidines 135; 134 and 135 (NR^1R^2 = 4-morpholinyl) showed some antireserpine activity and are considered potential antidepressants[522].

In the phenylpropyl series, the potential ß-adrenolytics 136 and analogues are mentioned as first. The synthesis of 136 started by reaction of 3-chlorophenylmagnesium bromide with epichlorohydrine and was concluded by reaction with 2-propylamine[245]. A further series of fluoxetin (74) analogues represented by 137 and 138 was prepared from N,N-dimethyl-3-chloro-3-phenylpropylamine[417]; the test in vivo could not prove the character of potential antidepressants. The 3-hydroxy-4-methylamphetamine (139) is known to cause hypermotility in mice which can be antagonized by cataleptic as well as noncataleptic neuroleptic agents[663]. It is thus a valuable tool for testing of neuroleptics. Its synthesis[664] was modified by us[363] which made this compound well accessible. 4-Hydroxy derivative of amphetamine and its N-monomethyl and dimethyl homologues were O-aminoalkylated[535] to a series of diamines **140** (n = 2 or 3, NR_2 = dimethylamino, diethylamino, 1-pyrrolidinyl, 1-piperidinyl, and R^1,R^2 = H or CH_3) accompanied in cases, when one of R^1R^2 is H, by the triamines like **141**; as potential antidepressants, **140** are inactive. Reaction of 4-(2-dimethylaminoethoxy)benzaldehyde with nitroethane gave 4-(2-dimethylaminoethoxy)benzonitrile as the only characterized product (cf. ref.[665]).

The amphetamine derivative **142** displayed properties of a potential antidepressant[534]. Its synthesis from ((2-phenylthio)phenyl)acetonitrile via ((2-phenylthio)phenyl)acetone proceeded smoothly. On the other hand, the synthesis starting by reaction of 2-(phenylthio)benzaldehyde with nitroethane was complicated in this first step by the unwanted formation of 2-(phenylthio)benzonitrile (cf. ref.[665]). Similar experiences were met in the series of methoxylated and hydroxylated analogues of **142** out of which **143** clearly showed the character of a potential antidepressant[553]. Reactions of 2-(methoxyphenylthio)benzaldehydes with nitroethane gave in addition to the wanted 1-aryl-2-nitropropenes also the corresponding benzonitriles and benzaldoximes (cf. ref.[665]). Only carefully purified 1-aryl-2-nitropropenes could be used in the syntheses of homogeneous amphetamine derivatives. The final methoxy amines (like **143**) were demethylated with pyridine hydrochloride or with boron tribromide to the corresponding phenolic amines[553]. The vinylogy between benzyl and cinnamyl led us to synthesize analogues of phenbenzamine (**111**) of formula **144** : cinnamaldehyde and its 4-methoxy derivative were transformed by reactions with aniline to the Schiff bases which were reduced with sodium borohydride to N-cinnamylanilines; these were alkylated with 2-dimethylaminoethyl chloride[211]. The antihistamine activity of **144** is weaker than that of **111**. In the series of sulfonium analogues of local anaesthetics, the sulfonium salts **145** and **146** were prepared[109]. The homologue of **127** is phenyltrimethonium (**147**), a potent ganglionic blocker[567,660], whose synthesis was also described in details[98]. A further adventure in the fluoxetine (**74**) series[415] consisted in the synthesis of **148** (R = methyl, ethyl, benzyl) by reactions of the potassium salts of 2-alkoxy(or benzyloxy)phenols with N,N-dimethyl-3-chloro-2-phenylpropylamine. Attempts at their partial demethylation by treatment with ethyl chloroformate led to cleavage of the molecules and obtaining of N-methyl-2-phenylallylamine after the hydrolysis. Two independent syntheses starting either from phenyl 2-propyl sulfide or 2-(4-aminophenylthio)propionic acid[545] led to the thia analogue of ibuprofen[666] of formula **149**; the antiinflammatory activity of the compound is comparable with that of ibuprofen, the toxicity is lower and the analgetic activity is higher.

A series of 1-phenylalkanols and dialkylphenylmethanols was transformed by reactions with 2-dimethylaminoethyl, 2-diethylaminoethyl and 2-(1-piperidinyl)ethyl chloride in the presence of sodium amide in benzene to series of thirteen ethers **150** and twenty one ethers **151** which were prepared as potential antihistaminics and antispasmodics[59]. The maximum antihistamine activity was attained by **150** (R = methyl; R^1 = butyl or pentyl), i.e. 12% that of diphenhydramine (cf. **164**), and by **151** (R = methyl; R^1 = butyl, isobutyl or pentyl; R^2 = methyl), i.e. 25 - 30% of the diphenhydramine activity in vitro. The most active antispasmodic (anticholinergic) of the series was **150** (R = ethyl, R^1 = isobutyl) which was considered a candidate for clinical testing[68] (it displayed 25 - 50% of the atropine activity in vitro). Compound **150** (NR_2 = 1-piperidinyl, R^1 = ethyl) had the highest myotropic antispasmodic activity (ten times higher than papaverine) (ref.[59]). Compound **150** (R = methyl, R^1 = hexyl) (ref.[21]) was prepared similarly. 1-Chloro-4-phenylbutan-2-ol was transformed to **152** which displayed clear ß-adrenergic blocking activity[245]. The bisquaternary ammonium salt **153** was prepared as a potential ganglionic blocker[117]. Double alkylation of phenylacetonitrile with 2-dimethylaminoethyl chloride opened the way to **154** – **156** (ref.[121]), derivatives of pentamethonium iodide (cf. the bromide **10**) with only low ganglionic blocking activity[568].

Multi-step syntheses led to the open heterocannabinoid models **157** and **158** (ref.[550]); compound **157** has high activity against the reserpine-induced ulcer formation in rats and **158** inhibits the spontaneous activity of mice. A series of aralkyl bromides was transformed by reactions with hydrazine hydrate to the corresponding aralkylhydrazines as potential monoamine oxidase inhibitors; compound **159** was the most active one in the test of potentiation of tryptamine convulsions in rats[252]. 2-Phenylpentanoic acid is a suitable component of molecules of antispasmodic agents. Its 2-chloroethyl ester gave by reaction with N,N-dimethylhydrazine the hydrazonium salt **160** (ref.[77]). Reaction of the acid chloride with 2-(methylthio)ethanol and the following addition of methyl iodide afforded the sulfonium salt **161** (ref.[74]). The sodium salt of 2-hydroxy-2-phenylpentanoic acid was reacted with 2-(methylthio)ethyl chloride and the product was treated with methyl iodide giving the antispasmodic **162** (ref.[116]).

4.2.2 *Diarylalkyl Derivatives*

4.2.2.1 Benzhydryl Derivatives

The 2-benzylphenol ether **75** (X = CH_2), phenyltoloxamine[623], was already mentioned. Its sulfonium analogue **163** was synthesized[41] from 2-hydroxydiphenylmethane by treatment with sodium ethoxide and 2-(methylthio)ethyl chloride in ethanol and by the following reaction with methyl iodide; it has considerable antihistamine activity in vitro but lower than ether **75** (X = CH_2).

Aminoalkyl benzhydryl ethers as a new group of antihistamine agents were discovered by Rieveschl at Parke and Davis in the U.S.A.[102]. The prototype is diphenhydramine (**164**, Benadryl ®) which is on the market since 1946 (ref.[667]). Our team devoted much effort to SAR investigations in this series and to attempts to find useful analogues of **164**. Ethers of this series were prepared by four methods: (*A*) from the benzhydrolate anion and aminoalkyl chlorides[10], (*B*) from benzhydryl bromide by heating with aminoalkanols and sodium carbonate[44,45], (*C*) from benzhydryl halide and sodium aminoalkoxides (1,1,2,2-tetraphenylethane was the usual by-product) (ref.[10]), (*D*) from benzhydryl haloalkyl ethers and amines[45]. Method *A* was new for the synthesis of **164** (ref.[45]);it was also used for the preparation of the less active **165** (ref.[10]). The piperidine analogue **166** (benzperidine, perastin(INN)) (cf. refs[139,169]) was prepared by methods *A*, *B* and *C* (ref.[10]) and was characterized in the form of several salts[10,21,42]; for the IR spectrum, cf. ref.[55]. Compound **166** was found unstable in boiling dilute hydrochloric acid; dibenzhydryl ether is the cleavage product[10]. The methiodide of **166** was transformed to the quaternary base which was cleaved on heating to benzhydrol, acetylene and 1-methylpiperidine[10].The hydrochloride of **166** was found equipotent with **164**.HCl (refs[667,668]) in pharmacological tests and its clinical usefulness was verified[669] which led to its introduction on the Czechoslovak market (Antihistamin ®) where it remained until 1962 when it was substituted by a more active agent[670]. Analytical methods and the article for the Czechoslovak Pharmacopoeia[671-673] were elaborated for **166**. A pharmacokinetic study was published[674] and a series of papers dealt with special aspects of biological activities of benzperidine[675-689]. Toxic effects of **166** in humans were found only after accidental ingestion of excessive doses in children[690,691]. The lower homologue of **164**, i.e. compound **167** was prepared by method *D* and was found much less active[45].

Method *A* using 1,3-bis(diethylamino)-2-propyl chloride gave **168** displaying poor activity[10]. Method *B* using 1,4-bis(2-hydroxyethyl)piperazine afforded according to the conditions used either the very active **169** (importantly exceeding the antihistamine activity of **164**) (ref.[58]) or the uninteresting **170** (ref.[21]). The chloro compound **171**, prepared from **169** (ref.[58]) displayed lower antihistamine activity and some adrenolytic effect. Compound **172** was prepared by method *B* from N,N'-bis(2-hydroxyethyl)-N,N'-dimethylethylenediamine and was found to be devoid of activity[58]. Method *B* produced also benzhydryl 6-dimethylaminohexyl ether[45] which was almost inactive. The benzhydrolate anion reacted with epichlorohydrine giving **173** which was transformed by treatment with secondary amines to amino alcohols **174** (R = diethylamino, 1-piperidinyl, 4-morpholinyl[8] and also benzhydrylamino[45]) which were not active. Method *B* using the corresponding *trans*-2-aminocyclohexanols afforded **175** (R = dimethylamino, diethylamino, 1-piperidinyl and 4-morpholinyl) with very low antihistamine activity[44]. Method *C* used in the same series gave 1,1,2,2-tetraphenylethane as the main product[44]. 2,6-Lutidine was reduced either with sodium and butanol or by pressure hydrogenation on Raney nickel to the mixture of isomeric 2,6-lupetidines which was separated by fractional crystallization of the hydrochlorides or of the N-(benzenesulfonyl) derivatives; the configuration was assigned on the basis of IR spectra. Both isomers were transformed by reactions with 2-chloroethanol to the amino alcohols which were converted by method *B* to *cis*- and *trans*-**176**, dimethyl homologues of **166** (ref.[55]). The work was intended as our first contribution to the problem of stereoselectivity of action but the result was poor because both isomers had only low antihistamine activity (10 – 20% of that of **166**).

Nuclear substitution in the benzhydryl ether series offered a further approach to potential antihistaminics. We started with the 2-, 3- and 4-methyl derivatives of **166** (ref.[8]) which were obtained by method *A*. The most active member of the series was the methiodide of **177** with 4-methyl which was more active than the hydrochloride. The morpholine derivative **178** (4-methyl), prepared by method *A*, had 20% of the activity of **164** (ref.[21]). Special attention was devoted to the 4-hydroxy derivative of diphenhydramine, i.e. **179**, which was considered a potential metabolite of **164**. In our first attempt[133], 4-acetoxybenzophenone was hydrogenated on Raney nickel in methanol to 4-acetoxybenzhydrol which on treatment with sodium amide and 2-dimethylaminoethyl chloride gave directly an oily base whose picrate showed correct analysis for the picrate of **179**. Because we could not exclude for our product the structure of the isomeric **180**, this compound was also synthesized[133] from 4-hydroxybenzophenone by reaction with sodium ethoxide and 2-dimethylaminoethyl chloride in ethanol and by the following reduction with lithium aluminium hydride; the difference of the final products was considered a proof of correctness of formula **179**. Our second approach[210] to **179** started from 4-hydroxybenzophenone which was transformed to the 2-tetrahydropyranyl ether. Reduction of the keto group with lithium aluminium hydride, following reaction with 2-dimethylaminoethyl chloride (sodium amide) and hydrolysis afforded unequivocally **179** which was found different from the product of the first approach[133]; this was finally identified as **181**. A new synthesis of **180** was also carried out[210].

Compound **182** was presented under the name of flunamine as an experimental antiparkinsonic, dopaminomimetic and potential antidepressant[692]. We prepared by method *A* (sodium hydride) its tertiary amine analogue **183** (ref.[473]) having a similar anticataleptic activity like **182**. The structure of our product, obtained by reaction of benzhydryl bromide with 2-aminoethanol (according to ref.[693]) and assumed to be 2-aminoethyl benzhydryl ether, was corrected by Pailer[694]: it is in fact 2-(benzhydrylamino)ethanol. The synthesis of **184** (ref.[533]) was stimulated by the fact that the dichlorobenzhydryl residue in this structure is the same like in some of the most active anxiolytic 1,4-benzodiazepines (cf. lorazepam[695]); compound **184** proved some anticonvulsant activity in the electroshock test in mice.

In the benzhydryl ether series a comparison of the influence of the character of the cationic head on the antihistamine activity was carried out. Reaction of **165** with ethyl iodide gave **185** having 10% of activity of **164** (all data in vitro) (ref.[97]). Benzhydryl 2-chloroethyl ether reacted with N,N-dimethylhydrazine to give **186** being four times as active as **164** (ref.[77]). Reaction of benzhydryl bromide with 2-(methylthio)ethanol and the following addition of methyl iodide afforded **187** displaying 60% of the activity of **164** (ref.[41]). 2-, 3- and 4-Methylbenzhydryl chlorides[49] gave similarly the corresponding methyl derivatives of **187** out of which the 4-methyl compound was twice as active as **164** (refs[41,73]). Alkylation of thiourea with benzhydryl 2-iodoethyl ether afforded the isothiuronium iodide **188** (ref.[77]) being almost inactive. Reaction of the same iodoethyl ether with triethylphosphine[97] gave **189** having 10% of the activity of **164** . Finally, reaction of benzhydryl 2-chloroethyl ether with trimethylarsine[62] gave **190** displaying in vivo and also in vitro 50% of the activity of **164**. In conclusion we proved the approximately equivalent influence of the various types of cationic heads on the activity; the atypical isothiuronium head is an exception and the lower activity of the ethylonium compounds (**185**, **189**) in comparison with the methylonium ones was well known[102]. Benzhydryl ethers containing instead of the cationic head only some hydrophilic groups were prepared[67] for checking the validity of our hypothesis on the possible mode of action of antihistaminics[81]. Reaction of benzhydryl bromide with glycerol in the presence of sodium carbonate gave a mixture which was separated by fractional distillation, the first fraction being evidently **191**. Substitution reaction of ethyl 3-bromopropionate with the benzhydrolate anion and the following alkaline hydrolysis afforded **192**. These compounds were devoid of antihistamine activity: the presence of the cationic head is indispensable. Two benzhydryl esters were prepared as the RC analogues (reversed carboxyl) of the antispasmodic diphenylacetic acid esters. Refluxing benzhydryl chloride with sodium 3-diethylaminopropionate in benzene[36] gave **193** (a papaverine-like antispasmodic) and N,N-diethylbenzhydrylamine together with benzhydryl acrylate as by-products. Reaction of benzhydrol with 3-(methylthio)propionyl chloride in the presence of pyridine[129] and the following addition of methyl iodide resulted in **194** which is a rather active anticholinergic antispasmodic. The attempts to prepare the sulfonium salts by reactions of benzhydryl 2-(methylthio)acetate and benzhydryl 2-(methylthio)propionate with methyl iodide led only to trimethylsulfonium iodide[129] (transalkylation). In the benzhydryl sulfide series, compound **195** (sulfide analogue of **166**) was prepared[10,15,42] either via 2-(1-piperidinyl)ethanethiol or via benzhydryl mercaptan[8]; it is almost devoid of antihistamine activity. Its methiodide was transformed to the quaternary base, the heating of which afforded benzhydryl vinyl sulfide and 1-methylpiperidine[15]. Sodium benzhydryl mercaptide reacted with 2-(methylthio)ethyl chloride and the following addition of methyl iodide gave **196** (very low antihistamine activity) (ref.[51]). Reaction of the same sodium mercaptide with N,N-diethyl-2,3-epoxypropylamine resulted in **197** (inactive) (ref.[8]). The observation that in the benzhydryl sulfide series there comes together with the disappearing of antihistamine activity to an increase of central depressant activity led to the development of **198** (captodiamine, Covatin ®) (ref.[696]) which was marketed as a psychosedative or ataractic agent with some anxiolytic component of action. Our manipulation with the structure of **198** (ref.[181]) led to **199** (dithiotolperidine), prepared via 4-(butylthio)-4'-methylbenzophenone. This compound significantly prolonged the narcotic action of thiopental in mice[697] and had only very low ataxic activity; it was recommended to clinical trials which, however, were withdrawn.

Benzhydrylamine and benzophenone derivatives were also the object of our synthetic studies. Some simple benzhydrylamine derivatives like **200** - **202** were prepared[81] in connection with our hypothesis on the mechanism of the antihistamine action. They were inactive which shows that there must be a certain distance between the benzhydryl carbon and the cationic head. Heating benzhydrylamine with ethyl 3-diethylaminopropionate to 200°C in the autoclave did not lead to the expected N-benzhydryl-3-diethyaminopropionamide[36]; the main product was **203** (aminolysis and amine exchange) accompanied by dibenzhydrylamine. Benzhydrylamines **204** and **205**, obtained via 2,3'-dichlorobenzhydryl chloride[533], had not interesting activity. On the other hand, compound **206**, designed as an analogue of the diazepam-like lorzafone[698], displayed anticonvulsant, central depressant and antinociceptive actions[533]. Esters **207** (R = diethylamino, 1-piperidinyl) (ref.[33]), prepared from benzophenone-2-carboxylic acid via the acid chloride, were only papaverine-like antispasmodics.

4.2.2.2 1,1-Diarylethyl Derivatives

1,1-Diarylethyl ethers and homologues are to be mentioned in the first line. Our systematic investigations of the antihistamine activity in series of homologues[17,28,39] led to the synthesis of 1,1-diphenylethyl ethers **208** and **209** (ref.[21]) by reactions of 1,1-diphenylethanol with 2-aminoethyl chlorides in the presence of sodium amide. The products proved important because while **209** was found equipotent with **166**, **208** was twice as active as **164** in vitro[668]. Testing in vivo[699] (histamine aerosol test and detoxication of histamine in guinea pigs) showed that **208** has six to twenty times higher activity than **164** and that it is a serious candidate for practical use (mephenhydramine, moxastine (INN)). In addition to the hydrochloride[21], some further salts were prepared[68,132] and for technical production its preparation by reaction of 1,1-diphenylethanol with 2-dimethylaminoethyl chloride hydrochloride in the presence of powdered sodium hydroxide was elaborated[154]; as a minor by-product of this procedure, a crystalline molecular complex of 1,1-diphenylethanol and **208** (1:1) was isolated, characterized and prepared from the components[272]. In comparison with **164**, the ether bond in **208** is even more unstable towards acid hydrolysis which was quantitatively confirmed in a study of the reaction kinetics[94]; the rate of the hydrolysis is approximately parallel with the degree of antihistamine activity which was in agreement with our hypothesis[81].

Analytical methods for the qualitative detection and quantitative determination of **208** were elaborated[700-702], a pharmacokinetic study was carried out[647], its influence on the growth of tissue cultures was investigated[703], and the antiulcer and gastric antisecretory effects in experiments were described[704-707]. The compound **208** was introduced on the market in 1955 by SPOFA (Alfadryl®) and it is still used as an antiallergic[708-710] and antiulcer agent[711,712]. Its CNS effects were also investigated[713]. The literature on mephenhydramine (**208**) was summarized in two reviews[139,169]. Reaction of the base **208** with 8-chlorotheophylline[68] gave a stable and crystalline molecular complex (1:1) which is an analogue of the anti-motion sickness agent dimenhydrinate (Dramamine ®) (ref.[714]). It was found[68] that our substance has higher antihistamine activity than **208** and also the central depressant activity was higher[715]. These were the reasons for its introduction in 1958 on the market as Theadryl® (mephenhydrinate, moxastine teoclate (INN)) as an antiemetic and anti-motion sickness agent (lower doses for children under the name Kinedryl ®), documented by many positive clinical reports[716-722]. Because of its sedative effect of the ataractic type it was also tested with positive results in the treatment of different psychoses[723-726]. Higher homologues of **208**, i.e. **210** (R = ethyl and propyl) were prepared similarly like **208** but their antihistamine activity is low[29].

Further step was the study of the influence of ring substitution in **208** on the antihistamine activity. To this end a series of 3- and 4-substituted derivatives with F, Cl, Br, I, OCH_3, SCH_3 and CN as substituents was prepared[138] from the correspondingly substituted acetophenones or benzophenones by Grignard reactions with arylmagnesium bromides or methylmagnesium iodide and the following reactions with 2-dimethylaminoethyl chloride in the presence of sodium amide. The 4-substituted compounds proved interesting with **211** (meflophenhydramine) and **213** (mebrophenhydramine, embramine (INN)) as the most active ones[727-729]. Without having knowledge of the work done in Germany[730,731] concentrated on the chloro compound **212** (chlorphenoxamine (INN), which was introduced as Systral ®) our pharmacologists could not find any superiority of this compound. After having taken into account the activity and toxicity[727-729], mebrophenhydramine (**213**) was selected for preclinical research[139,169]. Its synthesis from 1-(4-bromophenyl)-1-phenylethanol and 2-dimethylaminoethyl chloride hydrochloride in the presence of sodium hydroxide[154] was also feasible with good yields. Methods for its detection[732], quantitative determination[702], polarographic determination[733] and the use of capillary isotachophoresis in its analysis[734] were described. A contribution to its pharmacokinetics was published[735]. After a general discussion of metabolic fate of antihistaminics[736], a paper on the metabolic hydroxylation of **213** in homogenates of the rabbit's liver was published[737]. The identification of the metabolite as the 4'-hydroxy derivative of **213** was enabled by our synthesis of this compound[210] via 1-(4-bromophenyl)-1-(4-(2-tetrahydropyranyloxy)phenyl)ethanol.

The introduction of the hydrochloride of **213** on the market by SPOFA (Bromadryl®) was announced in 1961 – 1962 (ref.[738]) and an early report[739] dealt with its use in the radiation sickness. Most of the clinical papers[740-745] relate to its use in the treatment of allergic states. In addition to a report[746] on the dermatologic side effects of **213** coming from a direct contact of the skin with the substance, the central depressant and sedative side effects were reported[747] as the most important ones. This fact led to the introduction of a combination containing a small dose of phenmetrazine[748] (Bromadryl F ®) with which the sedative effects were completely removed and the drug was reported as useful in allergic states including bronchial asthma[741,749-753]. Another drug which found use in the treatment of asthma is the combination of **213.HCl** with ephedrine hydrochloride, theophylline and oxyphylline[754-761], marketed since 1962 as Xantedryl® and Xantedrylettae® (lower dosage for children). Mebrophenhydramine (**213**) was licensed to the British subsidiary of Smith Kline and French Co. and it was marketed in the U.K. and mainly in India (for years the most used antihistaminic in that country) as Mebryl®. The corresponding clinical documentation[762-768] was concentrated mainly to its use in the treatment of urticaria and urticarial pruritus, and also in asthma. The base **213** afforded also with 8-chlorotheophylline a crystalline and well characterized molecular complex (1:1) (ref.[155]) (mebrophenhydrinate, embramine teoclate (INN)) having antihistaminic and antiemetic properties with lower sedative side effects than mephenhydrinate (ref.[769]). It is marketed since 1968 as Medrin® and used mainly as an antiemetic[770-774].

Reactions of acetophenones with 2-substituted phenylmagnesium bromides (CH_3, Cl, SCH_3, and OCH_3) gave the corresponding tertiary alcohols and the first three of them were transformed to **214** by treatment with sodium amide and 2-dimethylaminoethyl chloride[272]; the 2-methoxy intermediate did not give the ether evidently due to the fact that the hydroxyl is very strongly hydrogen-bonded to the oxygen atom of the methoxy group (cf. IR). The ethers **214** are almost inactive as antihistaminics. Four ethers of the type **215** were prepared in connection with the already mentioned flunamine (**182**) and did not show any appreciable activity[473].

4.2.2.3 Further Diaryl- and Polyaryl-alkyl Derivatives

Ethyl diphenylacetate and benzilate were reduced with lithium aluminium hydride to the alcohols **216** and **217** which was one of the first applications of this reducing agent in this country[37]. Compound **216** was transformed to the ether **218** by treatment with 2-dimethylaminoethyl chloride and sodium amide[90]; **218** is a homologue of **164** and has 30% of its antihistamine activity in vitro. Methylation of diphenylacetonitrile with methyl iodide (sodium amide), the following hydrolysis of the methylated nitrile with dilute sulfuric acid to the amide and its degradation with potassium hypobromite afforded **219**, an antihistamine model compound[81]. Reduction of diphenylacetopiperidide with lithium aluminium hydride[90] gave **220**, a lower homologue of the antispasmodic fenpiprane[775]. 2-Chloroethyl diphenylacetate reacted with N,N-dimethylhydrazine under formation of **221** having some spasmolytic activity[77]. 2-(Methylthio)ethyl diphenylacetate (obtained from diphenylacetyl chloride and 2-(methylthio)ethanol) afforded sulfonium salts out of which the ethiodide **222** displayed a spasmolytic activity in vitro (6% of the atropine activity) (ref.[74]). A similar ester of benzilic acid[74] (dimethylsulfonium iodide) had 15% of the atropine activity. Diphenylacetonitrile was transformed via the O-ethyl imidate hydrochloride to 2,2-diphenylacetamidine[24]. Reaction of diphenylchloroacetyl chloride with 2-diethylaminoethanol gave an inhomogeneous base affording a crystalline hydrochloride considered to be the dihydrochloride of **223**. This product displayed a high antispasmodic (atropine-like as well as papaverine-like) activity and was introduced on the market after some pharmacological and toxicological studies as Prospasmin® (REMED) (ref.[1]). Carefull crystallization of this product[33] led to homogeneous **223.2HCl**, and from the mother liquor the hydrochloride of the benzilic ester **224** (benactyzine) was isolated. It was found that this component of Prospasmin® was responsible for its high atropine-like activity[776], whereas **223** is a papaverine-like antispasmodic. The ester **225** (ref.[33]) was evidently the intermediate of formation of **223** as well as of **224** (cf. ref.[2]).

Synthetic investigation on the basis of 2-(2-phenylethyl)benzoic acid led to compounds **226** – **229** (refs[222,240]) being structurally related to the antidepressants amitriptyline (cf. **367**) and imipramine. 1,2-Diphenylethanol was transformed by methods which were repeatedly described to the ether **230** (further homologue of **164**) and two analogues; their antihistamine activity was low[10]. 2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethanone was transformed in three steps to the dopamine derivative **231** which displayed opposite activity than expected[448]: it was procataleptogenic.

3,3-Diphenylpropionic acid was reduced with lithium aluminium hydride[37] to the alcohol **232** which was transformed to the ether **233** (further homologue of **164**), almost inactive as an antihistaminic[90]. 3,3-Diphenylpropyl bromide, obtained from **232**, gave in two steps the sulfonium salt **234**, a sulfonium analogue of fenpiprane[775], almost devoid of antihistamine activity[51]. The mentioned bromide reacted with hydrazine hydrate and gave the hydrazine derivative **235** as a potential monoamine oxidase inhibitor[252]. Reaction of sodium methanethiolate with 3-bromo-1-phenylpropanone, the following reaction with phenylmagnesium bromide and addition of methyl iodide afforded **236** (ref.[75]). 3,3-Diphenylpropionitrile was transformed via the corresponding O-ethyl imidate hydrochloride to the amidine **237** and two its analogues[24]; **237** displayed 10% of the antihistaminic activity of **164** in vitro. A further homologue of **164**, the ether **238**, was prepared from 1,3-diphenyl-2-propanol[21] and the amine **239** was obtained by reduction of the corresponding oxime by hydrogenation on Raney nickel[90]. As a potential dopaminomimetic, compound **240** was prepared[472] in five steps from 2-(3,4-dimethoxyphenyl)acetonitrile; in agreement with the expectation, this compound lowered the homovanillic acid level in corpus striatum of the rat brain.

Reaction of diphenylacetyl chloride with dimethylcadmium gave 1,1-diphenyl-2-propanone which was subjected to the Mannich reaction using dimethylamine, piperidine and morpholine[25]. For the resulting aminoketones two different formulations were possible out of which that corresponding to **241** was preferred[43] on the basis of negative results of the Lieben and Kuhn – Roth methods and of the result of degradation by melting with sodium hydroxide. Correctness of our formulation was confirmed after the appearing of our publication[43] by two other groups[777,778].

3-Chlorobenzophenone and some analogues were subjected to treatment with 3-dimethylaminopropylmagnesium chloride and the resulting tertiary alcohols were dehydrated by dilute sulfuric acid to the olefinic amines like **242** being the open models of the neuroleptic chlorprothixene (cf. **593**, R = 2-Cl) and displaying CNS depressant, antihistamine, antiserotonin and spasmolytic activity[214]. Reduction of the intermediate alcohols with hydroiodic acid gave the dihydro derivatives of **242**. Alkylation of 1,1-diphenylethane with 2-dimethylaminoethyl chloride (for the formation of the required carbanion, a reagent prepared from sodium and naphthalene in tetrahydrofuran[779] was used) afforded **243** showing some anticholinergic activity. The corresponding dibenzoylalkanes afforded in four steps the quaternary salts **244** (n = 2, 4, 8) (ref.[103]) out of which the lower member (n = 2) displayed a relatively high ganglionic blocking activity in cats[567], whereas the higher members (n = 4, 8) were peripheral myorelaxants[165]. The prenylamine[780] analogues **245** (R = H, OCH_3, dimethylamino; R^1 = H, methyl, ethyl) (ref.[496]) proved uninteresting; on the other hand, the intermediate **246** showed important anorectic activity which is in agreement with the literature report[781] on a lower homologue. The amino alcohol **247**, prepared from 3,4-diphenyl-2-butanone[498], proved indication of thymoleptic character (antireserpine activity). Aminoethyl ethers derived from triphenylmethanol and 1,1,2-triphenylethanol[10,42] are devoid of antihistamine activity.

4.3 ARYLCYCLOALKANE AND ARALKYLCYCLOALKANE DERIVATIVES

In the series of phenylcyclopentane derivatives, 4-cyclopentylacetophenone was the starting material. Its bromination, substitution reactions with amines and reduction of the keto group led to a series of amino alcohols[452] out of which **248** was the most active as a central stimulant. 4-Cyclopentylacetophenone oxime was transformed in four steps to **249** (ref.[420]), an analogue of the monoamine oxidase inhibitor pargyline[782]. 4-Cyclopentylaniline afforded in three steps a series of diamines with **250** being a potential antidepressant[450] (antireserpine activity). The easily accessible 1-phenylcyclohexanol was transformed to the ether **251** and some analogues[9]; **251** is almost devoid of antihistamine activity.

Ritter reaction with 1-benzylcyclopentanol led to the formamide **252** displaying some anticonvulsant activity; it was used for preparing a series of 1-benzylcyclopentylamines and their N-acyl derivatives[234,284]. Similar work on the basis of 1-benzylcyclohexanol was also carried out[234]. 2-Benzyl-1-methylcyclopentanol was subjected to the Ritter reaction and the resulting formamide was transformed[420] to amines like **253** showing hypotensive activity probably on the basis of ganglionic blockade. 1-Phenyl-3-(methylthio)-1-propanone was reacted with cyclohexylmagnesium bromide and the product treated with methyl iodide giving the weakly antispasmodic[75] sulfonium salt **254**, an analogue of the anticholinergic and antiparkinsonic trihexyphenidyl[783]. Esters of 2-, 3- and 4-(dimethylamino)benzoic acids were hydrogenated on platinum catalyst and the resulting dimethylaminocyclohexanecarboxylates were reacted with phenyl magnesium bromide[110]. Amino alcohols like **255** were obtained showing weak spasmolytic activity.

Esters of cyclohexylphenylacetic acid with a suitable cationic head in the molecule are powerful anticholinergic antispasmodics. Our group could confirm in this line the same relation like in the series of antihistaminic benzhydryl ethers: approximate equivalency of the various cationic heads from the point of view of the activity. Whereas the known drofenine (**256**, Trasentin H®) (ref.[139]) has only about 2% of the atropine activity in vitro, the quaternary salts **257** and **258** (refs[97,115]) have at least full atropine activity. The dimethylhydrazonium chloride **259**, obtained from 2-chloroethyl cyclohexylphenylacetate and N,N-dimethylhydrazine[77], is twice as active as atropine. The dimethylsulfonium salt **260** is much more active than atropine[74] and the triethylphosphonium iodide **261** has 20% of the atropine activity[97]. The pyridinium salt **262** (hexadiphenium bromide) (ref.[129]) is more active than atropine and was recommended together with **93** and **117** to clinical trials[784]. In the case of **262**, this was carried out[785] but the agent was found less active than **260**.

The most active antispasmodic of the just mentioned series is **260** (hexadiphensulfonium iodide, hexasonium iodide (INN)) which was first prepared from cyclohexylphenylacetyl chloride and 2-(methylthio)ethanol and by the following addition of methyl iodide[74]. A different method consisted in the reaction of 2-iodoethyl cyclohexylphenylacetate with sodium methanethiolate and in the following addition of methyl iodide[97]. A similar method on the basis of 2-bromoethyl cyclohexylphenylacetate was also used[124]; further methods consist in ester exchange of ethyl cyclohexylphenylacetate with 2-(methylthio)ethanol[124] and addition of methyl iodide, and finally in reaction of sodium cyclohexylphenylacetate with 2-(methylthio)ethyl chloride and treatment with methyl iodide[124]. Quite recently[786], cyclohexylphenylacetic acid mixed anhydride was used to esterify 2-(methylthio)ethanol. Crystal and molecular structure (preferred conformation) of **260** was investigated by the X-ray analysis[787,788]. Methods for analytical determination of **260** were worked up[789,790] and the stability of **260** was studied[791]. Pharmacological reports include general reviews on the activity of sulfonium salts as antispasmodics[792-795], papers on the spasmolytic activity of **260** (refs[796-798]), on its effects on the intestinal motility, cardiac action and salivation[799,800], on gastric secretion and gastric ulcers[801-808], on higher CNS activity[809], and on cholinesterases[810]. Compound **260** was introduced on the market by SPOFA in 1957 as Thiospasmin® as an oral preparation per 25 mg of the substance[811]. The first pharmacokinetic study used unlabeled **260** (ref.[812]), further studies in this line used [^{35}S]hexadiphensulfonium iodide[813-815]. Clinical studies of **260** dealt in the first line with treatment of spasms of the gastrointestinal, bile and uropoietic systems[816-819], further with treatment of gastric ulcers[820] and also with risks of therapeutic use of **260** (ref.[821]). A combination of **260** with tolazoline and phenobarbital was marketed by SPOFA as Syntospon® since 1963 (ref.[822]). A thioester **263** related to **260** was prepared from cyclohexylphenylacetyl chloride and sodium 2-(methylthio)ethanethiolate and by the following addition of methyl iodide[79]; it was found much less active than **260**.

Reaction of sodium hexahydrobenzilate with 2-(methylthio)ethyl chloride and the following addition of methyl iodide resulted in **264** (oxyphensulfonium iodide, oxysonium iodide (INN)) having at least comparable anticholinergic activity with that of **260** (ref.[116]). Its properties were described in several papers already mentioned[790,791,794,795,798,806-808] and in some further ones[823-825]. It is being used in therapeutic practice as the injection form of the preceding drug (Thiospasmin inj.®).

The dimethylhydrazonium analogue **265** of the preceding compound was obtained either from 2-bromoethyl hexahydrobenzilate and N,N-dimethylhydrazine or from sodium hexahydrobenzilate and N-(2-bromoethyl)-N,N-dimethylhydrazonium bromide[195]. It is a further extremely potent anticholinergic (oxyphenhydrazonium bromide) which was pharmacologically and clinically tested[825-827] with very encouraging results. The good position of oxyphenonium bromide (**266**, Antrenyl®) on the spasmolytic market[829] induced us to prepare a series of about twenty of its ring substituted (halogen, alkyl, methoxy, methylthio) derivatives and analogues[195]. The corresponding aryl substituted hexahydrobenzilic acids were mostly prepared by reactions of ethyl arylglyoxylates with cyclohexylmagnesium bromide and by final hydrolysis with aqueous potassium carbonate. The sodium salts of the acids were reacted with five aminoalkyl chlorides and the products were treated with methyl halides. The 3-fluoro derivative **267** (fluoxyphenonium bromide) proved to be the best from the point of view of activity and toxicity data and was successfully pharmacologically and clinically tested[828,830]. Compounds **265** and **267** were not introduced to practice because the well comparable **260** and **264** entered the market.

4.4 CONDENSED AROMATIC COMPOUNDS

4.4.1 *Indane and Indene Derivatives*

1-Indanone was hydrogenated on Raney nickel to 1-indanol and the same ketone was transformed by treatment with phenylmagnesium bromide to 1-phenyl-1-indanol; both alcohols gave by reactions with 2-dimethylaminoethyl chloride and sodium amide[29,40] the ethers **268** and **269** having 15 – 20% of the antihistamine activity of **164** in vitro. Mannich reaction with 1-indanone, paraformaldehyde and piperidine hydrochloride in ethanol afforded in addition to **270** (ref.[53]) the ethoxy derivative **271**, a new by-product of the Mannich reaction[54]. A similar reaction in butanol gave in addition to **270** the by-product **272** (ref.[54]). 1-Tetralone did not show a similar side reaction[54]. Reaction of **270** with phenylmagnesium bromide and the following dehydration gave **273** having high papaverine-like spasmolytic activity and some antihistamine effect[53]. Its hydrogenation on palladium proceeded under hydrogenolysis and gave 1-phenyl-2-methylindane[53]. The alcohol, obtained by reduction of **270** with lithium aluminium hydride[100], was esterified with 4-nitrobenzoyl chloride and the ester was reduced to **274** having significant local anaesthetic activity on the guinea pig's cornea[100]. The Schiff base, obtained from 1-indanone and aniline, was reduced with lithium aluminium hydride and the product was N-alkylated with 2-dimethylaminoethyl chloride to **275**, a cyclic analogue of **111**, practically devoid of the antihistammine activity[175].

With the aim to find new antispasmodics[46,82], indane-1-carbonitrile (**276**) was needed as the starting material. Its direct synthesis from 1-chloroindane was not successful; it was necessary to alkylate diethyl malonate with 1-chloroindane, to treat the malonic ester obtained with amyl nitrite and sodium ethoxide in ethanol and to dehydrate the intermediate 1-indanyloximinoacetic acid with acetic anhydride[46]. The nitrile **276** was then transformed to the amide and the corresponding acid which was converted to the ester **279**. Alkylation of **276** resulted on the one hand in the basic nitrile **277**, and in the benzyl derivative **278** on the other[46]. Alkaline hydrolysis of **278** gave the acid which was transformed via the acid chloride to the ester **280**. Alkylation of phenylacetonitrile with 1-chloroindane and the following processing of the nitrile obtained opened the access to the ester **281**, a further papaverine-like antispasmodic[46]. Processing of 3-phenyl-1-indanone[119] led to the ether **282** (a weak antihistaminic); the oxime of the said ketone opened the access to the amine **283** and its derivatives[119]. Cyclization of 3-(3-methoxyphenyl)propionyl chloride with stannic chloride gave 5-methoxyindanone (**284**) (with 7-methoxyindanone as a minor by-product) which was used as the starting material for the synthesis of estrogenic hormone model compounds[113]. 5-(Bromoacetyl)indane was subjected to substitution reactions with amines (e.g. benzylmethylamine), the products were reduced with lithium aluminium hydride and in the case of benzylamines subjected to final catalytic debenzylation with hydrogen on a platinum catalyst; **285**, a potential sympathomimetic, was one of the products[317].

4.4.2 *Naphthalene Derivatives*

1- Naphthol and 2-naphthol were transformed to 2-diethyaminoethyl ethers[10] and to their sulfonium analogues **286** which were almost inactive as antihistamine agents[41]. Heating 1-(1-naphthoxy)-2,3-epoxypropane with 1-methylcyclopentylamine, 1-methylcyclohexylamine and 1-methylcycloheptylamine afforded the amino alcohols **287**, analogues of propranolol[831], which displayed some β-adrenolytic activity[560]. Sodium salts of 1- and 2-thionaphthol were reacted with chloroacetonitrile and the products treated with hydroxylamine to give naphthylthioacetamidoximes **288** showing some antireserpine activity (potential antidepressants) (ref.[406]). 1-Naphthylphenylmethanol was transformed to the naphthalene analogue of **166** showing only 5 % of its antihistamine activity[14]. Compound **289** was prepared via 1-chloro-3-(1-naphthyl)-2-propanol[245] as a further potential β-adrenolytic agent. In the search after new neurotropic agents (potential antidepressants), 6-acetyl- and 6-propionyl-nerolin were reacted with 3-dimethylaminopropylmagnesium chloride and the alcohols obtained were dehydrated with dilute sulfuric acid to **290** (R = CH_3, C_2H_5) (ref.[268]). 2-Diethylaminoethyl di(1-naphthylmethyl)acetate[507] was synthesized as an analogue of the cerebral vasodilator naftidrofuryl[832].

4.4.3 *Tetraline Derivatives*

1-Tetralone was reduced to 1-tetralol and transformed by Grignard reaction to 1-phenyl-1-tetralol. Both alcohols were converted to the 2-dimethyalminoethyl ethers **291** and **292** as potential antihistaminics[29,40] (low activity). 2-(1-Piperidinylmethyl)-1-tetralone (the Mannich base) was reacted with phenylmagnesium bromide to give **293**, a relatively strong papaverine-like spasmolytic agent[53]. Its dehydration gave 1-phenyl-2-(1-piperidinylmethyl)-3,4-dihydronaphthalene. Attempts to saturate the double bond in this compound by hydrogenation on palladium proceeded under preferential hydrogenolysis via 2-methyl-1-phenyl-3,4-dihydronaphthalene to 2-methyl-1-phenyltetraline. Reduction of the mentioned Mannich base and two further steps resulted in **294**, a procaine analogue with high local anaesthetic activity[100]. Tetraline-1-carbonitrile (**295**, R = H) was prepared either by dehydration of the corresponding amide[46] or via 2-oximino-2-(1-tetralyl)acetic acid[82]. It was alkylated to **295** (R = alkyl, allyl, benzyl, 2-diethylaminoethyl) which were hydrolyzed with sodium or potassium hydroxides under severe conditions to mixtures of the corresponding acids and amides. Two of the acids were transformed to 2-diethylaminoethyl esters **296** (R = H or $CH_2C_6H_5$), potential antispasmodics[46]. The 1-allylnitrile **295** (R = allyl) was hydrolyzed under simultaneous cyclization to the hexahydrophenalene derivative[833].

2,2-Dimethyl-1-tetralone was reacted with methylmagnesium iodide, the product was dehydrated by heating with iodine, the olefinic product was subjected to Ritter reaction and the formamide obtained was reduced with lithium aluminium hydride[201] giving **297**; this sterically hindered amine displayed mild and brief hypotensive and ganglionic blocking effect. In the search after sulfonium analogues of local anaesthetics of the aminoacetanilide series, 5-(chloroacetamido)-6-methyltetraline was reacted with sodium methanethiolate to give **298** which, however, did not afford the methiodide[109].

4.4.4 6,7,8,9-*Tetrahydro-5H-benzocycloheptenes*

This skeleton was considered a suitable carrier system for biologically active molecules and our team devoted much effort to its functionalization; none of its derivatives, however, did find practical use; it was our first meeting with seven-membered ring systems. Compounds **299** - **302** were prepared[40,53,100] similarly like the analogues in the indane and tetraline series and also their pharmacological profiles were similar: **300**, antihistamine agent; **301**, papaverine-like antispasmodic; **302**, strong local anaesthetic. 6,7,8,9-Tetrahydrobenzocyclohepten-5-one was the starting material for many syntheses. The Schiff base, formed by its reaction with aniline, was reduced with lithium aluminium hydride and the product was alkylated with 2-dimethyalminoethyl chloride to **303**, a cyclic analogue of **111**, which was not found to have the expected antihistamine activity[274]. An attempt to cyclize 2,5-diphenylvaleric acid with polyphosphoric acid proceeded under decarbonylation and afforded 1-phenyltetraline[274].

6,6-Dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one was treated with 3-dimethylaminopropylmagnesium chloride[305] and the alcohol obtained was dehydrated to **304** (*E,Z*-mixture) which was devoid of antireserpine activity. Via the oxime, the ketone was transformed to the primary amine which was the basis of synthesis of the hypotensive **305**, the prenylamine[780] analogue **306**, and the propranolol[831] analogue **307** (ref.[274]). Reformatsky reaction of the ketone with ethyl 2-bromopropionate, the following dehydration and reduction with Raney nickel alloy in alkaline solution led to the acid **308** displaying some antiinflammatory activity[336]. Transformation of this acid to the amide and its Hofmann degradation gave the primary amine which was methylated to **309**, an amphetamine analogue having strong antireserpine activity in the test of ptosis. 5,7,8,9-Tetrahydrobenzocyclohepten-6-one[316] was also used for preparing a series of compounds; reduction of its oxime with sodium and ethanol gave **310** (amizoptene) displaying pronounced anorectic, antireserpine and mydriatic effects while the undesired stimulating effect was observed only after high doses. The amine **310** is also an analogue of amphetamine and its preparation by a different method was described by Seidl and Huisgen[834].

2-Acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene was another starting material in this area. Via the corresponding bromoacetyl compound[286], a series of amino ketones and amino alcohols was prepared out of which **311** displayed some hypotensive and spasmolytic activity. The tertiary alcohol obtained from the 2-acetyl compound by reaction with methylmagnesium iodide, afforded in attempts at dehydration (also Ritter reaction) instead of the isopropenyl derivative its dimer, identified as 1,3,3-trimethyl-1,2,3,4,5,6,7,8,9-octahydrocyclohept[*f*]indene (**312**). The known 2-acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene was hydrolyzed to the primary amine[304] which was converted via the 2-hydroxy compound to **313**, a further propranolol[831] analogue, which proved devoid of β-adrenolytic activity. Chloromethylation of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene, proceeding in position 2, served as another entry to the series. The chloromethyl compound gave easily the 2-(cyanomethyl) derivative which was reduced with lithium aluminium hydride to the primary amine displaying in addition to a mild stimulating effect a significant antireserpine activity[285]. The same nitrile was transformed by Claisen reaction with ethyl acetate and the following treatment with sulfuric acid to the corresponding arylacetone; the following reaction with methylmagnesium iodide, Ritter reaction, hydrolysis (and methylation) gave the phentermine[835] analogues **314** ($R' = H$ or CH_3) having – contrary to expectation – central depressant activity. Alkylation of diethyl acetamidomalonate with the chloromethyl compound and the following hydrolysis and decarboxylation afforded the phenylalanine analogue **315**. Friedel–Crafts reaction of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene with benzoyl chloride gave the 2-benzoyl derivative which was used[306] to prepare the O-(aminoalkyl)oxime **316**, the imine **317**, and the 3-dimethylaminopropylidene compound **318**; these compounds displayed central depressant activity.

4.4.5 *Tricyclic Condensed Aromatic Compounds*

4.4.5.1 *s*-Hydrindacenes

Cyclization of 5-(3-chloropropionyl)indane gave *s*-hydrindacen-1-one (**319**) which was an excellent entry to the *s*-hydrindacene series. This tricyclic system was almost completely neglected in the pharmaco-chemical research and was, therefore, an object of our attention. The oxime of **319** on the one hand was aminoalkylated to **320**, and reduced to **321** ($R^1 = R^2 = H$) on the other[353]. Alkylation of **321** ($R^1 = R^2 = H$) or its acylation and reduction gave several **321** ($R^1 = H$ or CH_3, $R^2 = CH_3$, C_2H_5, $CH_2C_6H_5$ or 2 = dimethylaminoethyl) displaying mild stimulating effects.

Reduction of **319** afforded *s*-hydrindacene which was acetylated to **322**, an important intermediate in the series[364]. Beckmann rearrangement of its oxime and the following hydrolysis with 100% phosphoric acid gave the amine **323** which was transformed in two steps into **324**, a mild tranquillizer with ataxic, hypothermic, thiopental potentiating, and spontaneous motility decreasing properties. Chloroacylation of **323** and the following substitution reactions with amines[435] led to a series of aminoacylamido compounds out of which **325** displayed local anaesthetic and antiarrhythmic activity. Bromination of **322** gave the bromoacetyl compound which was subjected to substitution reactions with amines (incl. alkylbenzylamines) and the products were reduced to amino alcohols and debenzylated by catalytic hydrogenation; **326** is an example of the products. Instead of the expected sympathomimetic character, the only effect observed was the hypothermic one[378]. Chloromethylation of *s*-hydrindacene[365] resulted in a mixture of the major **327** and the minor 4,8-bis(chloromethyl) derivative. After separation, both of these chloromethyl compounds were used for further syntheses. Reaction of **327** with benzylmethylamine, the following catalytic debenzylation, and alkylation with propargyl bromide afforded **328**, a pargyline[782] analogue; in agreement with the expectation, **328** potentiates the tryptamine-induced convulsions and has a mild stimulating effect. The 4,8-bis(chloromethyl) compound gave by reaction with 2-(1-piperazinyl)ethanol compound **332** having sedative, antiarrhythmic and surprisingly peripheral myorelaxant activity. Alkylation of diethyl formamidomalonate with **327** followed by hydrolysis and decarboxylation afforded the tricyclic phenylalanine analogue **329** (ref.[379]). The cyanomethyl compound, prepared from **327**, was transformed in two steps to (*s*-hydrindacene-4-yl)acetone whose oxime was used to prepare the amphetamine analogues **330** out of which especially the amino and dimethylamino compounds proved amphetamine-like properties (anorectic, antireserpine). A missleading hypothesis was the reason for multi-step syntheses of **331** ($n = 3$ or 4) as potential neuroleptics[419]; the products were devoid of this type of activity.

4.4.5.2 Acenaphthene and Fluorene Derivatives

Acenaphthene as a pharmacophore in the molecules of drugs is also rare. Our investigation in this series was of limited extent[268]. 2,2-Dimethylacenaphthen-1-one (**333**) was subjected to treatment with 3-dimethylaminopropylmagnesium chloride and the product was easily dehydrated to a mixture of geometric isomers of **334** out of which one homogeneous component was isolated. The ketone **333** was reduced with sodium borohydride to the alcohol which was transformed to the 2-dimethylaminoethyl ether **335**. The mentioned alcohol gave by treatment with hydrogen chloride the relatively unreactive 1-chloro compound affording by heating with 1-methylpiperazine only 19% of **336** (characterized only by the analysis of the picrate). None of these products did show any interesting properties.

9-Fluorenol as a cyclic analogue of benzhydrol was used to prepare aminoalkyl ethers like **337** which is almost devoid of antihistamine activity[14]. Fluorene-9-carboxylic acid is a cyclic analogue of diphenylacetic acid which led to the preparation of its 2-(methylthio)ethyl ester and the sulfonium salt **338** having about 10% of the spasmolytic activity of atropine in vitro[74]. Some fluorene compounds were also prepared as tricyclic models of the estrogenic hormones. In a model study, ethyl 2-methylcyclohexanone-2-carboxylate was treated with phenylmagnesium bromide and the product was transformed in three steps to crystalline and stereochemically probably homogeneous

2-phenyl-1-methylcyclohexane-1-carboxylic acid. Cyclization of its chloride with stannic chloride afforded the tetrahydrofluorenone **339** (ref.[84]). Using 4-methoxyphenylmagnesium bromide instead of phenylmagnesium bromide led to an analogous methoxy ketone which was demethylated by heating with pyridine hydrochloride to **340** (ref.[95]). In an attempt to prepare the methyl ether of B-nordoisynolic acid (**341**) by cyclization of the lactone **342** with aluminium chloride and hydrogen chloride[149], an inhomogeneous and estrogenically inactive acid $C_{18}H_{24}O_3$ was obtained. The inactivity indicates that the product is more likely the isomeric acid **343** (analogies[836,837]).

4.4.5.3 Anthracene and Phenanthrene Derivatives

The known spiroanthracene-9,1'-cyclopropan-10-one gave by treatment with 3-dimethylaminopropylmagnesium chloride[268] the expected alcohol **344** which, however, could not be dehydrated by an acid-catalyzed reaction under preservation of cyclopropane : treatment with hydrochloric acid gave **345**, with acetic anhydride **346**, with picric acid in boiling ethanol **347** (cf. also ref.[838]).

In the neurotropic field, 10,10-dimethyl-9,10-dihydrophenanthrene-9-one was transformed by treatment with 3-dimethylaminopropylmagnesium chloride to the alcohol **348** which was dehydrated by heating with phosphoryl chloride[268]. The product was found to be **349** (spectra); the primarily formed carbocation was stabilized under rearrangement. The by-product was identified as the known 9,10-dimethylphenanthrene.

The hydrophenanthrenecarboxylic acids **350** and **352** were described in the literature[5] as the estrogenically highly active degradation products of estrone and equilenine and named doisynolic (**350**) and bisdehydrodoisynolic acid (**352**); the methyl ethers **351** and **353** retain the high degree of activity. Our first original contribution in this area was the synthesis of the isomer of **353** with methoxyl shifted from position 7 to 9, i.e. **354** (ref.[83]). The synthesis started from methyl 9-methoxy-2-methyl-1-oxo-1,2,3,4-tetrahydrophenanthrene-2-carboxylate and proceeded in four steps. The product **354** was crystalline, probably homogeneous (ethyl and carboxyl probably in *cis*-position) and in the growth test estrogenically inactive.

In our synthesis of **351** we elaborated first the preparation of the two basic intermediates, i.e. 3-methoxyphenylacetylene[52,125] (from 3-methoxybenzaldehyde in four steps (cf. also ref.[838])) and methyl 2-ethyl-1-methyl-3-oxocyclohexane-1-carboxylate[118] (from Hagemann's ester in five steps). Reaction of these two components in the presence of potassium tert-butoxide in tert-butyl alcohol afforded the acetylenic lactone **355** (ref.[125]) which was hydrogenated on palladium in methanol to the crystalline saturated lactone **356**. Its cyclization with hydrogen chloride and aluminium chloride in benzene resulted in **351** as a stereoisomeric mixture having estrogenic activity comparable with that of estradiol benzoate. Further purification gave one homogeneous racemate, identified by the courtesy of Dr G. Anner (CIBA, Basel) by direct comparison with products of the total synthesis of the Swiss authors[849] as the Cα stereoisomer **357**. A similar synthesis starting from 3-methoxy-4-methylphenylacetylene[143] resulted in the crystalline and biologically active 6-methyldoisynolic acid methyl ether **358** having probably the same configuration like **357**. Reduction of **356** with lithium aluminium hydride[150] gave the crystalline diol **359** which was cyclized with polyphosphoric acid to a compound $C_{19}H_{26}O$ being most likely **360** (assigned on the basis of analogy of a similar reaction of 2-ethyl-1-methylcyclohexylmethanol and of the following hydrogenation); the cyclization was evidently accompanied by dehydration under Wagner – Meerwein rearrangement (cf. also ref.[841]). Compound **361** (inactive oily mixture of stereoisomers) was synthesized from ethyl 2-oxocyclohexanecarboxylate in ten steps[131] as an open model of **351**.

4.4.5.4 Dibenzo[*a*,*d*]cycloheptene Derivatives

Our team[137] was one of the first attacking the chemistry of this system within pharmaco-chemical investigations. The known ketone **362** was the best entry whose use led in the first study to fifteen dibenzo[*a*,*d*]cycloheptene derivatives including **363** – **366**. A modified procedure for preparing **362** consisted in the cyclization of 2-(2-phenylethyl)benzoic acid with a mixture of phosphoryl chloride and zinc chloride at 60°C (ref.[216]).The alcohol **363** was transformed to the 2-dimethylaminoethyl ether[137] and its methiodide **364** displaying quite important antihistamine activity in vitro. Attempts to acylate **363** by several acid chlorides in the presence of N,N-dimethylaniline led, surprisingly, to **366**. Reaction of **362** with 3-dimethylaminopropylmagnesium chloride gave the tertiary alcohol[168] which was dehydrated to **367**. This compound (proheptadiene) was recognized as having antireserpine, antihistamine and antiserotonin actions[842,843] and was recommended to clinical trials. In the meantime it appeared abroad[844] as amitriptyline and has been used with success until now in the treatment of mental depressions. Our clinicians[845-847] could only confirm these findings. Anyway, amitriptyline was introduced on the Czechoslovak market (Amitriptylin-SPOFA®) and for us it represented an important step on the way from antihistaminics to psychotropic agents, in this case especially to antidepressants. The transformation of **367** to the secondary amine **369** (nortriptyline) by treatment with ethyl chloroformate and by hydrolysis of the intermediate carbamate **368** was much improved and some independent synthetic ways were found[232] which enabled also the introduction of this antidepressant (Nortriptylin-SPOFA ®) on the Czechoslovak market[848-853].

Catalytic hydrogenation of **367** or reduction of its alcohol precursor with hydroiodic acid afforded the saturated side-chain amine **370**. Its lower homologue **372** was obtained from **371** by treatment with butyllithium and 2-dimethylaminoethyl chloride[168]. These saturated amines were less active as potential antidepressants. Carboxylic acid **373** was also accessible from **371** by lithiation and then carbonation[168]. The synthesis of **374**, the putative acid metabolite of amitriptyline[854], was carried out from **375** (ref.[501]).

Methods of preparing derivatives of **362** substituted in position 3 by atom of chlorine, methyl, methoxyl, and methylthio were worked up and these ketones were used to synthesize similarly[167] the corresponding amitriptyline derivatives out of which **376** in the form of a homogeneous geometrical isomer (chlorproheptadiene) was also clinically tested with interesting results[855]. The transformation of the 10,11-saturated ketones like **362** into the 10,11-dehydro analogues was possible and the unsaturated ketones were used[182] to prepare compounds **377** (proheptatriene, cyclobezaprine (INN)) and **378** (chlorproheptatriene). The former (**377**) was found interesting[856] and was used clinically for some time as an experimental antidepressant[857-861]. The synthesis of **379**, the lower homologue of **377**, was also carried out[232].

The 10-ketones **380** and **381** are accessible by cyclization of the corresponding 2-(2-benzylphenyl)acetic acids and were the source of preparation of several types of amines[207,231]. Both ketones were reduced with sodium borohydride to the secondary alcohols which were transformed to the ethers **382** and **383**; both compounds had antihistaminic, antiserotonin and sedative activity. The alcohols were further converted to the 10-chloro compounds giving by substitution reactions with 1-methylpiperazine compounds **384** and **385** (peraptene and chloroperaptene). They have strong sedative activity and **385** is a neuroleptic agent much more active than chlorpromazine. It was clear that this type was very promising in the line of antipsychotic activity but the fact that the priority in this area belonged to the Rhone – Poulenc company[862] led to discontinuation of our activity in this series. Interesting was the reaction of the oxime of **380** with 3-dimethylaminopropylmagnesium chloride[231]. The product was characterized as 4b-(3-dimethylaminopropyl)-5a,10-dihydroazirino[2,3-*m*]dibenzo[*a,d*]cycloheptene (**386**) which was hydrolyzed with picric acid in boiling ethanol to **387**.

4.4.5.5 Bridged Aromatic Tricycles

The known ketone **388** was transformed in the usual way into 9-(3-dimethylaminopropylidene)-6,7,8,9-tetrahydro-5*H*-5,8-methanobenzocycloheptene (**389**) (ref.[221]). Cyclization of 1-benzylcyclohexanol and its 3-chlorophenyl analogue with polyphosphoric acid gave 5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene and its 2-chloro derivative[221] which were oxidized with chromic anhydride to the ketone **390** and its 2-chloro derivative. Reduction of **390** afforded the corresponding alcohol which was converted to the ether **391** displaying some analgetic activity[148]. Ketones 390 (2-H and 2-Cl) were transformed to the olefinic amines **392** (2-H and 2-Cl) which were devoid of neurotropic activity[221].

4.4.6 *Tetracyclic Condensed Aromatic Compounds*

4.4.6.1 11*H*-Benzo[*a*]fluorenes

Compounds having this skeleton were prepared as analogues of the estrogenic hormone equilenine. Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate was reacted with 2-naphthylmagnesium bromide, the obtained mixture of stereoisomeric alcohols was dehydrated, the double bond was saturated by catalytic hydrogenation (Pd), the ester function was hydrolyzed and the resulting 1-methyl-2-(2-naphthyl)cyclohexane-1-carboxylic acid was cyclized in the form of the acid chloride with stannic chloride to **393** (ref.[95]). Similar synthesis using 6-methoxy-2-naphthylmagnesium bromide and leaving the double bond untouched[111] led to the crystalline ramic 11-oxo-14,15-dehydro-C-nor-D-homoequilenine methyl ether (**394**).

4.4.6.2 Direction to Hydrocyclopenta[*e*]phenanthrenes

Studies summarized in this paragraph are not classified according to the structure of the products prepared but according to the final goal of the work. Contributions to the total synthesis of the estrogenic hormones were the object of the studies (cf. also refs[6,72,152]). The main contribution consisted in the synthesis of the stereochemically homogeneous esters **395** (ref.[69]) and **396** (ref.[101]). Ethyl 3-(ethoxycarbonylmethyl)-1-methyl-2-oxo-3(4)-cyclohexene-1-carboxylate[69] was subjected to reaction with anisole and aluminium chloride according to the Indian authors[863-865] and **395** was obtained which was transformed by ester exchange to **396**. While refs[863-865] described **395** and **396** only as amorphous mixtures of stereoisomers, our products were crystalline and the dimethyl ester **396** was proven to be identical with an intermediate of an accomplished total synthesis of estrone[866] but obtained by a completely different way. Partial hydrolysis of **395** gave **397**, transformed in crude state to the acid chloride and cyclized with stannic chloride to an inhomogeneous and oily product assumed to be **398** (mixture of stereoisomers) (ref.[101]). Model synthetic experiments[157,174,177] proceeding via **399** – **401** were discontinued because of unsuccessful attempts to C-alkylate these compounds to the desired position (the reason was probably the complete enolization of these compounds).

In an attempt to prepare starting materials for the synthesis of equilenine, 6-acetylnerolin and 6-(3-(methoxycarbonyl)propionyl)nerolin were brominated and structures **402** and **403** were assigned to the products[112]. Dr J. Jacques (College de France, Paris) expressed doubts on the correctness of these structures[867]; in a common work[163], structures **404** and **405** were proven for our products and different methods leading to **402** and **403** were elaborated (bromination with phenyltrimethylammonium perbromide or with pyridinium bromide perbromide). Hydrindan-1,4-dione (**406**) was the object of our attention as a possible CD fragment of the molecules of estrogens. The first synthetic attempt[91] starting from dimethyl 3-nitrophthalate was discontinued after four steps in the stage of dimethyl 3-oxocyclohexane-1,2-dicarboxylate. The trials to reduce 4-methoxyindanone[113] with lithium in ammonia or sodium in ammonia did not afford characterized products. Finally, **406** was prepared[123] from 4-hydroxyindanone whose oxime was hydrogenated on platinum catalyst to the crystalline 1-aminohydrindan-4-ol (probably *cis* on the junction). Treatment with nitrous acid gave hydrindane-1,4-diol which was oxidized with chromic acid to **406** (probably *cis*) giving a crystalline and homogeneous bis(2,4-dinitrophenylhydrazone). In connection with an attempt to prepare 4-methoxy-1-tetralone as an intermediate, 4-methoxy-4-phenylbutyric acid was prepared from the known methyl 2-acetoxymercuri-3-methoxy-3-phenylpropionate in six steps[114]; an attempt at its cyclization in the form of the acid chloride in situ with stannic chloride resulted only in 4-chloro-4-phenylbutyric acid. An attempt to synthesize 7a-methyl-1,4-hydrindanedione (**407**) from 3,6-dihydroxyphthalonitrile by a multi-step procedure was finished in the stage of the mixture of stereoisomeric **408** (ref.[91]). Reaction of ethyl 3-bromo-1-methyl-2-oxocyclohexane-1-carboxylate with potassium acetate in boiling acetic acid gave the mixture of isomeric **409** which was separated and both isomers were characterized[105]. They were assumed to be potential intermediates in this area but many of their reactions[105] did not lead to useful results.

5 HETEROCYCLIC COMPOUNDS

5.1 HETEROMONOCYCLIC COMPOUNDS

5.1.1 *Furan, Thiophene, Pyrrole, Thiazole, and Pyrazole Derivatives*

Starting from furan-2-carboxaldehyde and proceeding via the secondary alcohol, the ether **410**, the furan analogue of **164**, was prepared[19]. Its methiodide displayed lower antihistamine activity than diphenhydramine (**164**) in vitro. A simultaneously appearing report[868] gave for the unstable acetate of **410** a higher activity. A modified synthesis[507] of the cerebral vasodilator naftidrofuryl **411** was described and the product was characterized as a mixture of two racemates in the ratio of 66:34. The analogous **412** was prepared from the known di(2-tetrahydrofurfuryl)acetic acid[507]. The synthesis of the very active anticholinergic spasmolytic agent penthienate bromide (**413**) was carried out[227] in the time when only pharmacological[869] and clinical[870] reports were available.

Our synthesis of the ganglionic blocker pentolonium bromide (**414**) was a similar case[99]; its high activity was confirmed[567]. The antidopaminergic neuroleptic agent sulpiride (**415**) was prepared by a modified route[509] together with some analogues. Ethyl 3-(ethoxycarbonyl)propionimidate hydrochloride reacted with ammonia in ethanol and instead of the expected amidine gave a product, identified as 5-imino-2-pyrrolidone[30]. The chain homologous imidates reacted normally and did not give the corresponding ring homologues[871]. The choline ester iodides **416** and **417** were prepared[556] from ethyl (2-oxo-1-pyrrolidinyl)acetate as a structural combination of the molecules of the nootropic agent piracetam[872] and acetylcholine which should play a role in memory deficits associated with aging. The 4-chloroanilide **418** was prepared from the chloride of the mentioned acid and was found to potentiate the anticonvulsant effect of diazepam in mice, to prolong the survival time of mice under conditions of nitrogen anoxia and to prolong the duration of the gasping reflex (acute brain ischemia induced by decapitation) in mice[556].

The thiazole derivative **419** was prepared as a potential local anaesthetic[66]. Attempts to prepare N'-isopropylcyancetohydrazide either by reduction of the corresponding acetone hydrazone with sodium borohydride or by reaction of methyl cyanoacetate with N-isopropylhydrazine gave a product $C_5H_{11}N_3O$ which was identified as the pyrazolidinone **420** (ref.[252]). This product, erroneously assumed to be the wanted isopropylcyanacetohydrazide, was used in a study[873] of its influence on the monoamine oxidase.

5.1.2 *Imidazole Derivatives*

In connection with our involvement in the group of antihistamine agents, we also were interested in the chemistry of histamine (**421**) and of its analogues[18]. Our contribution to the synthesis of histamine consisted in its preparation from 2-(4(5)-imidazolyl)acetonitrile by reduction with lithium aluminium hydride on the one hand[56], and by its pressure hydrogenation on Raney nickel on the other. N-Benzylhistamine (**422**), having neither histamine nor antihistamine activity, was prepared from **421** and benzaldehyde by catalytic hydrogenation on a platinum catalyst (reductive alkylation) (ref.[71]). Reaction of 4(5)-chloromethylimidazole with sodium methanethiolate gave **423** reacting with methyl iodide under transalkylation resulting in trimethylsulfonium iodide[104]. Reaction of 2-(4(5)-imidazolyl)acetonitrile with ethylenediamine in carbon disulfide[130] in the presence of water afforded **424** displaying clear histamine-like activity on the isolated intestine as well as on the blood pressure. 5-Methyl-1*H*-imidazole-4-ylmethanethiol was reacted with a series of aralkyl halides in the presence of sodium hydroxide[547]. Out of the products obtained, **425** and **426** showed some pharmacological properties which are considered predictive of antidepressant action.

In the 4,5-dihydroimidazole series, the histamine analogue **427** was prepared from 3-(benzamido)propionitrile via the O-ethyl imidate hydrochloride, by its reaction with ethylenediamine and acid hydrolysis[26]; compound **427** has neither histamine nor antihistamine activity. Reaction of benzhydrol with sodium in xylene, followed by treatment with 2-chloromethyl-4,5-dihydroimidazole resulted in **428** (diphenazoline, Antadril®) having in vitro 40% of the antihistamine activity[12] of diphenhydramine (**164**). Compound **428** was prepared almost simutaneously and independently on three other places[874-876]. Compound **429** (antazoline, Antistin®, Analergin®) is a mild but much used antihistamine agent[877]. Our contribution to its chemistry consisted in the preparation of its several new salts[132], in identification of the product of its alkaline hydrolysis[93] as N-(2-aminoethyl)-2-(N-benzylanilino)acetamide, and in the synthesis of its 4-methyl-, 4-methoxy - and 4-chlorobenzyl analogues[92] being altogether less active than **429**. Compound **430** (phentolamine, Regitin®) is a sympatholytic and hypotensive agent[878]. By reactions of correspondingly substituted diphenylamines with 2-(chloromethyl)-4,5-dihydroimidazole, our group[106] prepared three analogues of **430** for checking the dependence of activity on structure in this series : the desmethyl analogue was found to have the opposite effect, i.e. sympathomimetic; the *o*-tolyl analogue had about 50% of the activity of **430**; the *m*-tolyl analogue was found to be indifferent. Heating (2-phenylthiophenyl)acetonitrile with ethylenediamine tosylate led to **431** having mild antireserpine activity[522] (potential antidepressant). Similar reaction of 3,3-diphenylpropionitrile gave 2-(2,2-diphenylethyl)-4,5-dihydroimidazole and diphenylacetonitrile gave similarly the corresponding lower homologue[24]. Compound **432** was synthesized from the nitrile via the corresponding O-ethyl imidate hydrochloride[527]. The 2-amino-4,5-dihydroimidazole derivative **433** (clonidine, Catapresan®) is a very active antihypertensive and sympatholytic drug[879]. Our analogues **434** (ref.[327]) and **435** (ref.[435]) did not display interesting activity.

5.1.3 *Tetrahydrothiopyran Derivatives*

3,4,5,6-Tetrahydro-2*H*-thiopyran-4-ol was used to prepare the ester sulfonium salts **436** – **438** (ref.[136]). The former (**436**, mecyclosulfonium iodide) was found to be a very strong parasympathomimetic (cyclic analogue of acetylsulfocholine iodide); it was clinically tested but the limited usefulness of this type of neurotropic agents did not enable its production. The other two compounds (**437**, **438**) are strong anticholinergic spasmolytics. Reaction of the same alcohol with benzhydryl chloride in the presence of sodium carbonate gave the benzhydryl ether and addition of methyl iodide led to **439**, a weak antihistaminic[500]. Reaction of 4-tetrahydrothiopyranylmagnesium bromide with 10,11-dihydrodibenzo[*a*,*d*]cyclohepten-5-one, the following dehydration and addition of methyl iodide gave **440** which did not prove a potential antidepressant but a compound with antihistamine and anticholinergic properties[500]. The dimethylamino Mannich base derived from tetrahydrothiopyran-4-one was reacted with a series of arylmagnesium bromides giving ten amino alcohols (*cis*- and *trans*-mixtures). Compound **441**, which was separated to the major *trans*- and minor *cis*-component[505], is a thia analogue of the analgetic agent tramadol[880]. After our publication[505], another report on the synthesis of **441** was published[881]. Demethylation of *trans*-**441** gave *trans*-**442** proving higher analgetic activity than tramadol.

5.1.4 *Pyridine Derivatives*

A series of pyridinium salts was prepared by reactions of 2-(benzhydryloxy)ethyl iodide and chloride with pyridine and six of its homologues[76]; the unsubstituted **443** had the highest antihistamine activity (20% of that of **164** and **166**). Ethyl esters of all the three isomeric pyridinecarboxylic acids were reduced with lithium aluminium hydride to the isomeric pyridylmethanols[37] which was a very early use of this reducing agent. 3-Pyridylmethanol (Ronicol ®) which is a potent peripheral vasodilator, was also prepared from pyridine-3-carbonitrile by catalytic hydrogenation on Raney nickel and the following reaction of the obtained 3-(aminomethyl)pyridine with nitrous acid[50]. Further transformations to 3-(chloromethyl)pyridine and 3-pyridylmethylmercaptan were also described[50]. Reactions of 3-pyridylmethanol with sodium amide and benzhydryl bromide afforded the ether **444** (almost devoid of antihistamine activity) together with 1,1,2,2-tetraphenylethane[68]. Piperidine and morpholine analogues of the antihistaminic agents pyribenzamine[882] and mepyramine[883] (**445** and **446**, X = CH_2 or O) were prepared[23] by aminoalkylation of N-benzyl-2-aminopyridine and its N-(4-methoxybenzyl) analogue; the most active was found to be **445** (X = CH_2) having 50% of the activity of phenbenzamine (**111**). Out of the α-alkyl homologues of pyribezamine, the ethyl homologue **447** was found to be the most active[63] (twice as active as **111**). Combination of α-methylation and p-substitution in benzyl (cf. **448**, R = CH_3, Cl, F, Br) led to significant decrease of the antihistamine activity[178]. Also the vinylogues of pyribenzamine and mepyramine (**449**, R = H or OCH_3) were weak antihistamine agents[211]. The indane containing cyclic analogues **450** (R = H, Cl) are almost inactive[175].

N-(2-Pyridyl)benzamide was prepared on the basis of an erroneous report on its antihistamine activity[32]. N-(2-Pyridyl)chloroacetamide, obtained from 2-aminopyridine and chloroacetyl chloride[66], reacted with diethylamine under the formation of **451**, a potential local anaesthetic. A similar reaction with 1-methylpiperazine gave **452** which inhibits very potently the formation of indomethacine-induced gastric ulcers in rats but is rather weak as an antisecretory and anticholinergic agent[530]. 2-Amino-3-methylpyridine reacted with chloroacetyl chloride under the formation of **453** which could be transformed to **454** by treatment with diethylamine[66]. 3-Acetyl- and 3-propionylpyridine reacted with phenyl- and 4-tolylmagnesium bromide under the formation of the tertiary alcohols which were transformed to ethers by reactions with aminoethyl chlorides[16,42]. Combinations **455** and **456** were found most convenient from the point of view of antihistamine activity[17] (approximately equipotent with **164** and **166**). For the marketed 2-pyridyl analogue doxylamine (Decapryn®), a similar intensity of effect was reported[884].

Nicotinic acid is a well known peripheral vasodilating agent which was the reason for our efforts at finding more suitable agents of this type in the area of nicotinic acid derivatives. The hydrophilicity of such derivatives was one condition and this was the reason for preparing esters of nicotinic acid with alkylene glycols $HO(CH_2)_nOH$ with n = 2, 3, 5, 6. Reactions of nicotinoyl chloride with these glycols gave on one hand the hydroxyalkyl esters, and diesters on the other[64]. Out of the monoesters the lowest member of the series, i.e. **457** (ethiacine) proved the best and protracted vasodilating activity[885,886] and the agent was recommended to clinical trials. Its analytical determination[887] was worked out but the introduction to practice became impossible because of its instability in aqueous solutions. Reaction of nicotinoyl chloride with 2-(methylthio)ethanol and the following addition of methyl iodide[64,80] gave **458** which showed properties of a hypotensive ganglionic blocker[567]. In addition to the glycol dinicotinates, the similar esters of picolinic and isonicotinic acid were also prepared[70], transformed to dimethiodides which were hydrogenated on platinum and the saturated products transformed again to dimethiodides. Compounds **459** and **460** displayed some curare-like activity in some of the tests available[165,578]. The synthesis of benzyl or benzhydryl esters of nicotinic acid[49] presumed their easy hydrolysis and such esters were considered prodrugs of nicotinic acid. Compound **461** displayed considerable hypotensive activity but was relatively toxic[885]. Reactions of nicotinoyl chloride with benzylamine and aminopyridines gave the corresponding nicotinamides[64]; heating of nicotinic acid with N-phenylethylenediamine afforded N-(2-anilinoethyl)nicotinamide[31] having low antihistamine activity. The nicotinamide **462** displayed protracted hypotensive and peripheral vasodilating effect[234]. Compound **463** was obtained from nicotinoyl chloride and 4-(2-diethylaminoethoxy)aniline[484].

(3-Pyridyl)acetonitrile was used as the starting material for the synthesis of several derivatives of homonicotinic acid[60], e.g. **464** – **466**; the first two are weak antispasmodics, the latter has mild pressoric effect (the opposite effect to that of the phenyl analogue tolazoline[888]). Alkylation of phenylacetonitrile with 2-bromopyridine gave 2-phenyl-2-(2-pyridyl)acetonitrile[65] which was also used for further syntheses; one of the products was **467**. Several α-substituted 2-pyridylthioacetamides[514] were prepared as potential anti-ulcer agents. N-Alkylation of 4-phenyl-1,2,3,6-tetrahydropyridine with phenacyl chloride was the entry to the synthesis of potential analgetics like **468** and **469**.

5.1.5 *Piperidine Derivatives*

N-Monosubstituted piperidines as analogues of the corresponding dialkylamino compounds were mostly described in the preceding paragraphs. This chapter is devoted – with some exceptions – to C-substituted piperidines. N-Phenacylpiperidine and its methyl homologue were transformed by reactions with arylmagnesium bromides to the amino alcohols **470** (R = H or Cl, R^1 = H or CH_3) as potential antitussive agents[193]. The piperidine analogue of pentolonium bromide (**414**) was prepared[117] and was found to be less active as a ganglionic blocker[567] as 414. The amphetaminoid **471** (mixture of stereoisomers) was prepared by reductive amination of phenylacetone with 3-amino-1-ethylpiperidine and sodium borohydride[544]. 1-Methyl-4-piperidinol, 1-benzyl-4-piperidinol and 1-methyl-4-phenyl-4-piperidinol were transformed by nucleophilic substitution reactions with 2- or 4-fluorophenyl sulfides in dimethylformamide and in the presence of sodium hydride into the corresponding ethers[540] out of which **472** and **473** displayed activity in tests considered indicative of antidepressant activity.

N-(4-Piperidinyl)benzamides **474** and **475** were prepared as analogues of sulpiride (**415**) (refs[509,554]) and **475** proved to be an antidopaminergic neuroleptic with mild ataxic, cataleptic and antiapomorphine activities. 4-Aryl-4-substituted piperidines gave by treatment with S-methylisothiouronium sulfate compounds **476** which were prepared as potential blockers of the adrenergic neurones[327] but were devoid of antihypertensive activity. 1-(3-Chloropropyl)-4-phenylpiperidine was used to the synthesis of several 3-(4-phenyl-1-piperidinyl)propyl esters[227] out of which **477** was an anticholinergic antispasmodic and mydriatic agent. Compound **478** was obtained from 1-(4-chlorobutyryl)-4-cyclopentylbenzene and 4-phenyl-4-piperidinol[511] and had properties of a tranquillizer.

Penfluridol (**479**) is an oral and long-acting neuroleptic agent[889]. The need of a sample of this compound as a standard led us to search after more convenient synthetic routes than those described. The first new route started from 4,4'-difluorobenzophenone and proceeded via **481** which was processed by reaction with 4-chloro-3-trifluoromethylphenylmagneium bromide[303]. Another one used 4,4-bis(4-fluorophenyl)butyric acid and proceeded via **482** which was reduced with lithium aluminium hydride[303]. The best method found started by elaboration of a reliable synthesis of the mentioned acid by reaction of 4-(4-fluorophenyl)butyrolactone with fluorobenzene and aluminium chloride[374], the acid was reduced with sodium dihydridobis(2-methoxyethoxo)aluminate to the alcohol giving by treatment with hydrobromic acid 4,4-bis(4-fluorophenyl)butyl bromide. The final substitution reaction with 4-(3-chloro-4-trifluoromethylphenyl)piperidine-4-ol afforded **479**. This synthesis together with the following preclinical[890,891] and clinical studies[892] enabled the introduction of **479** to psychopharmacological practice in this country (Micefal®). Its decanoic ester **480**, described by our group[414], proved an ultralong acting depot neuroleptic in the tests of antiapomorphine activity in dogs. On the other hand, the cyclic analogue **483** proved inactive[374].

Compound **484** was prepared from 4-bromobenzophenone by treatment with 1-methyl-4-piperidinylmagnesium chloride and by the following dehydration[544]; it displayed a mild antihistamine effect in vivo and significant peripheral antiserotonin activity. A similar synthesis of the antihistamine and antiserotonin agent cyproheptadine (**485**) was published by us[183] two years before the publication of the original authors[893].

The analgetic activity of pethidine (**486**) (ref.[894]), a simple model of the morphine molecule, induced our extensive experimental work in this field starting mostly from norpethidine (**487**). A new synthesis[191] of oxpheneridine (**488**) (ref.[895]) and of its acetate was carried out; both compounds proved higher analgetic activity than **486**. The amine analogues[223] of oxpheneridine like **489** proved inactive. The same result was reached with **490** (ref.[393]). On the other hand, the amino alcohol **491**, obtained in two steps from **487**, was rather active as an analgetic[191]. 1-Methyl-4-piperidone reacted with 4-cyclopropylphenylmagnesium bromide and the product was acylated with propionyl chloride to give **492** (ref.[544]), the analgetically inactive cyclopropyl derivative of the reversed carboxyl analogue of pethidine having significant activity[896]. Much experimental work was devoted to the synthesis of analogues of the extremely potent analgetic fentanyl (**493**) (ref.[897]). Only the very near analogues **494** – **496** displayed activity near to that of **493** (ref.[544]).

5.1.6 *Morpholine Derivatives*

Some N-monosubstituted morpholines were mentioned in the preceding paragraphs as analogues of the dialkylamino derivatives. Morpholines **497** were unexpectedly obtained as products of reactions of 4-(alkylsulfonyl)phenacyl bromides with diethanolamine[485]. The methiodide of **497** ($R = CH_2CH(CH_3)_2$) showed peripheral myorelaxant effect.

5.1.7 *Pyrimidine Derivatives*

In the effort to prepare some pyrimidine analogues of histamine, the correspondingly substituted diethyl malonates were reacted with thiourea and the products were hydrolyzed to give **498** (ref.[34]). Attempt to cyclize 4-(4-chlorophenylthio)-2-(methylthio)pyrimidine-4-acetic acid with trifluoroacetic anhydride gave the enol **499** which was transformed by the action of sulfuric acid[347] into **500**.

5.1.8 *Piperazine Derivatives*

Some of the piperazine derivatives were already mentioned in the preceding paragraphs, many will be described in the following ones. Here some further compounds will be mentioned in whose molecules piperazine plays a cardinal role.

A series of variously Ar-substituted analogues of 1-phenyl-4,4-dimethylpiperazinium iodide (DMPP), a known stimulant of sympathetic as well as parasympathetic ganglia[898] was prepared[342] having instead of one methyl group 2-cyanoethyl, 2-aminocarbonylethyl or 2-ethoxycarbonylethyl; the products have ganglionic blocking, hypotensive and myorelaxant properties being at the same time considerably toxic. Out of the piperazine derivatives containing the 4-cyclopentylphenyl residue in the molecules[497,511,512] **501** displayed analgetic activity in the peritoneal test, **502** and **503** are tranquillizers with ataxic, antiamphetamine, thiopental potentiating, and locomotor activity inhibiting effects. In the sulpiride (cf. **415**) series, **504** and **505** proved the character of antidopaminergic neuroleptics with some ataxic and antiapomorphine activity[509,559]. A series of naphthyl- and tetralylpiperazines[320] was prepared by heating hydrochlorides of the naphthyl- and tetralylamines with diethanolamine hydrochloride, and by the following N-substitution; **506** was found to be a mild neuroleptic with ataxic, hypothermic, antiamphetamine, and cataleptic activity. One of our compounds, 1-(1-naphthyl)piperazine, was described more recently[899] as a 5-hydroxytryptamine-1B agonist. The prepared 1-(2-fluorenyl)piperazines were found uninteresting[352]. Series of piperazine-containing 2-substituted 6,7,8,9-tetrahydro-5*H*-benzocycloheptenes were prepared[304,317,318] : **507** is a potential antidepressant, **508** has central stimulating and hyperthermic effects, and **509** is a sedative.

The putative bioisosterism between pyridine and nitrobenzene[900] led to the synthesis of **510** having important anti-ulcer and anticholinergic activity and being thus similar to the tricyclic pyridine derivative pirenzepine[901]. Anti-ulcer activity was also found with 5-(2-(4-methyl-1-piperazinyl)acetamido)methyl-10,11-dihydrodibenzo[*a*,*d*]cycloheptene[523]. Some of the 1-(2,4,6-trimethylbenzyl)piperazines[345] showed mild central stimulating activity. 2,3,5,6-Tetrachloro-1,4-bis(4-methyl-1-piperazinylmethyl)benzene was peripheral vasodilator and hypotensive in rats[319]. Similar properties were shown by 1-(3-dimethylamino-3-phenylpropyl)-4-methylpiperazine[408]. The N-(2-Hydroxyethyl)piperazino analogues of penfluridol (cf. **479**) and their esters were inactive as neuroleptics[374]. Reactions of ethyl (2-oxo-1-pyrrolidinyl)acetate with monosubstituted piperazines gave a series of piperazides out of which **511** and **512** were more active than piracetam[872] by their antiamnesic effects in rats, by antagonizing the brain-damaging effects of cycloheximide in infantile rats and by their potentiation of the effects of anticonvulsant agents[557]. 4′-Chloro-4-fluorobutyrophenone was subjected to the substitution reaction with 1-(ethoxycarbonyl)piperazine, the product was hydrolyzed and subjected to further transformations[330]; all of the products were noncataleptic and **513** had strong ataxic activity. 1-Methyl-4-(1,2-diphenylethyl)piperazine, an open model of perathiepin (cf. **737**, R = H), did not influence the CNS (ref.[251]). Some further open models of this compound and of octoclothepin (cf. **737**, R = 8-Cl), e.g. **514** and **515**, were likewise inactive as neuroleptics[277,375]. Compound **515** and its analogues[506] showed some anthelmintic activity. A further open model of octoclothepin, i.e. **516**, was an anticonvulsant[359]. For the similarly constructed **517**, antidepressant activity was indicated in the literature; its synthesis by a different method was carried out together with the synthesis of a series of analogues but indications of antidepressant activity could not be noted[460].

Substitution reactions of 4-(alkylsulfonyl)phenacyl bromides with 1-arylpiperazines afforded a series of phenacylpiperazines out of which **518** (mesylphenacyrazine) was selected as a sedative with low toxicity for clinical testing[337]. Its pharmacology was investigated[902-907], the [^{14}C]substance (label in the CO group) was synthesized and pharmacokinetic and metabolic study was carried out[908]; compound **519** (main metabolite) (cf.[337]), N-phenylpiperazine, 4-(methylsulfonyl)benzoic acid, and 4′-hydroxy derivative of **518** (cf. ref.[337]) were identified as urine metabolites. Phase 1 of clinical trials[909,910] proved the sedative and hypnotic effect but showed also some side-effects (mainly of adrenolytic character) which resulted in stopping the experimentation with **518**. Several further analogues of **518** were found uninteresting[338,485]. The structure of the antitussive agent eprazinone[911] induced us to synthesize several fluorinated amino analogues **520** with comparable antitussive activity in rats and guinea pigs[454]. We were also involved in the investigation of the structural field of analgetic activity of the piperazine AP-237 (ref.[912]) and our product **521** proved more active than the prototype and had also antiinflammatory activity[424]. 1-(4-Methoxyphenoxyacetyl)-4-(2-phenylethyl)piperazine[508] was found to have sedative, antiarrhythmic and indications of thymoleptic activity. In the series of 1-acyl(or thioacyl)-4-benzylpiperazines, analogues of the antidepressant piberaline[913], compounds **522** and **523** displayed some activity of a similar type[546]. 1-(1-(4-Methoxyphenyl)-3-phenylpropyl)-4-methylpiperazine[275], a member of a longer series of analogues, displayed anticonvulsant, hypothermic, thiopental potentiating, and mydriatic activities. Compound **524**, prepared in four steps from 2-(3,4-dimethoxyphenyl)-1-(4-tolyl)ethanone[448] as a dopamine analogue, proved anti cataleptic activity.

5.2 HETEROBICYCLIC COMPOUNDS

5.2.1 *cis-2-Azabicyclo*[3.3.0]*octanes and cis-8-Azabicyclo*[4.3.0]*nonanes*

Compounds **525** and **526** were prepared[327] as analogues of the adrenergic neurones blocking agent guanethidine[914]; the latter (guanisoline, **526**) showed in a battery of tests properties similar to those of guanethidine and was used in an orientation clinical test with hypertonic patients using oral administration. Its antihypertensive effect was found unreliable and the clinical testing was stopped[327].

5.2.2 *Benzo[b]thiophene and Indole Derivatives*

(5-Chloro-2-(phenylthio)phenyl)acetothiomorpholide and its 5-methyl analogue gave on treatment with polyphosphoric acid **527** (R = Cl or CH_3) which constituted a new synthesis of benzo[*b*]thiophene skeleton[375,390]. Compounds **527** were transformed by acid hydrolysis to 2(3*H*)-benzo[*b*]thiophenones **528**.

Alkylation of indole with 3-dimethylaminopropyl chloride (NaH, dimethylformamide) gave 1-(3-dimethylaminopropyl)indole[239]. Acylation of 2,3-dihydroindole with chloroacetyl chloride and the following reaction with diethylamine afforded 1-

(diethylaminoacetyl)-2,3-dihydroindole as a potential local anaesthetic[66]. Japp-Klingemann reaction of ethyl 2-oxopiperidine-3-carboxylate with aryldiazonium chlorides and the following Fischer cyclization gave the 1-oxo-1,2,3,4-tetrahydrocarbolines which were hydrolyzed to the corresponding tryptamine-2-carboxylic acids. Decarboxylation by heating with hydrochloric acid gave in addition to tryptamine (**529**, R = H) its 5-methyl, 5-fluoro, 5-methoxy, 5-ethoxy, 5-methylthio and 7-methylthio derivatives[147], needed as intermediates. Another approach to substituted tryptamines started from the corresponding indoles giving by reactions with oxalyl chloride and the following ammonolysis the 3-indolylglyoxylic amides which were reduced with lithium aluminium hydride; in this way, in addition to 6-methoxy- the 6-ethoxy- and 5,6-methylenedioxytryptamine were obtained. 5-Hydroxytryptamine is an important biogenic amine[915] (serotonin); its modified synthesis was described by Vejdělek[916]. Series of tryptamine derivatives were synthesized[145,192] as model compounds related to the hypotensive alkaloid reserpine; their activity was unimportant.

5.2.3 2,1-*Benzisoxazole and Benzimidazole Derivatives*

5-Chloro-3-phenyl-2,1-benzisoxazole (**530**, Ar = C_6H_5) is an important intermediate in the synthesis of the anxiolytic 1,4-benzodiazepine derivatives and is formed in a high yield by reaction of 4-chloronitrobenzene with phenylacetonitrile in methanolic solution of sodium (or potassium) hydroxide. Our use of (6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)acetonitrile as a component[393] led easily to **531**. The use of *o*-substituted phenylacetonitriles affords on the other hand mixtures with low proportion of **530** and several by-products. (2-Chlorophenyl)acetonitrile gave only 12% of **530** together with **532**, **533** and **537** as the most typical by-products[404]. From the reaction of (2-fluorophenyl)acetonitrile only **532** (and its deoxygenated analogue) and **537** (R = 2-F) were obtained[404]. (2-Methylphenyl)acetonitrile gave 54% of **530** together with **534** (R = CH_3) and **536** (ref.[510]). (2-Methoxyphenyl)acetonitrile resulted in 27% of **530** together with **532** (and its deoxygenated analogue) (ref.[510]). Reaction of (2-methylthiophenyl)acetonitrile gave also 27% of **530** together with **534** (R = SCH_3) and a further atypical by-product[510]. Similar reactions of (3-chloro-4-methoxyphenyl)acetonitrile and (3,4-dimethoxyphenyl)acetonitrile gave about 75% of **530** and small amounts of less typical by-products, e.g. **535** (ref.[524]). Compounds **530** were used as intermediates for further synthetic work.

Alkylation of 2-(phenoxymethyl)benzimidazole with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride gave **537a** (n = 2 or 3) (ref.[239]). Reactions of 2-(4,4′-dihalobenzhydryloxy)ethyl bromide with 1-(4-piperidinyl)-2-benzimidazolone resulted in the flunamine (**182**) analogues **538** (R = F or Br) (ref.[473]). 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ol was transformed in four steps to **539**, a practically inactive analogue[516] of the antiallergic agent oxatomide[917].

5.2.4 *Pyrrolopyridines and Pyridoimidazoles*

5-Methyl-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine was transformed by alkyaltion with 2-dimethylaminoethyl chloride[61] to **540**, a heterocyclic analogue of phenbenzamine (**111**) which is practically devoid of antihistamine activity. Potassium salt of quinolinic acid imide was alkylated with 2-dimethylaminoethyl chloride, the product was reduced with lithium aluminium hydride and methyl iodide was added affording the 5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine derivative **541** displaying only weak hypotensive activity and lacking the ganglionic blocking effect[202] (for a similar work, cf. ref.[918]). The anomalous products of reactions of 2-(N-substituted amino)pyridines (phenyl, cyclohexyl, butyl, benzyl, 2-phenylethyl) with chloroacetyl chloride were designated on the basis of a detailed NMR study as 1-substituted 4-(chloromethyl)-2-oxopyrido[1,2-*a*]pyrimidin-5-ium-3-olates[530]. Dr Winkler (CIBA-GEIGY, Basel) expressed doubts on the correctness of this formulation and prefers the structure of 1-substituted 3-(chloroacetyl)-pyrido[1,2-*a*]imidazole-4-ium-2-olates **542** based partly on results published in ref.[920] which includes our 1-phenyl compound and for which a sydnone structure **543** was suggested. The case needs reinvestigation.

5.2.5 2,8-*Diazaspiro*[4.5]*decane and* 2-*Azabicyclo*[3.3.1]*nonane Derivatives*

Compound **544** (RS-86), accessible in several steps from 1-methyl-4-piperidone, is an analgetic and sedative agent with central muscarinic (cholinergic agonist) effect after oral administration[921]. A series of analogues was prepared[555] but only **545** proved interesting : it prolongs significantly the survival time of mice in the test of nitrogen anoxia and in high oral doses it induces the appearance of the parkinsonic syndrome which lasted for more than one month and of ataxia (mice) which persisted for more than one week. 2-Azabicyclo[3.3.1]nonane (**546**, morphan) is a fragment of the morphine molecule. We started its synthesis[11] from the oxime of ethyl (3-oxocyclohexyl)acetate which was hydrogenated on platinum and then hydrolyzed. The obtained amino acid had not tendency to form the lactam and was therefor evidently the *trans*-acid **547**. The synthesis of **546** was carried out shortly[922,923] after our work (cf. also ref.[924]).

5.2.6 1,4-*Benzodioxan*, 2-*Benzothiopyran, Quinoline and Isoquinoline Derivatives*

Compound **548** was prepared from 2-chloromethyl-2,3-dihydro-1,4-benzodioxan as a potential adrenolytic agent[108]; it proved some hypotensive action. (2-(2-Chlorophenyl)ethylthio)acetyl chloride cyclized by treatment with aluminium chloride under decarbonylation[562] to **549**, characterized as the methiodide and sulfone. 1-(2-Benzhydryloxyethyl)quinolinium iodide[76] was prepared as a potential antihistamine agent and 1-(diethylaminoacetyl)-1,2,3,4-tetrahydroquinoline[66] as a potential local anaesthetic. 2-Phenylquinoline was hydrogenated to a mixture of two tetrahydro products which was separated by acetylation and 1,2,3,4-tetrahydro compound was aminoalkylated[29]; **550** (a cyclic analogue of **111**) displayed in vitro the full antihistamine activity of **111**. On the other hand, 1-(2-dimethylaminoethyl)-2-methyl-1,2,3,4-tetrahydroquinoline[61] was inactive. 8-(2-Diethylaminoethoxy)quinoline[10] was also inactive. Compound **551**, prepared from 2-chlorocinchoninic acid chloride in two steps[109] as an analogue of the local anaesthetic cinchocaine, gave only the inactive monomethiodide. Starting from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, a series of N-substituted derivatives as potential analgetics was prepared[194]; compound **552** was the most potent one but had only 3% of the morphine activity. Using the Bischler – Napieralski reaction, followed by reduction and N-alkylation, a series of oxa and thia analogues of the analgetic methopholine[925] was prepared; the most active member of the series was **553** (ref.[225]). Compound **554** was prepared[198] as an open model of the corresponding berbine derivative. The cyclic dopamine analogue **555**, obtained from 2-(3,4-dimethoxyphenyl)-1-(4-tolyl)ethylamine by Bischler – Napieralski reaction, the following reduction and O-demethylation[448], displayed an opposite effect than expected : it was procataleptogenic.

5.2.7 *Benzoxepin, Benzothiepin and Benzoselenepin Derivatives*

8-Chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-one was obtained by cyclization of 4-(3-chlorophenoxy)butyric acid with polyphosphoric acid[279] and amine functions were introduced by many ways. As examples of the products, **556** (with some guanethidine-like hypotensive effect) and **557** (analogue of the already mentioned pargyline) may be shown. The Beckmann rearrangement of the ketone gave 9-chloro-2,3,4,5-tetrahydro-1,5-bezoxazocine-6-one (**558**) and the product of the reaction of the ketone with sodium azide and sulfuric acid was characterized as 9-chloro-5,6-dihydro-4*H*-tetrazolo-[5,1-*e*]-1,6-benzoxazocine (**559**). Cyclization of 4-(3-chlorophenoxy)-2-phenylbutyric acid gave 8-chloro-4-phenyl-2,3,4,5-tetrahydro-1-bezoxepin-5-one[280] which was also used as the starting material for the synthesis of amino compounds.

2,3,4,5-Tetrahydro-1-benzothiepin-5-one was transformed via the oxime to the 5-amino compound and its N-alkylated derivatives[244] and via the alcohol and chloride to a series of tertiary amines. The pargyline analogue **560** has higher antireserpine activity than pargyline itself. Reaction of the ketone with diethyl carbonate (NaH) gave the 4-(ethoxycarbonyl) derivative which reacted with phenylhydrazine and afforded 2-phenyl-2,3,4,5-tetrahydropyrazolo[3,4-*d*]-1-benzothiepin-3-one (**561**). The propranolol analogue **562** was prepared from 2,3,4,5-tetrahydro-1-benzothiepin in six steps[282] but proved inactive as a β-blocker. An attempt to cyclize 4-phenyl-4-(phenylthio)butyric acid with polyphosphoric acid in toluene[282] did not give the wanted 2-phenyl-2,3,4,5-tetrahydro-1-benzothiepin-5-one but 7-methyl-4-phenyl-1-tetralone (under cleavage of thiophenol and interaction with toluene). Cyclization of 2-phenyl-4-(phenylthio)butyric acid with polyphosphoric acid at 150°C took also an anomalous course[278] : an orange substance $C_{16}H_{10}S$ was formed for which several structures were suggested. The UV spectrum calculated for indeno[1,2-*c*]-1-benzothiopyran (**563**) was in best agreement with the experimental values and structure **563** was accepted for the product (the mechanism of its formation is unclear). The corresponding *p*-methylated acid cyclized smoothly and the ketone was transformed in four steps to **564** (stereoisomeric mixture) having some sedative and antireserpine activity[278]. 1,2,4,5-Tetrahydro-3-benzothiepin-5-one was reacted with phenylmagnesium bromide, the crystalline alcohol was dehydrated to oily $C_{16}H_{16}S$ which reacted with methyl iodide under a strange cleavage reaction and gave 3-methyl-1,2,4,5-tetrahydro-3-benzothiepinium iodide[562]. The synthesis of 2,3,4,5-tetrahydro-1-benzoselenepin-5-one was improved[253] and the ketone was transformed to the oxime and the secondary alcohol.

5.2.8 *Benzazepine Derivatives*

2,3,4,5-Tetrahydro-1*H*-1-benzazepine-2-one was reacted with primary amines and titanium tetrachloride to give the cyclic amidines, 2-amino-4,5-dihydro-3*H*-1-benzazepines[479], with indications of some peripheral neurotropic effects. The Beckmann rearrangement of the oxime of 7-fluoro-4-(4-fluorophenyl)-1-tetralone gave the 1-benzazepine derivative **565** as the main product and the naphthylamine **566** as a by-product[421] (Semmler – Wolff aromatization). The Schmidt reaction with the mentioned tetralone resulted in **565** as the main product and the isomeric **567** as the by-product[374]. Compound **565** was reduced to the amine which was used for preparing further derivatives[421]. 2,3,4,5-Tetrahydro-1*H*-3-benzazepine-2-one was also used as the starting point for preparing a series of amines including **568**, a cyclic analogue of pargyline[239]. Cyclization of the appropriately substituted N-(2-arylethyl)mandelamides with polyphosphoric acid gave lactams of the tetrahydro-3-benzazepine series (**569**, X = O) which were transformed by treatment with phosphorus pentasulfide to thiolactams **569** (X = S) (ref.[561]). Attempts to transform N-(2-phenoxyethyl)benzamide and N-(2-phenylthioethyl)benzamide to derivatives of 1,4-benzoxazepine and 1,4-benzothiazepine[240] by the Bischler – Napieralski reaction were unsuccessful; 2-phenyl-4,5-dihydrooxazole was the product in both cases.

5.2.9 1,4-*Benzodiazepines*

Most compounds we prepared in this group were used as intermediates or standards. The first two cases are exceptions. The benzisoxazole **531** was reduced with iron and acetic acid to 2-(2-amino-5-chlorobenzoyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene whose oxime was cyclized by reaction with chloroacetyl chloride to **570**. Final treatment with methylamine led under rearrangement[393] to the chlordizepoxide analogue **571** which did not show anticonvulsant activity. Nordazepam (**573**, R = H) was alkylated with 3-(4-phenyl-1-piperazinyl)propyl chloride to **572** having properties of a potential hypnotic agent[404]. Delorazepam (**573**, R = 2-Cl) was prepared by a modified route[404] : the bezisoxazole **530** (Ar = 2-chlorophenyl) was reduced with iron and acetic acid to 2-amino-5,2'-dichlorobenzophenone which was acylated with phthalimidoacetyl chloride. The product was cleaved by hydrazinolysis and simultaneously cyclized to **573** (R = 2-Cl). Similar processing of the benzisoxazoles **530** (Ar = 2-tolyl, 2-methoxyphenyl, 2-methylthiophenyl, 3-chloro-4-methoxyphenyl, 3,4-dimethoxyphenyl, and 4-chlorophenyl) gave the corresponding **573** (refs[486,510,524]), most of which were transformed by the action of phosphorus pentasulfide to the corresponding thiones. The 4-chlorophenyl compound **573** is the known benzodiazepine antagonist Ro 5-4864 (ref.[926]). The phthalimidoacetamido route was also used for the synthesis of 5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepine-2-one[486], an intermediate of the synthesis of the potent hypnotic agent flunitrazepam[927].

5.3 HETEROTRICYCLIC COMPOUNDS

5.3.1 *Heterotricyclic Compounds with Five- and Six-Membered Rings*

5.3.1.1 Dithienothiopyrans, Dibenzothiophenes and Thienobenzothiopyrans

Ethyl 2-bromo-5-ethylthiophene-3-carboxylate was transformed in two steps into 5-ethyl-2-(2-thienylthio)thiophene-3-carboxylic acid which was cyclized with polyphosphoric acid in toluene[387] to 2-ethyldithieno[2,3-*b*;3',2'-*e*]thiopyran-4-one (**574**). Reaction with 3-dimethylaminopropylmagnesium chloride gave the expected tertiary alcohol which decomposed in attempts at its dehydration.

Diazotization of 3-amino-2-(phenylthio)benzoic acid[236] gave **575** as one of the products; **576** was obtained similarly[430]. The acid **575** was better prepared by the Gomberg reaction from 2-(2-aminophenylthio)benzoic acid[237] and was used for the synthesis of amines with spasmolytic, local anaesthetic and hypotensive activities. The dihydroimidazole **577** in low doses had a positively inotropic effect. Cyclization of 2-(2-thienylthio)benzoic acid with polyphosphoric acid afforded thieno[2,3-*b*]-1-benzothiopyran-4-one[312] giving in two steps **578**, a very potent antihistamine agent in vivo. Similar procedure, starting from 2-(3-thienylthio)benzoic acid, stopped in the stage of the 9*H*-thieno[3,2-*b*]-1-benzothiopyran-9-ol derivative **579** which decomposed in attempts at its dehydration[329].

5.3.1.2 Carbazole, Cyclopent[*g*]isoquinoline and Benz[*c,d*]indole Derivatives

Acylation of carbazole with chloroacetic anhydride and the following reaction with diethylamine gave **580**, an extremely active local anaesthetic[66]. The oxime of *s*-hydrindacene-1-one was subjected to the Beckmann rearrangement with polyphosphoric acid[366]; the lactam **581** was the major product and the isomer **582** was the minor one. Compound **581** was used for preparing several amines for pharmacological screening. The benz[*c,d*]indole derivative naphthostyril (**583**) gave by alkylation **584** having antiserotonin activity[239]. Reactions of **583** with primary and secondary amines and titanium tetrachloride afforded cyclic amidines like **585** displaying several peripheral neurotropic activities.

5.3.1.3 β-Carboline Derivatives

Several N-substituted 1,2,3,4-tetrahydro-β-carbolines[145] were prepared as simple reserpine models. Reaction of tryptamine with glyoxylic acid was the entry to a series of 1,2,3,4-tetrahydro-β-carboline derivatives[171]; the alcohols **586** and **587** displayed weak reserpine-like hypotensive activity. Substituted benzaldehydes were reacted with tryptamine and the resulting Schiff bases were reduced with sodium borohydride to N-benzyltryptamines[192]. The Schiff bases were also cyclized to 1-aryl-1,2,3,4-tetrahydro-β-carbolines[192]. 1-Phenyl compound was transformed in two steps to **588** which inhibited the formation of the indomethacin-induced gastric ulcers in rats[515]. Bischler – Napieralski reactions of N-(cyclohexylacetyl)tryptamine and its 4-methoxy derivative followed by reduction gave 1-(cyclohexylmethyl)-1,2,3,4-tetrahydro-β-carboline and its 4-methoxy derivative[127] (short-acting hypotensives). Similar reactions starting from N-(arylalkanoyl)tryptamines led to 1-aralkyl-1,2,3,4-tetrahydro-β-carbolines out of which the simple 1-benzyl compound (**589**, phenoharman in the form of the methanesulfonate) was selected for clinical trials for its hypotensive effect in animals[128]. The synthesis of **589** was modified and improved[197], its reserpine-like character of action was confirmed in biochemical as well as pharmacological studies[928-934]. Clinical testing did not confirm the predicted hypotensive action in patients[935]; on the other hand, it indicated an important central action. Phenoharman was found ineffective in schizophrenia but was found useful in maniodepressive psychoses[936-938]; in some patients its use led to worsening of the humour (dysphoric acion). Clinical experimentation in various lines[939-942] continued for some time but finally phenoharman remained interesting only as an agent inducing experimental depression[943-945]. Some 1-(aryloxy- or arylthiomethyl)-1,2,3,4-tetrahydro-β-carbolines[225] were prepared as potential analgetics but were found inactive. Attempts to cyclize 4-arylthio-2-methylthiopyrimidine-3-carboxylic acids proceeded under decarbonylation and [1]benzothieno[3,2-*d*]pyrimidines (**590**) were the products[347].

5.3.2 *Heterotricyclic Compounds with Six-Membered Rings*

5.3.2.1 Xanthene, Thioxanthene and Selenoxanthene Derivatives

4-Methoxyxanthone and 4-methoxythioxanthone were transformed in three steps into **591** and **592** which did not show the presumed antidepressant activity[513]. Thioxanthene became a very important pharmacophore through the discovery of the Danish authors[946] of the neuroleptic action of **593**, especially those substituted in position 2. The synthesis of such compounds started by the easy cyclization of the 2-(arylthio)benzoic acids (mostly with sulfuric acid) to the thioxanthones which were reacted with 3-dimethylaminopropylmagnesium chloride and the tertiary alcohols obtained were dehydrated by acid catalyzed reactions to **593**. In the case of asymmetrically substituted **593**, mixtures of (*E*)- and (*Z*)-isomers were formed which were separated in many cases by crystallization of the bases or of the salts. The neuroleptic activity is stereoselective and only the (*Z*)-isomers are active. Our team contributed significantly to the knowledge of the structural field of neuroleptic activity in this group. First, we synthesized the unsubstituted prothixene (**593**, R = H) (ref.[206]). It is a strong antihistamine agent and was, therefore, recommended to clinical testing[947]. The assumed activity was confirmed but at the same time the strong sedative activity of prothixene disabled its practical use. Then, the synthesis of chlorprothixene (**593**, R = 2-Cl) was modified and the separation of the geometrical isomers was worked out. Patenting of a new synthetic way[206] enabled the introduction of manufacture of this agent in this country (Chlorprothixen-SPOFA®) and clinical investigations confirmed its antipsychotic activity in schizophrenic patients[948]. A spectrophotometric (IR) method[949] enabled the differentiation of the geometrical isomers and the determination of the (*Z*)-isomer in mixtures. Derivatives and analogues of prothixene were found to be inhibitors of the alcohol dehydrogenase[370]. 3-, 4-, 6- and 7-Hydroxy derivatives of chlorprothixene were synthesized[400] and used as standards in a metabolic study of chlorprothixene oriented especially to ist metabolic hydroxylation[474]. A series of 2-alkyl derivatives of prothixene (**593**, R = 2-alkyl) was synthesized[226], some members were separated to isomers and with (*Z*)-2-isopropyl compound the maximum central depressant effect was found. For preparing the 2-cyclopropyl derivative of **593**, the corresponding starting acid had to be cyclized with trifluoroacetic anhydride[315]; the product was of weak activity (probably the (*E*)-isomer). 2-Benzyl derivative of **593** was described together with several 2-alkoxy derivatives[217]. 2-Methoxythioxanthone was demethylated with hydrobromic acid to 2-hydroxythioxanthone opening the way to the 2-benzyloxy derivative of **593** and also to the 2-hydroxy derivative of prothixene (**593**, R = OH) in the form of both isomers[258].

Aminoalkyl ethers of 2-hydroxythioxanthone, 2-hydroxyprothixene and also of the intermediate 2-hydroxy amino alcohol were prepared and tested[258]. 2-(3-Alkylphenylthio)benzoic acids were cyclized with sulfuric acid to mixtures of 3-alkyl (major) and 1-alkyl (minor) derivatives of thioxanthone[425] which were separated and which opened the way to 1-ethyl, 3-methyl and 3-ethyl derivatives of prothixene (some sedative and cataleptic activity). In connection with the work in the ring-homologous series (dibenzo[*b*,*f*]thiepins), the 3-fluoro[372], 6-fluoro[331,359], 3,6-difluoro[372], 7-fluoro[331], and 6,7-difluoro[354] derivatives of chlorprothixene were prepared. The cataleptic activity was used as an indication of the (*Z*)-configuration (with regard to the position of the side chain and the 2-chlorophenyl). Some of the fluorinated compounds were strong neuroleptics with prolonged ataxic activity (oral administration). 2-(Bromomethyl)thioxanthone was used for the synthesis of **593** (R = 2-CH_2SCH_3); the product is a tranquillizer with low cataleptic activity[463]. 4-Dimethylamino(also pyrrolidino, piperidino and morpholino)thiophenols were synthesized, reacted with 2-iodobenzoic acid and processed to the corresponding 2-amino derivatives of **593** (they are only tranquillizers) (ref.[489]). The 1,2,4-trichloro and 2,4,5,6-tetrachloro derivatives of **593** were prepared only in the form of the inactive (*E*)-isomers[457].

2-Chloro-9-(1-methyl-4-piperidylidene)thioxanthene was demethylated with ethyl chloroformate, the carbamate was hydrolyzed and the secondary amine obtained was alkylated with 2-bromoethanol to **594** which was shown to be only a low-cataleptic tranquillizer[457]. Thioxanthone and 2-chlorothioxanthone were reacted with 3-(4-phenyl-1-piperidinyl)propylmagnesium chloride and the intermediates obtained were used to prepare the 3-(4-phenyl-1-piperidinyl)propylidene analogues of prothixene and chlorprothixene[227] (the isomer A of the chloro compound is a strong sedative agent). Reaction of thioxanthone with 3,4,5,6-tetrahydro-2*H*-thiopyran-4-ylmagnesium bromide started the synthesis of the sulfonium salt **595** showing only weak antihistamine and anticholinergic effects[500]. Thioxanthene-9-ol was treated with hydrogen chloride in ether and then with piperidine giving the unstable 9-(1-piperidinyl)thioxanthene[258] lacking any CNS action. Attempts at cyclizing thioxanthene-9-acetic acid with polyphosphoric acid resulted in an escape reaction[381] : acetic acid was cleaved and the formed thioxanthylium cation was disproportionated into thioxanthone and thioxanthene. Reaction of 2-chlorodibenzo[*b,f*]thiepin or 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin with acetyl chloride and aluminium chloride led under rearrangement of the skeleton to 2-acetyl-7-chloro-9-(chloromethyl)thioxanthene[377]. 2-(Arylseleno)benzoic acids were cyclized with sulfuric acid to selenoxanthone and its 2-chloro derivative which were transformed in two steps into **596** and **597**. The mixture of the isomeric bases **597** was separated by seeding with the crystals of the evidently isomorphic (*Z*)-chlorprothixene (**593**, R = 2-Cl). In this way (*Z*)-**597** and (*E*)-**597** were obtained, the former having 50% of the ataxic activity of (*Z*)-**593** (R = 2-Cl) (ref.[255]).

5.3.2.2 Acridine, Benz[*d,e*]isoquinoline, Julolidine, and Methanobenzazocine Derivatives

9,10-Dihydroacridine was aminoalkylated with 2-dimethylaminoethyl chloride and homologues[61] ($NaNH_2$) and **598** was found to be in vitro seven times as active as **111** as an antihistamine agent. Acylation of dihydroacridine with chloroacetyl chloride and the following treatment with diethylamine gave[66] the potential local anaesthetic **599**.

3-Methyl-7,8,9,9a-tetrahydro-1*H*-benz[*d,e*]isoquinoline was reduced with sodium borohydride to **600** which was alkylated with propargyl bromide to **601**, a cyclic analogue of the monoamine oxidase inhibitor pargyline[782]. Treatment of **600** with phenylacetyl chloride followed by reduction with lithium aluminium hydride gave an unexpected product identified as **602** (N-dealkylation with the acid chloride, N-acylation, reduction and hydrogenolysis) (ref.[479]).

Under the guidance of Prof. V. Prelog (Zurich), the author[22] hydrogenated julolidine on the Adams catalyst and the mixture of the hexahydro bases **603** was separated by fractional crystallization of the picrates; the main **603-A** and the minor **603-B** were obtained and characterized. Using a different way, Leonard[950] prepared a hexahydrojulolidine which gave evidence of resolution, is therefore the *cis-trans*-isomer and is identical with one of our stereoisomers[951]. Hydrogenation of julolidine was repeated by further authors[952]. Attempt to nitrosate julolidine to position 9 by treatment with nitrous acid led to $C_{24}H_{28}N_2$, identified as **604** (ref.[87]). 9-Methoxyjulolidine was demethylated with hydrobromic acid to 9-hydroxyjulolidine which was transformed to basic ethers **605** showing indications of antidepressant activity with some selectivity in favour of the adrenergic mechanism[560].

1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocine (6,7-benzomorphan) is an important part of the morphine molecule and its N-substituted 8-hydroxy-6,11-dimethyl derivatives exhibit strong morphine-like analgetic activity. We alkylated this basic hydroxydimethyl compound with 2-(2-chloroethyl)-1,3-dioxane and 2-(2-chloroethyl)-1,3-dioxolane[544] and obtained **606** out of which **606** (n = 1) had 25 % of the morphine activity in the Haffner test (collision with ref.[953]).

5.3.2.3 Thianthrene, Phenothiazine, 11*H*-Pyrido[2,3-*b*]quinazoline, and [1]Benzothiopyrano[3,2-*d*]pyrimidine Derivatives

Thianthrene (**607**) was obtained as one of the products of cyclization of 2-(2-bromophenylthiomethyl)thiophenol[430] with potassium carbonate and copper in dimethylformamide. The 3,8-dichloro derivative **608** was isolated as the by-product of the reaction of 4-chloro-2-fluorothiophenol with 2-chlorobenzaldehyde in hexamethylphosphoric triamide in the presence of sodium hydroxide at 100°C (ref.[469]). Our involvement in the very productive phenothiazine series was limited. Acylation of phenothiazine with 3-chloropropionyl chloride and following reactions with sodium methanethiolate and then methyl iodide gave the sulfonium salt **609** displaying some spasmolytic activity[129]. Phenothiazine and 2-chlorophenothiazine were alkylated with 3-(4-phenyl-1-piperidinyl)propyl chloride giving **610** (ref.[227]); compound **610** with R^1 = Cl was a long-acting central depressant agent. The synthesis of pecazine (**611, Pacatal®**) was described[126] in a time when only its biological properties have been published[954]; its pharmacology was verified and it was found that its central effects are much weaker than those of chlorpromazine. Modified syntheses of the mild neuroleptic agent thioridazine[955] (**612**) and of the antiemetic agent metopimazine[956] (**613**) were described[549]. The new syntheses utilized fluorinated aromatic intermediates and the nucleophilic displacement reactions of the aromatic fluorine atom activated by the *o*-standing sulfur atom (sodium hydride as the reagent).

The by-product of the reaction sequence starting from 5,11-dihydro-6*H*-pyrido[2,3-*b*]-1,4-benzodiazepin-6-one[514] and proceeding by treatment with chloroacetyl chloride followed by 1-methylpiperazine, which was isomeric with the main and expected product (pirenzepine[901]), was surprisingly identified (X-ray, NMR) as 11*H*-pyrido[2,3-*b*]quinazolin-11-one (**614**) (ref.[526]) (transacylation, recyclization, double bond and hydrogen shift, and finally nucleophilic substitution with methylpiperazine). Cyclization of 2-(methylthio)-5-(phenylthio)pyrimidine-4-carboxylic acid chloride[347] with aluminium chloride gave the desired 2-(methylthio)-[1]benzothiopyrano[3,2-*d*]pyrimidine-10-one (**615**); attempts at its transformation to the prothixene analogue were unsuccessful.

5.3.3 *Heterotricyclic Compounds with Seven-Membered Rings*

5.3.3.1 Benzocycloheptathiophenes

9,10-Dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophene derivatives **616** and **617** are the very important antimaigraine agent pizotifen[957] and the antiasthmatic ketotifen[958]. Our synthesis of their sulfonium analogues **619** and **620** (proved pharmacologically not interesting) (ref.[537]) led us closer to the chemistry of **617**. Some new possible intermediates were prepared and the last stages of the synthesis were slightly modified. Moreover, the chirality of ketotifen (**617**), which was indicated by isotachophoretic study[959], was proven by ^{1}H NMR spectroscopy. The resolution of racemic **617** was achieved by crystallization of salts with optically active O,O′-diacyltartaric acids. The X-ray crystallographic analysis of (+)-**617** (−)-O,O′-di(*p*-toluoyl)-(*R*)-tartrate led to the three-dimensional structure of the molecule of (+)-ketotifen and to determination of the (*R*) absolute configuration. This enantiomer was found to be the more active ketotifen enantiomer but the stereoselectivity of its action is only a partial one. One of the products of bromination of 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one was used to realize the synthesis of **618** which is much less active than **617** in the line of antihistamine activity. Reaction of 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one with 3,4,5,6-tetrahydrothiopyran-4-yl magnesium bromide gave in addition to the expected tertiary alcohol compound **621**, evidently the product of 1,6-addition and the following spontaneous dehydrogenation[537].

The isomeric benzo[5,6]cyclohepta[1,2-*b*]thiophene system was attacked only by our team[248]. Cyclization of (2-(2-thenyl)phenyl)acetic acid with phosphorus pentoxide in toluene afforded **622** which was transformed via the secondary alcohol to the 4-chloro compound. The final substitution reaction with 1-methylpiperazine gave 10*H*-

benzo[5,6]cyclohepta[1,2-*b*]thiophene as the main product (product of elimination) and **623** which proved to be a chlorpromazine-like neuroleptic agent[248].

5.3.3.2 Dibenzoxepin Derivatives

Dibenz[*b,e*]oxepin-11(6*H*)-one was reduced to the secondary alcohol which was transformed on the one hand to the ether **624**, and to **625** on the other[224]. The piperazine derivative **625** displayed antireserpine and central anticholinergic activity.

Cyclizations of 2-(4-substituted phenoxy)benzoic acids with polyphosphoric acid resulted in dibenz[*b,f*]oxepin-10(11*H*)-ones **626** (R = H, CH_3, Cl, OCH_3, SCH_3) which were transformed in three steps into the neuroleptically active **627** and **628** with the most active combinations **627** (R = SCH_3) and **628** (R = Cl) (ref.[251]). The similarly prepared 8-methyl-10-(4-(2-hydroxyethyl)-1-piperazinyl) analogue was transformed to esters[292] **629** (n = 8, 12) which were tested as potential depot neuroleptic agents. The enamine **630** was obtained from the ketone **626** (R = H) by treatment with 1-methylpiperazine and titanium tetrachloride in benzene[257]. The series of 10-piperazino-10,11-dihydrodibenzo[*b,f*]oxepins as potential neuroleptics was studies also by the teams of Hoffmann – La Roche and Rhone – Poulenc which was demonstrated only by patents.

5.3.3.3 6,11-Dihydrodibenzo[*b,e*]thiepin Derivatives

The fact that we lost the priority with amitriptyline (**363**) led us to investigate the 6,11-dihydrodibenzo[*b,e*]thiepin derivatives which are isosteric with the 10,11-dihydrodibenzo[*a,d*]cycloheptenes. We were not able to cyclize 2-(S-benzylthio)benzoic acid with polyphosphoric acid but its anhydride gave with aluminium chloride some **631** (R = H). It was found much better to cyclize 2-(phenylthiomethyl)benzoic acid (obtained by reaction of phthalide with the sodium salt of thiophenol) giving **631** (R = H) with high yield[179]. The following reaction with 3-dimethylaminopropylmagnesium chloride (cf. also ref.[468]) resulted in **636** (R = H) (refs.[179,467]) which was dehydrated by an acid catalyzed reaction to **632** (R = H).

This compound (prothiadene, dosulepin (INN), dothiepin (British approved name)) was found to have a suitable combination of antireserpine and central depressant activities[960-965] and was recommended to clinical trials. Our preliminary communication on prothiadene[179] was followed by reports of the teams of Boehringer – Mannheim[966,967] and of Sandoz[968] (cf. also ref.[969]) on the same compound but our team was the only one which brought prothiadene to stages of clinical testing and practical use. The double bond in **632** (R = H) and the asymmetry of the molecule gives the precondition for the existence of (*Z*)- and (*E*)-isomers. The product obtained by dehydration consists at least by 90% of one isomer which was isolated homogeneous and proved to be the (*E*)-isomer (IR spectra[249], X-ray crystallographic study[970], ^{1}H NMR[501]). The reason of such predominancy of the (*E*)-isomer is probably the conformation of the intermediate carbocation **638** in which the N and also the S atom are protonated and repulsion of the positive charges leads to preference of formation of the (*E*)-isomer by stabilization of **638** by loosing a proton. The demethylation of crude **632** (R = H) via **633** (R = H) to northiadene (**634**, R = H) gave a mixture containing more of the (*Z*)-isomer which enabled the preparation of homogeneous (*Z*)-**632** (R = H) (refs[249,501]). Also the application of the Wittig synthesis to **631** (R = H) led to mixtures out of which chromatography separated the homogeneous (*Z*)-prothiadene[501].

After a series of positive clinical results (mainly in various forms of mental depression) (refs[971-986]), the agent was introduced by SPOFA to practical use[987,988] (Prothiaden®). Later the drug was licensed first to Crookes Laboratories (U.K.) and then to Boots Company (U.K.) and more recently also to Kaken Pharmaceuticals (Japan). The coopereation with these companies multiplied the published information on prothiadene in all directions (cf. e.g. special symposia[989-992] in Moscow (1972), Paris (1974), Prague (1977) and Vienna (1978)). Many of the published reports on prothiadene deal with modifications of the last stages of the synthesis[993-1003], various methods of analytical determination in preparations and biological material including the differentiation of the isomers[1004-1017], biochemical effects[1018-1024], biochemical pharmacology[1025-1035], general pharmacology[1036-1042], pharmacokinetics[1043-1051], stability[1052-1054], electrophysiology and electroencephalography[1055-1059], influence on reproduction[1060-1064], toxicology, side effects in men and intoxications[1065-1084], interactions with other drugs[1085-1087], clinical trials in depression including comparative studies[1088-1127], clinical trials in neurology and other medical lines[1128-1146]; for monographic articles on prothiadene, cf. refs[1147-1149]. A combination of prothiadene with mebrophenhydramine (**213**) was introduced as an antihistaminic with antidepressant and hypnotic activity[1150-1153] (Prothidryl®). The pharmacokinetics[1043-1059,1154] and metabolism of prothiadene[1047,1155-1161] were investigated in several animal species and humans partly with [^{35}S]labeled prothiadene. Making use of synthetic northiadene (**634**, R = H) (refs[200,249]), dinorthiadene (**635**, R = H) (ref.[386]) (prepared from **631** (R = H) via the 11-cyclopropyl carbinol, (*E*)-11-(3-bromopropylidene) compound, the corresponding phthalimido compound and its hydrazinolysis), S-oxides of prothiadene and northiadene[200,249] (prepared by oxidation of the sulfides with hydrogen peroxide in acetic acid), and 2-hydroxy derivative of prothiadene (**632**, R = 2-OH) (ref.[386]) (was prepared in the form of both homogeneous geometrical isomers from **631** (R = 2-OCH_3) via **632** (R = 2-OCH_3) and by its demethylation with boron tribromide or hydrobromic acid) as standards, the named compounds were identified as urine metabolites. There was an indication that also the N-oxide of prothiadene could be a metabolite[1156,1157] but attempts at its synthesis by oxidation of **632** (R = H) with hydrogen peroxide in neutral solutions proceeded under Cope elimination and afforded 11-allylidene derivatives of 6,11-dihydrodibenzo[*b*,*e*]thiepin-S-oxide and -S,S-dioxide[386]. Japanese authors[1160] established in urine of humans the presence of two conjugated metabolites, derived from prothiadene and northiadene, which were identified as the quaternary ammonium-linked glucuronide and the corresponding tertiary N-glucuronide.

A series of nuclearly substituted derivatives of prothiadene (**632**) was prepared by the general route mentioned, i.e. starting from substituted thiophenols and phthalide (or substituted phthalides) via the 2-(arylthiomethyl)benzoic acids, **631** and **636**. The following prothiadene derivatives (**632**) were prepared : 2-methyl, 2-ethyl, 2-isopropyl, and 2-butyl[180,969], 2-fluoro (separated to geometrical isomers), 2-chloro, and 2-bromo[180,960], 3-methoxy[290], 3-chloro and 3-bromo[200,1162], 4-methyl[180,960], 3,8-difluoro[230] (with high anticataleptic activity[428]), 9-fluoro[428], 9-chloro[180], 9-bromo[521] (separated to (*E*) and (*Z*)-isomers), 2,9-difluoro[428], and 2,9-dichloro[180,960]. (*E*)-2-Bromo compound (**632**, R = 2-Br) was transformed by treatment with cuprous cyanide in hexamethylphosphoric triamide[521] to the (*E*)-2-cyano compound (**632**, R = 2-CN) (was obtained also from **631** (R = 2-Br) via **631** (R = 2-CN) and **636** (R = 2-CN)) which was found to be a selective inhibitor of 5-hydroxytryptamine re-uptake in the brain and is thus a potential antidepressant. Compound (*E*)-**632** (R = 9-Br) was similarly transformed to (*E*)-**632** (R = 9-CN) (ref.[521]).

Out of all of these compounds (**632**), the 2-methyl derivative (methiadene, medosulepin (Czech. Pharmacopoeia)) was found most interesting because of its high antihistamine activity, acceptable toxicity, good water-solubility of the hydrochloriode and stability of the aqueous solution[180,260]. The problem of its geometrical isomerism was solved[247], the (*E*)-isomer was again found as the major one and it was oxidized to the S-oxide and S,S-dioxide[247]. Some analytical, biochemical and pharmacological papers deal with methiadene[1006,1008,1163,1164]. It was introduced in injections in combination with calcium glucoheptonate (Methiaden-Calcium®) and it has been used until now in the treatment of allergic states of various origin[1165,1166]. Its successful use was reported in many papers[1167-1178].

The transformation of **632** (R = H) to northiadene (**634**, R = H) via the carbamate[200] was already mentioned. The same product was also obtained from **636** (R = H) via the carbamate, its hydrolysis and dehydration[249]. Northiadene was prepared in the form of both geometrical isomers which could be methylated to the corresponding prothiadenes (**632**, R = H) (refs[249,501]). The following Ar-substituted northiadenes (**634**) were prepared : 2-methyl[247] (both geometrical isomers), (*E*)-2-bromo (was transformed in three steps to (*E*)-2-cyano[521]), and 3-methoxy[290]. (*E*)-Northiadene (**634**, R = H) proved also high antireserpine activity[965,1036,1162] and a general pharmacological profile differing somewhat from that of prothiadene[1179-1181]. It was also clinically tested in mental depressions with positive results and was found rather similar to prothiadene[1182-1186]. (*E*)-Northiadene (**634**, R = H) was alkylated and the products were eventually further transformed to a series of products[444]. The lipophilic ester **639** was tested as a depot antidepressant with a completely negative result[444]. The treatment of (*E*)-northiadene with 4-chlorophenacyl bromide gave **640**, an analogue of lofepramine[1187], which was found less active than prothiadene[519]. Chloroacetylation of **634** (R = H) and the following reaction with 1-substituted piperazines gave compounds like **641**, potential anti-ulcer agents[531].

Side-chain modified analogues of prothiadene were prepared from **631** (R = H) by using the following Grignard reagents : 3-(1-piperidinyl)propylmagnesium chloride, 2-(1-methyl-2-piperidinyl)ethylmagnesium chloride, 1-methyl-3-piperidinylmethylmagnesium chloride, 3-(4-methyl-1-piperazinyl)propylmagnesium chloride[183], and 3-(4-phenyl-1-piperidinyl)propylmagnesium chloride[227] - and by the final dehydration of the alcohols obtained. Reaction of **631** (R = H) with 2-(dimethylaminomethyl)cyclohexylmagnesium chloride gave a mixture (**642**, R = H) out of which four homogeneous bases were separated by chromatography. Dehydration of the main component gave **646** (R = H) for which (*E*)-configuration was presumed[477]. Reactions of **631** (R = H) with 2-, 3- and 4-(dimethylaminomethyl)phenylmagnesium bromide gave **643** (R = H) (ref.[539]). Treatment of the 2-isomer with phosphoric acid proceeded with extrusion of sulfur[539] and led to **652**. Reactions of **631** (R = H, 2-Cl, 2-Br, 2-Cl-8-F) with 1-methyl-4-piperidinylmagnesium chloride gave the corresponding **644** (refs[183,455,521,531]). In the case of **644** (R = H), a by-product was isolated[531] and identified as the product of 1,6-addition and the following spontaneous dehydrogenation, i.e. **653** (R = H). Dehydration of **644** gave the corresponding **647** (R = H, 2-Cl, 2-Br, 2-Cl-8-F) out of which perithiadene (**647**, R = H) is practically equipotent with prothiadene in its antireserpine, antihistamine and sedative activities[960]; it was the object of further pharmacological studies[1188-1190]. Demethylation of **647** (R = H) by the ethyl chloroformate method and final hydrolysis gave **648** (R = H) which was chloroacetylated and the product subjected to substitution reactions with 1-substituted piperazines[531]; the products were potential anti-ulcer agents.

Similar demethylation[455] of **647** (R = 2-Cl) gave **648** (R = 2-Cl) which was converted via **649** (R = 2-Cl) to the corresponding decanoate. This compound – instead of being a depot neuroleptic agent – showed dopaminomimetic character: it potentiated the effects of apomorphine, had anticataleptic activity and decreased the level of homovanillic acid in corpus striatum of the rat brain. The 2-chloro-8-fluoro compound **647** had only properties of a tranquillizer[455]. Compound **647** (R = 2-Br) was converted by treatment with cuprous cyanide in hexamethylphosphoric triamide to **647** (R = 2-CN) (ref.[521]). Reactions of **631** (R = H and 2-CH_3) with 3,4,5,6-tetrahydro-2*H*-thiopyran-4-ylmagnesium bromide afforded mixtures of **645** (R = H and 2-CH_3) and **654** (R = H and CH_3). Dehydration of the former and addition of methyl iodide gave **650** (R = H and 2-CH_3) which were free of the central effects and had only low antihistamine activity[500]. Compound **651** (R = 2-Cl) was synthesized[458] as an analogue of the neuroleptic (*Z*)-pinoxepin[1191] from **631** (R = 2-Cl) via the cyclopropyl carbinol and the (*E*)-11-(3-bromopropylidene) compound. Our product (**651**, R = 2-Cl), being the (*E*)-compound, is inactive as a neuroleptic agent and its decanoate has neither properties of a depot neuroleptic, nor of a depot antidepressant.

Ketones **631** were reduced with sodium borohydride to **655** (R = H, 2-CH_3, 2-Br, 3-OCH_3) (refs[179,247,290,521]) which were transformed to **656** (R = H, 2-Br) by the action of hydrogen chloride or thionyl chloride[215,521]. 11-Unsubstituted compounds **657** (R = H, 2-CH_3, 3-OCH_3) were prepared by reduction of **655** with hydroiodic acid[200] or of **631** and their oximes with zinc and acetic acid[215,290,391]. Compounds **655** – **657** were used as intermediates for further synthetic work. Reduction of **636** (R = H) or of **632** (R = H) with hydroiodic acid[200,215] gave hydrothiadene (**637**, R = H) which was also obtained by reaction of **656** (R = H) with 3-dimethylaminopropylmagnesium chloride[215]. Similar methods resulted in Ar-substituted derivatives **637** (R = 2-F, 2-Cl, 2-Br, and 2,9-Cl_2). Hydrothiadene was found to have similar antireserpine activity like prothiadene[1162] which led to its more detailed pharmacological studies[1188-1190,1192-1194]. An attempt to resolve racemic hydrothiadene by isotachophoresis with *β*-cyclodextrine was reported[1195]. Clinical trials confirmed similarity of hydrothiadene with prothiadene in depressive states[1196-1199]. A compound of elemental composition corresponding to **637** (R = 2-CH_3) was obtained by alkylation of **657** (R = 2-CH_3) with 3-dimethylaminopropyl chloride (sodium amide) but the position of the side chain is uncertain[391]. 2-Bromo-**637** was transformed by cuprous cyanide to the 2-cyano analogue **637** (R = 2-CN) which is a strong and selective inhibitor of 5-hydroxytryptamine re-uptake in the brain and has antireserpine activity like a potential antidepressant[521]. Demethylation of hydrothiadene by the ethyl chloroformate method resulted in norhydrothiadene (**658**, R = H) (ref.[215], collision with Merck[1200]) which is a further potential antidepressant[1192-1194]. Compounds **651** (R = H, 2-Cl) were reduced with hydroiodic acid giving unhomogeneous products from which crystallization of the salts afforded **659** (R = H, 2-Cl) (ref.[458]).

Reduction of **632** and **636** is in general an unclean reaction complicated by the cleavage of the CH_2-S bond. This type of reduction of **644** (R = H) gave an insight into the proceeding reeactions[538]; the primary product was **647** (R = H) which was cleaved and recyclized affording the spiro(benzo[*b*]thiophene-2(3*H*),4′-piperidine) derivative **660** (NMR). The sulfone **661**, obtained by oxidation of **657** (R = H), gave by alkylation with 3-dimethylaminopropyl chloride[250] (sodium hydride) the sulfone related to hydrothiadene (**662**) having important antihistamine activity in vivo.

N-(Ethoxycarbonyl) derivative of **658** (R = H) was chlorinated with N-chlorosuccinimide, the product was reacted in situ with phenylmagnesium bromide and then reduced with lithium aluminium hydride giving **664** (ref.[538]). Prothiadene (**632**, R = H) S-oxide gave by the Pummerer reaction (heating with acetic anhydride) the 6-acetoxy derivative **665** which had no CNS activity[264]. The sulfone **663** gave by aminoalkylation[250] (sodium hydride) compound **666** (X = SO_2) which was reduced to the alcohol **667** (X = SO_2) (two racemates isolated). Aminoalkylation of the 11-methyl derivative of **657** (R = H) with 3-dimethylaminopropyl chloride (butyllithium) gave **668** (X = S) as a mixture of stereoisomers[538].

Reactions of **655** with the corresponding alkyl chlorides (sodium hydride or sodium amide) and of **656** (or tosylates of **655**) with the corresponding alcohols gave ethers. Compounds **669** and **670** (R = H) had important antihistamine activity[200,1162], their N-benzyl quaternary salts[250] had spasmolytic and mydriatic activity. Reaction of **655** (R = H) with excessive 3-dimethylaminopropyl chloride (sodium amide) gave a product with two side chains[391], identified as **677**. The 1-methyl-4-piperidinyl ethers **671** (R = H, CH_3) (ref.[490]) and the 3-quinuclidinyl ethers **672** (R = H, CH_3, Cl, Br) (ref.[518]) displayed important antireserpine, anticataleptic and antihistamine activities. The ether **673** (R = H) cleaved on treatment with methyl iodide[500] and gave 4-hydroxy-1-methyl-3,4,5,6-tetrahydro-2*H*-thiopyranium iodide. The aromatic ethers **674** (R = H, Br) are very acid-sensitive and are cleaved to **655** (ref.[552]). Reactions of **655** (R = 2-Cl, 2-CH_3) with 2-bromoethanol in the presence of sulfuric acid gave **675** (R = Cl, CH_3) which were subjected to substitution reactions with N-substituted piperazines[459] giving products like **676** (R = Cl, CH_3).

Compound **656** (R = H) was transformed via the isothiuronium salt[391] to the thiol **678** whose sodium salt was aminoalkylated giving **679** (n = 2, 3) which displayed significant antispasmodic and local anaesthetic activities. The aromatic sulfides **680** were prepared from the new 2-, 3- and 4-(dimethylaminomethyl)thiophenol[552] and were found to be devoid of antireserpine activity.

Substitution reactions of **656** with secondary amines gave the corresponding tertiary amines out of which especially the piperazines **681** (R = H) (ref.[215]), **682** (R = Cl) (ref.[458]) and **683** (R = H) (ref.[459]) have properties of potential antidepressants. Reaction of **656** (R = H) with 1-(ethoxycarbonyl)piperazine[516] gave the substitution product which was hydrolyzed to **684** (R = H) and this was alkylated with 1-(3-chloropropyl)-1,3-dihydro-2*H*-benzimidazole-2-one to **685** (R = H), an analogue of oxatomide[1201], having in the test of passive cutaneous anaphylaxis in rats similar activity like the prototype[516].

Compounds like **686** were prepared by substitution reactions of **656** with the corresponding amines[215,523]; compound **686** (R = CH_3) had antihistamine and antireserpine activity. Substitution reactions of **656** (R = H) with 2-, 3- and 4-(dimethylaminomethyl)aniline[552] gave the inactive **687**. On the other hand, the substitution products **688** (R = H, CH_3), obtained from **656** and 4-(2-dimethylaminoethoxy)aniline[552], displayed activity in several tests considered indicative of antidepressant effect.

Compound **689** was prepared on the one hand by bromination of **661**, and by reaction of **655** (R = H) S,S-dioxide with hydrobromic acid[250] on the other, and was transformed to **690**. The primary amine **691** was first obtained[215] from **656** via the phthalimide derivative and much better from **692** by heating with 2-aminoethanol to 170°C (ref.[402]). The urea derivative **693** was obtained by the same reaction at 130°C. Compound **694** was obtained from **691** and benzyl isocyanate[402]. Chloroacetylation of **691** and the following reactions with amines gave compounds like **695** (ref.[523]). Reaction of **691** with ethyl chloroacetate and the following hydrolysis gave **696** (ref.[523]). Compounds **693**, **694** and the amide of **696** displayed some anticonvulsant activity.

An attempt at carrying out the Leuckart reaction with **631** (R = H) led under extrusion of sulfur and involvement of formic acid or formamide to **697** which was also prepared by Leuckart reaction of 10-methyleneanthrone[402]. Compound **698** reacted with amines (with piperidine in the first line) in a surprising manner : mixtures of two isomers were formed which were separated and identified as compounds like **699** and **701** (ref.[427]). A similar course had also the reaction of **698** with 3-dimethylaminopropylmagnesium chloride; **700** and **702** were isolated and identified (NMR).

Reaction of **657** (R = H) with acetyl chloride and aluminium chloride gave an acetyl compound[297] which was identified as **703**. Its Willgerodt reaction led via the thiomorpholide to the acid **704** which displayed antiinflammatory activity in several tests. Reactions of **631** (R = H, 2-Br) with methoxymethylmagnesium chloride gave the corresponding alcohols which were dehydrated and hydrolyzed to the aldehydes **705** (refs[386,539]). Compound **705** (R = H) was reduced to **706** (R = H). The oxime of **705** (R = H) was dehydrated to the nitrile **707** (R = H) which was previously[215] obtained in a poor yield from **656** (R = H) and silver cyanide. The best method for preparing nitriles **707** (R = H, 2-CH_3, 2-Cl, 2-Br) was found in the reaction of the corresponding **656** with trimethylsilyl cyanide in the presence of stannic chloride[541]. Hydrolysis of **707** (R = H) gave the acid **708** (R = H) which was transformed to the amide **709** (R = H) (ref.[444]), having some anticonvulsant activity like the analogous cyheptamide[1202]. The chlorides **656** (R = H, 4-OCH_3) were transformed by the malonic ester synthesis to the acids **710** (R = H, 4-OCH_3) (refs[391,434]) which were transformed by the Curtius degradation to the amines **711** (R = H, 4-OCH_3) and further to the N-methylated homologues **712** and **713** which displayed antireserpine and anticataleptic activities like potential antidepressants[434]. The amine **711** (R = H) was transformed in two steps[523] into **714**, a potential anti-ulcer agent. Heating the nitriles **707** (R = H, 2-CH_3, 2-Cl, 2-Br) with ethylenediamine monotosylate resulted in the dihydroimidazoles **715** which have clear properties of potential antidepressants[541].

Reactions of **705** (R = H, 2-Br) with 2-, 3- and 4-(dimethylaminomethyl)phenylmagnesium bromide gave the secondary alcohols **716** whose oxidation to the corresponding ketones was attempted in many ways. Only in one case the oxidation with tetrabutylammonium chromate in chloroform was successful[539] and **717** (R = H) was obtained; it was accompanied by **657** (R = H) and **718**. The formation of **657** and the aldehydes **719** in similar cases was found to be a general reaction and was explained as a strange case of the retro-ene reaction[539]. The ketone **717** (R = H) showed a mild potentiation of yohimbine toxicity in mice and thus an indication of the antidepressant profile.

The nitrile **707** (R = H) was aminoalkylated[446] (sodium hydride) to **720** (n = 2, 3). Alkaline hydrolysis of **720** (n = 2) gave the amino acid **724** as the minor product and **725** as the major one[446]. Alkylation of **707** (R = H) with 1,2-dibromoethane and 1,3-dibromopropane in the presence of sodium hydride gave **721** (n = 2, 3) (ref.[446]). Their reactions with 4,4-disubstituted piperidines, especially with norpethidine (**487**), gave products like **722** which are analogues of diphenoxylate[1203] and proved similar antidiarrhoic activity[482]. An attempt to alkylate **707** (R = H) with 1,2-dibromoethane in the presence of sodium hydroxide or potassium carbonate and benzyltriethylammonium chloride[446] gave **723** and an isomeric by-product which was identified[504] by NMR spectra and by the X-ray crystallographic study[1204] as 11,12-dihydro-6*H*-6,12-methanodibenzo[*b,f*]thiocin-12-carbonitrile (cf. **997**). An attempt to reduce **723** with lithium aluminium hydride led surprisingly to **635** (R = H) (some strange allylic rearrangement must have been involved) (ref.[504]).

Reactions of **631** (R = H, CH_3) with vinylmagnesium bromide and the following treatment with hydrobromic acid gave **726** (R = H, CH_3) which were transformed via **727** to the acids **728** (R = H, CH_3);these were oxidized to sulfoxides and sulfones[501]. All of these acids are potential metabolites of prothiadene and methiadene (**632**, R = H, 2-CH_3). The acid **728** (R = H) was transformed to the dimethylamide which was reduced with lithium aluminium hydride giving (*E*)-**632** (R = H) which determined the configuration on the double bond in **728**. The ketone **631** (R = 2-CH_3) reacted with 2-(diethylamino)ethylamine in the presence of titanium tetrachloride[391] giving the imine **729** which had strong central depressant activity. The ketone **631** (R = 4-OCH_3) was demethylated with pyridine hydrochloride to **631** (R = 4-OH) which was transformed[528] to the ether **730** (indications of antidepressant-like activity).

Treatment of the ketones **631** (R = H, 2-F) with sodium hydride, the following methylation and hydrolysis proceeded under extrusion of sulfur and the anthracenes **731** – **733** together with anthraquinones were the products[531].

5.3.3.4 Dibenzo[*b,f*]thiepin Derivatives

Our work in this series was the most extensive one; it started in 1964 and lasted until the end of the author's scientific career, i.e more than for twenty years. The first stage of the medicinal chemistry of dibenzo[*b,f*]thiepins was reviewed[357] in 1977 (cf. also ref.[1205]). The more recent work was never reviewed. The present overview enables only to refer to all publications and patents of our team in this field but it is impossible to give details and to refer to publications of other teams. The cause of our concentration to this series was the fact that we found the dibenzo[*b,f*]thiepin system to be the most favourable pharmacophore in the series of neuroleptic agents; it was especially the combination of this system with piperazine[219,162] and for this reason I find advisable to start with this type which will not completely correspond to the chemical system.

The entry to the series are ketones **734** which are mostly obtained by cyclization of the (2-(arylthio)phenyl)acetic acids with polyphosphoric acid. The synthesis of the starting acids consisted in most cases in reactions of 2-halobenzoic acids with thiophenol and its Ar-substituted derivatives, in the following reduction of the 2-(arylthio)benzoic acids to alcohols with lithium aluminium hydride, sodium dihydridobis(2-methoxyethoxy)aluminate or with diborane, the following transformation of the alcohols to 2-(arylthio)benzyl chlorides with thionyl chloride and then to nitriles which are hydrolyzed. In some cases the Willgerodt reaction of the 2-(arylthio)acetophenones proved useful. The ketones are reduced with sodium borohydride to **735** which are converted by the action of hydrogen chloride to **736**, very reactive components in substitution reactions. These reactions with 1-methylpiperazine give **737** which are formed together with dibenzo[*b,f*]thiepins **738** as elimination products. Another important reaction is the formation of enamines **739** by reactions of **734** with 1-methylpiperazine in the presence of titanium tetrachloride.

The first compound, which was synthesized by the mentioned procedure, was perathiepin (**737**, R = H) (refs[207,220]). It was shown to have an extremely high ataxic activity (higher than chlorpromazine), inhibiting effect on the spontaneous locomotor activity, hypothermic, antihistamine, and antiserotonin activity[1206-1208]. This finding indicated for perathiepin neuroleptic activity which led to its clinical testing in this line[1209-1212]; there were surprising cases of therapeutic success in schizophrenics but most of the patients did not respond to perathiepin and the testing was stopped. Some biochemical and physiological papers[1213-1215] deal with perathiepin. For preparing the metabolic study of perathiepin (**737**, R = H), several potential metabolites were prepared as standards. Reaction of **736** (R = H) with 1-(ethoxycarbonyl)piperazine afforded the carbamate **740** (R = H) which was hydrolyzed to norperathiepin[212] (**741**, R = H). Oxidation of perathiepin with hydrogen peroxide under various conditions[291] gave the S-oxide **742** (R = H), N-oxide **743** (R = H) and S,N-dioxide **744** (R = H). Oxidation with the excess of hydrogen peroxide in boiling acetic acid led to cleavage of the molecule and to the formation of the sulfone corresponding to **738** (R = H) (ref.[212]).

The nuclearly hydroxylated perathiepin derivatives were prepared via the corresponding methoxy compounds (**737**, R = OCH_3) which were demethylated with boron tribromide. The cyclization of the methoxylated acids to **734** (R = OCH_3) were carried out with polyphosphoric acid in boiling toluene. The synthesis of the 2-hydroxy derivative **737** (R = 2=OH) started from **734** (R = 2-NH_2) which was transformed with nitrous acid to **734** (R = 2-OH), this was methylated to **734** (R = 2=OCH_3) and the synthesis proceeded then normally[360]; the product had week activity. The synthesis of the 3-hydroxy derivative **737** (R = 3-OH) proceeded along the general scheme[384] and the product was found more active than perathiepin in the line of ataxic and cataleptic activity. The way to the 2,3-dihydroxy derivative[349] (**737**, R = 2,3-$(OH)_2$) met with two anomalies. The first was the formation of a heptacyclic by-product (cf. **1074**, 12,13,16,17-tetramethoxy) in the cyclization aiming at **734** (R = 2,3-$(OCH_3)_2$). The second was the reaction of **735** (R = 2,3-$(OCH_3)_2$) with hydrogen chloride in chloroform giving a 1:1 mixture of **736** (R = 2,3-$(OCH_3)_2$) and **745** (Wagner – Meerwein rearrangement) which was separated by crystallization. The remaing part of the synthesis proceeded normally; the product was practically inactive. The enamine **739** (R = 2,3-$(OCH_3)_2$) was also prepared[349]. The 6-hydroxy derivative **737** (R = 6-OH) was prepared along the general scheme[328]; the final product was less active than perathiepin and was oxidized to the S-oxide (**742**, R = 6-OH). The enamine **739** (R = 6-OCH_3) was also synthesized[328]. For preparing the 7-hydroxy derivative (**737**, R = 7-OH), the 7-methoxy compound was first prepared which was not possible by the normal way[287]. Reaction of **735** (R = 7-OCH_3) with hydrogen chloride led only to the product of elimination (**737**, R = 3-OCH_3). It was, therefore, necessary to transform the ketone **734** (R = 7-OCH_3) to the enamine **739** (R = 7-OCH_3) which was reduced with diborane in situ to **737** (R = 7-OCH_3) showing considerable antihistamine activity. All attempts at its demethylation as well as modified procedures[287,351,401] were unsuccessful; the final product was **738** (R = 3-OH). After this experience, the syntheses aiming at the 3,7-dihydroxy and 7,8-dihydroxy derivatives of perathiepin were stopped in the stage of dimethoxy compounds[413] (**737**, R = 3,7-$(OCH_3)_2$ and 7,8-$(OCH_3)_2$); they had to be carried out also via the enamines **739**. The oxygen function in position 7 makes evidently the bond between C-10 and N of piperazine very labile. The neuroleptically very active 8-hydroxy compound (**737**, R = 8-OH) was the first hydroxy compound prepared in the series[300]. In addition to the normal way, it was also obtained by debenzylation of the 8-benzyloxy compound **737** (R = 8-$OCH_2C_6H_5$) and also by air oxidation of the Grignard reagent prepared from 8-bromo-**737**. The 2,8-dihydroxy and 3,8-dihydroxy compounds (**737**, R = 2,8-$(OH)_2$ and 3,8-$(OH)_2$) were prepared by the normal route[385] and were found less active than perathiepin. The metabolic study using the urine of rats and patients led only to identification of norperathiepin (**741**, R = H) and S-oxide (**742**, R = H) as metabolites[1216]. Racemic perathiepin was resolved with dibenzoyl-(+)-tartaric an di(*p*-toluoyl)-(–)-tartaric acids to enantiomers. Only the (+)-enantiomer was tested and its ataxic activity was found similar to that of the racemate; there was no stereoselectivity of action in this direction[212].

On the basis of analogy with the known neuroleptics chlorpromazine and chlorprothixene (**593**, R = 2-Cl), whose molecules contain the atom of chlorine in position corresponding to 8 in **737**, the 8-chloro derivative of perathiepin (octoclothepin, clorotepin (INN), **737**, R = 8-Cl) was the first of the chlorinated perathiepin derivatives, which was prepared by the mentioned route[235]. It also was prepared from **740** (R = 8-Cl) by reduction with complex hydrides[293] and in low yield by Leuckart reaction from 734 (R = 8-Cl) and 1-methylpiperazine[293]. Octoclothepin was found to be an extremely potent neuroleptic agent with the intensity of effects at least comparable to those of perphenazine[269,1217-1221]. This finding led to preclinical investigations[1222-1226] which enabled clinical trials[1227-1232]. The therapeutic activity of octoclothepin in schizophrenic psychoses was clearly recognized (accompanied by the usual extrapyramidal side effects) and the agent in the form of maleate was introduced by SPOFA[1233] as an oral neuroleptic to pharmacotherapy of schizophrenia (Clotepin®).

Further chemical work with octoclothepin included first the oxidation reactions leading to the S-oxide[235,291] (**742**, R = 8-Cl), N-oxide[291] (**743**, R = 8-Cl), and S,N-dioxide[291] (**744**, R = 8-Cl). For preparing the sulfone **747** it was necessary to oxidize **736** (R = 8-Cl) to **746** which was subjected to the substitution reaction with 1-methylpiperazine[291]. Further oxidation led to the sulfone N-oxide **748**. Analogy of the described method led from **736** (R = 8-Cl) to noroctoclothepin (**741**, R = 8-Cl) (ref.[267]) which was oxidized to the S-oxide[291]. The cyclic hydroxylamine derivative **749** could also be considered a potential metabolite of octoclothepin. It was prepared from **741** (R = 8-Cl) by reaction with benzoyl peroxide[339,368] and by the following hydrolysis of the obtained **750**; compound **751** was a by-product and is also a potential metabolite[368].

Out of the nuclearly hydroxylated derivatives of octoclothepin, the following were prepared by the mentioned methods : 2-hydroxy (**737**, R = 2-OH-8-Cl) which is practically inactive; 3-hydroxy (**737**, R = 3-OH-8-Cl) which is highly active[313]; 3-hydroxy S-oxide (**742**, R = 3-OH-8-Cl) (ref.[368]); 3-hydroxy derivative of noroctoclothepin (**741**, R = 3-OH-8-Cl) which was prepared[368] via **740** and **741** (R = 3-OCH_3-8-Cl); 2,3-dihydroxy[349] (**737**, R = 2,3-$(OH)_2$-8-Cl); 6-hydroxy (**737**, R = 6-OH-8-Cl) and the related S-oxide, N-oxide, 6-hydroxy-nor and its S-oxide[369]; 2,6-dihydroxy (**737**, R = 2,6-$(OH)_2$-8-Cl) and 3,6-dihydroxy[411] (**737**, R = 3,6-$(OH)_2$-8-Cl). Attempts to prepare the 7-hydroxy and 3,7-dihydroxy derivatives[355,362] were unsuccessful similarly like in the perathiepin series; they were discontinued in the stage of the methoxy compounds (**737**, R = 7-OCH_3-8-Cl, 3,7-$(OCH_3)_2$-8-Cl).

The enamine **739** (R = 8-Cl, dehydroclothepin) was prepared from **734** (R = 8-Cl) by three methods : (i) by heating with 1-methylpiperazine and 4-toluenesulfonic acid in benzene (low yield), (ii) by reaction with 1-methylpiperazine and titanium tetrachloride in benzene[257] (collision with refs[1234,1235]) and (iii) by heating with 1-methylpiperazine 4-toluenesulfonate in vacuo to 190°C[293]. This compound was found even more active than octoclothepin in several tests[257].

After the introduction of octoclothepin, many further papers dealing with this agent were published in the lines of pharmacology[1236,1237], further clinical experiences[1241-

[1248], and the use of very high doses[1249-1251]. The methanesulfonate[293] of octoclothepin was introduced on the market as an injection form (Clotepin inj.®) (refs[1252-1255]) and the oily solution of the octoclothepin base was introduced as a semi-depot preparation for intramuscular administration (Clotepin oleosum inj.®) (refs[1256-1261]). Analytical methods for determination of octoclothepin were elaborated[1262,1263] and its pharmacokinetics with [^{35}S] and [^{14}C]labeled substances was studied[1264,1265]. The metabolic studies used the synthesized potential metabolites as standards and the metabolites were isolated from urine and faeces of rodents and humans, from bile and liver homogenates[1266-1274]. The following compounds were identified as metabolites : octoclothepin S-oxide, N-oxide, S,N-dioxide, noroctoclothepin, its S-oxide, 2- and 3-hydroxy derivatives of octoclothepin, 3-hydroxy S-oxide and the 6-hydroxy derivative of noroctoclothepin. The reduction of the N-oxide in the liver back to octoclothepin was demonstrated[1272].

Octoclothepin has been used as the racemate. The resolution with dibenzoyl-(+)-tartaric and (+)-tartaric acid was carried out[293] and afforded the enantiomers which were first pharmacologically tested in the form of maleates. On the basis of the almost equal discoordinating effect of both enantiomers and an incorrect interpretation of the results in the test of catalepsy, we concluded erroneously that the neuroleptic action of octoclothepin is not stereoselective. Swiss authors[1275], using our substances, carried out a crystallographic and difractometric study of racemic and (+)-octoclothepin, they described the preferred conformation of the (+)-enantiomer and determined the absolute configuration at C-10 as (*S*). They published then[1276,1277] the finding of stereoselectivity of the neuroleptic effects of octoclothepin in the tests of catalepsy, of antiapomorphine and antiamphetamine action : in the racemic octoclothepin, the (*S*)-(+)-enantiomer is the active component. Shortly thereafter this finding was confirmed by our group[326]. The enantiomers were prepared in greater amounts and their clinical comparison was carried out[1278]. It was found that the (*S*)-(+)-enantiomer is antipsychotically more potent and brings about more extrapyramidal side reactions. The (*R*)-(−)-enantiomer, however, is not completely inactive which indicated that the stereoselectivity of the octoclothepin effects has only a certain limited degree. This was confirmed by further in vitro experiments using the water-soluble methanesulfonates of the enantiomers[437]. These substances were evaluated from the view-point of their affinity to brain dopamine receptors using crude homogenates of caudate nucleus from calf brains with [^{3}H]spiperone as the radioactive ligand[388], preparation of the rat-brain striatal membranes with [^{3}H]haloperidol as the ligand[1279], and finally using the determination of the influence on the homovanillic acid concentration in the rat corpus striatum[1280]; the incomplete stereoselectivity of action was explained by the relative flexibility of the octoclothepin molecule which is thus able to a certain adjustment to the shape and binding sites of the receptor[388]. Two monographical articles[1281,1282] were devoted to octoclothepin.

Further 8-halo derivatives of perathiepin, i.e. 8-fluoro and 8-bromo (**737**, R = 8-F, 8-Br) were prepared by the route outlined[235]; the 8-iodo compound (**737**, R = 8-I) had to be synthesized in a modified way[302]. The ketone **734** (R = 8-I) was obtained from the 8-amino ketone (**734**, R = 8-NH_2) and the remaining part of the synthesis proceeded along the scheme. All the three halo compounds are very active neuroleptics; the 8-iodo compound was the most active one in the test of catalepsy[302]. The following 8-alkyl derivatives of perathiepin (**737**, R = 8-alkyl) were prepared using the scheme : 8-methyl[238], 8-ethyl, 8-isopropyl, 8-butyl[315], 8-(tert-butyl) (ref.[238]) and 8-octyl[315]; the ethyl and isopropyl derivative are equipotent (especially in the test of catalepsy) with octoclothepin[315]. In the synthesis of the 8-cyclopropyl compound (**737**, R = 8-cyclopropyl) it was necessary to cyclize the starting acid to **734** (R = 8-cyclopropyl) with trifluoroacetic anhydride[315]. The synthesis of the 8-cyclopentyl compound proceeded normally[315]. The cyclopropyl derivative attained the activity of octoclothepin[315]. The 8-isopropyl, 8-butyl and 8-cyclopentyl enamines **739** were prepared by the titanium tetrachloride method[315] and the first of them was ten times more active than octoclothepin in the test of catalepsy. For the 8-alkoxy derivatives of perathiepin, the ketone **734** (R = 8-OCH_3) (obtained by cyclization of the corresponding acid with polyphosphoric acid in boiling toluene) was a common intermediate[238,300]. It was demethylated with pyridine hydrochloride to the 8-hydroxy ketone **734** (R - 8-OH) which was O-alkylated with ethyl bromide, butyl bromide, benzyl chloride and 2-bromopyridine to the corresponding ketones which were then processed in the described manner and gave **737** (R = 8-OCH_3, 8-OC_2H_5. 8-OC_4H_9, 8-$OCH_2C_6H_5$, 8-O-2-pyridyl) (ref.[300]). The 8-methoxy compound (octomethothepin) is an extremely active neuroleptic agent[238].

A further interesting group were the 8-alkylthio derivatives of perathiepin out of which 8-methylthio, 8-ethylthio, 8-propylthio, 8-isobutylthio, and 8-dodecylthio compounds[238,308] were prepared. The first two members of the series (**737**, R = 8-SCH_3, 8-SC_2H_5) are very active and especially the 8-methylthio compound (methiothepin, metitepine (INN)) became world-wide known because of its central antiserotonin action, which was discovered by the researchers of Hoffmann – La Roche Company, collaborating with us in the line of this compound. For references to biological information on methiothepin until 1977, cf. the review[356]. Methiothepin was prepared also via the enamine **739** (R = 8-SCH_3) by its reduction with zinc in acetic acid[397]. Normethiothepin (**741**, R = 8-SCH_3) was prepared from **736** (R = 8-SCH_3) via the corresponding carbamate **740** (ref.[267]). Oxidation products of methiothepin and normethiothepin were prepared as potential metabolites[291] : S^8-oxide, S^5,S^8-dioxide, N-oxide, S^5,S^8,N-trioxide and normethiothepin-S^5,S^8-dioxide. Oxidation of methiothepin with hydrogen peroxide in boiling acetic acid resulted in cleavage and formation of **738** (R = 2-SO_2CH_3) 5,5-dioxide[437]. Further compounds prepared were **741** (R = 8-SO_2CH_3) and its 5-oxide[403], the 8-methylthio analogue of **751** (ref.[397]), the similar 8-methylsulfonyl analogue and its 5-oxide[403]. Out of the Ar-hydroxylated derivatives of methiothepin only the 2-hydroxy (737, R = 2-OH-8-SCH_3) and the 3-hydroxy compound (737, R = 3-OH-8-SCH_3) were prepared[475]. The latter was identified as a metabolite and it is a strong neuroleptic agent. The question of stereoselectivity of the methiothepin action (cf. ref.[356]) was reinvestigated[1283,1284]. Many additions to the knowledge of biochemical, pharmacological, endocrinological and behavioural actions of methiothepin were published out of which only a selection is cited here[1285-1306].

It was clear that variously 8-substituted derivatives of perathiepin (737, 8-R) represent a big family of very active neuroleptic agents[228]. Twenty further members of this family were synthesized. The 8-(methylseleno) ketone (734, R = 8-$SeCH_3$) served as the starting material for preparing 737 (R = 8-$SeCH_3$) and the corresponding enamine 739 (ref.[281]); both compounds are more active as neuroleptics than octoclothepin. The 8-nitro compound (737, R = 8-NO_2), which was prepared along the scheme[233], is a potent neuroleptic with high ataxic, hypothermic and thiopental potentiating effects. Its S-oxide was prepared by oxidation[233]. It could be directly transformed to the 8-amino compound (737, R = 8-NH_2) (ref.[233]) which was also prepared by a modification of the total synthesis: the alcohol 735 (R = 8-NH_2) was transformed by treatment with trifluoroacetic anhydride and by methanolysis to 735 (R = 8-$NHCOCF_3$). This was transformed to 736 (R = 8-$NHCOCF_3$) giving in one step by the substitution reaction with 1-methylpiperazine and treatment with hydrochloric acid the desired 737 (R = 8-NH_2) with strong cataleptic and hypothermic activities[233]. Acetylation of 734 (R = 8-NH_2) gave the N-acetyl derivative which was converted in three steps to 8-acetamido derivative of perathiepin (737, R = 8-$NHCOCH_3$) (as a neuroleptic weaker than the amino compound[281]). Similar syntheses starting from 734 (R = 8-NH_2) led to 8-(ethoxycarbonylamino) and 8-(methanesulfonamido) derivatives of perathiepin[302] with low neuroleptic activity. From the new 4-(dimethylamino)thiophenol and 4-(4-morpholinyl)thiophenol via the corresponding 8-amino ketones 734 and via the enamines 739 (R = 8-$N(CH_3)_2$, 8-morpholino), the 8-dimethylamino and 8-(4-morpholinyl) derivatives of perathiepin were prepared[499]; the former is a typical incisive neuroleptic agent with strong ataxic, cataleptic, antiapomorphine and antiadrenergic activities. Diazotization of 734 (R = 8-NH_2) in hydrochloric acid and reaction of the diazonium salt with sulfur dioxide in the presence of cuprous chloride gave the sulfonyl chloride 734 (R = 8-SO_2Cl) which was processed in situ by reactions with dimethylamine and pyrrolidine. The obtained 8-(aminosulfonyl) ketones were processed in three usual steps to 8-(dimethylaminosulfonyl) and 8-(pyrrolidinosulfonyl) derivatives of perathiepin[301] (737, R = 8-$SO_2N(CH_3)_2$, 8-$SO_2NC_4H_8$). The 8-(dimethylaminosulfonyl) ketone was also transformed to the enamine 739 (R = 8-$SO_2N(CH_3)_2$). Both dimethylaminosulfonyl compounds are stronger neuroleptics than octoclothepin.

For preparing the 8-trifluoromethyl ketone (734, R = 8-CF_3) it was necessary to carry out the cyclization step with hydrogen fluoride[246] (hydrolysis of trifluoromethyl to carboxyl was the side reaction); the usual three steps gave **737** (R = 8-CF_3) which was milder than octoclothepin in the ataxic activity but stronger in cataleptic effect. 8-Cyano derivative of perathiepin (**737**, R = 8-CN) was prepared by two ways. The first[256] used the conversion of the 8-bromo ketone (**734**, R = Br) to the 8-cyano ketone with cuprous cyanide and then the usual three steps. The other[314] used the conversion of **737** (R = 8-Br) to the 8-cyano compound with cuprous cyanide in hexamethylphosphoric triamide. The second method was complicated by the formation of the carboxamide **737** (R = 8-$CONH_2$) as the by-product. Whereas the amide was weak as a CNS agent, the nitrile (**737**, R = 8-CN) was equipotent with octoclothepin[256]. Hydrolysis of the cyano ketone gave the keto acid **734** (R = 8-COOH) which was transformed in the three usual steps to the 8-carboxy derivative of perathiepin (**737**, R = 8-COOH) which was devoid of CNS activity[256]. Reduction of the nitrile **737** (R = 8-CN) with lithium aluminium hydride[256] gave the 8-(aminomethyl) compound **737** (R = 8-CH_2NH_2) being a very weak CNS agent. A similar reduction with lithium aluminium triethoxyhydride gave in addition to the mentioned 8-(aminomethyl) compound the desired aldehyde **737** (R = 8-CHO) which is equipotent with octoclothepin[314]. Deamination of **737** (R = 8-CH_2NH_2) with nitrous acid in acetic acid gave the mixture of the 8-(hydroxymethyl) and 8-(acetoxymethyl) compounds (**737**, R = CH_2OH and CH_2OCOCH_3) which was separated; both products have similar neuroleptic activity like octoclothepin[314]. 8-Acetyl and 8-propionyl derivatives of perathiepin[314] were prepared by applying the Beech method in the stage of **735** : the 8-amino alcohol (**735**, R = 8-NH_2) was diazotized, the diazonium salt was treated with semicarbazones of acetaldehyde and propionaldehyde and the products were hydrolyzed to **735** (R = 8-$COCH_3$, 8-COC_2H_5). Two usual steps gave **737** (R = 8-$COCH_3$, 8-COC_2H_5). The acetyl compound is about three times as active as octoclothepin, the propionyl compound is equipotent. At least twenty two 8-substituted derivatives of perathiepin were found to be very potent neuroleptic agents and most of them could probably be useful in the treatment of schizophrenic psychoses. Two attempts to evaluate the structure-activity relations in this series by the QSAR methods were undertaken[350,536].

N-Methyl is not the only N-substituent favourable for the activity when connected with a suitable 8-substituent. Variously N-substituted perathiepin derivatives were prepared (i) by N-alkylation of **741**, (ii) by N-acylation of **741** and the following reduction with lithium aluminium hydride, (iii) by substitution reactions of **736** with correspondingly N-monosubstituted piperazines, (iv) by addition of **741** to compounds like acrylonitrile, (v) by reactions of compounds like **763** with primary amines, and (vi) by transformation of the functional groups in the N-substituents. Out of the **752** (R = 8-Cl) only those with R^1 = ethyl, isopropyl and tert-butyl are active as neuroleptics[348], N-allyl, N-propargyl and N-(2-dimethylaminoethyl) are much weaker[267]. Compound **753** (R = 8-Cl) is more active than the homologue **754** (R = 8-Cl) (ref.[267]). Compounds **752** with R^1 being aryl, pyridyl, benzyl, higher aralkyl (including 4-

fluoroaralkyl) are almost devoid of neuroleptic activity[212,235,267,321,394]. Very positive influence on the activity is executed by lower hydroxyalkyls as R^1 substituents, documented especially by **755** (noroxythepin (R = H) and 8-substituted derivatives[212,267]) and **756** (oxythepin (R = H) and 8-substituted derivatives[212,267,301,315,403]). The following further 8-substituted hydroxyalkyl derivatives **757** proved interesting (R^1 given): 2-hydroxypropyl[341], 3-hydroxy-2-methylpropyl[341], 2-hydroxybutyl[437], 3-hydroxybutyl[267], 4-hydroxybutyl[267], 4-hydroxypentyl[437], and 2,3-dihydroxypropyl[341]. The propionamide (**758**, R = 8-Cl) and propionamidoxime (**759**, R = 8-Cl) derivatives preserve also a high degree of activity[267]. Lower esters (acetates, propionates) of the hydroxyalkyl derivatives **755** and **756** are active[267]; esters with acids like 3,4,5-trimethoxybenzoic[267], mandelic and benzilic[437] are inactive. Esters with long-chain fatty acids are very useful as depot neuroleptics (long-acting) and will be described separately. Compounds **760** and **761** (R = 8-Cl, 8 = SCH_3) with the cyclic acetal groups[309] have very high activity which equals that of octoclothepin and methiothepin. Compounds **762** were prepared by alkylation of **741** with 1-(3-chloropropyl)-1,3-dihydro-2*H*-benzimidazole-2-one[516] as antiallergics; compound **762** (R = H) proved in the test of passive cutaneous anaphylaxis in rats more active than oxatomide[1201], used as the prototype.

Noroxyclothepin (**755**, R = 8-Cl) was best prepared by the substitution reaction of **736** (R = 8-Cl) with 2-(1-piperazinyl)ethanol[267] and because of the high activity was considered for some time a candidate for clinical testing. The analogous enamine **764** (R = 8-Cl) was prepared by heating **734** (R = 8-Cl) with the monotosylate of 2-(1-piperazinyl)ethanol to 190°C in vacuo[341]. Its unstable N-oxide[341] was found extremely active in the test of catalepsy. A pharmacokinetic study of noroxyclothepin[1307] was carried out with substance labelled with ^{14}C in position 10 and the metabolic study detected twenty metabolites; only two were identified with the help of synthetic standards: **741** (R = 8-Cl) and the S-oxide of **755** (R = 8-Cl) (ref.[341]). Noroxyclothepin N-oxide was also prepared[341]. The enol ether **766** was prepared by heating **755** (R = 8-Cl) with cyclododecanone dimethyl ketal in toluene in the presence of 4-toluenesulfonic acid[341] as a potential depot neuroleptic; it did not show this presumed property. As a further potential metabolite, compound **767** (R = H) was expected but the attempt at its preparation via **767** (R = CH_3) was unsuccessful. For this reason, a different method was used[389] : the ketone **734** (R = 3-OCH_3-8-Cl) was demethylated with pyridine hydrochloride to **734** (R = 3-OH-8-Cl) which was reduced to the corresponding alcohol. This was treated with methanesulfonyl chloride and gave **769**. Treatment of this compound with 2-(1-piperazinyl)ethanol proceeded under substitution and aminolysis and gave the desired **767** (R = H). Oxyclothepin **756** (R = 8-Cl) was prepared similarly[267], had similar activity and gave similarly the N-oxide[291]. Its 3-hydroxy derivative (**768**, R = H) as a potential metabolite was prepared by the same method like described for **767** (R = H) (ref.[389]). Compounds **767** and **768** (R = H) had only low CNS activity – probably due to the significant decrease of lipophilicity (cf. ref.[383]).

The 8-methylthio compound **756** (R = 8-SCH_3, oxyprothepin) is the most important out of the neuroleptic amino alcohols of this series[271]. It was first prepared from **741** (R = 8-SCH_3) by the addition to methyl acrylate and by the following reduction with lithium aluminium hydride[267]. Further synthetic methods are the substitution reaction of **736** (R = 8-SCH_3) with 3-(1-piperazinyl)propanol[341] (for a minor by-product, cf. ref.[494]) and by reduction of the enamine **765** (R = 8-SCH_3) which was prepared from **734** (R = 8-SCH_3) (ref.[341]). Oxyprothepin was carefully pharmacologically investigated and found to be more potent than octoclothepin[1308-1320]. An important reason for its introduction on the market (Meclopin ®) was the fact that it could be used as the basis for a depot ester preparation[478]. Its therapeutic usefulness in schizophrenic psychoses and other mental diseases was demonstrateed in many communications; only selected papers are cited[1321-1348]. An X-ray crystallographic study of racemic oxyprothepin gave information on the preferred conformation of its molecule[1349]. Synthesis of potential metabolites of oxyprothepin proceeded together with the metabolic studies. Some of the potential metabolites are identical with those of methiothepin (normethiothepin and its oxidation products). The following potential metabolites with the intact 3-hydroxypropyl side chain were synthesized : 8-S-oxide[291,397], 5,8-dioxide[291,397], N-oxide[291], 8-sulfone (**756**, R = 8-SO_2CH_3), its 5-oxide, N-oxide and 5,N-dioxide[403], 2-hydroxy derivative[475], 3-hydroxy derivative[335] (for discussion of its surprisingly low neuroleptic activity, cf. ref.[383]), 2-hydroxy-8-sulfone[476], and 3-hydroxy-8-sulfone[476]. The pharmacokinetics (partly with ^{14}C and ^{3}H-labelled preparations) was studied in rats and humans[1350-1352]. The metabolic studies in rats and humans led to the identification (mostly with the help of synthetic standards) of the following substances[1350,1353-1356] : 8-S-oxide, 5,8-dioxide, N-oxide, 5,8,N-trioxide, 8-sulfone, 5-oxide-8-sulfone, 3-hydroxy derivative, a partly characterized hydroxy-8,N-dioxide, and normethiothepin.

Long-chain fatty acid esters of neuroleptic aminoalkanols have properties of depot neuroleptic agents[276,478,1357] : an intramuscular injection of such esters in vegetable oils forms in the muscle an oily depot from which the ester only slowly penetrates to the blood stream where it is quickly hydrolyzed by esterases[1358] and the free amino alcohol enters the brain and finds the sites of action. The esters per se are practically inactive in acute experiments, e.g. on the oral administration. Our amino alcohols **755** and **756** (and also **765** (ref.[292])) were used for the preparation of esters with butyric, oenanthic, caprylic, caprinic (decanoic), lauric, and palmitic acid. These esters were prepared (i) by acylation of the amino alcohols with acid chlorides or acid anhydrides[292,315,339], (ii) by reactions of the amino alcohols with the acids in boiling xylene under conditions of azeotropic distillation[292,339], (iii) similarly in dichloromethane in the presence of carbonyldiimidazole[397], (iv) by substitution reaction of **736** (R = 8-SCH_3) with N-(3-

decanoyloxypropyl)piperazine[339,397] (especially for the case o f 771), and (v) by alkylation of **741** (R = 8-Cl) with 2-(decanoyloxy)ethyl chloride[437] (for the case of **772**). Method (i) in the case of using an excess of the acid chloride is complicated by a cleavage reaction to **736** (R = 8-SCH_3) and 1-decanoyl-4-(3-decanoyloxypropyl)piperazine[339] (for the case of **771**). Three of the esters were pharmacologically tested : oxyprothepin oenanthate (**770**) (ref.[1359]), noroxyclothepin decanoate (**772**) (ref.[1360,1361] and oxyprothepin decanoate (**771**) (ref.[1362,1363]); the duration of the antiapomorphine effects in rats and dogs after a single intramuscular injection was evaluated. The most prolonged effects were found with oxyprothepin decanoate which was handed over to extensive clinical trials including double-blind comparisons with the most renowned depot neuroleptic agents used abroad[1364-1395]. The results were positive (a single injection maintains the antipsychotic effects for three to four weeks and our compound brings about less extrapyramidal side-effects than the agents used for comparison including fluphenazine decanoate and the drug was introduced on the market (Meclopin inj.®). Several esters like **770** – **772** but with R = C_2H_5, $CH(CH_3)_2$, C_4H_9 (ref.[315]) and esters of noroxyclothepin with unsaturated, branched-chain, alicyclic (including **773**), araliphatic and dicarboxylic acids[339] were prepared but were found less convenient. Neither the aza analogue **774** of oxyprothepin decanoate[397] did evoke attention; it was prepared from **756** (R = 8-SCH_3) and octyl isocyanate in boiling toluene.

The following Ar-mono- or disubstituted derivatives of perathiepin (**737**), the corresponding enamines (**739**), nor compounds (**741**), and amino alcohols (**755**, **756**) with the exception of the 8- (already described), 2- and fluoro substituted derivatives (will be described in the following paragraphs) were prepared using the general procedure or the specified modification : 1-chloro (**737**, R = 1-Cl) (the hydrolysis of the intermediate (6-chloro-2-(phenylthio)phenylacetonitrile) stopped in the stage of the amide and it was necessary to cyclize this amide with polyphosphoric acid which proceeded well[236], the other steps proceeded along the scheme; the final product lacks CNS activity); 3-chloro[236] (**737**, R = 3-Cl) (the synthesis proceeded normally, the product has low ataxic activity); 4-chloro[236] (**737**, R = 4-Cl) (normal procedure, very low ataxic activity); 6-chloro[236] (**737**, R = 6-Cl) (normal procedure, low ataxic activity); 6-chloronor (**741**, R = 6-Cl) (practically inactive[487]); 6-methyl (**737**, R = 6 = CH_3) (the cyclization step required very mild conditions[551]; at 150°C instead of **734** (R = 6-CH_3), the heptacyclic product of its dehydration and dehydrogenation was obtained[487]; the remaining part of the synthesis was normal; the final product is a noncataleptic tranquillizer[551]); 6-methyl-nor (**741**, R = 6-CH_3) (the product potentiates yohimbine in mice like a potential antidepressant); 6-ethyl-nor (**741**, R = 6-C_2H_5) (synthesis was normal[487], the product has antireserpine activity like a potential antidepressant); 6-methoxy-nor (**741**, R = 6-OCH_3) (potential antidepressant[487]); 7-chloro[236] (**737**, R = 7-Cl) (normal procedure, 10% of the ataxic activity of that of perathiepin); 7-methyl[425] (**737**, R = 7-CH_3) (normal synthesis, antihistaminic activity in vivo); 7-ethyl[425] (**737**, R

= 7-C_2H_5) (high antihistamine activity in vivo); 6,7-dichloro[407] (737, R = 6,7-Cl_2) (normal synthesis, weak sedative and relatively strong cataleptic activity);2-acetyl-8-chloro and 3-acetyl-8-chloro[377] (737, R = 2-$COCH_3$-8-Cl and 3-$COCH_3$-8-Cl) (Beech reaction used for obtaining 735 (R = 2-$COCH_3$-8-Cl, 3-$COCH_3$-8-Cl)); 7-trifluoromethyl[401] (737, R = 7-CF_3) (cyclization with polyphosphoric acid in dichlorobenzene at 190°C gave 734 (R = 7-CF_3) as the main product which was accompanied by two by-products – 734 (R = 7-COOH) and 775 giving on alkaline hydrolysis 734 (R = 9-COOH); the final,product has relatively strong ataxic and cataleptic activity); 7,8-dichloro[340] (737, R = 7,8-Cl_2) and also the 3-hydroxypropyl analogue and its octanoate (the synthesis was normal; low ataxic, medium cataleptic and anti-apomorphine effects); 7-trifluoromethyl-8-chloro[355] (737, R = 7-CF_3-8-Cl) (cyclization at 180°C gave in addition to 734 (R = 7-CF_3-8-Cl) some 734 (R = 7-COOH-8-Cl) and 776 giving on alkaline hydrolysis 734 (R = 8-Cl-9-COOH); low ataxic and cataleptic activity).

The 9-chloro compound (737, R = 9-Cl) was not accessible by the normal route because the cyclization of (2-(3-chlorophenylthio)phenyl)acetic acid afforded exclusively the 7-chloro ketone[236] (734, R = 7-Cl). A method of synthesis of 734 (R = 9-Cl) from 2-(3-chlorophenylthio)benzoic acid in five steps was elaborated[298], the crucial step being the oxidation of 1-chloro-9-methylenethioxanthene with thallic nitrate in methanol proceeeding under rearrangement of the skeleton and giving 777 which was hydrolyzed to 734 (R = 9-Cl); a by-product was 734 (R = 1-Cl). The rest of the synthesis proceeded normally affording the neuroleptically inactive 737 (R = 9-Cl). An attempt to cyclize (2-(2-acetamido-5-chlorophenylthio)phenyl)acetic acid with polyphosphoric acid in toluene[298] gave two isomeric Schiff bases – products of interaction with toluene – one of them being 778. The synthesis of the 6,9-dichloro compound 737 (R = 6,9-Cl_2) led in the cyclization step (PPA, 170°C) to a mixture of the major 779 and the minor 734 (R = 6,9-Cl_2) which was used for concluding the work[299]; the product was inactive. Thus, only substitution in position 8 in the molecule of perathiepin led to very active neuroleptic agents. The influence of the substitution in position 2 will be treated in one of the following paragraphs.

The fact that neuroleptics of the perathiepin series are partly metabolized to Ar-hydroxylated compounds (hydroxylation proven in positions 2, 3 and 6) which are hydrophilic and as such quickly eliminated from the organism, led to the idea to block the critical positions by fluorination which could result in potent compounds with prolonged action even after the oral administration[344,373]. The synthesis of the fluorinated compounds used the general scheme via 734 – 736 and 741, and resulted in the corresponding 737, 739, 756 and others. Fluorinated compounds having the atom of chlorine in position 2 will be treated in the paragraph devoted to noncataleptic neuroleptics. The 2-fluoro compound (737, R = 2-F) was prepared by the general method[323] and was found to be a relatively weak neuroleptic agent. The synthesis of the 3-fluoro compound **737** (R = 3-F) was complicated in the stage of cyclization[384] by the formation of the heptacyclic furan (cf. **1074**) as a by-product; the final product had high and prolonged ataxic action and was noncataleptic. The synthesis of the 6-fluoro compound (**737**, R = 6-F) was connected with the similar phenomenon in the cyclization step[380] and the final product has a perathiepin-like activity (free of the cataleptic affect). The 7-fluoro compound (**737**, R = 7-F) and the corresponding **739** (R = 7-F) were prepared by the general route[401]; the former showed low activity but the latter had high ataxic and especially cataleptic activity. The 8-fluoro compound (**737**, R = 8-F) is a strong incisive neuroleptic agent[235,302] with high ataxic and cataleptic activity. 2-Fluoro derivatives of octoclothepin, oxyclothepin, dehydroclothepin, methiothepin and oxyprothepin[324,331] are the first cases of neuroleptic agents in this series with blocked metabolic hydroxylation in position 2; compound **737**, (R = 2-F-8-Cl) and **756** (R = 2-F-8-Cl) are weaker neuroleptics than octoclothepin; **739** (R = 2-F-8-Cl) has high ataxic and cataleptic activity; the 8-methylthio compounds **737** and **756** (R = 2-F-8-SCH_3) are equipotent with the nonfluorinated prototypes. 2-Fluoro-8-isopropyl compounds **737** and **755** (R = 2-F-8-$CH(CH_3)_2$) were obtained by the normal way[465] and display some ataxic and cataleptic activity. The 3,7-difluoro compound (**737**, R = 3,7-F_2) was prepared normally[412] (with the heptacyclic by-product in the cyclization step) and was found to have high ataxic (clear prolongation of the effect), sedative, cataleptic and antiapomorphine activities.

3-Fluoro-8-chloro compounds represent interesting derivatives of octoclothepin and N-modified analogues with blockade of hydroxylation in position 3. 3-Fluoro-8-chloro compounds **737**, **739**, **756** (ref.[331]), **755** and **760** (ref.[359]) were prepared without complications and were mostly found to be more active than octoclothepin with clear signs of prolongation of the effects. On the other hand, compounds prepared from **736** (R = 3-F-8-Cl) by substitution reactions with N-(4-fluoroaralkyl)piperazines[405] proved uninteresting. The 3-fluoro-8-bromo compound **755** was found similar to the 3-fluoro-8-chloro analogue[412]. The 3-fluoro-8-iodo ketone (**734**, R = 3-F-8-I) was prepared from the 3-fluoro-8-amino ketone (**734**, R = 3-F-8-NH_2) by diazotization and reaction with potassium iodide and in the usual way [412] it was transformed to **755** (R = 3-F-8-I) which was very potent in the test for ataxic and cataleptic activity with mild protraction of the effects.

In the series of 3-fluoro-8-alkyl compounds[462,494] the following were prepared by the standard methods : **737** (R = 3-F-8-C_2H_5, 3-F-8-$CH(CH_3)_2$), **739** (R = 3-F-8-$CH(CH_3)_2$), **755** (R = 3-F-8-CH_3, 3-F-8-$CH(CH_3)_2$) and **764** (R = 3-F-8-$CH(CH_3)_2$) (ref.[551]). All of these compounds are extremely active neuroleptics with clearly protracted effects after oral administration out of which isofloxythepin (**755**, R = 3-F-8-$CH(CH_3)_2$) was selected for further studies[382,478]. In the main chemical paper[494], we described its synthesis by the final substitution reaction and the identification of a minor by-product, its resolution to enantiomers and preparation of four potential metabolites by oxidation reactions wiz the S-oxide, N-oxide, S,N-dioxide and des-(hydroxyethyl) S-oxide. For metabolic studies, the synthesis of hexadeuterio (in isopropyl) and trideuterio (in ring C) analogues were prepared[503]. Pharmacological papers[1396-1406] and reports on its biochemical pharmacology[1407-1421] described the various faces of its neuroleptic action and its high antidopaminergic activity. The activity of isofloxythepin was found to be stereoselective[423,1422,1423] : the (−)-enantiomer was found to be the active component of the racemate which is the opposite than in the case of octoclothepin where the (+)-enantiomer was the active one. Nevertheless it is assumed that the absolute configuration on the chiral centre of (−)-isofloxythepin is the same like in the case of (+)-octoclothepin, i.e. (*S*) (ref.[494]). In toxicological papers[1424-1426] some possible side effects were studied and the determination of small amounts of the compound, especially in biological material, was worked up[1427-1431]. Pharmacokinetic studies in animals and humans[1432-1435] used partly the [10-^{14}C]labelled compound. The metabolic studies in rats[1432,1436] indicated as metabolites the N,S-dioxide (standard available[494]), further **780**, **781** (formed evidently from **780** via **782**), and the enamine **764** (R = 3-F-8-$CH(CH_3)_2$); some further metabolites were characterized only partly. Compound **780** was synthesized[503] from (4-fluoro-2-iodophenyl)acetic acid and 2-(4-mercaptophenyl)propionic acid in six steps. The enamine **764** (R = 3-F-8-$CH(CH_3)_2$) was prepared[551] by both methods mentioned for similar cases and was found to have similar neuroleptic activity[1437] like isofloxythepin. Many papers[1438-1453] were devoted to results of clinical trials of isofloxythepin in all usual phases and characterized the agent to be a highly potent neuroleptic with prolonged action (the effect of a single dose lasts for two to seven days). The practical use of isofloxythepin in this country was approved but the manufacture was not started due to the pretentious synthetic process. A monographical article[1454] was devoted to the agent. Isofloxythepin decanoate[503] displayed in experiments properties of a supra-long acting depot neuroleptic.

Several N-substituted analogues of isofloxythepin were prepared via the corresponding **736** or **741** out of which the N-ethyl and N-(3-hydroxypropyl) compounds were the most active[503]. The following further 3-fluoro-8-substituted compounds **737** and **755** were prepared and most of them proved very active and had protracted action : 3-Fluoro-8-trifluoromethyl compounds **737** and **755** (ref.[416]) (for the cyclization of the corresponding acid, the reagent consisting of methanesulfonic acid and phosphorus pentoxide proved the only useful and gave **783** which was hydrolyzed to the ketone; final products are extremely active). 3-Fluoro-8-methoxy, 3-fluoro-8-hydroxy, 3-fluoro-8-ethoxy and 3-fluoro-8-(ethylthio) compounds **737** (ref.[422]) were obtained by the standard procedures and all of them were very active neuroleptics. 3-Fluoro-8-methylthio compounds **737** and **756** were prepared similarly[324] and had similar properties. The 3-fluoro-8-nitro compound **755** was prepared by the standard procedure[447] and was found most active in the antiapomorphine tests but its activity is not protracted; it was reduced to the 3-fluoro-8-amino compound **755** which was low-cataleptic but the other effects were significantly protracted. 3-Fluoro-8-(dimethylsulfamoyl) compound **755** was found less active than the analogues[447] (the ketone **734** (R = 3-F-8-$SO_2N(CH_3)_2$) was prepared from the corresponding 8-amino ketone by diazotization, reaction with sulfur dioxide in hydrochloric acid in the presence of cuprous chloride and by the following reaction of the formed sulfonyl chloride with dimethylamine). In the synthesis of the 3-fluoro-8-cyano compound **755**, the crucial step was the conversion of **735** (R = 3-F-8-I) to **735** (R = 3-F-8-CN) by reaction with cuprous cyanide in hexamethylphosphoric triamide[447]; the 3-fluoro-8-(aminocarbonyl) compound was the by-product in the final step of the synthesis. The 3-fluoro-8-acetyl compound **755** was found to be a strong incisive neuroleptic agent with protracted effects[447] (acetyl was introduced in the stage of **735** (R = 3-F-8-NH_2) which was diazotized and subjected to the Beech reaction with acetaldehyde semicarbazone and the intermediate was hydrolyzed to **735** (R = 3-F-8-$COCH_3$).

Now, the other fluorinated perathiepin derivatives (with the exception of those with Cl in position 2) will be mentioned. In the first attempt to synthesize the 2,3-difluoro derivative of octoclothepin[354], it was found that in the intermediate 2-bromo-4,5-difluorobenzonitrile, the *p*-standing fluorine is more active than the *o*-standing bromine. This was used to prepare 2-bromo-5-fluoro-4-methoxybenzonitrile which was transformed in nine steps to the 2-fluoro-3-methoxy derivative of octoclothepin which was demethylated to the 2-fluoro-3-hydroxy analogue (**737**, R = 2-F-3-OH-8-Cl); it was less active than octoclothepin. The synthesis of 2,3-difluoro derivative of octoclothepin[396] requested twenty steps, started from methyl anthranilate and proceeded via 2-(4-chlorophenylthio)-4,5-difluorobenzyl alcohol; the final product was less active than the 3-fluoro derivative of octoclothepin. The 6-fluoro derivative of octoclothepin[380] was prepared by the standard procedure and had protracted ataxic activity. The 3,7-difluoro derivative of octoclothepin[362] had high and protracted ataxic activity and also high cataleptic and antiapomorphine effects in rats but a comparison with pimozide[1455] in the animal experiments was not in favour of our compound[362]. Its analogues with N-(4-fluoroaralkyl) substituents[405] instead of methyl had high and protracted ataxic activity but low cataleptic activity. The 3-methoxy-7-fluoro derivative of octoclothepin[362] was prepared by the standard way and was demethylated with boron tribromide to the 3-hydroxy-7-fluoro analogue which was rather active. The isomeric 3-fluoro-7-methoxy derivative of octoclothepin[362] could be prepared only by reduction of the corresponding enamine and its demethylation gave **738** (R = 3-F-7-OH-8-Cl). The 3-chloro-8-fluoro derivative of perathiepin and the corresponding enamine[335] were prepared by the standard ways; the former is a rather strong CNS depressant agent but is low-cataleptic. The 7-fluoro derivative of octoclothepin (**737**, R = 7-F-8-Cl) is an interesting compound[340] : ten times less toxic than octoclothepin and more active in the antiapomorphine tests in rats; its **755** analogue was also prepared and transformed to the octanoate as a potential depot neuroleptic. The isomeric 7-chloro-8-fluoro compound is less interesting. The corresponding enamines **739** were also synthesized[340]. The 6,9-difluoro derivative of perathiepin (**737**, R = 6,9-F_2) was prepared smoothly but was found practically inactive[395].

The substituent in position 8 (the neuroleptic substituent) in molecules like **737**, **739**, **755** and **756** is in most cases connected with appearing of neuroleptic and antischizophrenic activity but unfortunately also with high cataleptic activity which indicates the unwanted extrapyramidal side effects. For this reason, the discovery of clozapine[1456] as a noncataleptic piperazinotricycle which showed very useful antischizophrenic activity and had the atom of chlorine as the nuclear substituent in the quasi-symmetrical position corresponding in our series to position 2, was an impetus for searching after further noncataleptic neuroleptics[520] and our team participated intensively in these efforts[322]. Very early, we had doclothepin (**737**, R = 2-Cl), prepared by the general method[236], which had relatively strong ataxic activity but was much weaker than octoclothepin and was, therefore, considered uninteresting. By the standard methods, the following 2-substituted derivatives of perathiepin (**737**) and noroxythepin (**755**) were prepared in the search after noncataleptic neuroleptic agents: 2-fluoro[323], 2-chloro[236,323], 2-bromo[323], 2-iodo[323], 2-nitro[360] (nitration of **734** (R = H) gave the 11,11-dinitro derivative[333] and was thus not of synthetic value), 2-amino[333], 2-acetamido[333], 2-methoxy[334], 2-hydroxy[360], 2-methylthio[334], 2-methyl[390], 2-trifluoromethyl[334], 2-(dimethylsulfamoyl) (ref.[334]), 2-acetyl[333]; most of these compounds with the exception of the 2-chloro compounds, were found to be noncataleptic, having low ataxic activity and mostly without influence on the level of homovanillic acid in the rat brain striatum which means lack of antidopaminergic activity.

Both of the 2-chloro compounds – doclothepin (**737**, R = 2-Cl) and docloxythepin (**755**, R = 2-Cl) were also practically noncataleptic, rather strongly ataxic and clearly antidopaminergic. Docloxythepin was selected as the candidate for clinical trials[322]. It was prepared not only by the substitution reaction of **736** (R = 2-Cl) with 2-(1-piperazinyl)ethanol[323] but also by reduction of the enamine **764** (R = 2-Cl) with zinc and acetic acid[361]. The starting enamine was prepared from **784** together with **785** by the action of 2-(1-piperazinyl)ethanol in the presence of potassium tert-butoxide[361]; the participation of the dehydro compound **786** as an intermediate cannot be excluded. A simplified method of synthesis of the intermediate (5-chloro-2-(phenylthio)phenyl)acetic acid using the Willgerodt reaction and 2,5-dichloroacetophenone as the starting material[375] made docloxythepin relatively easily accessible. Out of the possible metabolites of docloxythepin, the following were prepared[392] : S-oxide, N-oxide, S,N-dioxide, des(hydroxyethyl) **741** (R = 2-Cl), its S-oxide, the ethylenediamine **787** and its S-oxide, and finally the primary amine **788** and its S-oxide. This primary amine was prepared from **734** (R = 2-Cl) by the Leuckart reaction via the N-formyl derivative which was formed together with the heptacyclic pyridine derivative **789**. Out of the hydroxylated derivatives of docloxythepin as further potential metabolites, only 6-hydroxy[410] and 8-hydroxy[351] were prepared; an attempt to prepare the 7-hydroxy compound[351] was interrupted in the stage of **735** (R = 2-Cl-7-OCH_3). Some esters of docloxythepin with hydrophilic acids (e.g. methoxyacetic, morpholinoacetic) were prepared as potential prodrugs[488] but did not prove interesting; neither docloxythepin decanoate[323] did awake attention. Out of the docloxythepin analogues **790** (2-Cl; X = O, S; R = CH_3, C_2H_5, C_6H_5; n = 2, 3) only the 3-methoxypropyl and 2-(methylthio)ethyl compounds[483] had properties of noncataleptic neuroleptics (free of antiapomorphine activity against sterotypies in rats and increasing the homovanillic acid concentration in the rat brain striatum); the similar octoclothepin analogues (**790**, 8-Cl) are incisive neuroleptics with cataleptic, antiapomorphine and strong ataxic activities[483].

The first pharmacological studies[1457,1458] proved that docloxythepin possesses an intensive sedative activity but is practically devoid of cataleptogenic and antiapomorphine effects. In contrast to clozapine, it did not produce the central antioxotremorine effect in mice. These data were supplemented[1459] by studies of antagonism to amphetamine-induced stereotypies, inhibition of conditioned reactions and protective effect from the adrenaline toxicity. It was also found to antagonize the N,N-dimethyltryptamine-induced hyperthermia[1460]. Electroencephalographic studies in rabbits and rats[1458,1461] suggested that docloxythepin had a certain degree of anticholinergic and antidopaminergic activities. Biochemical studies[1462,1463] proved that docloxythepin raises the homovanillic acid level in rat corpus striatum, and consenquently enhances the dopamine turnover in a similar way like clozapine and other neuroleptics. A contribution to the pharmacokinetics was the determination of docloxythepin level in the rat blood and bile[1464,1465]. A more profound pharmacokinetic study in rats was carried out with [10-^{14}C]labelled compound[1466]. In the urine of rats given labelled or unlabelled substance, there were detected[1467] three S-oxides and two N-oxides. Comparison with the synthetic standards suggested that the metabolites were the docloxythepin derived S-oxide, N-oxide, S,N-dioxide, and des(hydroxyethyl) S-oxide. The mechanism of docloxythepin S-oxidation was investigated in the rat liver in vitro[1468]. In view of the suspected hepatotoxicity in dogs[1469], docloxythepin was approved solely for phase 1 clinical trial, i.e. single administration to healthy volunteers. In this trial, it was compared with clozapine[1470] in the same dosage. Docloxythepin produced a mild hypotensive effect lasting longer than that after clozapine. Subjectively, docloxythepin was reported as a stronger sedative and its action as longer lasting than that of clozapine. Similarly to clozapine, docloxythepin modified the EEG recordings[1471] but its effect was stronger and longer lasting owing to its two to four times higher miligram efficacy; nevertheless its further development was discontinued.

Docloxythepin proved in principle to be the correct molecule. For this reason, its slight modifications were investigated. The synthesis of the compounds used in general the standard procedure. Introduction of further chlorine atoms into the aromatic nuclei were tried first. The 3-chloro derivative (**791**, R = 3-Cl) was noncataleptic, mildly sedative but without effect on the homovanillic acid level in the rat brain[471]. The 4-chloro and 4,8-dichloro derivatives (**791**, R = 4-Cl, 4,8-Cl_2) were evaluated only in behavioural tests[418] : they were noncataleptic and only weakly sedative. The 6-chloro compound (**791**, R = 6-Cl) was almost noncataleptic and showed some antidopaminergic activity[492] (weaker than clozapine). The 7-chloro compound (**791**, R = 7-Cl) was more interesting being in the homovanillic (HVA) test more active than clozapine and almost noncataleptic[492]. The most interesting proved to be the 8-chloro compound (**791**, R = 8-Cl) whose molecule contains the neuroleptic as well as the pseudoneuroleptic substituent (positions 8 and 2) (refs[236,492]). It is a multipotent psychotropic and neurotropic agent with a high affinity to striatal dopamine receptors, a low influence on the HVA level, almost noncataleptic and free of the antiapomorphine effects, with a high antiamphetamine effect, strong tranquillizing and hypothermic activity, and moreover, antihistamine, antispasmodic and strong α-adrenolytic action. None of these compounds, however, was recommended for preclinical research. Another series of compounds, containg in their molecules the neuroleptic and at the same time the pseudoneuroleptic substituent, were the 2-halogeno-8-isopropyl compounds[465] out of which **791** (R = 8-$CH(CH_3)_2$) and its 2-fluoro analogue were clearly cataleptic. On the other hand, the iodo compound **792** was noncataleptic, had high affinity to dopamine receptors in striatum in the [^{3}H]spiperone binding assay (higher than clozapine) and raised the level of HVA in striatum more potently than clozapine. It was devoid of antiapomorphine activity (stereotypies in rats) and was a medium strong tranquillizer. In general, it was an interesting noncataleptic neuroleptic agent which resembled clozapine by its activity profile; its further development was prevented by two facts : difficulties with the synthesis and presence of iodine in the molecule.

Simultaneously with docloxythepin, 2-chloro-7-fluoro derivatives **737**, **755** and **756** (R = 2-Cl-7-F) were synthesized[323] and attracted attention by their low acute toxicity and high ataxic activity in mice. On the other hand, they displayed medium cataleptic activity in rats and for this reason their studies were discontinued. After the failure of docloxythepin, we returned to this interesting type and attempted to suppress the cataleptogenic character by finding a suitable N-substituent[493]. This happened using 2-(aminocarbonyl)ethyl to this end and we arrived at compound **793**, called cloflumide in the form of the methanesulfonate[502,520]. Its synthesis started from 3-fluorothiophenol and used the Willgerodt reaction for preparing the intermediate (5-chloro-2-(3-fluorophenylthio)phenyl)acetic acid which was cyclized to **734** (R = 2-Cl-7-F). The final step consisted either in the addition of **741** (R = 2-Cl-7-F) to acrylamide[493] or in the substitution reaction of **736** (R = 2-Cl-7-F) with 3-(1-piperazinyl)propionamide[551]. Cloflumide proved to have strong sedative and ataxic activity in mice[1472,1473], inhibited significantly the apomorphine-induced agitation but not the stereotypies, it was quite active in the test of inhibition of apomorphine emesis in dogs and five times more active than clozapine in the test of apomorphine-induced climbing behaviour in mice. It increased intensively the HVA level in corpus striatum and tuberculum olfactorium of the rat brain[1474] (clozapine had only 10% of activity in both brain structures mentioned). Cloflumide had also important affinity to dopamine receptors in both brain structures ([^{3}H]spiperone binding assay). Its pharmacokinetics was studied using [^{3}H]cloflumide in rats[1475]. Because of some doubts about the statement that cloflumide is noncataleptic at 50 mg/kg orally[493], the study of cataleptic effect in rats was repeated and it was found [520,521] that the ED_{50} is slightly below of 50 mg/kg; cloflumide was thus identified as being only low-cataleptic which resulted in interruption of its development. The 6-fluoro derivative of docloxythepin[380] (**791**, R = 6-F) and the 8-fluoro derivative of doclothepin[323] (**737**, R = 2-Cl-8-F) were synthesized but their activity was not interesting.

11-Substituted derivatives of perathiepin did not escape to our attention. The known 11-methyl ketone **734** was transformed via **735** and **736** (R = 11-CH_3) to **737** (R = 11-CH_3) with unknown configuration[212] which was much less active than **737** (R = H). Attempts to prepare 11-methyl- and 11,11-dimethyl derivatives of **734** by cyclization reactions of 2-(2-(phenylthio)phenyl)propionic and 2-methyl-2-(2-(phenylthio)phenyl)propionic acid[461] led to mixtures out of which an oily product $C_{15}H_{12}OS$, characterized as **734** (R = 11-CH_3), was isolated with difficulties; side reactions were cleavage of one methyl group and the passage into the thioxanthene series. Similar experience was made with the cyclization of 2-phenyl-2-(2-(phenylthio)phenyl)acetic acid[551] with polyphosphoric acid or phosphoric ester. Seven products including the wanted 734 (R = 11-C_6H_5) were isolated and identified (two of them thioxanthene derivatives). On the other hand it was possible to prepare ketones **734** (R = 8-Cl-11-$CH_2C_6H_5$, 8-Cl-11-(2-dimethylaminoethyl), 8-Cl-11-(3-dimethylaminopropyl), 8-Cl-11-(2-methyl-3-dimethylaminopropyl)) by the following way[346] : 2-(2-(4-chlorophenylthio)phenyl)acetonitrile was C-alkylated (sodium amide) with the corresponding chlorides, the obtained nitriles could be hydrolyzed only to the stage of the corresponding amides which were cyclized to **734** with polyphosphoric acid. The ketones obtained were reduced with sodium borohydride to *cis*-8,11-disubstituted **735** which were transformed to the corresponsing *trans*-**736**; the synthesis of 8-chloro-11-substituted **737** was not carried out.

Ketones **734** (R = H, 8-Cl, 2-Cl, and 8-OCH_3) were brominated to the corresponding 11-bromo ketones[212,300,361,437]. Their substitution reactions with 1-methylpiperazine gave mixtures of equal parts of the 11-oxo-perathiepins (**737**, R = H, 2-Cl, 2-OCH_3) which are little active, and the diketones **794** (R = H, 2-Cl, 2-OCH_3) undergoing easily the benzilic acid rearrangement to thioxanthene derivatives[212,300]. The ketone **734** (R = 11-Br-8-Cl) was reacted with 2-(1-piperazinyl)ethanol and the product **755** (R = 2-Cl-11-oxo) was reduced to *cis*-**735** (R = 2-Cl-11-OH). All attempts [361] to remove selectively the 11-OH group and transform the alcohol to docloxythepin (**791**, R = H) failed. Oxidation of **734** (R = H) with hydrogen peroxide in boiling acetic acid[212] gave the S,S-dioxide of **794** (R = H). Mannich reaction of **734** (R = H) resulted in **795** which was reduced to **796** with undetermined configuration[212]; both compounds were inactive. Wolff – Kishner reduction (Huang – Minlon modification) of **734** (R = H, 8-Cl) gave the 10,11-saturated compounds **797** (R = H, 2-Cl) (refs[207,298]). Three di- and trisubstituted **797** were obtained as by-products of reduction of the corresponding enamines **739** with zinc and acetic acid[362,413].

Nitrosation of **741** (R = H) gave **798** ($R^1 = R^2 = H$) which was reduced with lithium aluminium hydride[212] to **799** ($R^1 = R^2 = H$). Similar reactions in the 2-chloro, 8-chloro and 2,8-dichloro series[436] led to **799** which were transformed by reactions with benzaldehydes to hydrazones **800**, prepared as potential anticonvulsants but which were found only to be tranquillizers. Substitution reactions of **736** (R = 8-Cl, 8-SCH_3) with 2-methylpiperazine or 2,5-dimethylpiperazine gave the corresponding **801** and **802** which were transformed via the N-formyl derivatives[348] to the corresponding N-methyl compounds **801** and **802**; as neuroleptics these compounds are much less active than the piperazine-C-nonmethylated analogues.

Substitution reaction of **736** (R = 8-Cl) with octahydropyrrolo[1,2-*a*]pyrazine gave the stereochemically inhomogeneous **803** which proved a relatively highly potent neuroleptic on parenteral administration[437]. Substitution reactions of **736** (R = 8-Cl, 8-SCH_3) with 8-methyl-3,8-diazabicyclo[3.2.1]octane and 3-methyl-3,8-diazabicyclo[3.2.1]octane[266] resulted in **804** and **805** (R = Cl, SCH_3); the former displayed a high degree of neuroleptic activity.

The chloro compounds **736** (R = H, 8-Cl) were transformed to amines **806** by reactions with dimethylamine[207], 2-diethylaminoethylamine[207], pyrrolidine[257], piperidine[207], 4-hydroxypiperidine[212] and 4-(ethoxycarbonyl)-4-phenylpiperidine[207]; these products were inactive as neuroleptics. The primary amines **807** (R = H, Cl) were obtained by the Leuckart reaction via the corresponding N-formyl compounds[207,367] (these were reduced to **808**); further transformations led to the pargyline analogue **809** (R = Cl) having not pargyline-like activity[367], and to the amineptine[1476] analogue **810** (R = Cl), found to be a mild tranquillizer[367]. The homopiperazine analogue **811** (R = H) of perathiepin had only 10% of its ataxic activity[212]. A systematic search after antidepressants among the 2-chloro-10-amino-10,11-dihydrodibenzo[*b,f*]thiepins[542] led to **812** having the pharmacological profile of a potential antidepressant. Compound **807** (R = Cl) was used to prepare a series of carbamates and ureas as potential anticonvulsants[367]; some of them really displayed this type of activity.

The phenolic ketone **734** (R = 6-OH) was transformed to several aminoalkyl ethers as potential antidepressants[529]; only **813** showed indications in this line. The alcohols **735** treated with 2-dimethylaminoethyl chloride and sodium amide gave ethers **814** (R

= H, Cl, OCH_3) showing ataxic and also cataleptic activity, i.e. the neuroleptic character[207,235,238]. Compound **735** (R = 8=Cl) reacted with 2-bromoethanol in the presence of boron trifluoride etherate giving **815** which underwent substitution reaction with N-monosubstituted piperazines resulting in products[456] like **816**. These compounds were interesting low-cataleptic neuroleptic agents with strong ataxic activity, significantly active in the antiapomorphine tests in rats, free of the adrenolytic component, little toxic, and clearly raising the HVA level in the rat striatum.

This finding led to a systematic investigation in the isomeric noncataleptic 2-chloro series and resulted in clopithepin (**817**) as a further candidate for clinical testing as a noncataleptic neuroleptic agent[517]. Its pharmacological profile was summarized in ref.[520]: less toxic and much less sedative than clozapine, at 50 mg/kg orally noncataleptic like clozapine, without influence on the apomorphine stereotypies in rats but at the same time antiemetic in the apomorphine test in dogs, in the test of apomorphine-induced climbing in mice less active than clozapine, stronger antidopaminergic than clozapine (the HVA assay and the [^{3}H]spiperone binding assay), practically lacking the peripheral adrenolytic effect, and having a very low anticholinergic effect. After these encouriging results of comparison of clopithepin with clozapine, the comparison with chlorpromazine[551] gave less favourable results and clopithepin was dropped.

Alkylation of **734** (R = H) with 2-dimethylaminoethyl chloride (sodium amide) gave mixtures of the enol ether **818** (major) and the C-alkylated product **819**; use of an excess of the alkylating agent led to **818** and **820** which was separated[257]; acid hydrolysis of **820** resulted in homogeneous **819**.

Azeotropic distillation of the mixture of **734** (R = 2-Cl), 2-bromoethanol and 4-toluenesulfonic acid in benzene[551] gave **821** which was transformed by substitution reaction to **822**, the 10,11-dehydro analogue of clopithepin; the compound had a similar pharmacological profile like **817**.

Via the corresponding isothiuronium chlorides, **736** (R = 2-Cl, 8-Cl) were transformed to the thiols **823** which were S-alkylated to the sulfides **824** (refs[367,543]). The secondary amine **825** (R = 2-Cl) displayed a clear profile of an antidepressant[543]. Reactions of **823** (R = 2-Cl) with ethyl chloroalkanoates and the following hydrolysis gave acids like **826** (R = 2-Cl) displaying some antiinflammatory and analgetic activity[543].

Dibenzo[*b,f*]thiepin derivatives with carbon bond to position 10 of the skeleton were also the object of our studies. In fact, the first goal in the series was the synthesis of the prothiadene analogue of formula **827**. The synthesis was complicated by the fact that the reaction of **734** (R = H) with 3-dimethylaminopropylmagnesium chloride[207] gave only 3% of **828** (due to the almost complete enolization of **734** under the conditions of the Grignard reaction); the product was easily dehydrated to **827** (the exocyclic position of the double bond was confirmed by the UV spectrum). The product (**827**) did not show any indication of the antidepressant profile. Reactions of **736** (R = H, 8-

CH_3) with 1-methyl-4-piperidylmagnesium chloride led to compounds **829** (R = H, OCH_3) which have clearly the neuroleptic character[212,238]. Especially the 8-methoxy compound **829** (R = OCH_3) is a strong neuroleptic. The practical equivalency of 4-methyl-1-piperazinyl with 1-methyl-4-piperidinyl as substituents in position 10 of the 10,11-dihydrodibenzo[*b,f*]thiepins from the point of view of the neuroleptic activity shows that not the stability (or better lability) of the bond between C-10 and the substituent but the distance of the strongly basic nitrogen atom and some site in (or on) the tricyclic carrier (maybe the substituent in position 8 including hydrogen) is of the primary importance.

Addition of bromine to **738** (R = H) gave the mixture of the stereoisomeric dibromides **830** which was dehydrobrominated with collidine to **831** (ref.[212]). The similar chloro compound **832** was obtained either from (2-(phenylthio)pheny)acetic acid or from **734** (R = H) with phosphoryl chloride and zinc chloride[212]. Heating **831** with cuprous cyanide in dimethylformamide gave **833** which was reduced with sodium borohydride to **834** (the corresponding carboxamide and carboxylic acid were also prepared[445]). Similar work starting from **738** (R = 2-Cl, 2,8-Cl_2) was much more complicated due to the formation of mixtures of isomers[445]. The nitrile **834** could be alkylated to **835** and analogues[445]. Compound **836** was obtained from **834** by alkylation with 2-(2-tetrahydropyranyloxy)ethyl chloride, by the following acid hydrolysis and reaction of the product with phosphorus tribromide[445]. Reactions of **836** with 4-substituted piperidines gave several potential antidiarrhoic agents out of which **837** proved the desired activity[482]. Addition of 3-dimethylaminopropylmagnesium chloride to **833** and the following mild hydrolysis gave a mixture of *cis*- (major) and *trans*-**838** which were separated and characterized (NMR). The *cis*-isomer proved some antireserpine activity[445].

An attempt to prepare A-hexahydro derivative of perathiepin (**839**, R = H) was unsuccessful; Kyburz and Dostert[1477] on the other hand were able to prepare *cis*- and *trans*-hexahydro derivatives of octoclothepin (**839**, R = Cl) and prove their neuroleptic inactivity. Unexpected formation of the dibenzo[*b,f*]thiepin skeleton was encountered in two cases. Reaction of bis(4-chlorophenyl) sulfide with chloroacetyl chloride in dichloromethane gave a crystalline $C_{16}H_9Cl_3O_2S$ which was preliminarily characterized as the hydrogen bond-fixed enol **840** (R = Cl) (ref.[293]). After several years the whole work was reinvestigated[461] and in addition to the sulfide mentioned, bis(4-fluorophenyl) sulfide, bis(4-bromophenyl) sulfide and bis(4-methylphenyl) sulfide were used. Compounds **840** (R = Cl, F, Br, CH_3) were obtained in all cases and only in the case of the methyl compound **841** was isolated as a second and main product (cf. refs[1478,1479]). Another surprising case was the attempt to hydrolyze and decarboxylate 2-acetyl-2-(2-(3-methoxyphenylthio)phenyl)acetonitrile by heating with 85% phosphoric acid[553]; four products were isolated and two were identified as **842** and **734** (R = 7-OCH_3).

5.3.3.5 Dibenzo[*c,e*]thiepin, Dibenzoselenepin and Dibenzo[*b,f*]silepin Derivatives

5,7-Dihydro[*c,e*]thiepin (**843**) did not prove convenient as a starting material for preparing derivatives suitably functionalized in position 5 and 7. Its reaction with n-butyllithium resulted in the partial sulfur extrusion under formation of the 9,10-dihydrophenanthrene-9-thiolate anion (sulfur analogy of the Wittig rearrangement). Further reactions (hydrolysis, alkylation with 2-dimethylaminoethyl chloride, and spontaneous dehydrogenation) led to phenanthrene-9-thiol, N,N-dimethyl-2-(9-phenanthrylthio)ethylamine, N,N-dimethyl-2-(9,10-dihydro-9-phenanthrylthio)-ethylamine and phenanthrene[495]. Only after oxidation to the sulfone **844**, the desired reactions became possible. Treatment with butyllithium and following carbonation afforded the acid **845** (together with the 5,7-diacid) which was transformed via the dimethylamide to **846**. Lithiation or treatment with sodium hydride and the following action of 3-dimethylaminopropyl chloride gave **847** showing clear indications of thymoleptic activity as a potential antidepressant[495].

Reaction of phthalide with selenophenol gave 2-(phenylselenomethyl)benzoic acid which was cyclized with polyphosphoric acid to dibenzo[*b,e*]selenepin-11(6*H*)-one (**848**). Its reaction with 3-dimethylaminopropylmagnesium chloride afforded **849** which was dehydrated to (*E*)-**850**, the selenium analogue of prothiadene[254]. Partial demethylation led to the northiadene analogue **851** and reduction with hydroiodic acid to the hydrothiadene analogue **852**. This compound was the most active one as a potential antidepressant in the series : it displayed similar antireserpine activities like imipramine[254]. Reactions of selenophenol and its 4-chloro derivative with 2-iodobenzoic acid gave the corresponding 2-(arylseleno)benzoic acids which were transformed in four steps to (2-arylselenophenyl)acetic acids. Their cyclization with polyphosphoric acid afforded dibenzo[*b,f*]selenepin-10(11*H*)-one (**853**, R = H) and its 8-chloro derivative[253]. The ketones were reduced to alcohols which, in turn, were transformed to the 10-chloro derivatives. Substitution reactions with 1-methylpiperazine afforded the selenium analogues of perathiepin and octoclothepin **854** (R = H, Cl); the latter proved a potent neuroleptic agent with high cataleptic and ataxic activity. The by-products of the substitution reactions were **855** (R = H, Cl). The enamines **856** (R = H, Cl) were prepared from **853** by the titanium tetrachloride method[257].

The known 10-bromo-5,5-dimethyl-10,11-dihydrodibenzo[*b,f*]silepin (**857**) was transformed by the substitution reaction with 1-methylpiperazine[348] to **858** which was practically devoid of neuroleptic activity.

5.3.3.6 Morphanthridine, Dibenz[*b,f*]azepine and 3,7-Methano-1*H*-2-benzazonine Derivatives

Schmidt reaction of anthraquinone, carried out in larger batches, produced 6,11-dioxo-5,6-dihydromorphanthtridine which was reduced to 5,6-dihydro-11*H*-morphanthridine

(859). Its aminoalkylation and chloroacylation followed by further transformations produced compounds like **860** and **861** (ref.[120]). Bischler – Napieralski reaction of N-formyl, N-acetyl and N-benzoyl derivatives of 2-benzylaniline by polyphosphoric acid and phosphoryl chloride[205] gave **862** (R = H, CH_3, C_6H_5) which were reduced with sodium borohydride to **859** and its 6-methyl and 6-phenyl derivatives; the latter was transformed to the 6-phenyl derivative of **860**. Out of the many morphanthridine derivatives prepared (there was collision with the teams of Cilag[1480] and Ciba[1481]), compound **860** (propazepine, prazepine (INN)) proved most interesting. It attracted first by its enormous antihistamine activity in vitro[1482]; the fact that it was a position isomer of the antidepressant imipramine, led to its pharmacological and biochemical comparison with this drug[1483-1489] and finally to its clinical testing as an antidepressant[1490,1491]. It was found active in patients with mental depressions in slightly higher doses than imipramine and it was not introduced to the therapeutic practice.

In the isomeric dibenzo[*b,f*]azepine series we published[514] a contribution to the synthesis of bis(norimipramine) (**863**) which was needed for a metabolic study. Dibenzo[*b,f*]azepine and its 10,11-dihydro derivative were acylated with chloroacetyl chloride and the products were reacted with 1-methylpiperazine giving **864** and **865**. The latter displayed significant anti-ulcer and anticholinergic activities[514].

The Beckmann rearrangement of the oxime of 5,6,7,8,9,10-hexahydro-5,9-methanobenzocycloocten-10-one[148] gave the lactam **866** (UV, IR) which was reduced with lithium aluminium hydride to **867** (R = H). Conventional reactions led to its N-methyl and N-(2-phenylethyl) derivatives (**867**, R = CH_3, $CH_2CH_2C_6H_5$).

5.3.3.7 11*H*-Dibenzo[*b,e*]-1,4-dioxepin, 6*H*-Dibenz[*b,e*]-1,4-oxathiepin, 11*H*-Dibenz[*b,f*]-1,4-oxathiepin and 11*H*-Dibenzo[*b,e*]-1,4-dithiepin Derivatives

11*H*-Dibenzo[*b,e*]-1,4-dioxepin (depsidan, **868**, X = O) and the corresponding lactone **869** (X = O) (depsidone) are known but they are not of use for preparing the potential antidepressants and neuroleptics of general formulae **870** and **871** (X = O). For obtaining such side chain-functionalized compounds (like **870**, X = O, $R^1 = R^2$ = H), it was necessary to cyclize intermediates like **873** (X = O, $R^1 = R^2$ = H) containg already the amino group in the side chain. 2-(2-Fluorophenoxy)benzaldehyde was reacted with 3-dimethylaminopropylmagnesium chloride and gave the intermediate **873** (X = O, $R^1 = R^2$ = H) which was cyclized with sodium hydride in dimethylformamide[430]. The obtained **870** (X = O, $R^1 = R^2$ = H) was found to have mild ataxic and anticataleptic activity; it is not a clear potential antidepressant.

In the series of 6*H*-dibenz[*b,e*]-1,4-oxathiepin, compounds **868** and **869** (X = S) were synthesized[432] but were also found unsuitable as precursors of **870** (X = S). The successful and already mentioned procedure, starting in this case from 2-(2-fluorophenylthio)benzaldehyde and proceeding via **873** (X = S, $R^1 = R^2$ = H) led to the desired **870** (X = S, $R^1 = R^2$ = H) which displayed antireserpine activity and the pharmacological profile of a potential antidepressant[432]. Using 1-methyl-4-piperidylmagnesium chloride as the Grignard reagent and the same method for cyclization led to **871** (X = S, $R^1 = R^2$ = H) which was found to be a strongly ataxic tranquillizer with hypothermic activity which potentiated the cataleptic action of perphenazine[432] (similar profile like perathiepin). The passage to strong neuroleptics was realized by introduction of neuroleptic substituents as R^1 (Cl, OCH_3, CF_3, SCF_3) and by the combined introduction of fluorine as R^2 (refs[431,433]). The synthesis of such compounds was possible by using the appropriately substituted benzaldehydes as the starting materials. The intermediates **873** and **874** were used in crude state and the final products **870** and **871** were isolated by chromatography in addition to at least eight different types of byproducts. The most interesting of them were the 2-substituted thioxanthones (2-H, Cl, OCH_3, CF_3) resulting evidently from the starting aldehydes by treatment with sodium hydride[433]. The preferred product was cloxathiepin (**871**, X = S, R^1 = Cl, R^2 = H), the synthesis of which was repeated[469] and which is in the line of intensity of the neuroleptic effect comparable with octoclothepin but has much lower adrenolytic activity. Compound **871** (X = S, R^1 = Cl, R^2 = F) which is a strong incisive neuroleptic, was demethylated using the ethyl chloroformate method and the following hydrolysis. The secondary amine obtained was N-alkylated with 2-bromoethanol giving **872** (X = S, R^1 = Cl, R^2 = F) which was transformed to the decanoate[431] being a medium long-acting depot neuroleptic agent. Shifting the neuroleptic substituent to the pseudo-symmetrical position[469] (2-(4-chloro-2-fluorophenylthio)benzaldehyde was used as the starting material) led to the practically noncataleptic compound **875** which, however, had also only low antidopaminergic activity (HVA assay).

Reactions of 2-hydroxythiophenol with 2-halobenzyl halides and their 5-substituted derivatives gave 11*H*-dibenz[*b,f*]-1,4-oxathiepin **876** and derivatives with R = Cl and CF_3. These compounds are useful intermediates. They can be lithiated or chlorinated in position of R^1 or first oxidized to the sulfones giving the carbanions by treatment with sodium hydride[429]. The following carbonation gave the acid **877** (R = H) which was transformed in three steps to **878** (R = H) with intensive antireserpine activity. Alkylation with 3-dimethylaminopropyl chloride led to **879** (R = H, Cl). The 11-chlorinated intermediates gave by treatment with 1-methyl-4-piperidylmagnesium chloride compounds **880** (R = Cl, CF_3) which are potent incisive neuroleptics[429]. The acid **877** (R = H) was transformed in six steps to the isobutaclamol open model **881** (R = H) which proved antidopaminergic activity in the HVA assay[481].

Reaction of benzene-1,2-dithiol with 2-bromobenzyl bromide in dimethylformamide in the presence of potassium carbonate and copper or the cyclization of 2-(2-bromophenylthiomethyl)thiophenol under similar conditions resulted in 11*H*-dibenzo[*b,e*]-1,4-dithiepin (**882**). This also was lithiated and transformed to the acid **883** and to the dimethylaminoalkyl derivatives **884** (n = 2, 3) which display high antagonistic activity against reserpine-induced hypothermia in mice[430] like potential antidepressants.

5.3.3.8 Dibenz[*b,f*]-1,4-oxazepine, Dibenzo[*b,f*]-1,4-thiazepine and 5*H*-Dibenzo-[*b,e*]-1,4-diazepine Derivatives

The Bischler – Napieralski reaction approach was used for preparing dibenz[*b,f*]-1,4-oxazepines **885** – **887** (R^1 and R^2 = H or Cl). Their catalytic hydrogenation on palladium led to the 10,11-dihydro analogues **888** which were aminoalkylated to **889** having some antihistamine, peripheral anticholinergic and antiserotonin effects[190].

Reactions of methyl thiosalicylate with 2-chloronitrobenzene and 2,5-dichloronitrobenzene, the following reduction of the nitro group and thermic cyclization afforded the lactams **890** and **891** which were reduced with lithium aluminium hydride to 10,11-dihydrodibenzo[*b,f*]-1,4-thiazepine and its 8-chloro derivative **892** (R = H, Cl). These compounds[122,134] were transformed to a series of N-(aminoalkyl) and N-(aminoacyl) derivatives displaying antihistamine, antireserpine, antiserotonin, local anaesthetic and spasmolytic properties[1482,1486]. Compounds **893** (R = H, Cl) are cyclic homologues of promazine and chlorpromazine without displaying really interesting properties. The Bischler – Napieralski reaction approach leading to **894** – **896** enabled the synthesis of the 11-methyl and 11-phenyl derivatives of homo-promazine (**897**, **898**) having also antireserpine and antiserotonin activities[204]

Following our hypothesis assuming that the antischizophrenic effect of the noncataleptic neuroleptic clozapine could be explained by its metabolic conversion to the 2-hydroxy derivative (metabolic introduction of a neuroleptic substituent), we synthesized[376] via **899** and **900** the supposed metabolite **901**; it was shown that this compound per se is noncataleptic but potentiates the cateleptic effect of perphenazine. This result cannot be considered a confirmation of our hypothesis.

5.3.3.9 Thieno[2,3-*c*]-2-benzothiepin Derivatives

This tricyclic system was unknown before our work and the entry to it was the cyclization of 2-(2-thienylthiomethyl)benzoic acid (obtained from phthalide and 2-thiophenethiol) to **902** (R = H) first with polyphosphoric acid in boiling toluene in a low yield[200], much better with phosphorus pentoxide in toluene[229] which was also used for preparing the 6-substituted ketones[229] **902** (R = Cl, Br). The first task of the work was to prepare the thiophene isostere of our antidepressant prothiadene. Reactions of **902** (R = H, Cl, Br) with 3-dimethylaminopropylmagnesium chloride gave the alcohols **908** which were dehydrated by acid catalyzed reactions to **903** (refs[200,229]).

Whereas **903** (R = Cl, Br) showed some activity in tests typical for neuroleptics[229], 903 (R = H) (dithiadene, bisulepin (Czech. Pharmacopoeia)) had only low central activity (including the effects in the antireserpine tests) but displayed a surprisingly high antihistamine activity in vivo (significantly more active than promethazine[200]). The crude **903** (R = H) was separated by crystallization of the hydrogen sulfate which led to isolation and characterization (IR, NMR) of the major (*E*)-isomer (dithiadene) and the minor (*Z*)-isomer which, more recently, was prepared also by the Wittig reaction[312,440]. Both isomers were oxidized to the 10-oxides[312] (sulfoxides). The dithiadene sulfone (10,10-dioxide) was prepared from **902** (R = H) which was oxidized with hydrogen peroxide in acetic acid to the sulfone which was transformed to **908** (R = H) sulfone and this was dehydrated[229]. The (*Z*)-isomer of dithiadene has similar antihistamine activity like dithiadene[312]; out of the S-oxidated dithiadene derivatives, which were prepared as potential metabolites, only (*E*)-dithiadene S-oxide maintains antihistamine activity (lower than the parent compound). Dithiadene was selected for preclinical and clinical studies in the form of the hydrochloride. Its pharmacology was described[1188-1190,1492,1493], various methods of its analytical determination were elaborated[1494-1497] and the pharmacokinetic study in rats[1498] was carried out with the [10-^{35}S]labelled substance. The metabolic study in rats[1499] led to identification of the sulfoxide and the N-demethylated compound[312] as metabolites. Dithiadene was introduced on the market (Dithiaden®) first as an oral, more recently also in injections on the basis of extensive clinical studies[1501-1515] for being used in the treatment of allergic states (including asthma) and for the hyperkinetic syndrome in children. A combination of dithiadene with (−)-phenylephrine underwent preclinical testing[1516] as a potential agent for the common cold.

Compound **904** (R = Cl) was prepared from **902** (R = Cl) via **909** (R = Cl) as a potential neuroleptic agent[312]. It was a mixture of geometrical isomers which did not show the character of a neuroleptic. Reaction of **902** (R = H) with 2-(dimethylaminomethyl)cyclohexylmagnesium chloride gave a mixture of stereoisomeric **910** (R = H) of which three homogeneous components were separated[477]. Dehydration of the mixture gave (*E*)- and (*Z*)-**905** (R = H) which were isolated. Their mixture, which was tested, showed antireserpine activity in two tests and thus the character of a potential antidepressant. Reactions of **902** (R = H, Cl) with 1-methyl-4-piperidylmagnesium chloride afforded **911** (R = H, Cl) (ref.[440]). In the former case, compound **913** was a by-product[440] (formed evidently by the 1,6-addition and the following spontaneous dehydrogenation). The alcohols **911** were dehydrated to **906** (R = H, Cl) out of which the former was found to be an extremely potent antihistamine, antireserpine and antiserotonin agent[229]. Structural and pharmacological similarity between the antimigraine agent pizotifene[1517] and our **906** (R = H) (pipethiadene) (ref.[1518]) led to development of our compound as a potential anti-migraine agent in the form of hydrogen (+)-tartrate[443]. As standards for metabolic studies the following pipethiadene derivatives and analogues were prepared by conventional methods[440] : S-oxide, N-oxide, S,N-dioxide, nor-pipethiadene (N-demethyl analogue), its S-oxide and finally the CH_3-[$^2H_3$] labelled compound. Pharmacology, biochemical pharmacology and toxicology of pipethiadene was described in several papers[1519-1535], the pharmacokinetic study in rats used [^{3}H]pipethiadene[1536,1537]. The metabolic studies working with rat urine and faeces and using the N-methyl deuterated substance and GC-MS identified as metabolites the S-oxide, N-oxide, S,N-dioxide, norpipethiadene N-oxide and Ar-hydroxylated norpipethiadene S-oxides[1538,1539]. After clinical testing[1540,1541], pipethiadene was released for practical use (Migrenal®). The sulfonium analogue **907** (R = H) of pipethiadene was prepared from **902** (R = H) via **912** (R = H) (ref.[500]). The reaction of the ketone with 3,4,5,6-tetrahydro-2*H*-thiopyran-4-ylmagnesium bromide was complicated by the formation of **914**, again a product of 1,6-addition and dehydrogenation. The final product had only mild antihistamine and anticholinergic effects[500].

Reduction of **902** (R = H) with sodium borohydride produced the alcohol **915**. An attempt at its transformation to the 4-chloro compound by treatment with hydrogen chloride gave only the ether **916** and reaction of **915** with sodium amide and 2-dimethylaminoethyl chloride gave surprisingly the 4-saturated **917** (ref.[229]). Acetylation of **902** (R = H) and of **917** gave the 2-acetylated derivatives[229,440]. The tosylate[229] and mesylate[490,516] of **915** in situ were used as equivalents of the unknown chloride for preparing the ethers **918** – **920** (refs[229,490]) and the amines **921** – **923** (refs[229,516]). Compounds **918** and **922** had some ataxic and antihistamine activities, **919** and **920** were in addition anticataleptic. Compound **923** had some H-1 antihistaminic effect but in comparison with oxatomide it lacked the antianaphylactic effect. Reduction of **903** (R = H) and **911** (R = H) with hydroiodic acid gave the saturated **924** and **925**, the former being highly active in a series of tests considered predictive of antidepressant efficacy[538].

5.3.3.10 Further Thienobenzothiepins

Cyclization of 5-bromo-2-(2-thienylthio)benzoic acid in the form of the chloride with zinc chloride afforded 6-bromothieno[2,3-*c*]-1-benzothiepin-4(10*H*)-one (**926**, R = Br) together with 5-bromo-1,2-benzodithiole-3-one[521]. Reaction with 3-dimethylaminopropylmagnesium chloride and the following dehydration gave **927** (R = Br) as the (*E*,*Z*)-mixture which was separated and the components were characterized. They were then transformed by treatment with cuprous cyanide in hexamethylphosphoric triamide to (*E*)- and (*Z*)-**927** (R = CN). Both isomers proved to be potential antidepressants and selective inhibitors of 5-hydroxytryptamine re-uptake in the brain. Cyclization of 2-(3-thienylthiomethyl)benzoic acid with phosphoric ester in toluene gave thieno[3,2-*c*]-2-benzothiepin-10(5*H*)-one (**928**) which was transformed in two steps[329] to **929** (a homogeneous hydrochloride but assignment of configuration was not possible) having very intensive H-1 histamine antagonistic activity. Cyclization of 2-(2-bromo-3-thienylthiomethyl)benzoic acid with phosphorus pentoxide in toluene gave 3-bromothieno[3,4-*c*]-2-benzothiepin-10(5*H*)-one (**930**) as the minor product[329] in addition to the major **928** (debromination proceeded prior to cyclization).

The thieno[2,3-*b*]-1-benzothiepin system was more typical for our work. The ketone **931** was obtained by cyclization of (2-(2-thienylthio)phenyl)acetic acid with phosphorus pentoxide in toluene. It was reduced to **932** which was transformed on the one hand to the ether **933**, and via **934** to **935** (peradithiepin) to the other; compound **936** was simultaneously formed by elimination[242]. Peradithiepin showed the strong ataxic activity like octoclothepin and also important peripheral antiserotonin action. The enamines **937** and **938**, prepared from **931** using the titanium tetrachloride method, had enormous cataleptic activity[273]; compound **938** was transformed to the caprylate as a potential depot neuroleptic[292]. Cyclization of (2-(5-chloro-2-thienylthio)phenyl)acetic acid gave **939** (R^1 = Cl, R^2 = R^3 = H) which was transformed in three steps to the 2-chloro derivative of **940** (ref.[263]), a strong, incisive neuroleptic agent. Shifting the atom of chlorine to the pseudo-neuroleptic position 7 led via **939** (R^2 = Cl, R^1 = R^3 = H) to the 7-chloro derivative of **941**, a low-cataleptic tranquillizer lacking the antidopaminergic activity in vivo[442]. Introduction of fluorine into position 8 led via the (4-fluoro-2-(2-thienylthio)phenyl)acetic acid and **939** (R^3 = F, R^1 = R^2 = H) to the 8-fluoro derivative of **940**, a neuroleptic with high ataxic and cataleptic activities but lacking the antiapomorphine effect[387]. Finally, the difficult synthesis of **940** (R^1 = Cl, R^2 = H, R^3 = F) was carried out along the same lines[409] and the product was found to be only a tranquillizer with protracted action.

5.3.3.11 [1]Benzothiepino[2,3-*b*]pyridines and Further Heterotricycles with a Seven-Membered Central Ring

An attempt to attack the thieno[2,3-*c*]-2-benzoselenepin system[283] was unsuccessful. Attempts to cyclize the acid **942** (obtained from phthalide and selenophenol) with polyphosphoric acid gave on the one hand the product of decarboxylation (**943**), and the Pailer's[1542] benz[*d*]indeno[1,2-*b*]pyran-5,11-dione (**944**) on the other.

Attempts to cyclize the acids **945** and **946** did not lead in our hands to the desired [1]benzothiepino[3,4-*b*]pyridine-5(11*H*)-ones[229,290]. On the other hand, (2-(phenylthio)-3-pyridyl)acetic acid and its 4-chlorophenyl and 4-isopropylphenyl analogues cyclized easily[288,289] to [1]benzothiepino[2,3-*b*]pyridine-6(5*H*)-ones **947** (R = H, Cl, $CH(CH_3)_2$) which were transformed to the corresponding **948** (together with **949**) and to the enamines **950**. Compounds of this series are much weaker neuroleptics than the corresponding dibenzo[*b,f*]thiepins.

Cyclizations of 2-(2-thienylthio)acetanilide and -benzanilide by the Bischler–Napieralski reaction[243] gave the thieno[2,3-*b*]-1,5-benzothiazepines **951** and **952**. They were reduced to **953** and these were alkylated with 3-dimethylaminopropyl chloride. Out of the obtained **954**, only that having R = CH_3 showed some antihistamine and antiserotonin activity but it was devoid of the CNS activity. The synthesis of 5,11-dihydropyrido[2,3-*b*]-1,4-benzodiazepine-6-one (**955**) was investigated in connection with the synthesis of the anti-ulcer agent pirenzepine[514]; several interesting by-products were identified (cf. **614**). An attempt to cyclize (5-ethyl-2-(2-thienylthio)-3-thienyl)acetic acid[387] did not lead to the desired 6-ethyldithieno[2,3-*b*;3′,2′-*f*]thiepin-3(4*H*)-one.

5.3.3.12 Heterotricycles with Angular Annelation and a Seven-Membered Central Ring

Reactions of 8-fluoro-5-(4-fluorophenyl)-1,3,4,5-tetrahydro-1-benzazepine-2-thione with acetic, propionic, methoxyacetic, (methylthio)acetic, benzoic, phenylacetic and nicotinic acid hydrazides in boiling butanol[421] resulted in the 1-substituted 6-(4-fluorophenyl)-9-fluoro-5,6-dihydro-4*H*-*s*-triazolo[4,3-*a*]-1-benzazepines **956** (R = CH_3 etc.) having no CNS activity in nontoxic doses. 1-Phenyl-4,5-dihydro-3-benzazepine-2(1*H*,3*H*)thione and its 8-chloro derivative reacted with acetohydrazide to give products which were assigned to be 3-methyl-11-phenyl-5,6-dihydro-11*H*-*s*-triazolo[3,4-*b*]-3-benzazepines **957** (R = H, Cl) (ref.[561]).

6-Aryl-8-halo-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines represent the family of the extremely potent hypnotic agent triazolam (**958**, R^1 = Cl, R^2 = 2′-Cl) whose synthesis was slightly modified[451]. Reactions of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepine-2-thione with a series of S-substituted 2-mercaptoacetic acid hydrazides afforded a series of triazolam analogues[451] out of which **959** (R^1 = Cl, R^2 = 2′-Cl) was the most active member as an anticonvulsant but still weaker than triazolam. Similar compounds **958** and **959** with R^2 = 2′-CH_3, 2′-OCH_3, 2′-SCH_3, 3′-Cl-4′-OCH_3 and 3′,4′-$(OCH_3)_2$ were almost inactive[510,524]. On the other hand compounds **958** and **959** with R^1 = Br and R^2 = 2′-Cl are almost equipotent in the tests for anticonvulsant activity with the R^1 = Cl analogues[453]. Reactions of the said thione and its 8-Br and 2′-H analogues with alkanesulfonylglycine and alkanesulfonylalanine hydrazides gave the series of **960** and **961** with R^3 = CH_3 or C_2H_5 which have only slightly the profile of anxiolytics and hypnotics[525]. Compounds of the series **961** were characterized (NMR) as mixtures of two diastereoisomers (it was attempted to explain this phenomenon). A compound of the series with R = Br, R^1 = Cl and R^2 = 2′-Cl was transformed by substitution reactions with N-monosubstituted piperazines[441] to compounds **962** in which the member having R^3 = $(CH_2)_2OCH_3$ was very active as an anticonvulsant and was more active than triazolam against pentetrazole-induced convulsions in mice. Compounds **962** with R^3 = 2-phenoxyethyl or 2-(phenylthio)ethyl were prepared via **962** (R^3 = H) and by its alkylation with 2-phenoxyethyl bromide and 2-(phenylthio)ethyl bromide[441]. The homologues **963** were prepared from the corresponding thione and the 2-(4-substituted 1-piperazinyl)acetic hydrazides[438]. The most simple **963** (R^1 = Cl, R^2 = 2′-Cl, R^3 = CH_3) is a rather active anticonvulsant.

In the 6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-a]-1,4-diazepine series compounds **966** were similarly prepared[464] via **964** or **965**; as CNS agents, they were found less active than the chlorobenzo analogues.

5.3.4 *Heterotricyclic Compounds with Eight-Membered Rings*

Attempts to cyclize 3-(2-(phenylthio)phenyl)propionic acid and its chloro derivative did not lead to 6,7-dihydrodibenzo[*b,g*]thiocin-5-ones but afforded the annelated thioxanthenes **967** and **968** as the most typical products[381], formed probably via the spirocyclic cations **969**; indanones of the type **970** were also formed. For obtaining the eight-membered ketone, it was necessary to use the Dieckmann cyclization of ethyl 3-(2-(4-chloro-2-ethoxycarbonylphenylthio)phenyl)propionate (sodium hydride in toluene) and the high dilution technique[399]. The product was **971** which was hydrolyzed and decarboxylated to **972**. Two further steps led to **973**, the B-homo-octoclothepin lacking the character of a neuroleptic. 2-(Benzylthiomethyl)benzoic acid did not cyclize to 5*H*-dibenzo[*c,f*]thiocin-12(7*H*)-one with polyphosphoric acid; 2-thiophthalide was the only product characterized[200].

Beckmann rearrangement of the oxime of **376** gave the lactam **974** which was reduced with lithium aluminium hydride to 5,6,7,12-tetrahydro[*b,e*]azocine (**975**). Aminoalkylation led to **976**, a homologue of the antidepressant imipramine, displaying high antireserpine activity[207]. Bischler – Napieralski cyclizations of 2-(2-phenylethyl)-formanilide, -acetanilide and -benzanilide led evidently to 11,12- dihydrodibenz[*b,f*]-azocines **977** which, however, were hydrolyzed during attempts at their transforming to salts to the amino ketones **978**. Only in the case of **977** (R = C_6H_5), which was reduced in situ with sodium borohydride, compound **979** was obtained[240].

6,12-Dihydrodibenzo[*b,f*]dithiocin (**980**) was obtained as a product of distillation of the crude 2-(benzylthio)benzyl chloride[222] and as a by-product of cyclization of 2-(2-bromophenylthiomethyl)thiophenol[430] in addition to **607** and **882**. The fluorinated compound **981** was obtained as a by-product of the preparation of 4-fluoro-2-(5-chloro-2-thienylthio)benzyl chloride[409]. Reactions of (2-(2-aminophenylthio)phenyl)acetic acid and its 2-amino-5-chloro analogue with polyphosphoric acid led to 5*H*-dibenzo[*b,g*]-1,4-thiazocine-6(7*H*)-ones **982** and **983** (ref.[298]); the former was transformed by treatment with isobutylamine and titanium tetrachloride to **984** (R^1 = H). Reaction of (2-(2-acetamido-5-chlorophenylthio)phenyl)acetic acid with polyphosphoric acid in boiling toluene afforded **985** (R^1 = Cl) as one of the products[298] (interaction with toluene, a case of the extramolecular Bischler – Napieralski reaction). The lactam **982** was transformed by treatment with phosphorus pentasulfide to the corresponding thiolactam[439] which reacted with hydrazine and gave instead of the wanted hydrazone the corresponding azine.

5.4 HETEROTETRACYCLIC COMPOUNDS

5.4.1 *Annelated Thioxanthene and Dibenzothiepin Derivatives*

Cyclization of 2-(1-naphthylthio)benzoic acid with sulfuric acid gave benzo[*c*]thioxanthone (**986**) which was reacted with 3-dimethylaminopropylmagnesium chloride and the mixture of **987**, obtained after dehydration, was separated to both isomers[217]. 2-(1-Naphthylthiomethyl)benzoic acid and its 5-chloro derivative were cyclized to benzo[*e*]naphtho[1,2-*b*]thiepin-7(12*H*)-ones **988** (R = H, Cl) which were converted in two steps[200] to homogeneous **989** (R = H, Cl); the former showed important peripheral antiserotonin effect. 2-(5-Indanylthio)benzoic acid was transformed in six steps to 8,9-dihydro-7*H*-indeno[5,6-*b*]-1-benzothiepin-11(12*H*)-one (**990**) which was further transformed to the perathiepin analogue **991** and to the corresponding enamine[307]; both compounds were weak neuroleptic agents. Similar processing of 2-(2-naphthylthio)benzoic acid[325] led to benzo[*b*]naphtho[2,3-*f*]thiepin-12(13*H*)-one (**992**, R = O) and further to **992** (R = 4-methyl-1-piperazinyl) and the corresponding enamine (weak neuroleptics). 2-(1-Naphthylthio)benzoic acid was converted in five steps[310] to benzo[*b*]naphtho[2,1-*f*]thiepin-7(8*H*)-one (**993**, R = O) which was transformed in three further steps to the perathiepin analogue **993** (R = 4-methyl-1-piperazinyl) which is almost inactive[310].

Cyclization of 8-(phenylthio and 4-chlorophenylthio)-1-naphthoic acids with polyphosphoric acid gave mixtures of benzo[*f*]naphtho[1,8-*b*,*c*]thiepin-12-ones (**994**, R = H, Cl) and the isomeric **986** (9-H, 9-Cl) (ref.[332]). Ketones **994** were the primary products which were converted to **986** by using higher temperature or longer reaction time (reversibility of the Friedel – Crafts cyclization). The ketone **994** (R = H) was transformed to the prothiadene analogue **995** (R = H) which proved to be a clear thymoleptic agent with antireserpine and anticataleptic actions. The ketone **994** (R = Cl) was used to prepare the octoclothepin analogue **996** (R = Cl) lacking the character of a neuroleptic agent.

One of the products of alkylation of **707** (R = H) with 1,2-dibromoethane[446] was identified by a detailed analysis of the NMR spectra[504] and by the X-ray crystallographic study[1204] as 11,12-dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-carbonitrile (**997**). It was oxidized to the 5-oxide and 5,5-dioxide and reduced with aluminium hydride to **998**. Methylation by the Eschweiler – Clarke method resulted in **999** which was inactive as a potential antidepressant.

5.4.2 *Berbine and Berbane Derivatives*

N-(3-Methoxyphenylacetyl) derivatives of 2-(3-methoxyphenyl)ethylamine and homoveratrylamine were cyclized by the Bischler – Napieralski reaction and the products were reduced with sodium borohydride to the corresponding 1,2,3,4-tetrahydroisoquinolines[198] which were subjected to reactions with formaldehyde (Pictet – Spengler reaction) to give the berbines **1000** and **1001** out of which the latter was new. The former was reduced with lithium and ethanol to an unstable tetrahydro derivative, characterized as **1003**. Similar synthesis of **1002**, carried out in connection with the chemistry of some dopamine analogues[448], started from N-(2-(3,4-dimethoxyphenyl)-1-(4-tolyl)-3,4-dimethoxyphenylacetamide.

Further experimental work was carried out in connection with total syntheses in the field of reserpine analogues[188]. Alkylation of 2-(3-methoxyphenyl)ethylamine with ethyl *trans*-2-(bromomethyl)cyclohexaneacetate proceeded under simultaneous intramolecular acylation and formation of **1004**. This was cyclized with phosphoryl chloride and the product was directly reduced with sodium borohydride to 7-methoxyberbane (**1006**) or the crude product of cyclization was transformed to the perchlorate **1005** which was reduced with zinc in perchloric acid to the same **1006**.

Reactions of 2-(3-methoxyphenyl)ethylamine and homoveratrylamine with the aldehyde ester **1007**, the alicyclic component of the Woodward's total synthesis of reserpine[1543-1545] gave the corresponding Schiff bases which were immediately reduced with sodium borohydride and cyclized to **1008** ($R^1 = R^2 = H$; $R^1 = OCH_3$, $R^2 = H$) (refs[162,188]). Methanolysis produced the corresponding **1009** which were acylated with 3,4,5-trimethoxybenzoyl chloride followed with sodium perchlorate giving the perchlorates **1011**. Reduction with sodium borohydride gave the alloberbanes **1012**, whereas reduction with zinc in acidic medium gave the epialloberbanes **1013**, corresponding stereochemically to racemic reserpine ("methoxy- and dimethoxy-despyrrolodeserpidines"). The series was completed by Pelz et al.[1546] by synthesis of the mescaline analogue **1013** ($R^1 = R^2 = OCH_3$). The analogue of **1009** in the alloberbane series (**1012**, $R^1 = R^2 = H$) was transformed to the 4-bromobenzenesulfonic ester which was subjected to hydrogenolysis with lithium aluminium hydride giving the alcohol **1014** of the alloberbane series[188]. Starting with 2-phenylethylamine[188], the syntheses proceeded until the stage of the seco-lactams (type **1010**); their cyclization by the Bischler – Napieralski reaction did not proceed. In the "despyrroloreserpine" series, there was a collision with the work of the Roussel – Uclaf team[1547,1548].

Similar synthesis starting from homopiperonylamine[186] resulted in the most interesting member of the series, mediodespidine (**1015**). In comparison with reserpine, this compound was a hypotensive agent without any significant CNS depressant activity. Separation of both lines of the reserpine effects by modification of structure was the main goal of the extensive work undertaken in the series. On the basis of pharmacological and biochemical experiments, mediodespidine[1549-1551] was selected for clinical trials; this endeavour was prevented by difficulties with its synthesis in larger scale.

5.4.3 *Remaining Heterotetracyclic Compounds*

Whereas the described synthesis[1552] of N-methylmorphinan (**1016**) was found easily reproducible, the attempts to prepare its 3-nor[107] and 9-nor analogue[1553] were unsuccessful. Reaction of 10-(2-hydroxyethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile with phosphorus tribromide in benzene[445] gave 2'-imino-4',5'-dihydrospiro(dibenzo[*b,f*]thiepin-10(11*H*),3'(2'*H*)-furan) (**1017**), i.e. the spirocyclic imidate. Its acid hydrolysis afforded the spirocyclic lactone **1018**.

An attempt to carry out the substitution reaction of *trans*-2,11-dichloro-10-(2-dimethylaminoethyl)-10,11-dihydrodibenzo[*b,f*]thiepin with 1-methylpiperazine[346] led to cyclization to the methochloride of 11-chloro-1-methyl-2,3,3a,12b-tetrahydro-1*H*-pyrrolo[2,3-*m*]dibenzo[*b,f*]thiepin (**1019**, n = 1), displaying some spasmolytic and antihistamine activities. A similar reaction of 2,11-dichloro-10-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[*b,f*]thiepin[346] produced the methochloride of 12-chloro-1-methyl-1,2,3,4,4a,13b-hexahydropyrido[2,3-*m*]dibenzo[*b,f*]thiepin (**1019**, n = 2) having similar activity. Compound **890** and its 2-chloro and 8-chloro derivatives were transformed by the action of phosphorus pentasulfide to the thiones affording by treatment with hydrazine the corresponding "hydrazones". Their reactions with triethyl orthoformate gave **1020** (R^1,R^2 = H, Cl) which were brominated to **1021**. Substitution reactions with 1-methylpiperazine afforded **1022** ($R^1 = R^2$ = H; R^1 = H, R^2 = Cl; R^1 = Cl, R^2 = H) which are rather toxic and lack CNS activity[439].

2-(2-Fluorophenylthio)phenylmagnesium bromide reacted with 1-(ethoxycarbonyl)-4-piperidone and the obtained tertiary alcohol was cyclized with sodium hydride in dimethylformamide[480] to 1'-(ethoxycarbonyl)spiro(dibenz[*b,e*]-1,4-oxathiepin-6,4'-piperidine) (**1023**). Reduction with sodium dihydridobis(2-methoxyethoxy)aluminate gave **1024** having antireserpine activity in two tests but only low affinity to imipramine binding sites in the rat brain.

5.5 HETEROPENTACYCLIC COMPOUNDS

5.5.1 [1]*Benzothiepino*[2,3,4-*ed*]*pyrido*[2,1-*a*]*isoquinoline Derivatives*

The extremely high and strictly stereoselective neuroleptic activity of the pentacyclic butaclamol[1554] and isobutaclamol[1555] induced us to the effort to synthesize analogues containg the dibenzo[*b,f*]thiepin tricycle in the skeleton[470]. Compound **834** was reduced with aluminium hydride to 10-(aminomethyl)-10,11-dihydrodibenzo[*b,f*]thiepin. This was formylated with acetic formic anhydride and the formamide obtained was cyclized by the Bischler – Napieralski reaction to **1025**. Addition of methyl vinyl ketone gave a mixture of stereoisomeric **1026** which was separated by chromatography and on the basis of analogy[1554,1555], the major component was assigned to be the 3b,9a-*cis*-isomer and the minor one the correct 3b,9a-*trans*-isomer.

This was reacted with t-butylmagnesium chloride and isopropyllithium which resulted in mixtures out of which **1027** and **1028** were isolated. The secondary alcohol **1029** was a by-product. 5-t-Butyl-3b,9a-*trans*-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino-[2,3,4-*ed*]pyrido[2,1-*a*]isoquinoline-5-ol is the 15-thia analogue of isobutaclamol and displays high affinity to dopamine receptors in the striatum in the rat brain (which confirms the correctness of the assignment or relative configuration of C-3b and C-9a.

5.5.2 *2H-Benzo[g][1]benzothieno[2,3-a]quinolizine Derivatives*

The named system corresponds to that of 1-deaza-1-thiayohimbane. In this area, our team[187] tried to synthesize racemic 1-deaza-1-thiadeserpidine. 2-(3-Thianaphthenyl)-ethylamine was reacted with **1007**, the Schiff base formed was reduced in situ with sodium borohydride and the acetoxylactam was transformed via the hydroxylactam to **1030**. The cyclization with phosphoryl chloride and reaction with sodium perchlorate gave the quaternary perchlorate **1031**. Its reduction with sodium borohydride resulted in the crystalline racemic 1-deaza-1-thia-3-isodeserpidine (**1032**). Reduction of **1031** with zinc in the presence of perchloric acid gave a mixture of equal amounts of **1032** and of an oily base which was evidently the wanted racemic 1-deaza-1-thiadeserpidine. After our work, an independent synthesis of racemic 1-deaza-1-thiareserpine was carried out[1556] (for the synthesis of the skeleton, cf. refs[1557,1558]).

5.5.3 *Yohimbane Derivatives and Reserpoids*

In the middle of fiftieth, Rauwolfia alkaloids[563] and reserpine (11,17α-dimethoxy-16β-methoxycarbonyl-18β-(3,4,5-trimethoxybenzoyloxy)-3-epi-20-alloyohimbane) as their most important representative, were in the centre of general attention in the field of drug research. The Woodward's total synthesis of reserpine[1543] was followed by efforts to use its principle for technical purpose[564,1544] and for the synthesis of its close analogues[1544,1559-1562]. The author of this review expressed his view that the total synthesis became the most progressive method of drug manufacture[141] and initiated extensive experimental work in the line of total synthesis of reserpoids using the principle of the Woodward's synthesis[140,153].Ten years later, the interest in this topic was practically over[241]. The work of our team started with working up of the individual steps of both Woodward's variants[1543] and of the Velluz' modifications[1544] of the preparation of the alicyclic component **1007** of the total synthesis of reserpine.

The first step, i.e. the stereoselective addition of benzoquinone to methyl vinylacrylate giving **1033** was developed to a high-yield process[146]. Also the reduction of this compound with aluminium isopropoxide to **1035** was importantly improved[146]. The idea to start from isopropyl vinylacrylate and to proceed via **1034** was found erroneous[161] : the Meerwein reduction of **1034** stopped in the stage of **1037** (only reduction of the sterically more accessible keto group). The next step was the reaction of **1035** with bromine in methanol giving the bromo compound **1038** which could be transformed to the methoxy compound **1039** either directly, i.e. by treatment with sodium methoxide[146] or better via the unsaturated lactone **1044** obtained from **1038** either by dehydrobromination with collidine[146] or with potassium acetate in boiling acetone[199]. All steps of the Woodward synthesis[1543] proceeded stereoselectively, i.e. the relative configurations on all centres in **1033**, **1035**, **1038** and **1044** are defined but the compounds are racemates.

One of the aims of our work was to carry out the resolution in some of these early stages of the synthesis. Compound **1038** gave by alkaline hydrolysis the unsaturated hydroxy acid **1046** which was resolved in the form of the salt with brucine[151]. Only the (–)-acid **1046** was obtained crystalline and it was cyclized with dicyclohexylcarbodiimide to (–)-**1044**. The following addition of methanol afforded (+)-**1039** which was found identical with the Velluz' optically active substance obtained differently[1544] and found to belong to the natural reserpine series. More recently[176], it was found more favourable to resolve racemic **1046** with (–)-ephedrine. The unwanted (–)-ephedrine salt of (+)-**1046** crystallized quantitatively and from the mother liquor, the desired (–)-**1046** was obtained in excellent yield. The problem of resolution was thus solved but further work proceeded in the racemic series. Nevertheless there was another episode aiming at an easy passage to the optically active series. Compound **1035** was oxidized with chromic anhydride in acetic acid[146] to the ketone **1047** and it was tried to reduce the keto group enantioselectively with baker's yeast[166] and then with six different microorganisms[172]. Most surprisingly, the only isolated product was **1048**, i.e. the saturation of the double bond proceeded instead of the expected reduction of the keto group. In the meantime, Roy and Wheeler[1563] studied the catalytic hydrogenation of **1047** in the presence of rhodium and palladium catalysts and obtained **1048** which was carefully characterized. With regard to the fact that they found some differences in properties of their product and those given by us[166,172], they expressed doubts on the correctness of the structure of our product. There came to a common reinvestigation of the case[209]. The samples were exchanged and were directly compared (melting points, IR spectra, reactions). The identity of the samples was established and correctness of structure **1048** for the yeast metabolite was proven. Another independent synthetic experiment started from **1036**, obtained by acetylation[146] of **1035**. Addition of bromine and dehydrobromination[170] gave **1049** which reacted with silver acetate in boiling dioxane under allylic rearrangement and gave the unwanted **1050**. Further steps leading from **1039** to **1007** were carried out in principle according to the literature already cited[1543-1545]. It was found that the unsaturated lactone **1044** adds not only methanol (leading to **1039**) but also the most various nucleophiles[196], e.g. ethanol, amines (cf. the dimethylamine adduct **1040**) and also the Grignard reagents (cf. the methylmagnesium iodide addition and hydrolysis product **1041** and the similar ethylmagnesium bromide product **1042**). It was also reduced with sodium borohydride to **1043**. These addition reactions gave extensive opportunities for the synthesis of reserpoids modified in position 17 which, unfortunately, were only partly used (the use of **1041** – **1043** will be mentioned in the next paragraphs).

In the final stages, the first attack was directed to racemic reserpine[160] and used combination of the published[1543-1545] and the own modifications. 6-Methoxytryptamine (**529**, R = 6-OCH_3) was reacted with **1007** and the obtained Schiff base was reduced with sodium borohydride under cyclization to **1051a** (R^1 = 6-OCH_3). Cyclization with phosphoryl chloride and reaction with sodium perchlorate gave **1052a** (R^1 = 11-OCH_3) which was reduced with zinc in perchloric acid and deacylated by methanolysis to a mixture 3:1 of methyl reserpate **1053b** (R^1 = 11-OCH_3) and methyl 3-isoreserpate **1054b** (R^1 = 11-OCH_3); this was separated by chromatography. Acylation of methyl reserpate with 3,4,5-trimethoxybenzoyl chloride using a modified procedure gave 72% of racemic reserpine (**1053c**, R^1 = 11-OCH_3). The procedure used was shorter than those of Woodward[1543] and Velluz[1544]. A similar scheme was adopted for the synthesis of racemic deserpidine[160] (**1053c**, R^1 = H) which was easier because the reduction of **1052a** (R^1 = H) with zinc and perchloric acid proceeded stereoselectively and the following methanolysis produced the homogeneous methyl deserpidate (**1053b**, R^1 = H). Two modified synthese of racemic deserpidine (**1053c**, R^1 = H) were carried out by our colleagues[1564,1565] who completed also a similar synthesis of racemic 19-methyldeserpidine[1566,1567] with undetermined configuration on C-19.

Our team proceeded then to the synthesis of reserpine analogues modified in ring A, i.e. in positions 10, 11 and 12. The starting materials were 5-fluoro-, 5-methyl-, 5-methoxy-, 5-ethoxy-, 5-(methylthio)- and 7-(methylthio)-tryptamine[147] (**529**, R = 5-F, 5-CH_3, 5-OCH_3, 5-OC_2H_5, 5-SCH_3 and 7-SCH_3). The syntheses of the corresponding A-substituted racemic deserpidines proceeded via **1051a** – **1051c** and **1052c**. In the synthesis of racemic 10-fluorodeserpidine[164] (**1053c**, R^1 = 10-F), the reduction of **1052c** (R^1 = 10-F) proceeded easily and resulted directly in the homogeneous product which was found to have similar hypotensive activity like racemic deserpidine but its sedative activity was ten times lower than that of racemic reserpine. This was a success because the separation of these two effects by molecular manipulation was just the main object of our efforts. The combination of these two very strong effects in the case of reserpine was its main disadvantage and resulted finally in the strong decrease of its use in the therapeutic practice in both of its lines: hypertension and schizophrenia. In cases of the 10-methyl-, 10-ethoxy- and 10-(methylthio)-deserpidines[156,] the work was more complicated because the reductions of **1052c** (R^1 = 10-CH_3, 10-OC_2H_5 and 10-SCH_3) with zinc in perchloric acid were not unequivocal and mixtures of the wanted 3-epialloyohimbane and undesired alloyohimbane (3-iso) derivatives were formed which had to be separated by chromatography or by crystallization of the perchlorates. The prepared racemic **1053c** (R^1 = 10-CH_3, 10-OC_2H_5, 10-SCH_3) had hypotensive and sedative reserpine-like activities somewhat lower than deserpidine[156]. A similar situation was met in the 12-(methylthio) series[185]: the reduction of **1052c** (R^1 = 12-SCH_3) gave an inhomogeneous **1053c** (R^1 = 12-SCH_3) which was purified by chromatography and crystallization which led also to the isolation of the homogeneous 3-isomer **1054c** (R^1 = 12-SCH_3). Racemic 12-(methylthio)deserpidine (methiopidine, **1053c**, R^1 = 12-SCH_3) proved a very interesting substance: a potent antihypertensive almost free of the sedative component of action[1551,1568] (cf. also[1569]). Its clinical trial was prevented only by its difficult accessibility.

A special case was the synthesis of racemic methyl O-(O-ethoxycarbonylsyringoyl)-10-methoxydeserpidate[159] (**1053d**, R^1 = 10-OCH_3). Starting from 5-methoxytryptamine[147] and **1007**, the synthesis proceeded to **1051a** (R^1 =5-OCH_3), this was cyclized with phosphoryl chloride and the product was transformed to the perchlorate **1052a** (R^1 = 10-OCH_3) which was reduced with zinc in perchloric acid. A 1:1 mixture of **1053a** and **1054a** (R^1 = 10-OCH_3) was obtained and separated by chromatography. The stereochemically correct (in all cases, the configuration at C-3 was settled by IR) **1053a** (R^1 = 10-OCH_3) was deacetylated by methanolysis and the product was acylated with O-(ethoxycarbonyl)syringoyl chloride in pyridine to the wanted **1053d** (R^1 = 10-OCH_3) which represented a structural combination of two hypotensive reserpoids in which the sedative component was importantly suppressed and which, therefore, were introduced to the antihypertensive pharmacotherapy: the partially synthetic methyl (–)-O-(O-ethoxycarbonylsyringoyl)reserpate[1570,1571] (syrosingopine (INN), Singoserp®) and the totally synthetic (–)-10-methoxydeserpidine[1544,1572,1573] (methoserpidine (INN), Decaserpyl®). In spite of this fact, our compound was not found interesting in this sense. It is necessary to add that our synthetic sequences in the reserpine field were carefully followed in all steps by paper chromatography[1574-1576].

The last stage of our totally synthetic efforts in the reserpine field was the use of the epoxy lactones **1041** – **1043** which were obtained by addition of the Grignard reagents to **1044** and by its reduction with sodium borohydride[196]. By their reactions with N-bromosuccinimide in dilute sulfuric acid[173,203], the bromohydrins **1055a** – **1055c** were obtained which were oxidized with chromic anhydride to **1056a** – **1056c**. The following reduction with zinc and acetic anhydride gave **1057a** – **1057c** (all in analogy with ref.[1543]) which were *cis*-dihydroxylated with barium perchlorate with a small amount of osmium tetroxide to **1058a** – **1058c**. Oxidative cleavage with periodic acid followed by esterification with diazomethane led to the corresponding modified "alicyclic components" **1059a** – **1059c**.

In the methyl and ethyl series[173], **1059a** and **1059b** were reacted with 6-methoxytryptamine, the products were reduced in situ with sodium borohydride to **1060a** and **1060b** which were subjected to methanolysis yielding **1061a** and **1061b**. These compounds were esterified with 3,4,5-trimethoxybenzoyl chloride to **1062a** and **1062b**. The following Bischler – Napieralski cyclization with phosphoryl chloride and reaction with the perchlorate anion afforded the perchlorates **1063a** and **1063b** which were reduced with zinc and perchloric acid to racemic 17α-methyl-17-demethoxyreserpine (**1064a**) and 17α-ethyl-17-demethoxyreserpine (**1064b**) which had similar hypotensive activity like reserpine but their sedative activity was importantly lower; especially ethyserpine (**1064b**) attracted the interest of the pharmacologists[1569]. In the case of the 17-demethoxy compounds[203], tryptamine was reacted with **1059c** and the product was transformed via **1060c** to **1063c**. Reduction with zinc in perchloric acid gave the racemic 17-demethoxydeserpidine (**1064c**) and reduction with sodium borohydride afforded the 3-isomer **1065c**.

Addition of diazomethane to **1044** and the following thermic decomposition of the product gave **1045** (ref.[196]) which was reduced with sodium borohydride to **1066**, a stereoisomer of **1041**. This compound was used by Ernest[1577] in our team to the synthesis of the racemic 17β-methyl-17-demethoxyreserpic acid lactone and its 3-isoreserpic isomer. The same author[1578] equilibrated **1059c** in acid medium to a mixture with **1067** which was used for the synthesis of racemic apoyohimbine and opened the way to further yohimbane and epiyohimbane derivatives. The last contribution of Ernest[1579] consisted in the finding that the introduction of the γ-lactone ring into **1007** is connected with the isomerization to **1068** which was used for preparing racemic 3-iso-20-alloreserpic acid lactone.

Esterification of (–)-methyl reserpate, accessible by methanolysis of natural reserpine, was described[1570] as a partially synthetic way leading to new reserpoids in which the hypotensive and neuroleptic (sedative) components could be more or less separated. Our first contribution in this line[184] used the acylation of (–)-methyl reserpate with chlorides of 3,5-dimethoxy-4-ethoxybenzoic, 3,5-diethoxy-4-methoxybenzoic, 3,5-diethoxy-4-(ethoxycarbonyloxy)benzoic, 3,5-dimethoxy-4-methylbenzoic, phenoxyacetic and the three monomethoxyphenoxyacetic acids in pyridine. Out of the compounds obtained, the 3,5-diethoxy-4-methoxybenzoate (bishomoreserpine, **1069**) and the (4-methoxyphenoxy)acetate (methoxyphenoserpine, **1070**) proved rather interesting. Bishomoreserpine showed increased central activity in behavioural and biochemical tests[1551,1569,1580-1582] and when used in psychopharmacotherapy as a neuroleptic agent, it could not be distinguished from reserpine[973]. The other compound, methoxyphenoserpine, on the other hand, appeared to be a "clean" antihypertensive with strongly diminished CNS effects with the exception of the ulcerogenic effect which is similar like with reserpine (refs[1551,1568,1569,1581,1583,1584]). The utility of methoxyphenoserpine in the pharmacotherapy of hypertension was confirmed by clinical testing[1585,1586]; one negative report[1587] in this line caused discontinuation of the clinical trials. The synthesis of a second series of (–)-methyl reserpate esters[208] used mainly reactions of methyl reserpate with the acids in the presence of dicyclohexylcarbodiimide. The most interesting seemed to be the 2,4-dichlorophenoxyacetate (**1071**) showing an even more convenient ratio of hypotensive to sedative activity than methoxyphenoserpine[208], and the (4-methoxyphenylthio)acetate (methoxyphenthioserpine, **1072**) which showed the same effect on the monoamine level in the brain and heart of mice like methoxyphenoserpine[1551].

5.6 HETEROPOLYCYCLIC COMPOUNDS

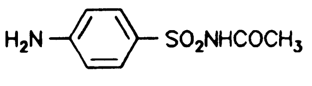
Such compounds were obtained mainly as by-products (cf. already **789**) and they are only mentioned. Reaction of compound **745** with 1-methylpiperazine[349] gave a nitrogen-free crystalline compound $C_{32}H_{28}O_4S_2$ which was characterized (MS etc.) as 2,3,2′,3′-tetramethoxydispiro(9*H*-thioxanthene-9,1′-cyclobutane-3′,9′-9*H*-thioxanthene) (**1073**) (cyclodimerization of an olefin without conditions for photochemical reactions but without protection from the day-light). Furo[2,3-*m*;4,5-*m′*]bis(dibenzo[*b*,*f*]thiepins) (**1074**) accompany often the ketones **734** formed by cyclizations of (2-(arylthio)aryl)acetic acids with polyphosphoric acid especially when higher temperatures and longer reaction periods are used. The following **1074** were isolated and characterized: 1,9-difluoro[380], 1,9-dimethyl[487], 3,7-dichloro[351], 13,16-dichloro[351], 12,17-difluoro[384], 3,7,12,17-tetrafluoro[412], 12,13,16,17-tetramethoxy[349], and 2,8-dichloro-3,7-difluoro[340]. We do not consider these compounds to be by-products but we presume their formation from the ketones **734** via the corresponding dienol ethers (formed by dehydration) and by their following spontaneous cyclization under dehydrogenation; for analogies, cf. refs[1588-1590]. In the dibenzo[*b*,*f*]selenepin series[253], the similar **1075** was obtained and characterized. In the benzo[*b*]naphtho[2,1-*f*]thiepin series[310], compound **1076** was obtained.

6 INDEX OF NONCHEMICAL NAMES OF THE ORIGINAL PRODUCTS

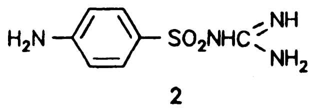
Name	Formula Number
acetylthiosulfocholine iodide	33
Alfadryl ®	208
amizoptene	310
Antihistamin®	166
benzamsulfonium iodide	117
benzperidine	166
bishomoreserpine	1069
Bromadryl®	213
Bromadryl F®	213
carbmethosulfonium iodide	34

chloroperaptene	**385**
chlorproheptadiene	**376**
chlorproheptatriene	**378**
cloflumide	**793**
clopithepin	**817**
clorotepin (INN)	**737** (R = 8-Cl)
Clotepin®	**737** (R = 8-Cl)
Clotepin inj.®	**737** (R = 8-Cl)
Clotepin oleosum inj.®	**737** (R = 8-Cl)
cloxathiepin	**871** (X = S, R^1 = Cl, R^2 = H)
cyclomethonium iodide	**45**
dehydroclothepin	**739** (R = 8-Cl)
Dimecamin®	**63**
dimecamine	**63**
dinorthiadene	(*E*)-**635** (R = H)
Dithiaden®	(*E*)-**903** (R = H)
dithiadene	(*E*)-**903** (R = H)
dithiotolperidine	**199**
doclothepin	**737** (R = 2-Cl)
docloxythepin	**755** (R = 2-Cl)
dosulepin (INN)	(*E*)-**632** (R = H)
dothiepin (Brit. Approved Names)	(*E*)-**632** (R = H)
embramine (INN)	**213**
embramine teoclate (INN)	**213**
Enterina®	**2**
ethiacine	**457**
ethyserpine	**1064b**
fluoxyphenonium bromide	**267**
guanisoline	**528**
hexadiphenium bromide	**262**
hexadiphensulfonium iodide	**260**

7 STRUCTURES OF COMPOUNDS PRESENTED IN THIS REVIEW



1



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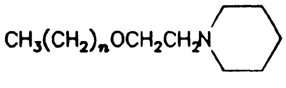
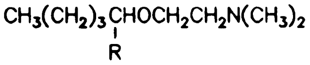


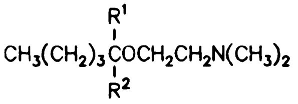
$n = 1$ **3**

$n = 5$ **4**



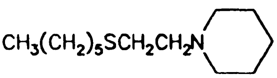
$CH_3(CH_2)_3\underset{R}{C}HOCH_2CH_2N(CH_3)_2$

5



$CH_3(CH_2)_3\overset{R^1}{\underset{R^2}{C}}OCH_2CH_2N(CH_3)_2$

6

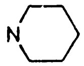


7

$C_2H_5OCSSCH_2CH_2R$

$R = N(C_2H_5)_2$ **8**

R =



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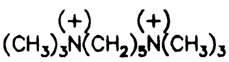
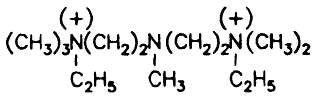


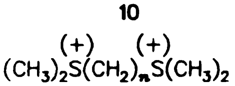
$(CH_3)_3\overset{(+)}{N}(CH_2)_5\overset{(+)}{N}(CH_3)_3$ 2 Br $^{(-)}$

10



$(CH_3)_3\overset{(+)}{\underset{C_2H_5}{N}}(CH_2)_2\underset{CH_3}{N}(CH_2)_2\overset{(+)}{\underset{C_2H_5}{N}}(CH_3)_2$ 2 Br $^{(-)}$

11

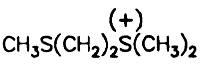


$(CH_3)_2\overset{(+)}{S}(CH_2)_n\overset{(+)}{S}(CH_3)_2$ 2 I $^{(-)}$

12

$CH_3S(CH_2)_nSCH_3$

13



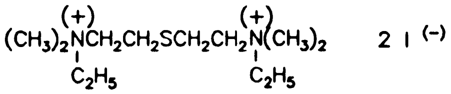
$CH_3S(CH_2)_2\overset{(+)}{S}(CH_3)_2$ I $^{(-)}$

14

$CH_3SCH_2CH_2SCH_2CH_2SCH_3$ $(CH_3)_2\overset{(+)}{S}CH_2CH_2SCH_2CH_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$

15 **16**

$RCH_2CH_2SCH_2CH_2R$



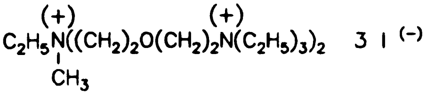
$(CH_3)_2\underset{C_2H_5}{\overset{(+)}{N}}CH_2CH_2SCH_2CH_2\underset{C_2H_5}{\overset{(+)}{N}}(CH_3)_2\quad 2\ I^{(-)}$

17 **18**

$(CH_3)_3\overset{(+)}{N}(CH_2)_{10}\overset{(+)}{N}(CH_3)_3\quad 2\ Br^{(-)}$ **19**

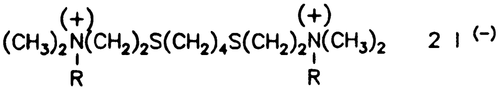
$(CH_3)_3\overset{(+)}{N}CH_2CH_2OCOCH_2CH_2COOCH_2CH_2\overset{(+)}{N}(CH_3)_3\quad 2\ I^{(-)}$ **20**

$(C_2H_5)_3\overset{(+)}{N}(CH_2)_2O(CH_2)_nO(CH_2)_2\overset{(+)}{N}(C_2H_5)_3\quad 2\ I^{(-)}$ **21**



$C_2H_5\underset{CH_3}{\overset{(+)}{N}}((CH_2)_2O(CH_2)_2\overset{(+)}{N}(C_2H_5)_3)_2\quad 3\ I^{(-)}$ **22**

$C_2H_5\overset{(+)}{N}((CH_2)_2O(CH_2)_2\overset{(+)}{N}(C_2H_5)_3)_3\quad 4\ I^{(-)}$ **23**



$(CH_3)_2\underset{R}{\overset{(+)}{N}}(CH_2)_2S(CH_2)_4S(CH_2)_2\underset{R}{\overset{(+)}{N}}(CH_3)_2\quad 2\ I^{(-)}$ **24**

$(CH_3)_2\overset{(+)}{S}(CH_2)_2O(CH_2)_5O(CH_2)_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$ **25**

$(CH_3)_2\overset{(+)}{S}(CH_2)_2S(CH_2)_nS(CH_2)_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$ **26**

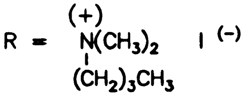
$(CH_3)_3\overset{(+)}{N}(CH_2)_2SCO(CH_2)_2COS(CH_2)_2\overset{(+)}{N}(CH_3)_3\quad 2\ I^{(-)}$ **27**

$(CH_3)_2\overset{(+)}{S}(CH_2)_2OCO(CH_2)_2COO(CH_2)_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$ **28**

$(CH_3)_2\overset{(+)}{S}(CH_2)_2SCO(CH_2)_2COS(CH_2)_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$ **29**

$(CH_3)_2\overset{(+)}{S}(CH_2)_2COO(CH_2)_2OCO(CH_2)_2\overset{(+)}{S}(CH_3)_2\quad 2\ I^{(-)}$ **30**

$HOCH_2CH_2R$



$R = \underset{(CH_2)_3CH_3}{\overset{(+)}{N}}(CH_3)_2 \quad I^{(-)}$ 31

$R = \overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ 32

$CH_3COSCH_2CH_2\overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ 33

$ROCOCH_2CH_2\overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ $R = CH_3$ 34

$R = C_2H_5$ 35

$(CH_3)_3CCOOCH_2CH_2N(CH_3)_2$ 36

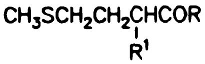
$CH_3(CH_2)_nCOOCH_2CH_2N(CH_3)_2$ 37

$(CH_3CH_2CH_2)_2CHCOR$ 38

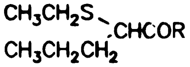
In formulae 38–40

a, $R = OH$

b, $R = NH_2$

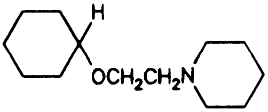


$CH_3SCH_2CH_2\underset{R^1}{C}HCOR$ 39



$\begin{matrix} CH_3CH_2S \\ CH_3CH_2CH_2 \end{matrix} \!\!> CHCOR$ 40

$(CH_3CH_2CH_2)_2CHCOOCH_2CH_2NHCOOC_2H_5$ 41



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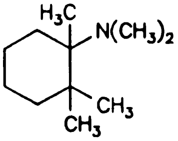

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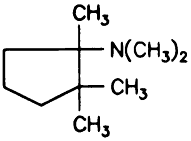

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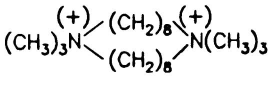
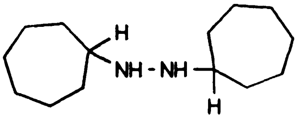
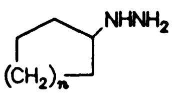


$2\ I^{(-)}$

45



46



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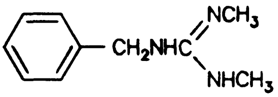

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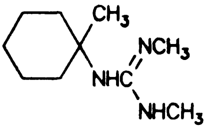
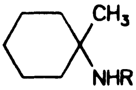
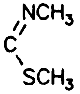


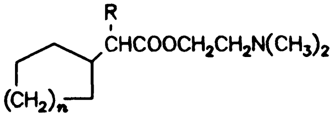
49



R = $CSNHCH_3$ **50**

R = 

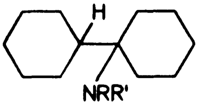
$C(=NCH_3)SCH_3$ **51**



R = H, n = 1 **52**

R = H, n = 3 **53**

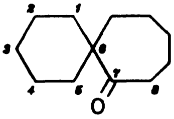
R = $(CH_2)_3CH_3$, n = 1 **54**



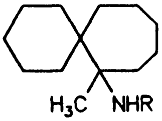
R = CHO, R' = H **55**

R = R' = H **56**

R = R' = CH_3 **57**

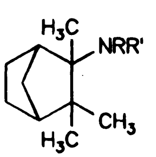


58



R = CHO **59**

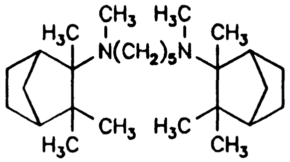
R = CH_3 **60**



$R = H, R' = CH_3$ **61**

$R = R' = H$ **62**

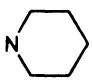
$R = R' = CH_3$ **63**



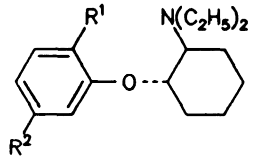
64

$C_6H_5O(CH_2)_nR$

$R = N(C_2H_5)_2,\ n = 2$ **65**

R =  , $n = 2$ **66**

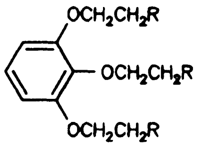
$R = N(CH_3)_2,\ n = 3$ **67**



$R^1 = R^2 = H$ **68**

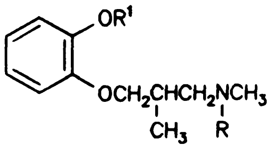
$R^1 = CH(CH_3)_2$ **69**

$R^2 = CH_3$



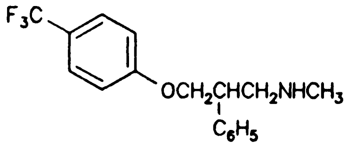
$R = N(C_2H_5)_2$ **70**

$R = \overset{(+)}{N}(C_2H_5)_3\ I^{(-)}$ **71**

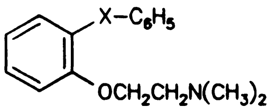


$R = CH_3$ **72**

$R = H$ **73**



74



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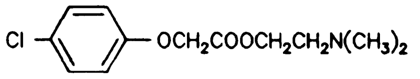
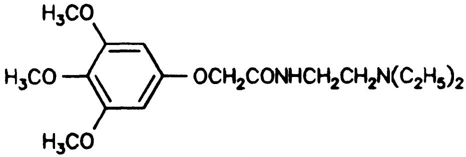
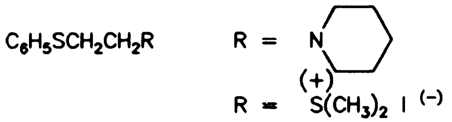


76

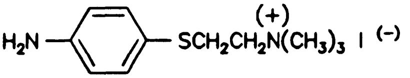


77

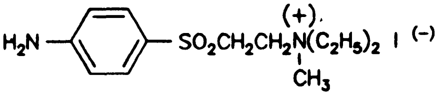


78

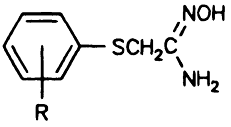
79



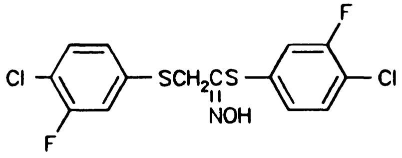
80



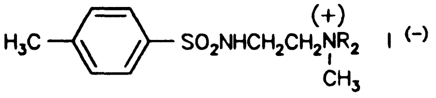
81



82

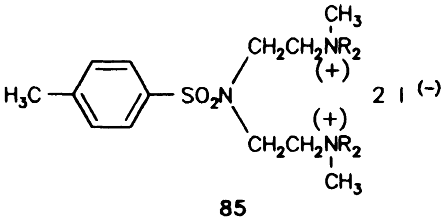


83



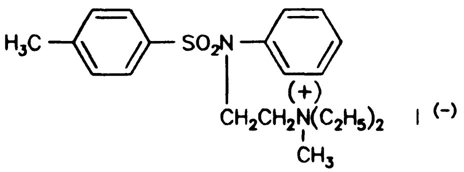
(R = CH_3, C_2H_5)

84

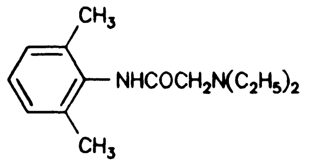


(R = CH_3, C_2H_5)

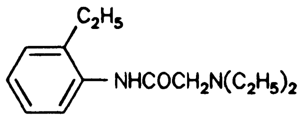
85



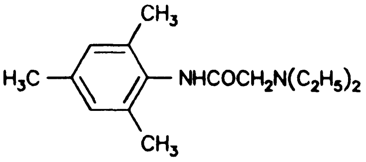
86



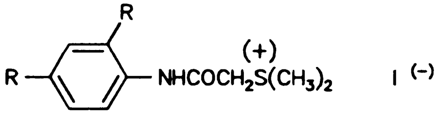
87



88

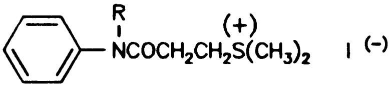


89



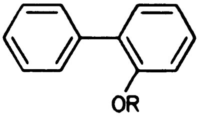
R = CH_3 **90**

R = H **91**



R = C_2H_5 **92**

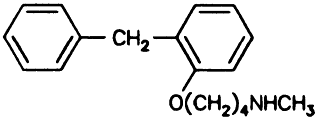
R = C_6H_5 **93**



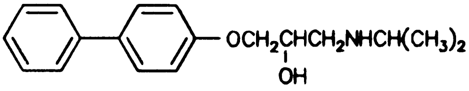
R = $(CH_2)_4NHCH_3$ **94**

R = $(CH_2)_2CN$ **95**

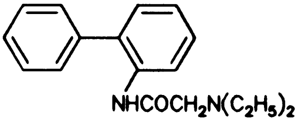
R = $(CH_2)_2COOH$ **96**



97

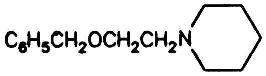


98

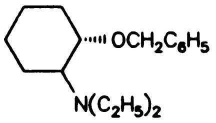


99

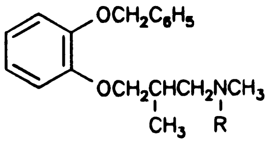
$C_6H_5(CH_2)_nOCH_2CH_2N(C_2H_5)_2$ n = 1–3 100



101

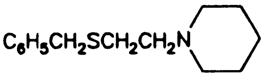


102

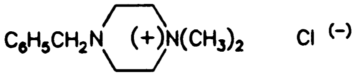


R = CH_3 103

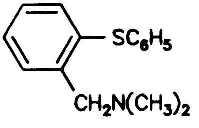
R = H 104



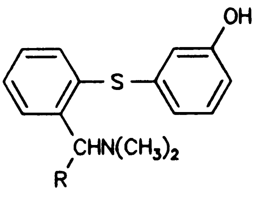
105



106

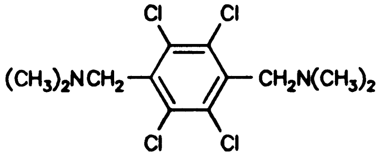


107

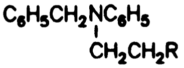


R = H 108

R = CH_3 109

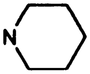


110



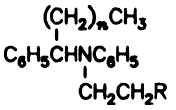
$$\begin{array}{l} C_6H_5CH_2\underset{|}{N}C_6H_5 \\ \qquad\quad CH_2CH_2R \end{array}$$

$R = N(CH_3)_2$ 111

R =  112

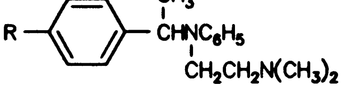
$R = OCH_3$ 113

$R = \overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 114

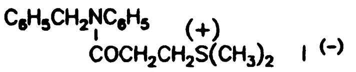


$$\begin{array}{l} \qquad (CH_2)_nCH_3 \\ \qquad\ | \\ C_6H_5CHNC_6H_5 \\ \qquad\quad | \\ \qquad\quad CH_2CH_2R \end{array}$$

$n = 0\text{–}3$ 115

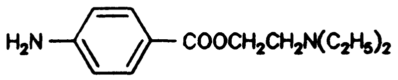


116

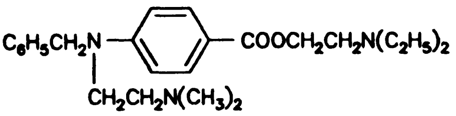


$$\begin{matrix} C_6H_5CH_2NC_6H_5 \\ COCH_2CH_2\overset{(+)}{S}(CH_3)_2\ \ I^{(-)} \end{matrix}$$

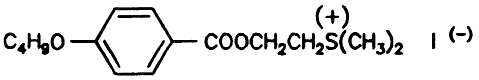
117



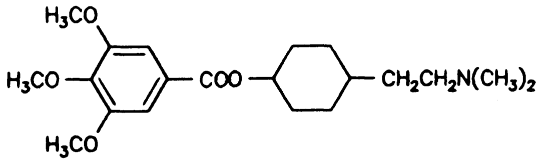
118



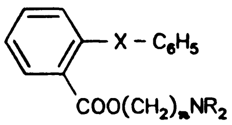
119



120



121

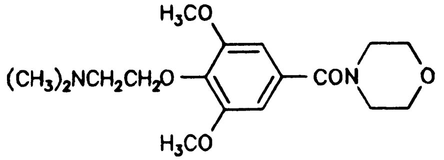


X = O, S, CH$_2$S

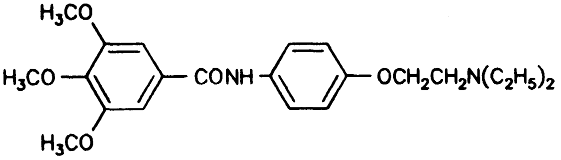
n = 2, 3

R = CH$_3$, C$_2$H$_5$

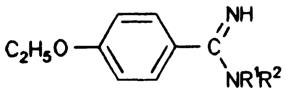
122



123

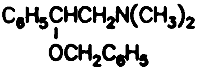


124



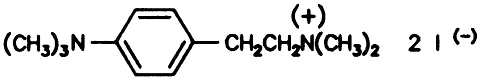
R^1, R^2 = H, CH$_3$

125

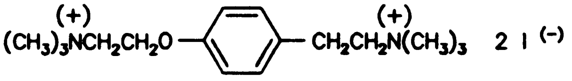


$C_6H_5\underset{OCH_2C_6H_5}{\underset{|}{C}}HCH_2N(CH_3)_2$

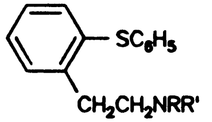
126



127

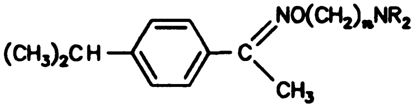


128



R, R' = H, CH_3

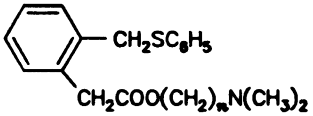
129



n = 2, R = H **130**

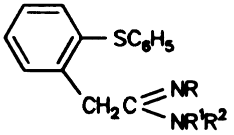
n = 3, R = CH_3 **131**

$C_6H_5CH_2COOCH_2CH_2SCH_3$ **132**



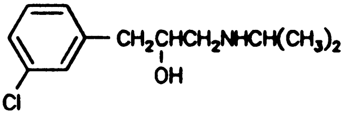
n = 2, 3

133

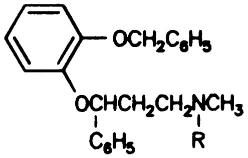


R = OH,
R^1 = R^2 = H **134**

R = H **135**

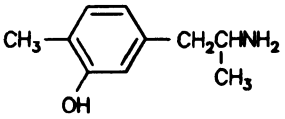


136

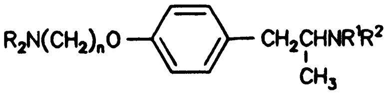


R = CH_3 **137**

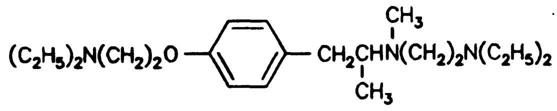
R = H **138**



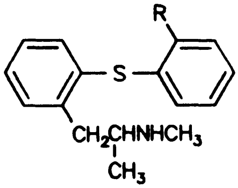
139



140

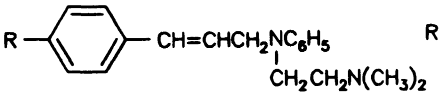


141

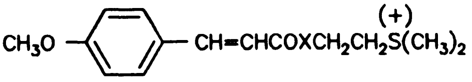


R = H 142

R = OCH_3 143

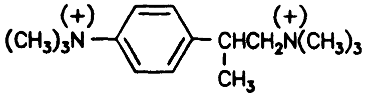


R = H, OCH_3 144

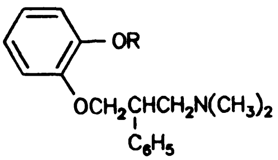


$I^{(-)}$ X = O 145

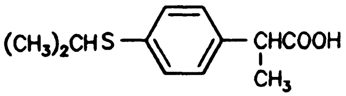
X = S 146



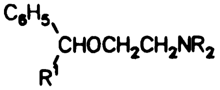
$2\ I^{(-)}$ 147



148

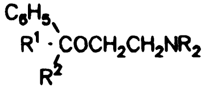


149



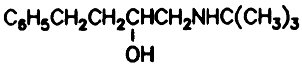
$C_6H_5(R^1)CHOCH_2CH_2NR_2$

150



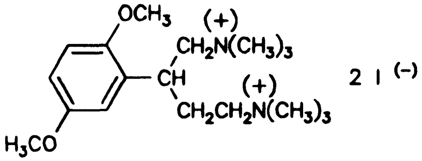
$C_6H_5(R^1)(R^2)COCH_2CH_2NR_2$

151

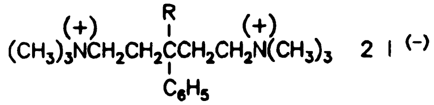


$C_6H_5CH_2CH_2CH(OH)CH_2NHC(CH_3)_3$

152



153

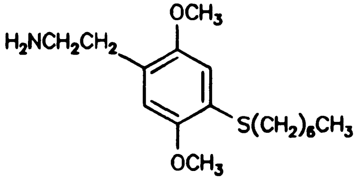


$\overset{(+)}{(CH_3)_3N}CH_2CH_2C(R)(C_6H_5)CH_2CH_2\overset{(+)}{N}(CH_3)_3 \quad 2\ I^{(-)}$

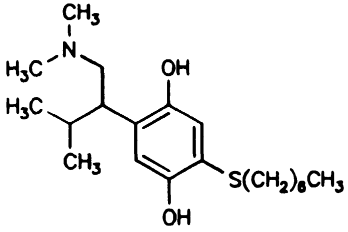
R = CN 154

$R = CONH_2$ 155

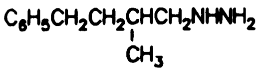
$R = CH_2\overset{(+)}{N}(CH_3)_3 \quad I^{(-)}$ 156



157

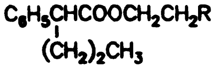


158

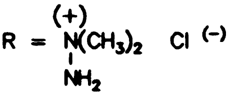


$C_6H_5CH_2CH_2CH(CH_3)CH_2NHNH_2$

159

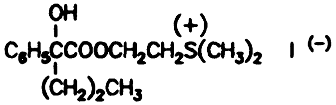


$C_6H_5\underset{(CH_2)_2CH_3}{CH}COOCH_2CH_2R$

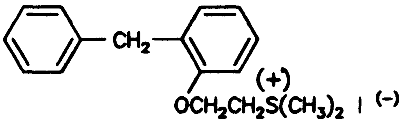


$R = \underset{NH_2}{\overset{(+)}{N}}(CH_3)_2 \quad Cl^{(-)}$ 160

$R = \overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ 161



$C_6H_5\underset{(CH_2)_2CH_3}{\overset{OH}{C}}COOCH_2CH_2\overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ 162

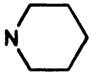


163

$(C_6H_5)_2CHOCH_2CH_2R$

$R = N(CH_3)_2$ 164

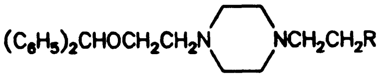
$R = N(C_2H_5)_2$ 165



R = 166

$R = NHCH_3$ 167

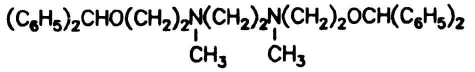
$(C_6H_5)_2CHOCH(CH_2N(C_2H_5)_2)_2$ 168



R = OH 169

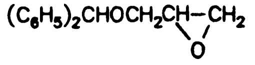
R = $OCH(C_6H_5)_2$ 170

R = Cl 171

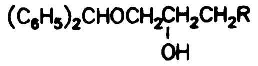


$(C_6H_5)_2CHO(CH_2)_2\underset{CH_3}{N}(CH_2)_2\underset{CH_3}{N}(CH_2)_2OCH(C_6H_5)_2$

172

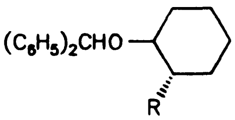


173

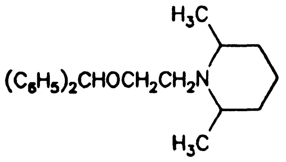


$(C_6H_5)_2CHOCH_2\underset{OH}{C}H_2CH_2R$

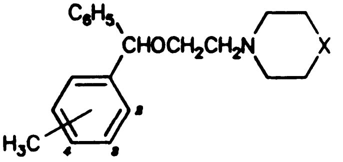
174



175

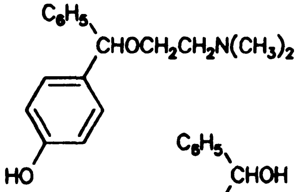


176

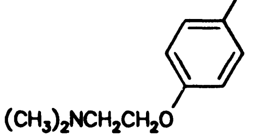


X = CH_2 177

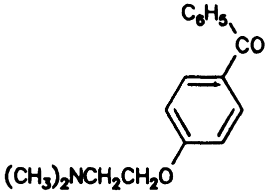
X = O 178



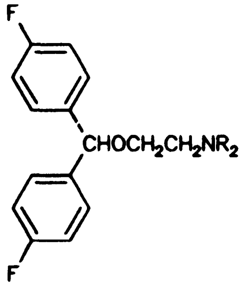
179



180

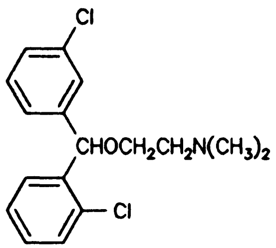


181



R = H 182

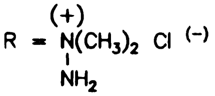
R = CH_3 183



184

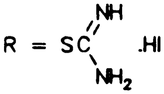
$(C_6H_5)_2CHOCH_2CH_2R$

$R = \overset{(+)}{N}(C_2H_5)_3\ I^{(-)}$ 185



$R = \underset{NH_2}{\overset{(+)}{N}}(CH_3)_2\ Cl^{(-)}$ 186

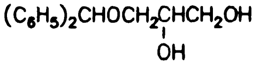
$R = \overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 187



R = SC(=NH)NH$_2$ .HI 188

$R = \overset{(+)}{P}(C_2H_5)_3\ I^{(-)}$ 189

$R = \overset{(+)}{As}(CH_3)_3\ Cl^{(-)}$ 190



$(C_6H_5)_2CHOCH_2\underset{OH}{C}HCH_2OH$ 191

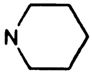
$(C_6H_5)_2CHOCH_2CH_2COOH$ 192

$(C_6H_5)_2CHOCOCH_2CH_2R$

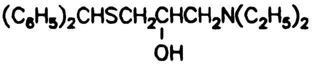
$R = N(C_2H_5)_2$ 193

$R = \overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 194

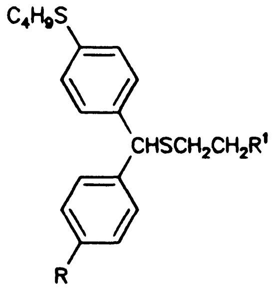
$(C_6H_5)_2CHSCH_2CH_2R$

R =  195

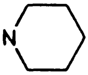
$R = \overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 196



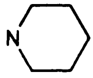
$(C_6H_5)_2CHSCH_2\underset{OH}{C}HCH_2N(C_2H_5)_2$ 197

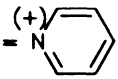


$R = H,\ R^1 = N(CH_3)_2$ 198

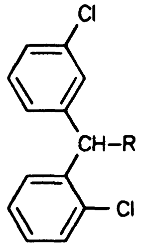
$R = CH_3,\ R^1 =$  199

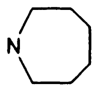
$(C_6H_5)_2CHR$ R = $N(CH_3)_2$ 200

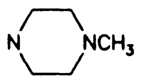
R =  201

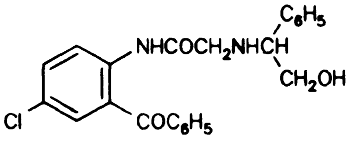
R =  Br (-) 202

$(C_6H_5)_2CHNHCOCH_2CH_2NHCH(C_6H_5)_2$ 203

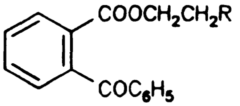


R =  204

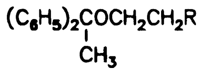
R =  205



206

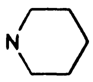


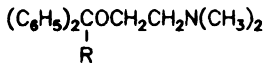
207



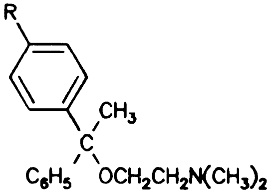
$(C_6H_5)_2\underset{CH_3}{C}OCH_2CH_2R$

R = $N(CH_3)_2$ 208

R =  209



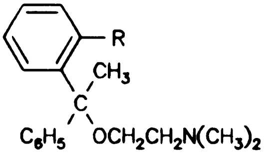
$(C_6H_5)_2\underset{R}{C}OCH_2CH_2N(CH_3)_2$ 210



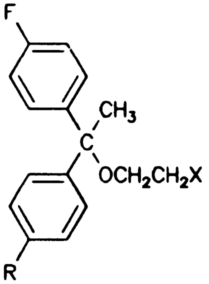
R = F **211**

R = Cl **212**

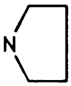
R = Br **213**



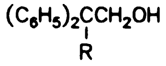
214



R = F, Br;

X = $N(CH_3)_2$, 

215



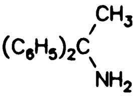
$(C_6H_5)_2\underset{R}{C}CH_2OH$

R = H **216**

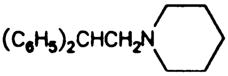
R = OH **217**

$(C_6H_5)_2CHCH_2OCH_2CH_2N(CH_3)_2$

218

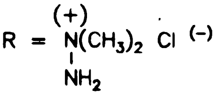


219

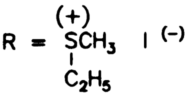


220

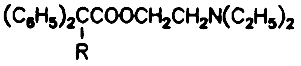
$(C_6H_5)_2CHCOOCH_2CH_2R$



$R = \overset{(+)}{\underset{NH_2}{N}}(CH_3)_2\ Cl^{(-)}$ **221**



$R = \overset{(+)}{\underset{C_2H_5}{S}}CH_3\ I^{(-)}$ **222**

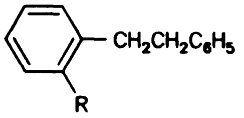


$(C_6H_5)_2\underset{R}{C}COOCH_2CH_2N(C_2H_5)_2$

R = $OCH_2CH_2N(C_2H_5)_2$ 223

R = OH 224

R = Cl 225

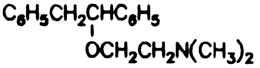


R = $COO(CH_2)_2N(CH_3)_2$ 226

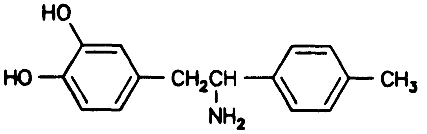
R = $CO(CH_2)_3N(CH_3)_2$ 227

R = $CH{=}CH(CH_2)_2N(CH_3)_2$ 228

R = $\underset{CH_2C_6H_5}{N}(CH_2)_3N(CH_3)_2$ 229



$C_6H_5CH_2\underset{OCH_2CH_2N(CH_3)_2}{C}HC_6H_5$ 230



231

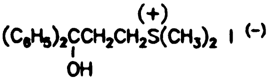
$(C_6H_5)_2CHCH_2CH_2R$

R = OH 232

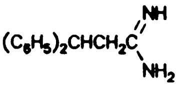
R = $OCH_2CH_2N(CH_3)_2$ 233

R = $\overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 234

R = $NHNH_2$ 235



$(C_6H_5)_2\underset{OH}{C}CH_2CH_2\overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 236

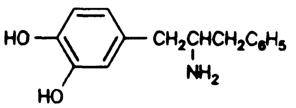


$(C_6H_5)_2CHCH_2C(=NH)NH_2$ 237

$(C_6H_5CH_2)_2CHR$

R = $OCH_2CH_2N(CH_3)_2$ 238

R = NH_2 239



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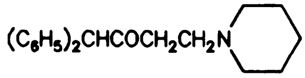

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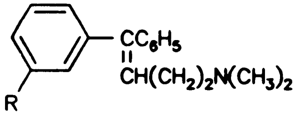

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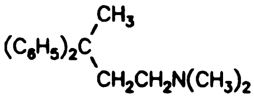
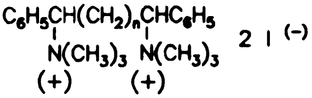
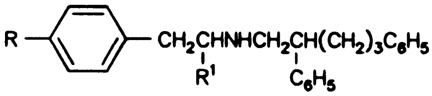


243

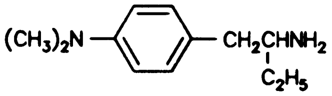


$$\underset{\underset{(+)}{N(CH_3)_3}}{C_6H_5CH}(CH_2)_n\underset{\underset{(+)}{N(CH_3)_3}}{CH}C_6H_5 \quad 2\ I^{(-)}$$

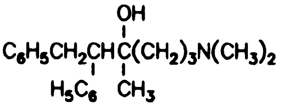
244



245

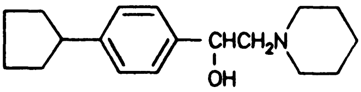


246

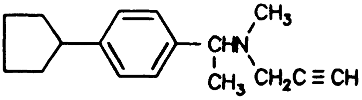


$$C_6H_5CH_2\underset{H_5C_6}{CH}\overset{OH}{\underset{CH_3}{C}}(CH_2)_3N(CH_3)_2$$

247



248



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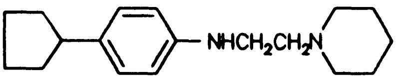

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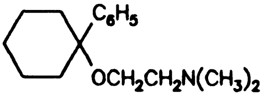

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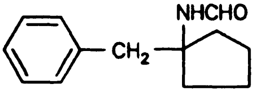

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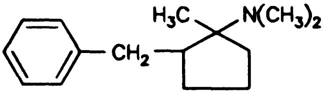
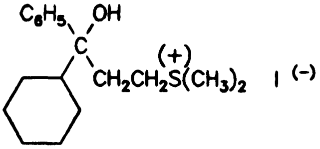


253



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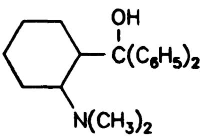
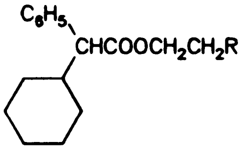


255



$R = N(C_2H_5)_2$ **256**

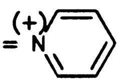
$R = \overset{(+)}{N}(CH_3)_3 \quad I^{(-)}$ **257**

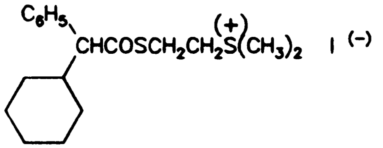
$R = \overset{(+)}{N}(C_2H_5)_3 \quad I^{(-)}$ **258**

$R = \overset{(+)}{\underset{NH_2}{N}}(CH_3)_2 \quad Cl^{(-)}$ **259**

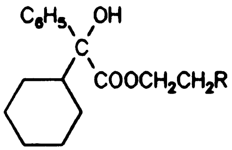
$R = \overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ **260**

$R = \overset{(+)}{P}(C_2H_5)_3 \quad I^{(-)}$ **261**

R =  Br $^{(-)}$ **262**



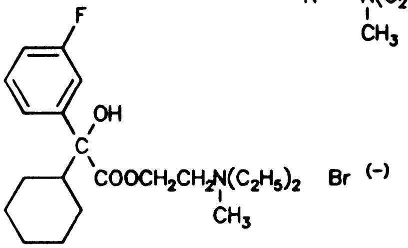
263



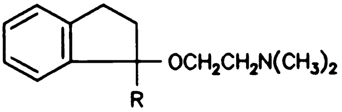
$R = \overset{(+)}{S}(CH_3)_2 \quad I^{(-)}$ **264**

$R = \overset{(+)}{\underset{NH_2}{N}}(CH_3)_2 \quad Br^{(-)}$ **265**

$R = \overset{(+)}{\underset{CH_3}{N}}(C_2H_5)_2 \quad Br^{(-)}$ **266**

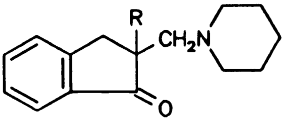


267



R=H **268**

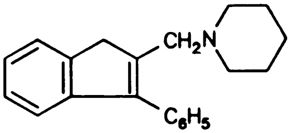
R=C_6H_5 **269**



R=H **270**

R=OC_2H_5 **271**

R=$O(CH_2)_3CH_3$ **272**



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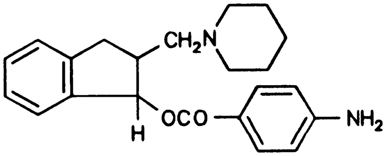

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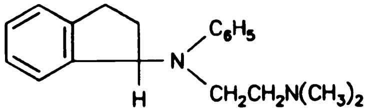

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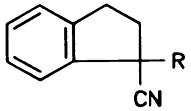
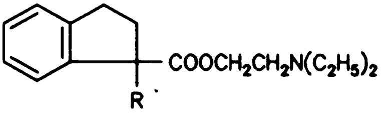


R = H **276**

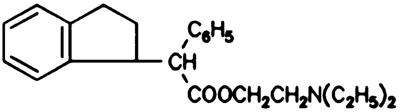
R = $CH_2CH_2N(C_2H_5)_2$ **277**

R = $CH_2C_6H_5$ **278**

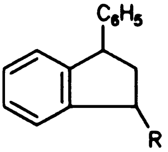


$R = H$ **279**

$R = CH_2C_6H_5$ **280**

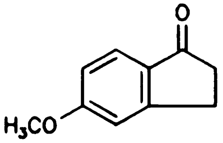


281



$R = OCH_2CH_2NCH_3)_2$ **282**

$R = NH_2$ **283**



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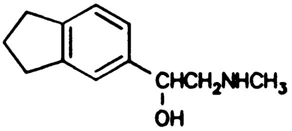

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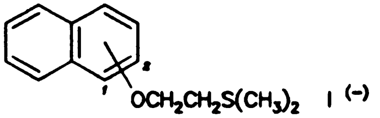

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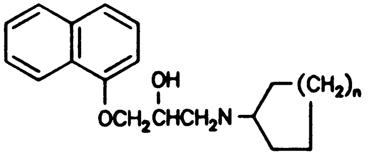
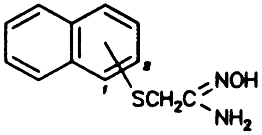


$n = 1, 2, 3$ **287**



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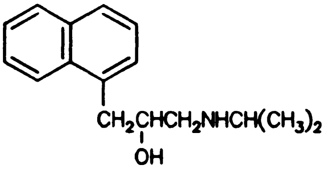

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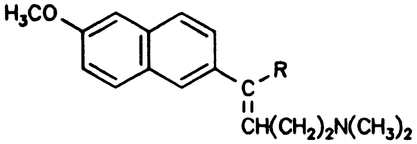

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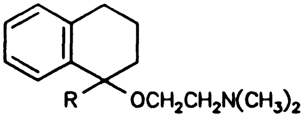
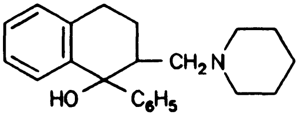


R = H **291**

R = C_6H_5 **292**



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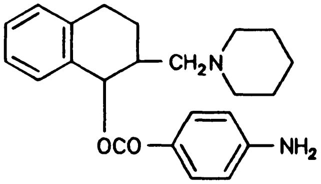

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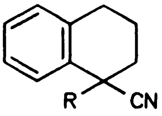

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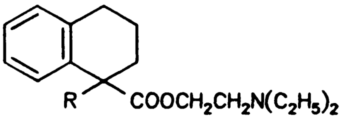

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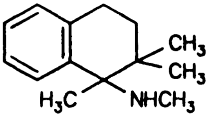

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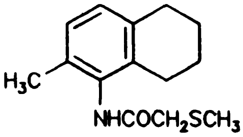

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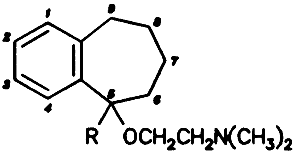
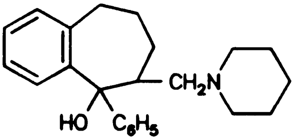


R = H 299

R = C_6H_5 300



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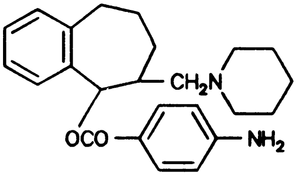

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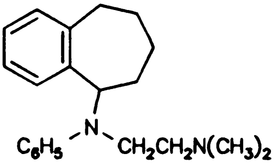

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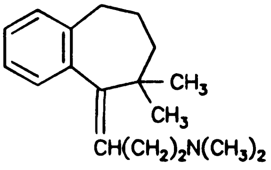

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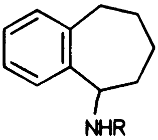
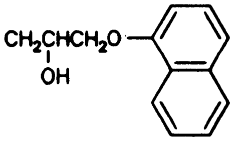


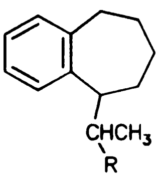
R = C_2H_5 305

R = $CH_2CH_2CH(C_6H_5)_2$ 306

R =

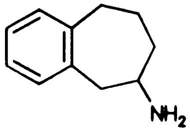


307

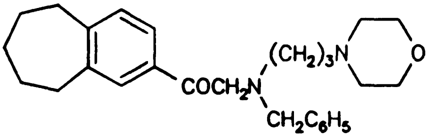


R = COOH 308

R = $N(CH_3)_2$ 309



310



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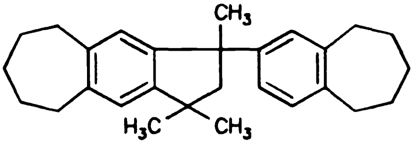

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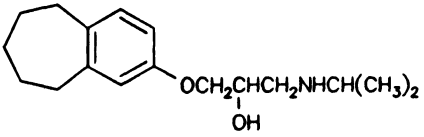

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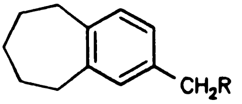
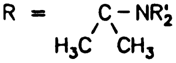
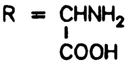
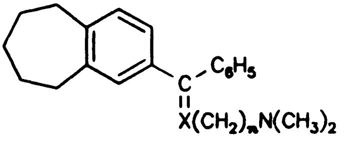




$R = C(CH_3)_2-NR'_2$ 314



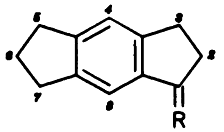
$R = CH(NH_2)COOH$ 315



X = NO, *n* = 2 316

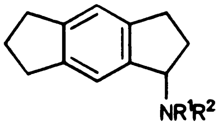
X = N, *n* = 3 317

X = CH, *n* = 2 318

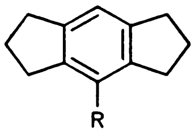


R = O **319**

R = $NO(CH_2)_2N(CH_3)_2$ **320**

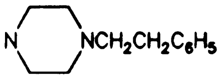


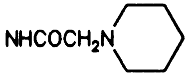
321

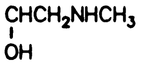


R = $COCH_3$ **322**

R = NH_2 **323**

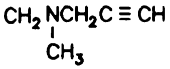
R =  **324**

R =  **325**

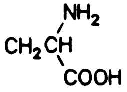
R =  **326**

$CH(OH)CH_2NHCH_3$

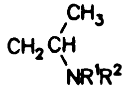
R = CH_2Cl **327**

R =  **328**

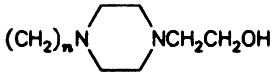
$CH_2N(CH_3)CH_2C\equiv CH$

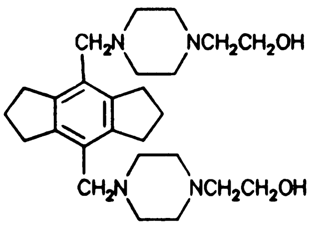
R =  **329**

$CH_2CH(NH_2)COOH$

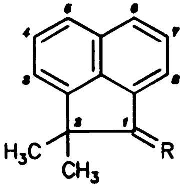
R =  **330**

$CH_2CH(CH_3)NR^1R^2$

R =  **331**



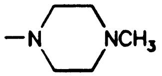
332

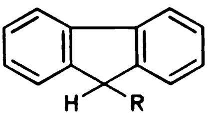


R = =O 333

R = $=CH(CH_2)N(CH_3)_2$ 334

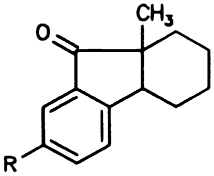
R = $-O(CH_2)N(CH_3)_2$ 335

R =  336



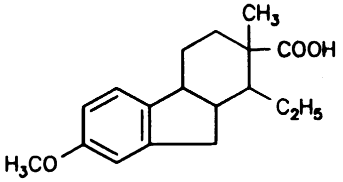
R = $OCH_2CH_2N(CH_3)_2$ 337

R = $COOCH_2CH_2\overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 338

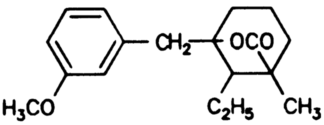


R = H 339

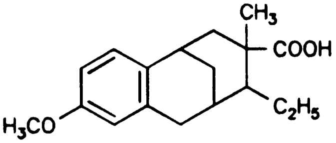
R = OH 340



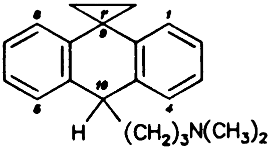
341



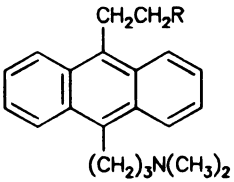
342



343



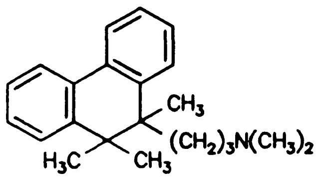
344



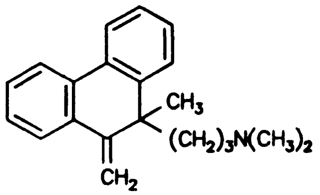
R = Cl 345

R = $OCOCH_3$ 346

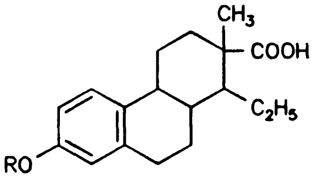
R = OC_2H_5 347



348

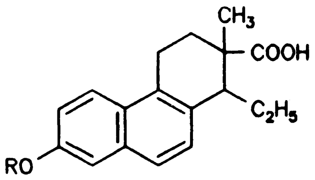


349



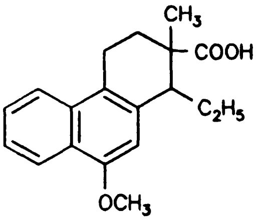
R = H **350**

R = CH_3 **351**

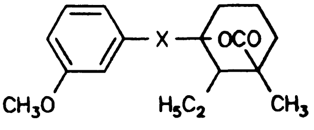


R = H **352**

R = CH_3 **353**

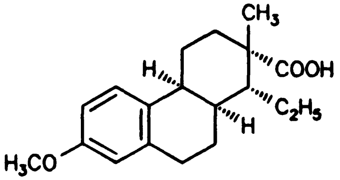


354

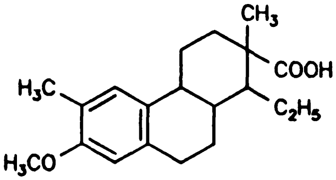


X = —C≡C— **355**

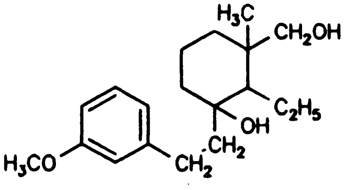
X = $-CH_2CH_2-$ **356**



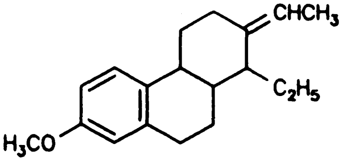
357



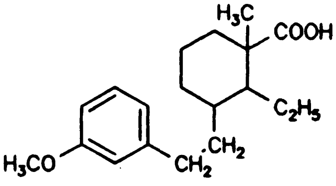
358



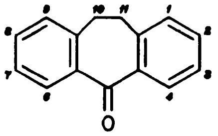
359



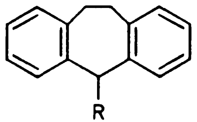
360



361



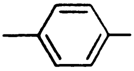
362

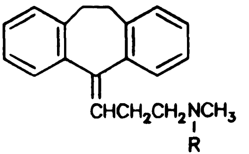


R = OH 363

R = $OCH_2CH_2\overset{(+)}{N}(CH_3)_3\ I^{(-)}$ 364

R = Cl 365

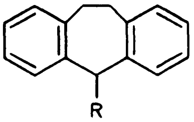
R =  $N(CH_3)_2$ 366



R = CH_3 367

R = $COOC_2H_5$ 368

R = H 369

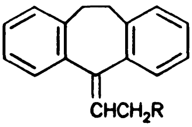


R = $(CH_2)_3N(CH_3)_2$ 370

R = H 371

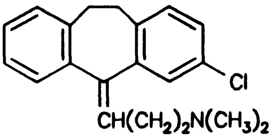
R = $(CH_2)_2N(CH_3)_2$ 372

R = COOH 373

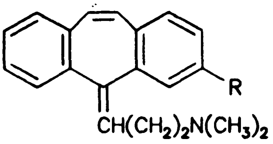


R = COOH 374

R = Br 375

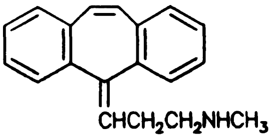


376

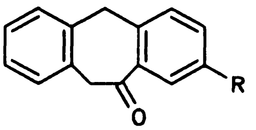


R = H 377

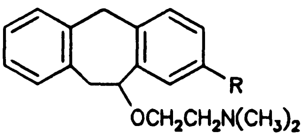
R = Cl 378



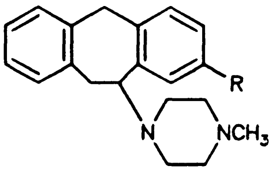
379



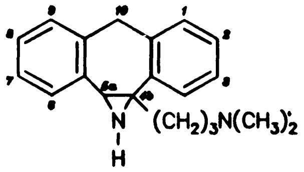
R = H 380
R = Cl 381



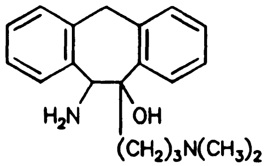
R = H 382
R = Cl 383



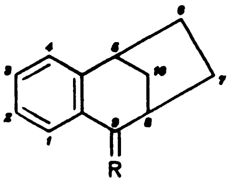
R = H 384
R = Cl 385



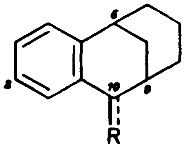
386



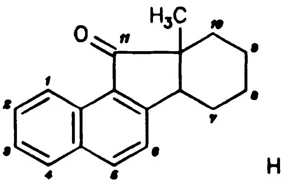
387



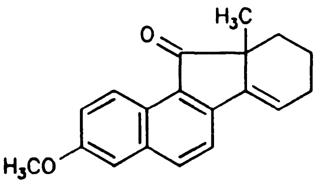
R = O 388
R = $CHCH_2CH_2N(CH_3)_2$ 389



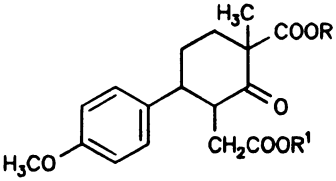
R = O 390
R = $OCH_2CH_2N(CH_3)_2$ 391
R = $CHCH_2CH_2N(CH_3)_2$ 392



393



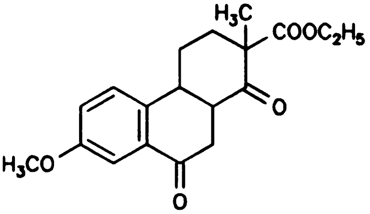
394



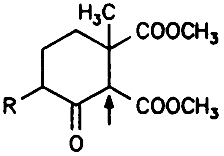
$R = R^1 = C_2H_5$ **395**

$R = R^1 = CH_3$ **396**

$R = C_2H_5, R^1 = H$ **397**

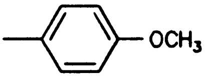


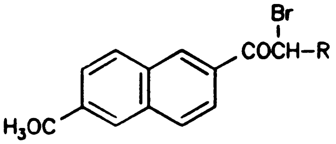
398



$R = CH_3$ **399**

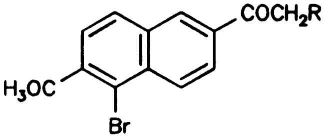
$R = C_6H_5$ **400**

R =  **401**



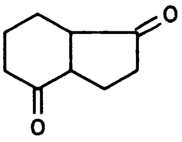
$R = H$ **402**

$R = CH_2COOCH_3$ **403**

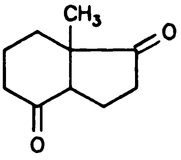


$R = H$ **404**

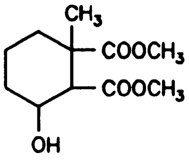
$R = CH_2COOCH_3$ **405**



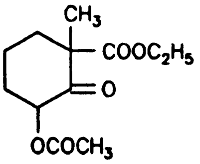
406



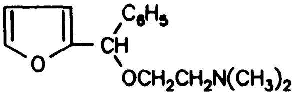
407



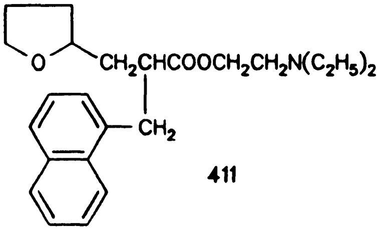
408



409



410



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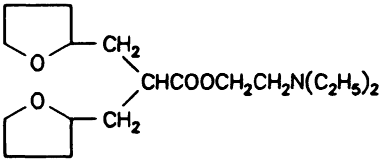
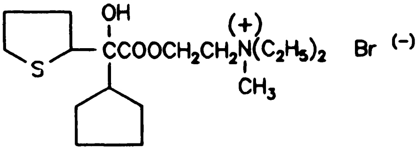
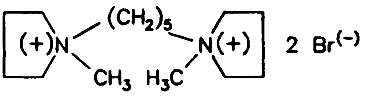


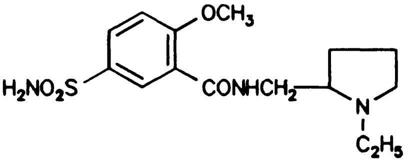
412



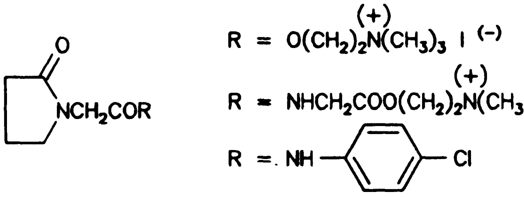
413



414



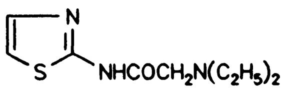
415



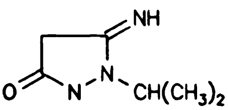
$R = O(CH_2)_2\overset{(+)}{N}(CH_3)_3\ I^{(-)}$ **416**

$R = NHCH_2COO(CH_2)_2\overset{(+)}{N}(CH_3)_3\ I^{(-)}$ **417**

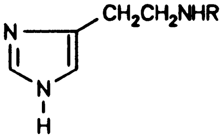
R = NH–C6H4–Cl **418**



419

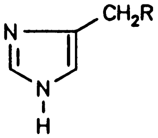


420

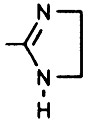


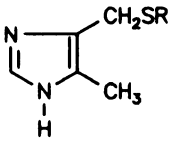
R = H **421**

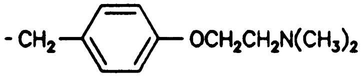
R = $CH_2C_6H_5$ **422**



R = SCH_3 **423**

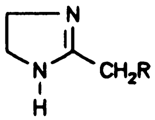
R =  **424**



R =  **425**

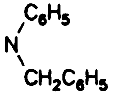
$-CH_2-C_6H_4-OCH_2CH_2N(CH_3)_2$

R = $(CH_2)_3C_6H_5$ **426**

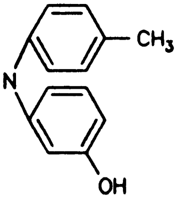


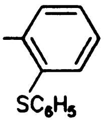
R = CH_2NH_2 **427**

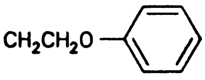
R = $OCH(C_6H_5)_2$ **428**

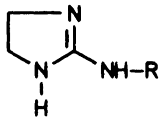
R =  **429**

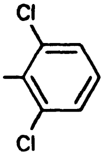
$N(C_6H_5)CH_2C_6H_5$

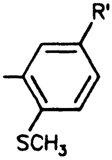
R =  **430**

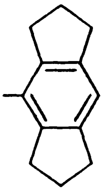
R =  **431**

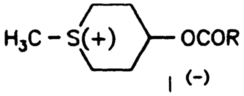
R =  **432**



R =  433

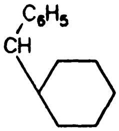
R =  R' = H, Cl 434

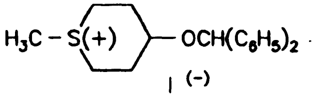
R =  435



R = CH_3 436

R = $CH(C_6H_5)_2$ 437

R =  438



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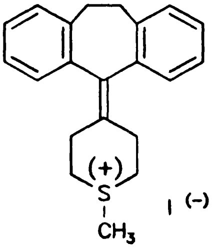

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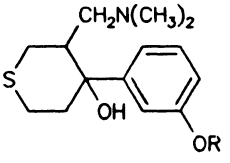
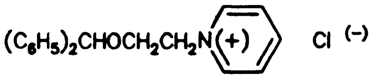


R = CH_3 441

R = H 442



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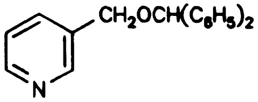

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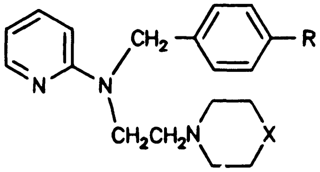
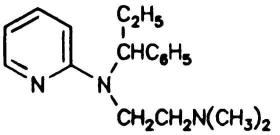
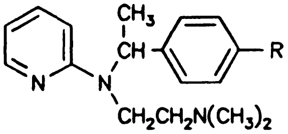


$R = H$ **445**

$R = OCH_3$ **446**



447



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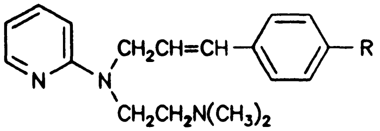

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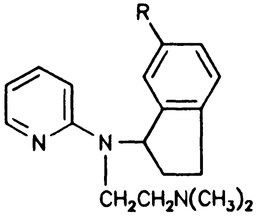

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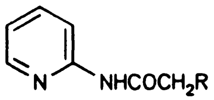
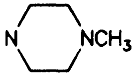


R = $N(C_2H_5)_2$ 451

R = 

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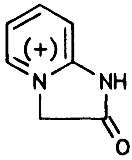

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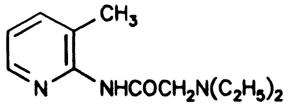
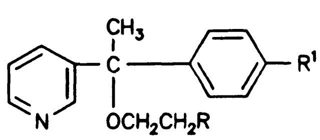
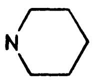
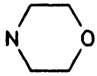


454

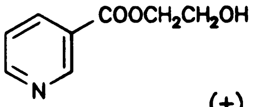


R = 

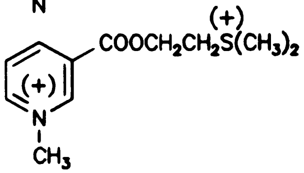
, R^1 = H 455

R = 

, R^1 = CH_3 456

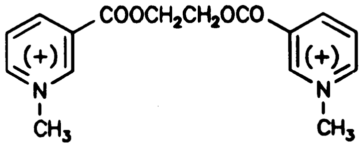


457



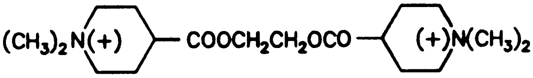
2 I$^{(-)}$

458



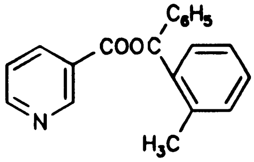
2 I$^{(-)}$

459

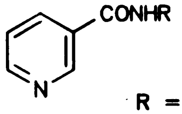


2 I$^{(-)}$

460



461



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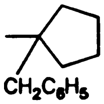

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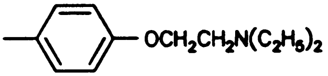
R =



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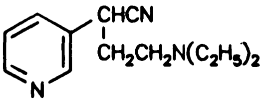

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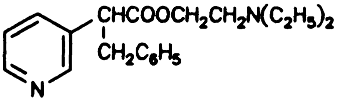

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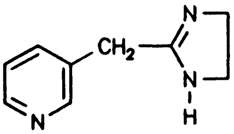

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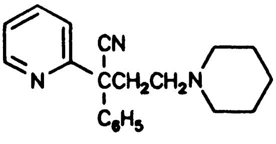

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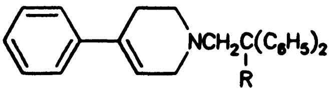
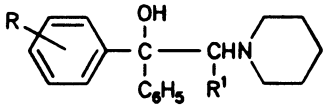


R = H 468

R = OH 469



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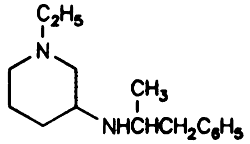

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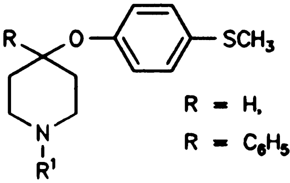
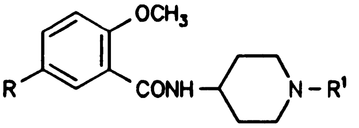


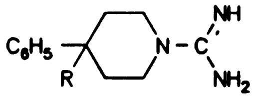
$R = H$, $R^1 = CH_2C_6H_5$ **472**

$R = C_6H_5$, $R^1 = CH_3$ **473**

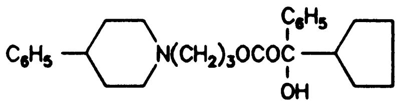


$R = SO_2NH_2$, $R^1 = CH_3$ **474**

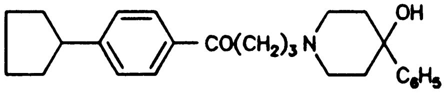
$R = NHCH_3$, $R^1 = CH_2C_6H_5$ **475**



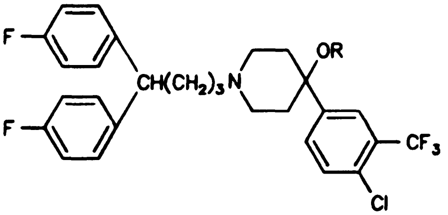
$R = OH, CONH_2, CH_2OH$ **476**



477

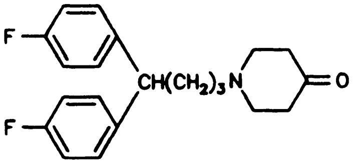


478

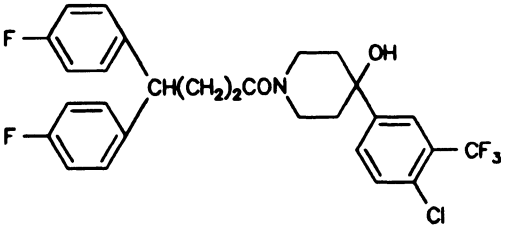


R = H 479

R = $CO(CH_2)_8CH_3$ 480



481



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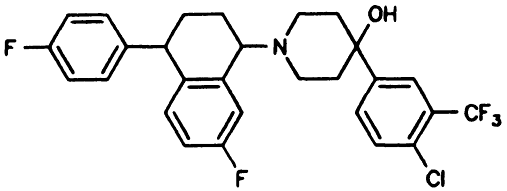

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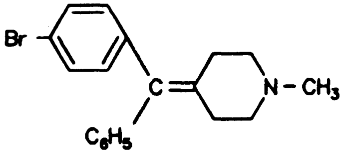
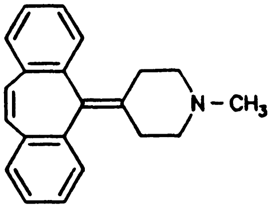


484



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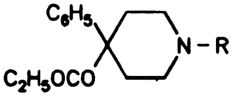
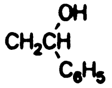
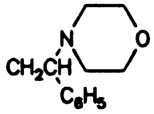


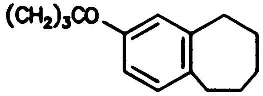
R = CH_3 **486**

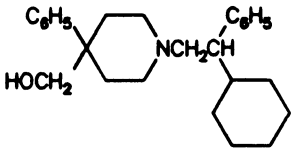
R = H **487**

R =  **488**

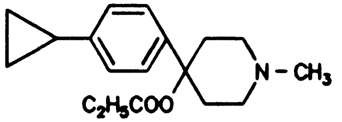
$CH_2CH(OH)C_6H_5$

R =  **489**

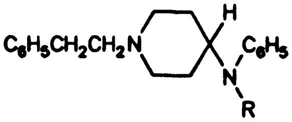
R =  **490**



491



492

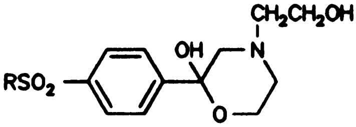


R = COC_2H_5 **493**

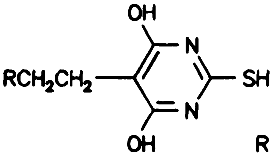
R = CSC_2H_5 **494**

R = $COCH_2OCH_3$ **495**

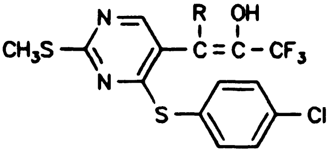
R = $COCH_2SCH_3$ **496**



497

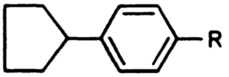


R = COOH or $N(C_2H_5)_2$ 498

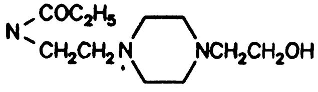


R = COOH 499

R = H 500

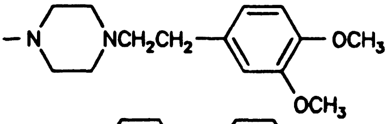


R =



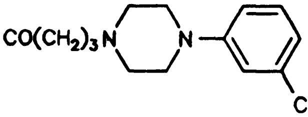
501

R =

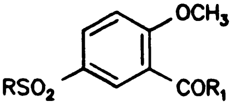


502

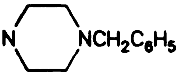
R =



503



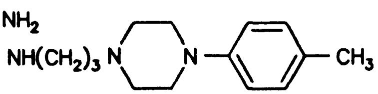
R = R_1 =



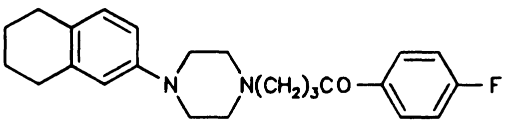
504

R = NH_2

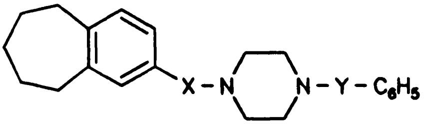
R_1 =



505



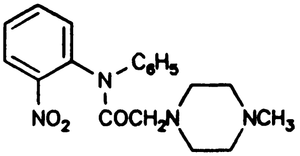
506



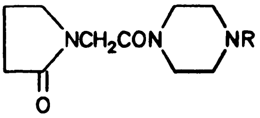
$X = -$, $Y = (CH_2)_3$ **507**

$X = -\underset{\text{OH}}{\text{CH}}\text{CH}_2-$, $Y = CH_2$ **508**

$X = CH_2$, $Y = -$ **509**

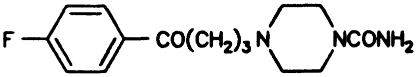


510

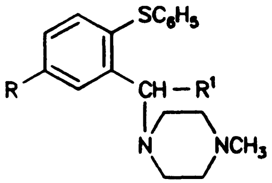


$R = CH_3$ **511**

$R = CH_2CH_2OCH_3$ **512**

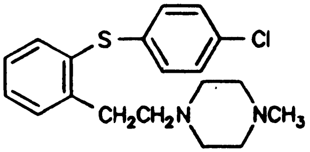


513

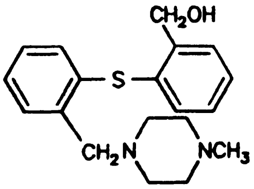


$R = R^1 = H$ **514**

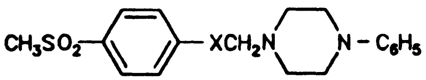
$R = Cl$, $R^1 = CH_3$ **515**



516

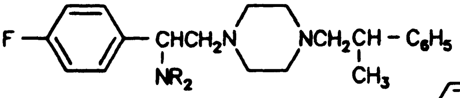


517

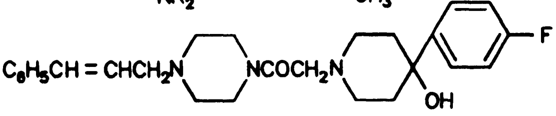


X = CO 518

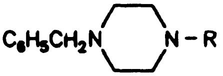
X = CHOH 519

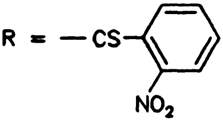


520



521





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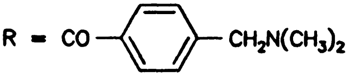
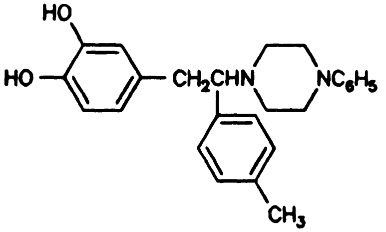
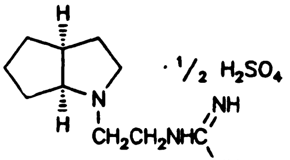


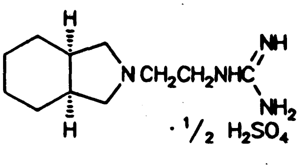
523



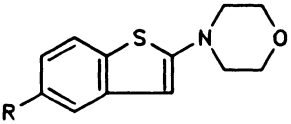
524



525



526



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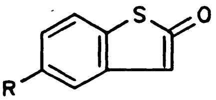

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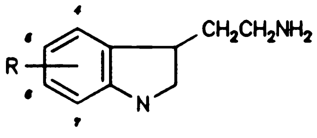

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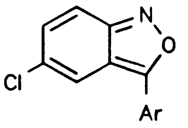
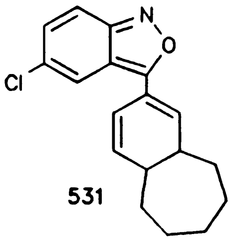


530



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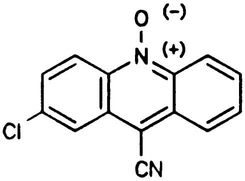
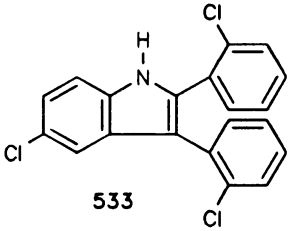
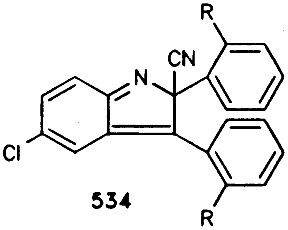


532



533



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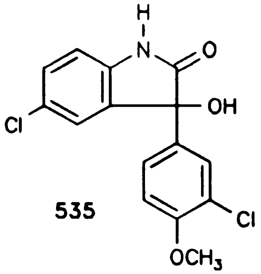
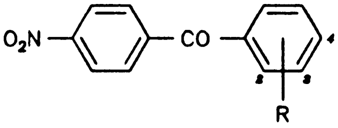


535



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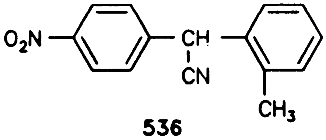
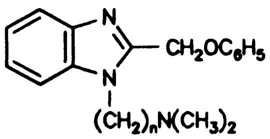
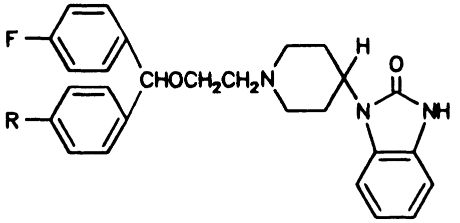


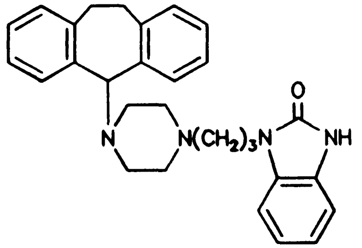
536



537a



538



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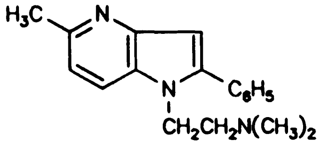

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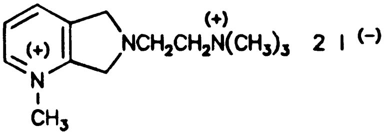

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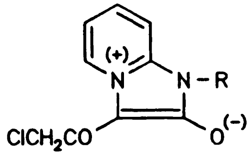

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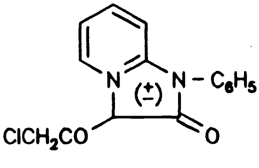

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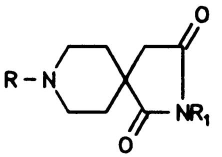
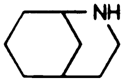
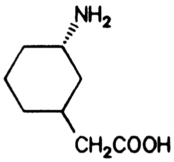


R = CH_3, R^1 = C_2H_5 **544**

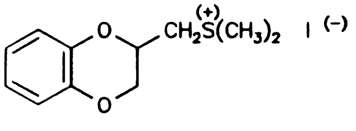
R = CH_2CH_2Cl, R^1 = $CH(CH_3)_2$ **545**



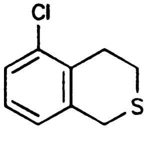
546



547



548



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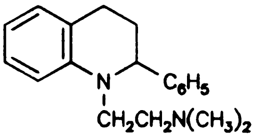

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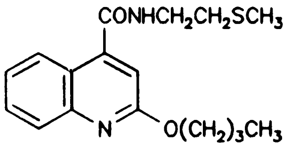

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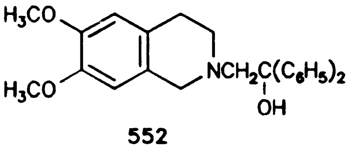

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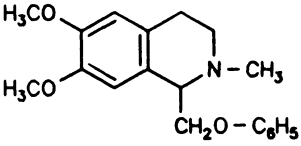

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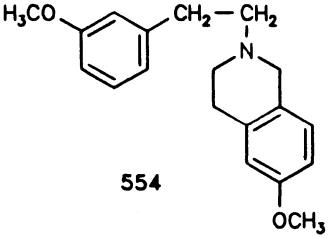

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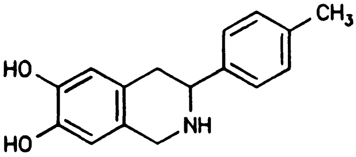

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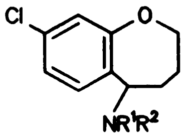
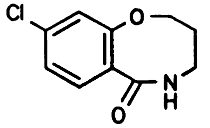
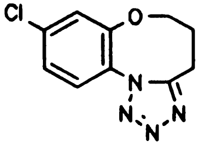


R^1 = H, R^2 = $\overset{NH}{\underset{NH_2}{C}}$ **556**

R^1 = CH_3, R^2 = $CH_2C\equiv CH$ **557**



558



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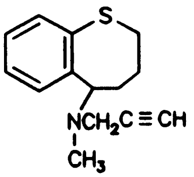

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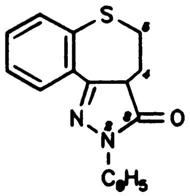
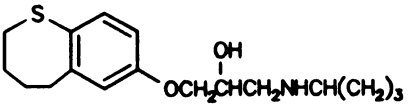


561



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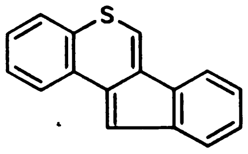

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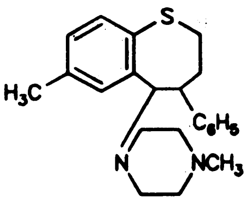
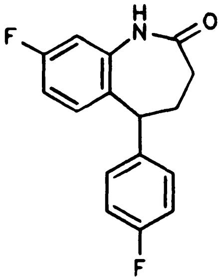


564



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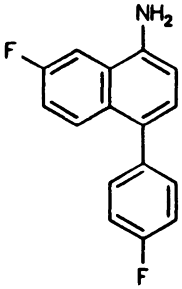

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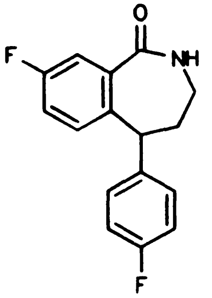
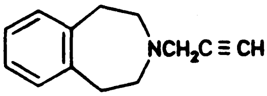


567



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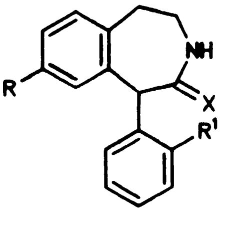
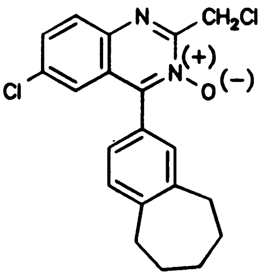
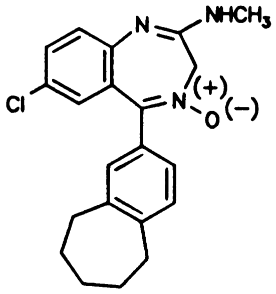


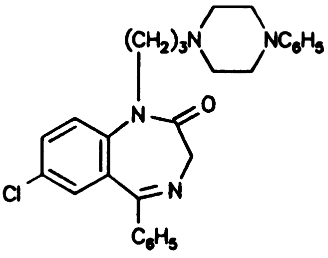
569



570



571



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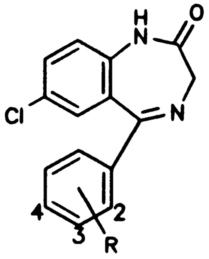

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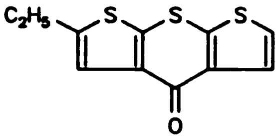

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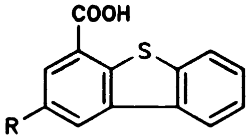
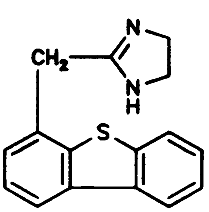


R = H 575

R = Cl 576



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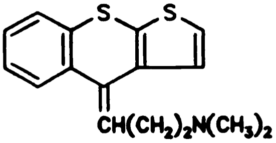
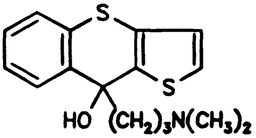


578



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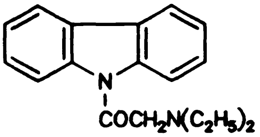

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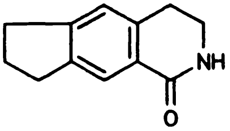

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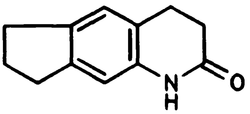

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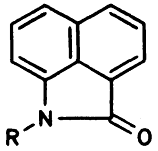
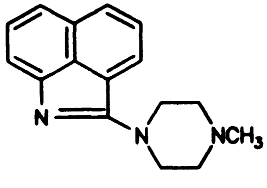


R = H 583

R = $(CH_2)_3N(CH_3)_2$ 584



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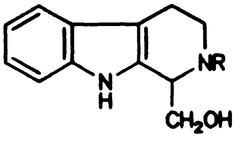
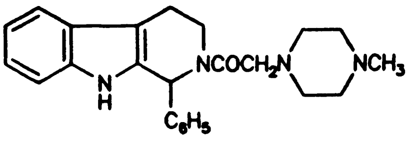


R = H 586

R = C_2H_5 587



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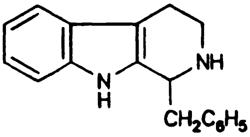

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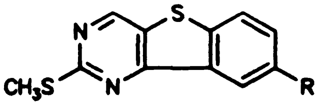

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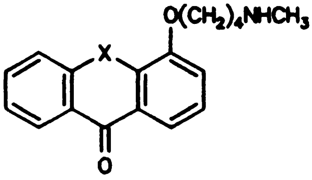
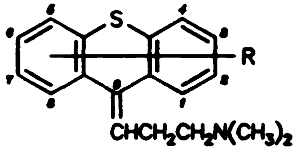
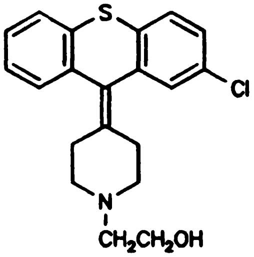


X = O **591**

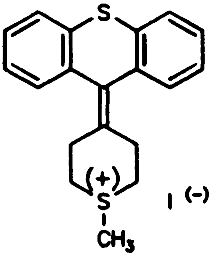
X = S **592**



593



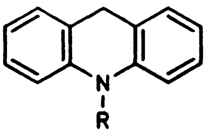
594



595

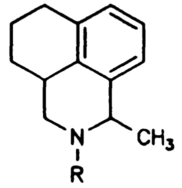
R = H **596**

R = Cl **597**



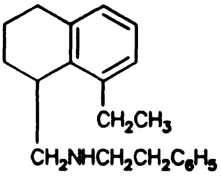
R = $CH_2CH_2N(CH_3)_2$ **598**

R = $COCH_2N(C_2H_5)_2$ **599**

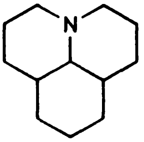


$R = H$ **600**

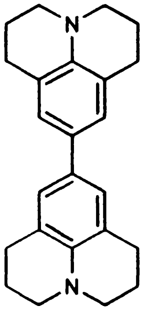
$R = CH_2C\equiv CH$ **601**



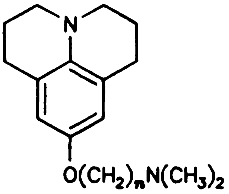
602



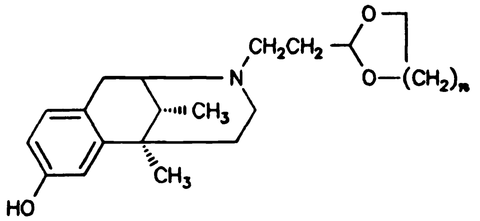
603



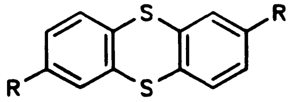
604



605 $n = 2, 3$

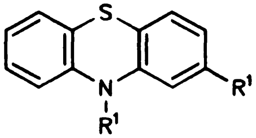


606 $n = 1, 2$



R = H 607

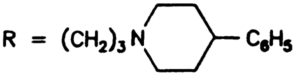
R = Cl 608



$R = COCH_2CH_2\overset{(+)}{S}(CH_3)_2\ I^{(-)}$

$R^1 = H$

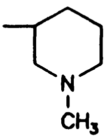
609



$R^1 = H, Cl$

610

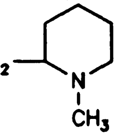
$R = CH_2$–



$R^1 = H$

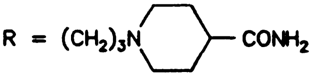
611

$R = CH_2CH_2$–



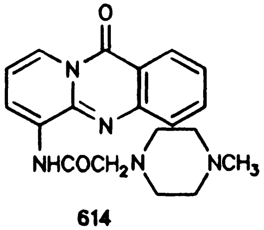
$R^1 = SCH_3$

612

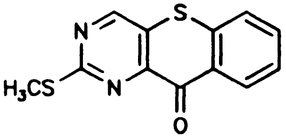


$R^1 = SO_2CH_3$

613



614



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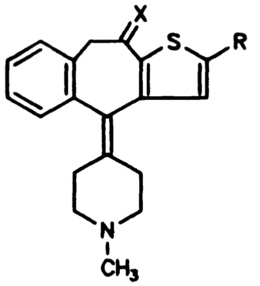
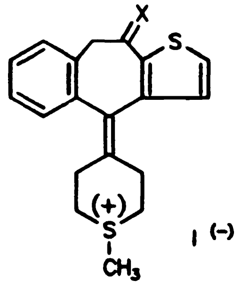


X = H_2, R = H **616**

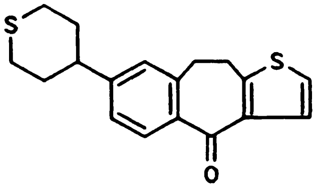
X = O, R = H **617**

X = O, R = Br **618**

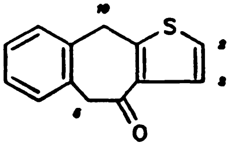


X = H_2 **619**

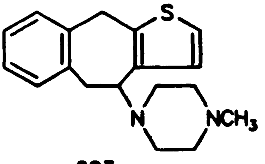
X = O **620**



621



622



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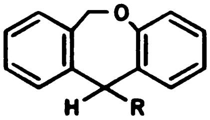
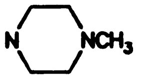
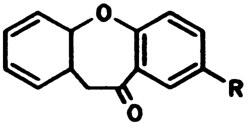
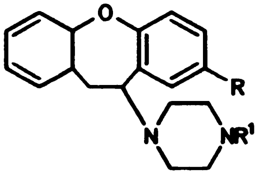


R = $OCH_2CH_2N(CH_3)_2$ **624**

R =  **625**



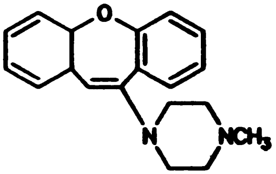
626



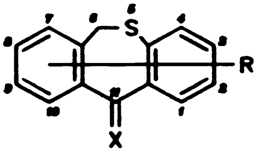
R^1 = CH_3 **627**

R1 = $(CH_2)_3OH$ **628**

R^1 = $(CH_2)_2OCO(CH_2)_nCH_3$ **629**

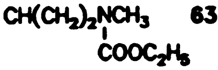


630



X = O **631**

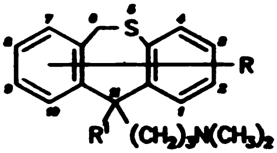
X = $CH(CH_2)_2N(CH_3)_2$ **632**

X =  **633**

$$X = CH(CH_2)_2\underset{\displaystyle COOC_2H_5}{\underset{|}{N}}CH_3$$

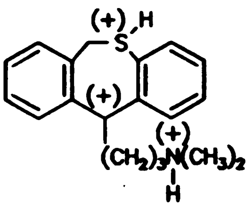
X = $CH(CH_2)_2NHCH_3$ **634**

X = $CH(CH_2)_2NH_2$ **635**

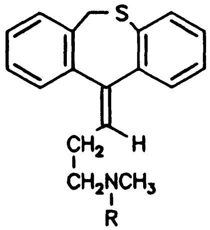


R^1 = OH **636**

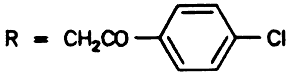
R^1 = H **637**



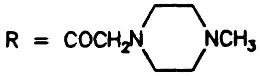
638



R = $(CH_2)_3OCO(CH_2)_8CH_3$ 639



640



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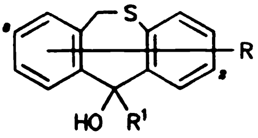
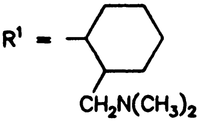
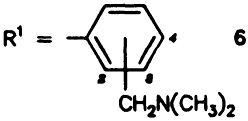




642



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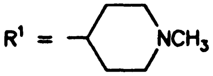
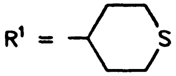


644



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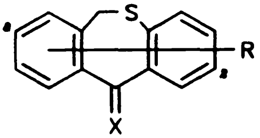

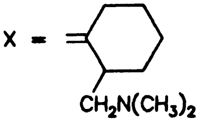

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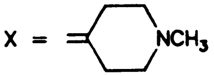

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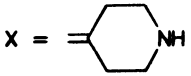

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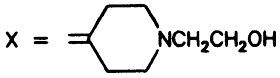

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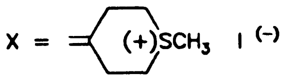

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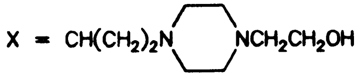
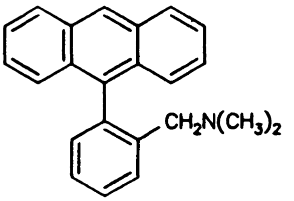


651



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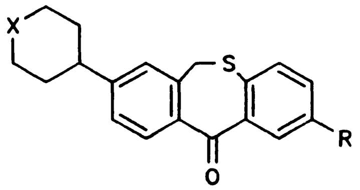
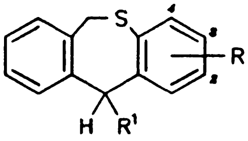


X = NCH_3 653

X = S 654

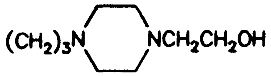


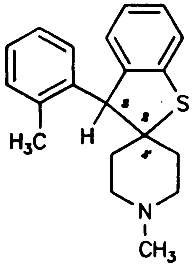
R^1 = OH 655

R^1 = Cl 656

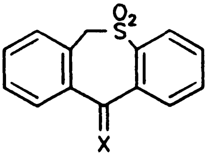
R^1 = H 657

R^1 = $(CH_2)_3NHCH_3$ 658

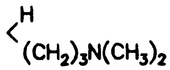

R^1 = $(CH_2)_3N\langle C_4H_8 \rangle NCH_2CH_2OH$ 659



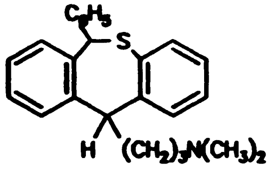
660



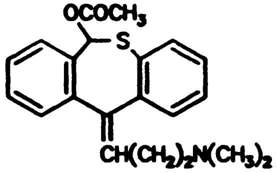
X = H_2 661


X = $<^{H}_{(CH_2)_3N(CH_3)_2}$ 662

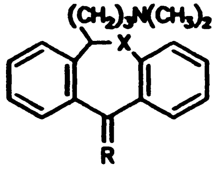
X = =O 663



664



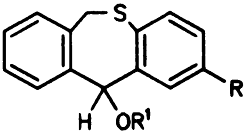
665



R = $=O$ **666**

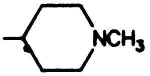
R = $<^{H}_{OH}$ **667**

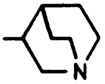
R = $<^{H}_{CH_3}$ **668**

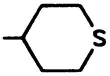


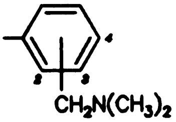
$R^1 = CH_2CH_2N(CH_3)_2$ 669

$R^1 = (CH_2)_3N(CH_3)_2$ 670

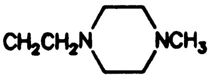
R^1 =  671

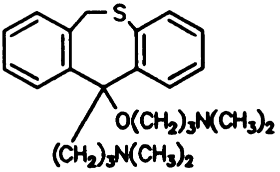
R^1 =  672

R^1 =  673

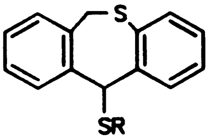
R^1 =  674

$R^1 = CH_2CH_2Br$ 675

R^1 =  676

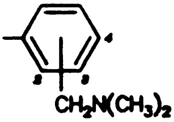


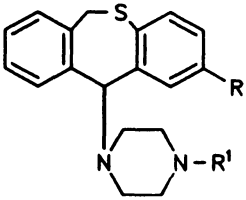
677



R = H 678

$R = (CH_2)_nN(CH_3)_2$ 679

R =  680

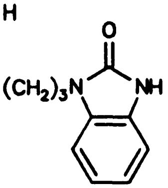


$R^1 = CH_3$ **681**

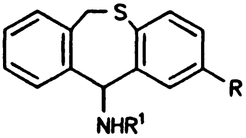
$R^1 = CH_2CH_2OH$ **682**

$R^1 = CH_2CH_2OCH_3$ **683**

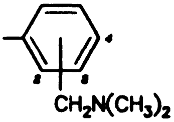
$R^1 = H$ **684**

$R^1 =$


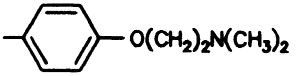
685



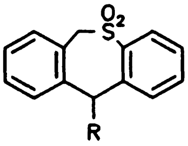
$R^1 = (CH_2)_2N(CH_3)_2$ **686**

$R^1 =$


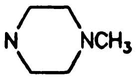
687

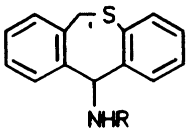
$R^1 =$


688



R = Br 689

R =  690



R = H 691

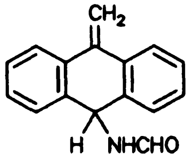
R = $COOC_2H_5$ 692

R = $CONHCH_2CH_2OH$ 693

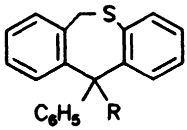
R = $CONHCH_2C_6H_5$ 694

R = $COCH_2N(CH_3)_2$ 695

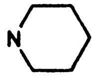
R = CH_2COOH 696



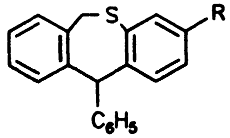
697

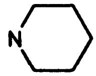


R = Cl 698

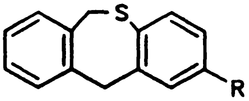
R =  699

R = $(CH_2)_3N(CH_3)_2$ 700



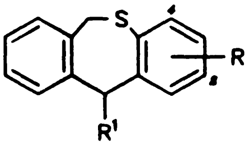
R =  701

R = $(CH_2)_3N(CH_3)_2$ 702



R = $COCH_3$ 703

R = CH_2COOH 704



R¹ = CHO 705

R¹ = CH_2OH 706

R¹ = CN 707

R¹ = COOH 708

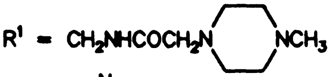
R¹ = $CONH_2$ 709

R¹ = CH_2COOH 710

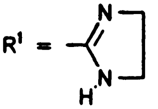
R¹ = CH_2NH_2 711

R¹ = CH_2NHCH_3 712

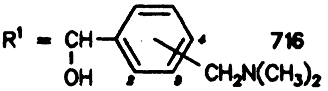
R¹ = $CH_2N(CH_3)_2$ 713



714



715



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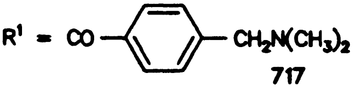
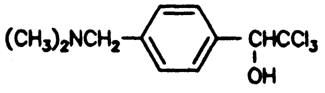
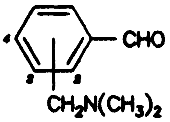


717



718



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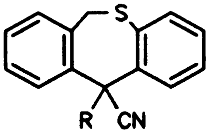
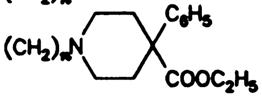


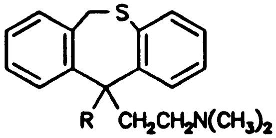
R = $(CH_2)_nN(CH_3)_2$ 720

R = $(CH_2)_nBr$ 721

R = 

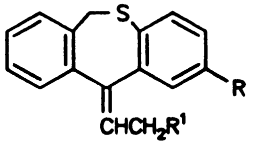
722

R = $CH{=}CH_2$ 723



R = COOH 724

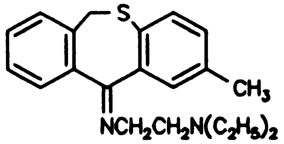
R = H 725



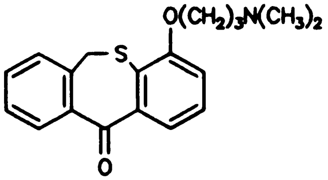
R^1 = Br 726

R^1 = CN 727

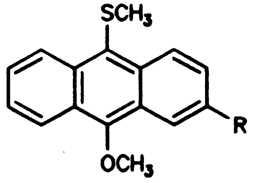
R^1 = COOH 728



729



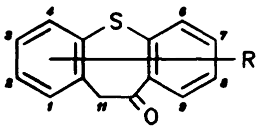
730



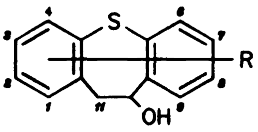
R = H 731

R = F 732

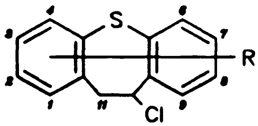
R = OCH_3 733



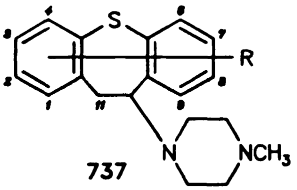
734



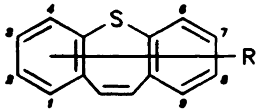
735



736



737



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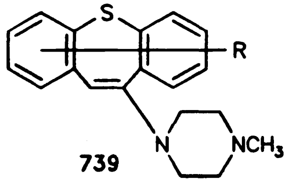
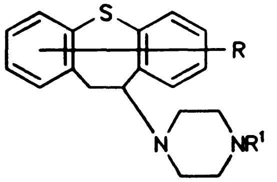
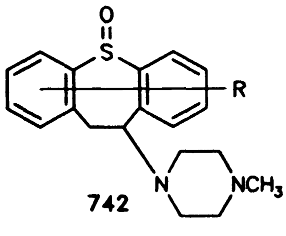


739

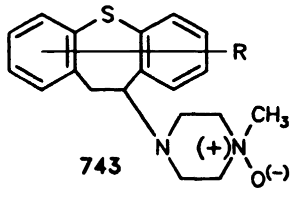


R^1 = $COOC_2H_5$ 740

R^1 = H 741



742



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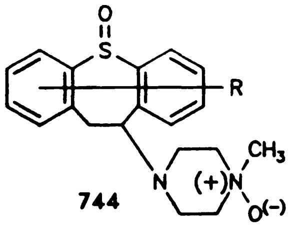
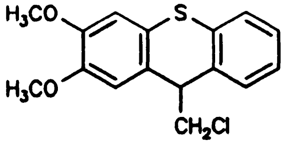
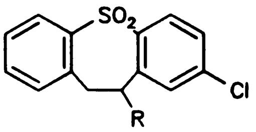


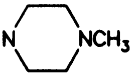
744

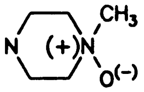


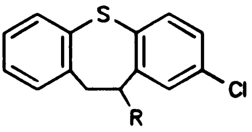
745

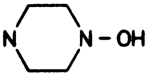


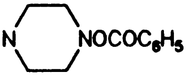
R = Cl 746

R =  747

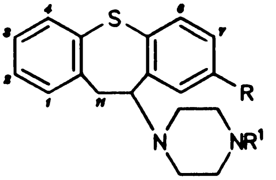
R =  748



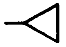
R =  749

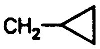
R =  750

R = $NHCH_2CH_2NH_2$ 751



R^1 = alkyl etc. 752

R^1 =  753

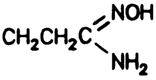
R^1 =  754

R^1 = CH_2CH_2OH 755

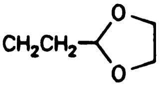
R^1 = $(CH_2)_3OH$ 756

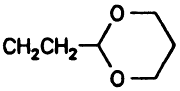
R^1 = $(C_nH_{2n})OH$ 757

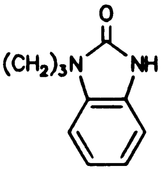
R^1 = $CH_2CH_2CONH_2$ 758

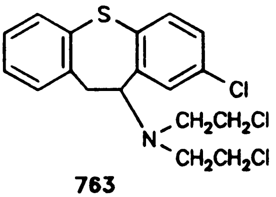
R^1 =  759

$CH_2CH_2C(=NOH)NH_2$

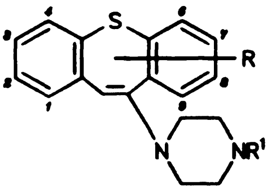
R^1 =  760

R^1 =  761

R^1 =  762

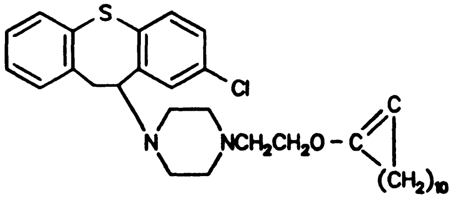


763

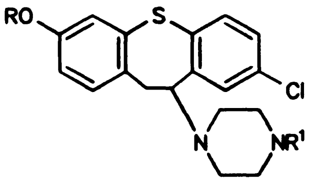


R^1 = CH_2CH_2OH 764

R^1 = $(CH_2)_3OH$ 765

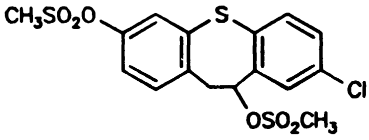


766

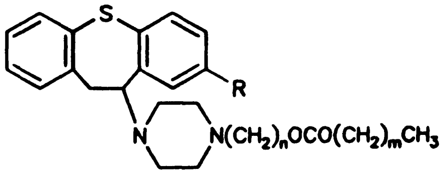


R^1 = CH_2CH_2OH 767

R^1 = $(CH_2)_3OH$ 768



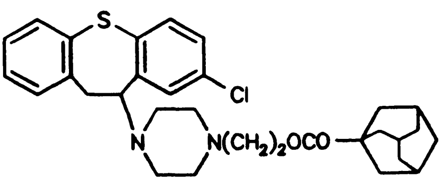
769



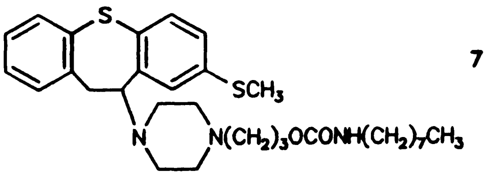
R = SCH_3 , n = 3, m = 5 770

R = SCH_3 , n = 3, m = 8 771

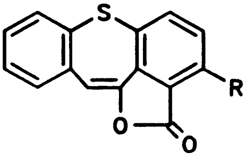
R = Cl , n = 2, m = 8 772



773

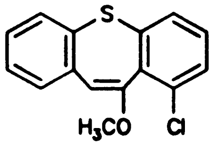


774



R = H 775

R = Cl 776



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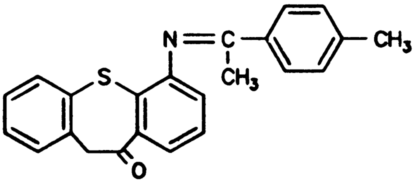
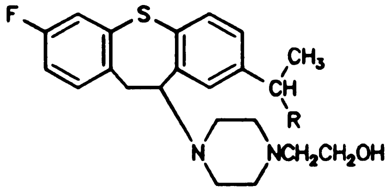


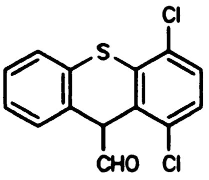
778



R = CH_2OH 780

R = H 781

R = COOH 782



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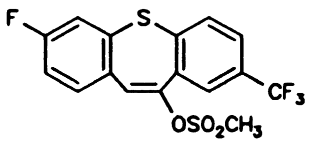

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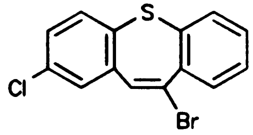
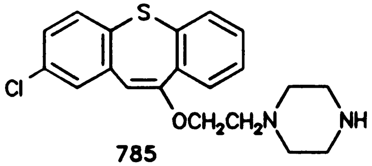


784



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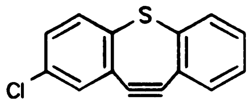
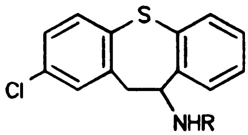
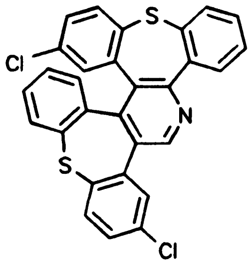


786



R = $CH_2CH_2NH_2$ 787

R = H 788



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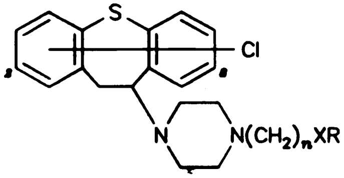
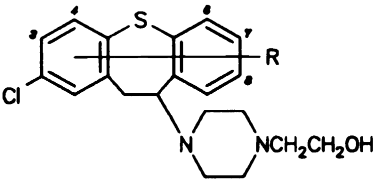


790



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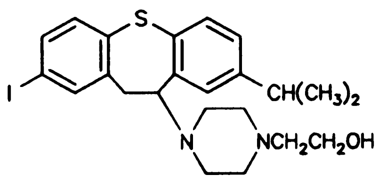

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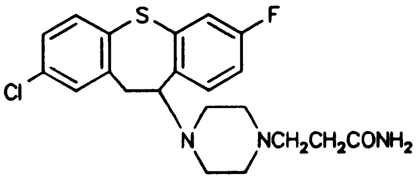
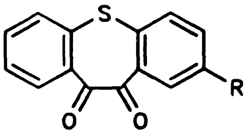
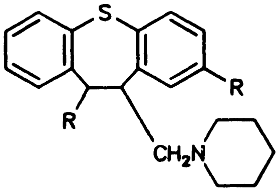


793

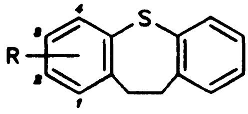


794

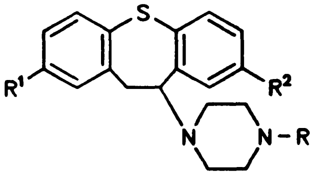


R = =O **795**

R = OH **796**



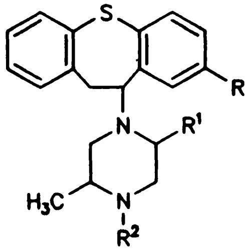
797



R = NO **798**

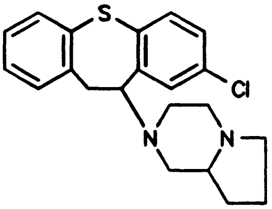
R = NH_2 **799**

R = N=CHAr **800**

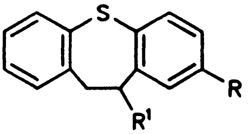


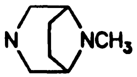
$R^1 = R^2 = H(CH_3)$ **801**

$R^1 = CH_3$, $R^2 = H(CH)_3$ **802**

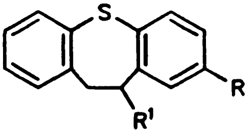


803



R^1 =  804

R^1 =  805



R^1 = NR^2R^3 806

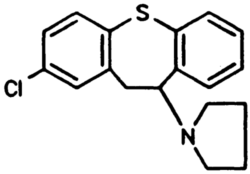
R^1 = NH_2 807

R^1 = $NHCH_3$ 808

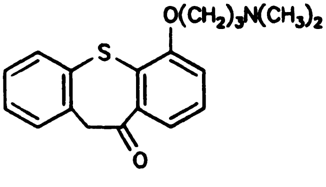
R^1 = $N(CH_3)CH_2C \equiv CH$ 809

R^1 = $NH(CH_2)_4COOH$ 810

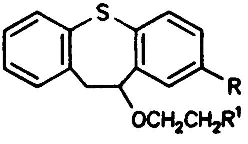
R^1 =  811



812

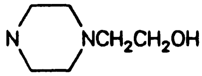


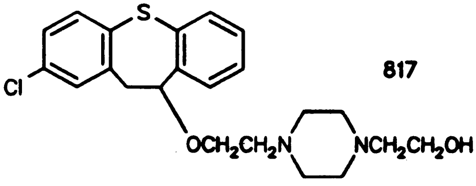
813



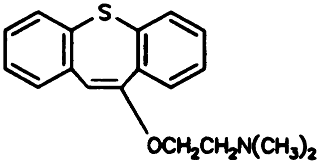
R^1 = $N(CH_3)_2$ 814

R^1 = Br 815

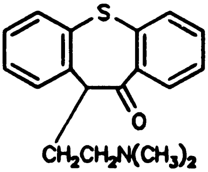
R^1 =  816



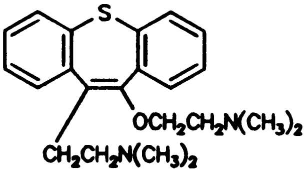
817



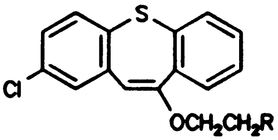
818



819

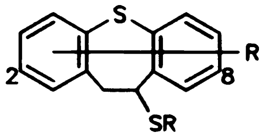


820



R = Br **821**

$R = N\quad NCH_2CH_2OH$ **822**

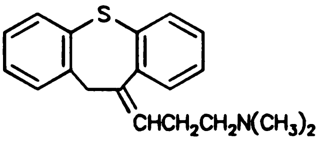


$R = H$ **823**

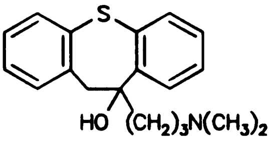
$R = CH_2CH_2N(CH_3)_2$ **824**

$R = CH_2CH_2NHCH_3$ **825**

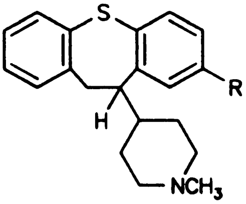
$R = CH_2COOH$ **826**



827



828



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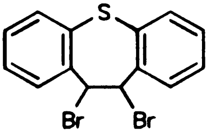
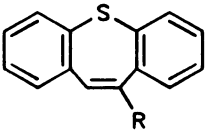


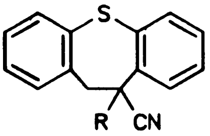
830



R = Br **831**

R = Cl **832**

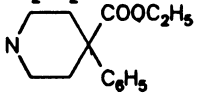
R = CN **833**

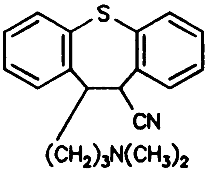


R = H **834**

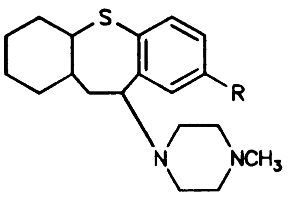
R = $CH_2CH_2N(CH_3)_2$ **835**

R = CH_2CH_2Br **836**

R =  **837**



838



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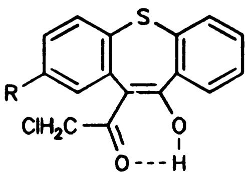
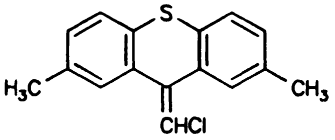
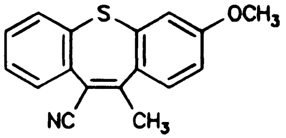


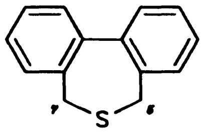
840



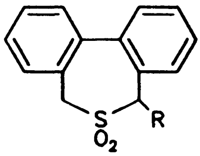
841



842



843

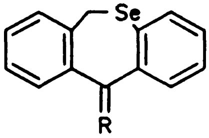


R = H 844

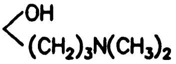
R = COOH 845

R = $CH_2N(CH_3)_2$ 846

R = $(CH_2)_3N(CH_3)_2$ 847



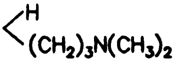
R = O 848

R =  849

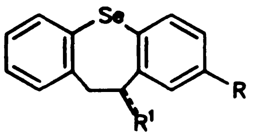
$$R = {<}\begin{matrix}OH\\(CH_2)_3N(CH_3)_2\end{matrix}$$

R = $=CH(CH_2)_2N(CH_3)_2$ 850

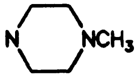
R = $=CH(CH_2)_2NHCH_3$ 851

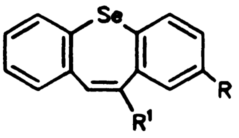
R =  852

$$R = {<}\begin{matrix}H\\(CH_2)_3N(CH_3)_2\end{matrix}$$



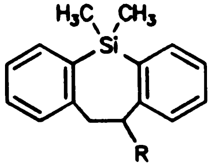
R^1 = O **853**

R^1 =  **854**

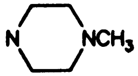


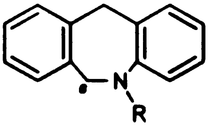
R^1 = H **855**

R^1 =  **856**



R = Br **857**

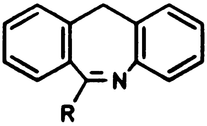
R =  **858**



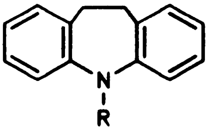
R = H 859

R = $(CH_2)_3N(CH_3)_2$ 860

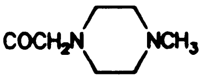
R = $COCH_2CH_2\overset{(+)}{S}(CH_3)_2\ I^{(-)}$ 861

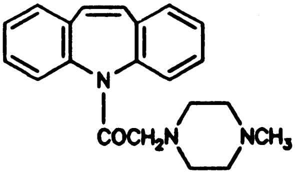


862

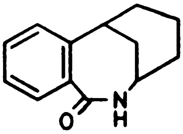


R = $(CH_2)_3NH_2$ 863

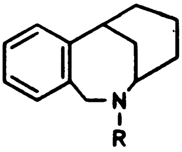
R =  864



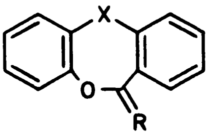
865

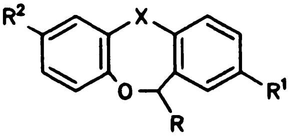


866



867

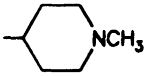


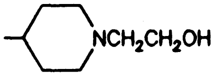


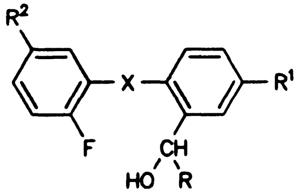
R = H_2 **868**

R = O **869**

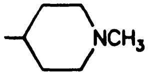
R = $(CH_2)_3N(CH_3)_2$ **870**

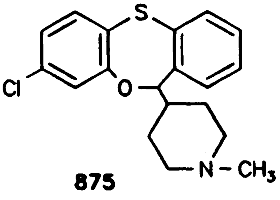
R =  **871**

R =  **872**

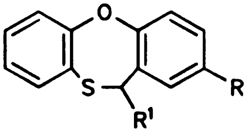


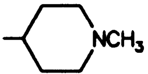
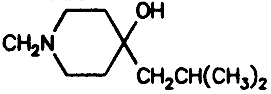
R = $(CH_2)_3N(CH_3)_2$ **873**

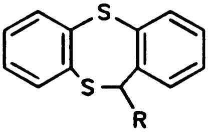
R =  **874**



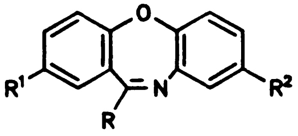
875



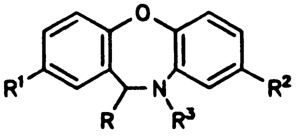
R^1 = H	876
R^1 = COOH	877
R^1 = $CH_2N(CH_3)_2$	878
R^1 = $(CH_2)_3N(CH_3)_2$	879
R^1 = 	880
R^1 = 	881



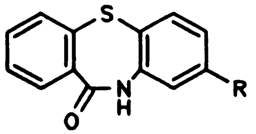
R = H	882
R = COOH	883
R = $(CH_2)_nN(CH_3)_2$	884



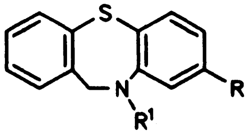
R = H **885**
R = CH_3 **886**
R = C_6H_5 **887**



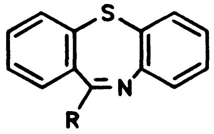
R^3 = H **888**
R^3 = $(CH_2)_3N(CH_3)_2$ **889**



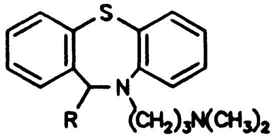
R = H **890**
R = Cl **891**



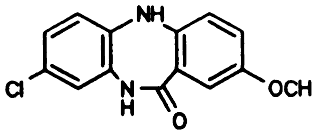
R^1 = H **892**
R^1 = $(CH_2)_3N(CH_3)_2$ **893**



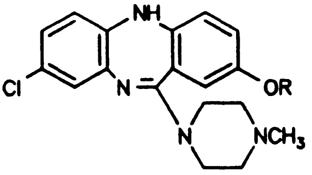
R = H **894**
R = CH_3 **895**
R = C_6H_5 **896**



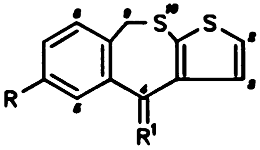
R = CH_3 **897**
R = C_6H_5 **898**



899

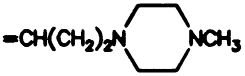


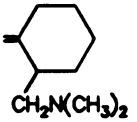
R = CH_3 **900**
R = H **901**

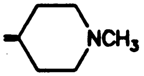


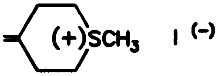
R^1 = =O **902**

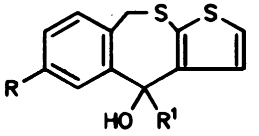
R^1 = $=CH(CH_2)_2N(CH_3)_2$ **903**

R^1 =  **904**

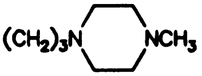
R^1 =  **905**

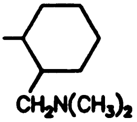
R^1 =  **906**

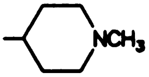
R^1 =  **907**

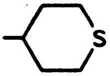


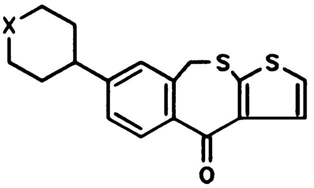
R^1 = $(CH_2)_3N(CH_3)_2$ **908**

R^1 =  **909**

R^1 =  **910**

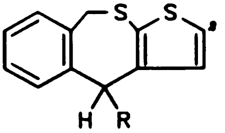
R^1 =  **911**

R^1 =  **912**

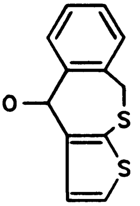


X = NCH_3 **913**

X = S **914**

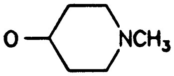


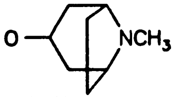
R = OH 915

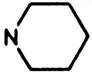
R =  916

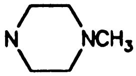
R = H 917

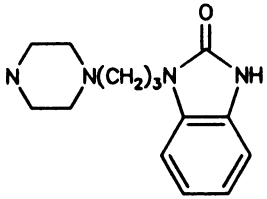
R = $O(CH_2)_2N(CH_3)_2$ 918

R =  919

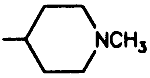
R =  920

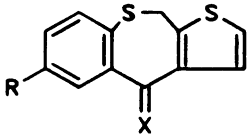
R =  921

R =  922

R =  923

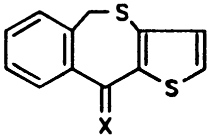
R = $(CH_2)_3N(CH_3)_2$ 924

R =  925



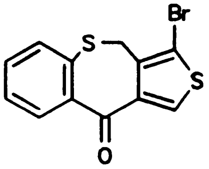
X = =O **926**

X = $=CHCH_2CH_2N(CH_3)_2$ **927**

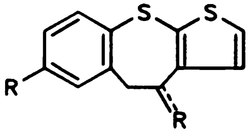


X = =O **928**

X = $=CHCH_2CH_2N(CH_3)_2$ **929**



930

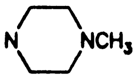


R = =O **931**

R = OH **932**

R = $OCH_2CH_2N(CH_3)_2$ **933**

R = Cl **934**

R = 

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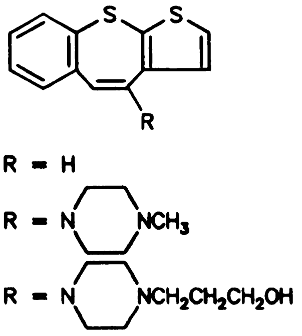
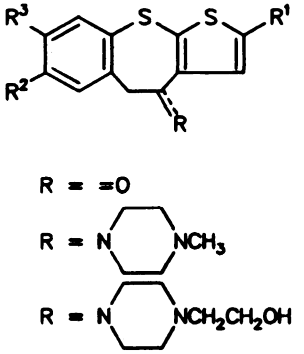


936

937

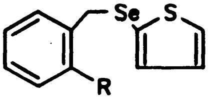
938



939

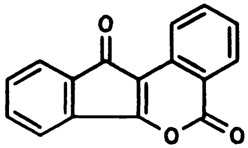
940

941

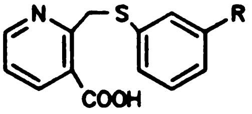


R = COOH 942

R = H 943

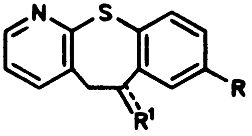


944

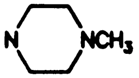


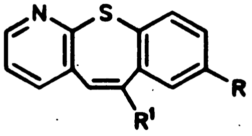
R = H **945**

R = OCH_3 **946**



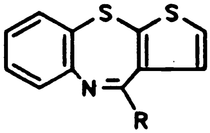
R^1 = =O **947**

R^1 =  **948**



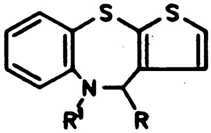
R^1 = H **949**

R^1 =  **950**



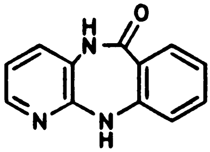
R = CH_3 **951**

R = C_6H_5 **952**

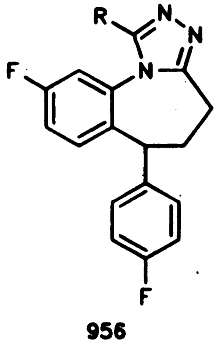


R^1 = H **953**

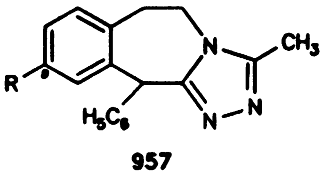
R^1 = $(CH_2)_3N(CH_3)_2$ **954**



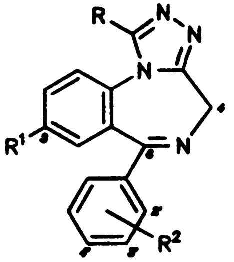
955



956



957

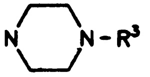


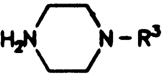
R = CH_3 958

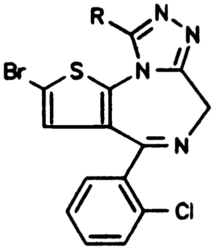
R = CH_2SCH_3 959

R = $CH_2NHSO_2R^3$ 960

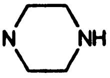
R = $CH(CH_3)NHSO_2R^3$ 961

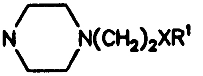
R =  962

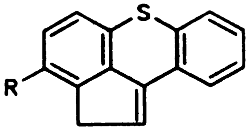
R = CH_2 963



R = Br 964

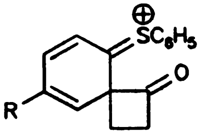
R =  965

R =  966

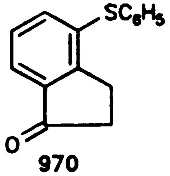


R = H 967

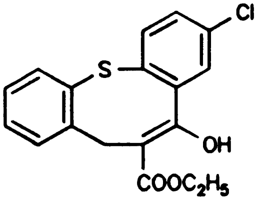
R = Cl 968



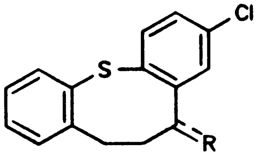
969



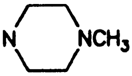
970

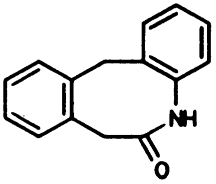


971

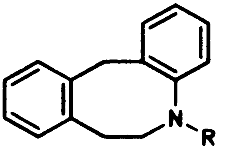


R = =O 972

R =  973

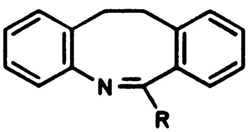


974

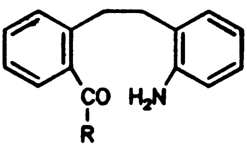


R = H **975**

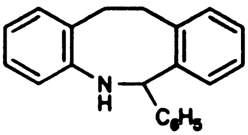
R = $(CH_2)_3N(CH_3)_2$ **976**



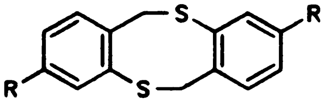
977



978

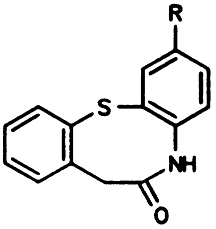


979



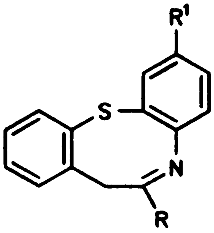
R = H **980**

R = F **981**



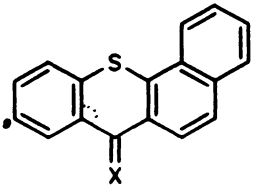
R = H **982**

R = Cl **983**



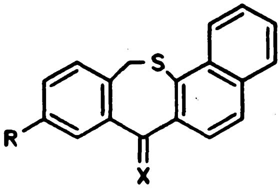
R = $NHCH_2CH(CH_3)_2$ **984**

R =  CH_3 **985**



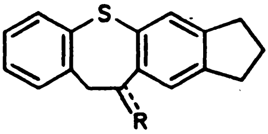
X = O **986**

X = $CH(CH_2)_2N(CH_3)_2$ **987**

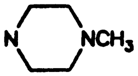


X = O **988**

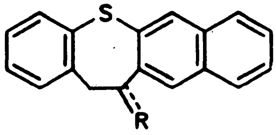
X = $CH(CH_2)_2N(CH_3)_2$ **989**



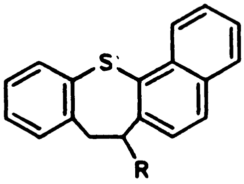
R = =O **990**

R = 

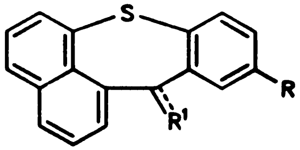
991



992



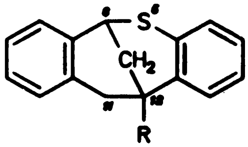
993



R^1 = =O 994

R^1 = $CH(CH_2)_2N(CH_3)_2$ 995

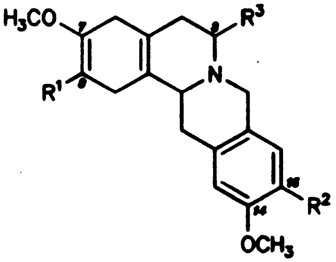
R^1 =  996

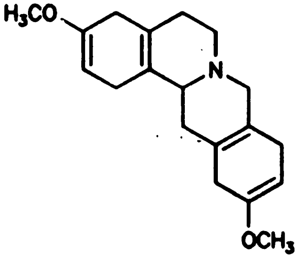


R = CN 997

R = CH_2NH_2 998

R = $CH_2N(CH_3)_2$ 999

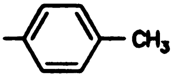




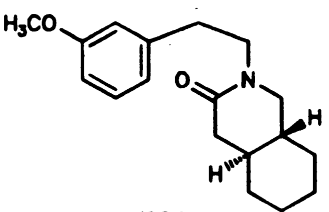
R^1 = R^2 = R^3 = H 1000

R^1 = OCH_3; R^2 = R^3 = H 1001

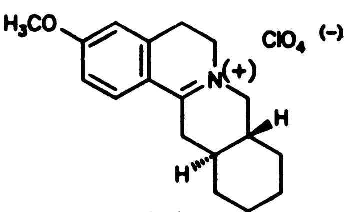
R^1 = R^2 = OCH_3; 1002

R^3 = 

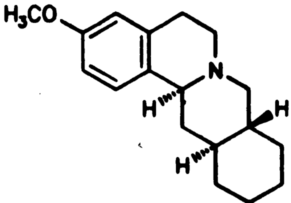
1003



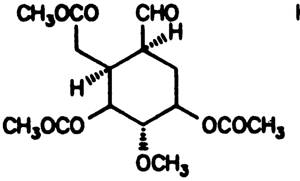
1004



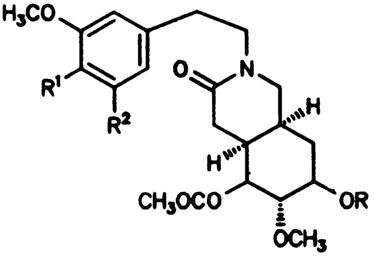
1005



1006

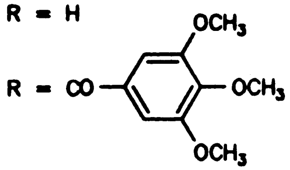


1007

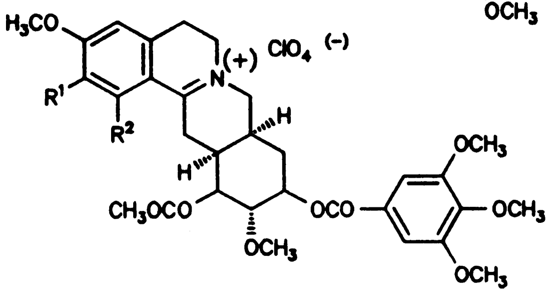


R = $COCH_3$ **1008**

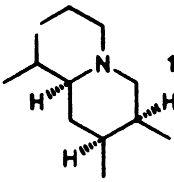
R = H **1009**



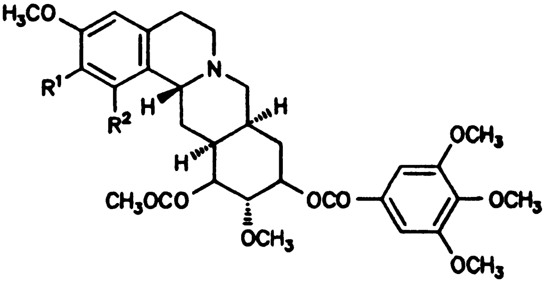
1010



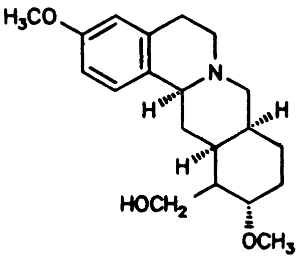
1011



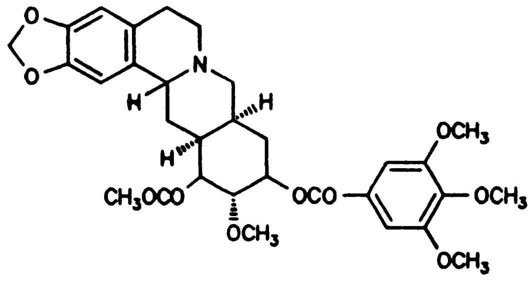
1012



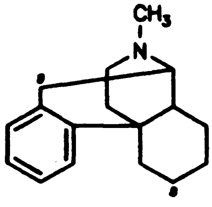
1013



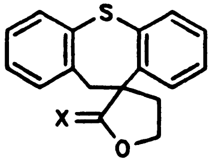
1014



1015

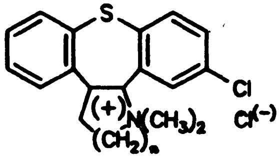


1016

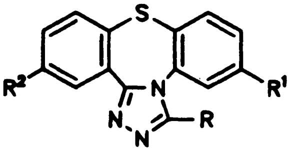


X = NH **1017**

X = O **1018**



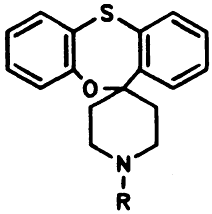
1019



R = H **1020**

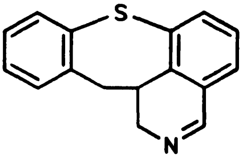
R = Br **1021**

R =  **1022**

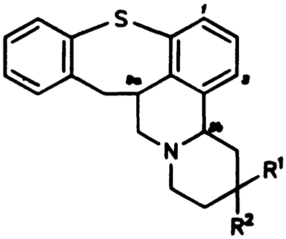


R = $COOC_2H_5$ **1023**

R = CH_3 **1024**



1025

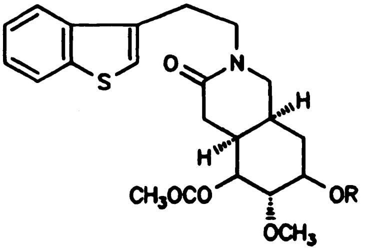


$R^1R^2 = {=}O$ 1026

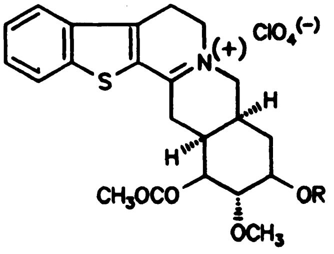
$R^1 = OH, R^2 = C(CH_3)_3$ 1027

$R^1 = OH, R^2 = CH(CH_3)_2$ 1028

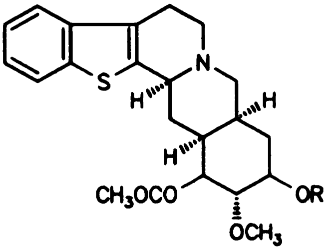
$R^1 = OH, R^2 = H$ 1029



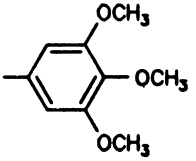
1030

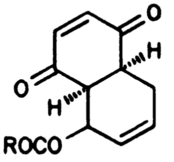


1031



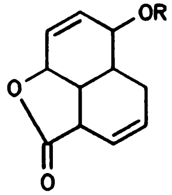
1032

In formulae 1030–1032, R = CO–




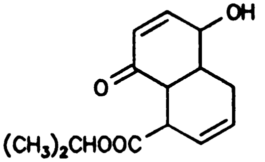
R = CH_3 1033

R = $CH(CH_3)_2$ 1034

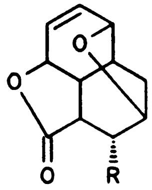


R = H 1035

R = $COCH_3$ 1036



1037



R = Br 1038

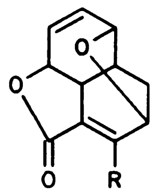
R = OCH_3 1039

R = $N(CH_3)_2$ 1040

R = CH_3 1041

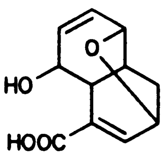
R = C_2H_5 1042

R = H 1043

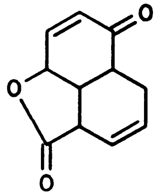


R = H 1044

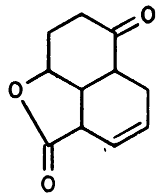
R = CH_3 1045



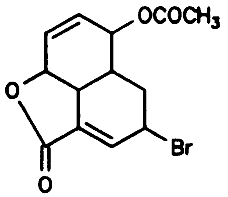
1046



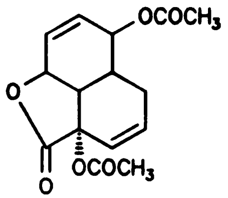
1047



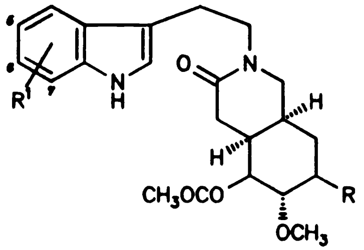
1048



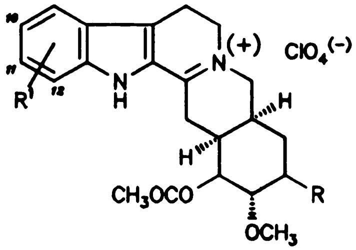
1049



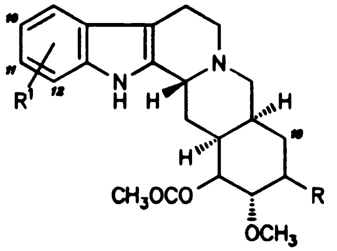
1050



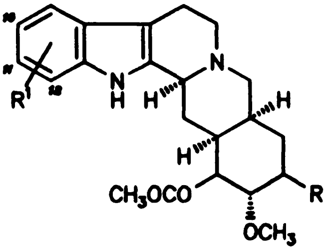
1051



1052



1053



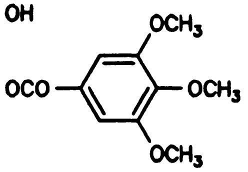
1054

In formulae 1051–1054

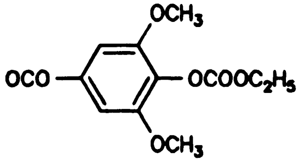
a) R = OCOCH$_3$

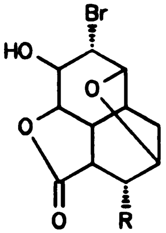
b) R = OH

c) R =

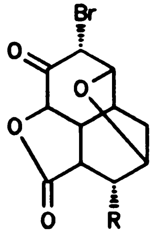


d) R =

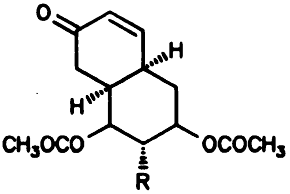




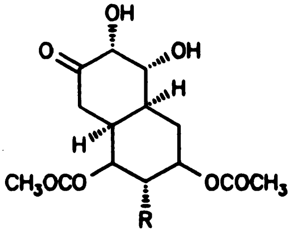
1055



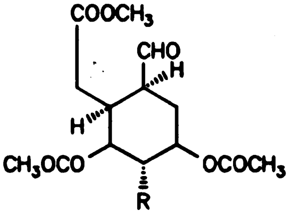
1056



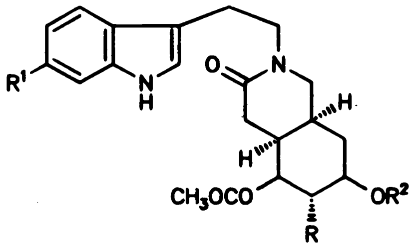
1057



1058



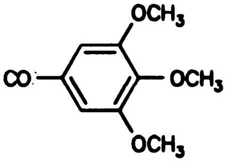
1059



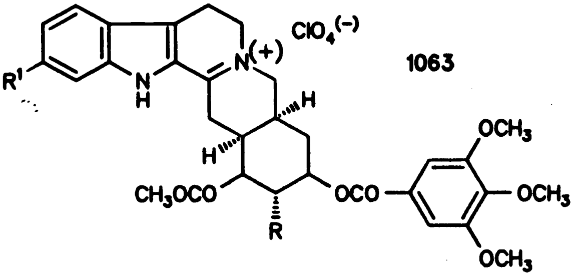
R^2 = $COCH_3$ **1060**

R^2 = H **1061**

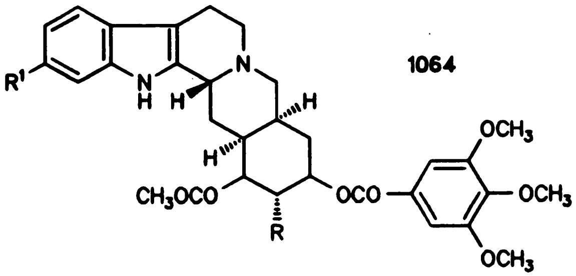
R^2 =



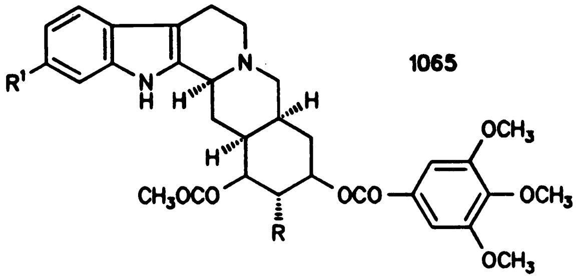
1062



1063



1064

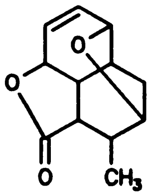


1065

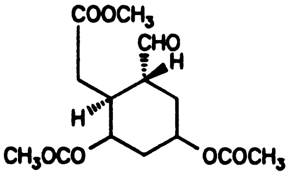
In formulae 1055–1065 a) $R = CH_3$, $R^1 = OCH_3$

b) $R = C_2H_5$, $R^1 = OCH_3$

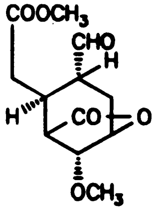
c) $R = R^1 = H$



1066



1067



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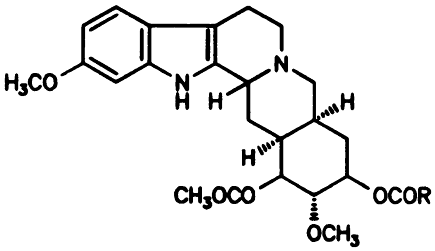

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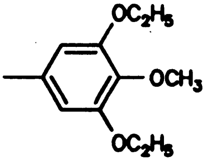

1069

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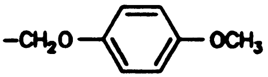

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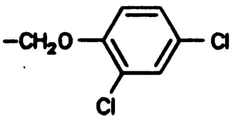

1071

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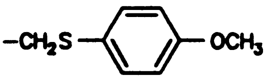
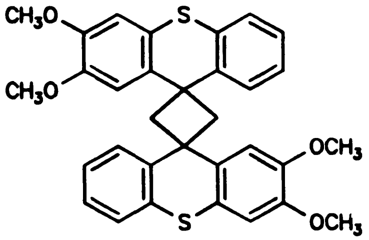
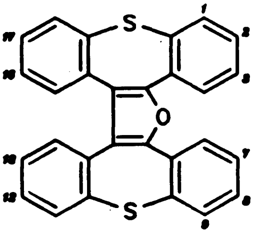


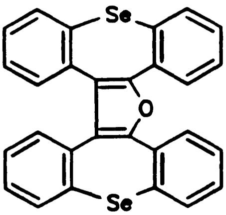
1072



1073



1074



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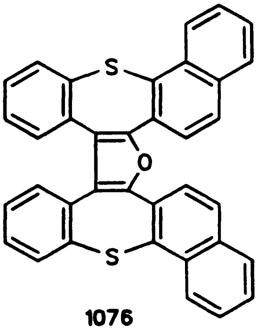

1076

8 REFERENCES

8.1 PART A

This part represents a condensed bibliography of papers and patents prepared by the author of this review. The main part of the bibliography is formed by citations of the original articles and review articles. Communications (lectures) are cited only in cases when their full text was published or the abstract appeared as a journal publication or in an internationally accessible medium. Preliminary communications and patents are cited together with the corresponding original papers. The overlapping of patents and original papers is mostly not perfect; the patents are cited only once. The references are arranged according to the years and within the years according to the alphabetical order of the authors.

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8.2 PART B

This part contains references to papers or patents of other authors which are connected in some way with the work mentioned in Part A. Most of the references in this part deal with the further fate of the selected compounds described in the review. They refer to their pharmacology, toxicology, pharmacokinetics, metabolism, various other properties and results of their clinical testing. Some of the references here document the connection of our chemical work with that of other chemical teams, i.e. independent work in similar lines proceeding before our experimental work, simultaneously or after it. Papers which were used by our group as starting points for our own work and papers describing the chemistry or biological properties of standard drugs, used by us as prototypes, were also partly included in this section of references.

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