NONCATALEPTIC NEUROLEPTIC AGENTS: 2-HALOGENO-8-ISOPROPYL-10-PIPERAZINO--10,11-DIHYDRODIBENZO[*b,f*]THIEPINS*

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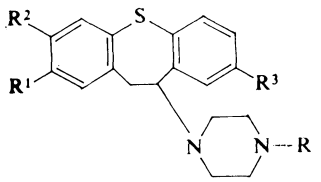
Received May 10th, 1983

Reactions of 5-fluoro-, 5-chloro- and 5-bromo-2-iodobenzoic acid with 4-isopropylthiophenol in solutions of potassium hydroxide in the presence of copper gave the acids *VIIabc* which were transformed *via* the intermediates *VIIIabc*—*Xabc* to 2-[5-halogeno-2-(4-isopropylphenylthio)-phenyl]acetic acids *XIabc*. Their cyclization with polyphosphoric acid resulted in 2-halogeno-8-isopropyldibenzo[*b,f*]thiepin-10(11*H*)-ones *XIIabc*. The 2-iodo ketone *XIId* was obtained from 2-(2-chloro-5-nitrophenyl)acetic acid by treatment with 4-isopropylthiophenol, by the following reduction of the resulting nitro acid *XIe* with hydrazine to the amino acid *XIf*, by its cyclization to the amino ketone *XIIf* and finally by its diazotization and reaction with potassium iodide. The ketones *XIIa*—*d* were reduced to the alcohols *XIIIa*—*d* giving by treatment with hydrogen chloride the chloro compounds *XIVa*—*d*. Substitution reactions with 1-methylpiperazine and 1-(2--hydroxyethyl)piperazine afforded the title compounds *Vabc* and *VIa*—*d*. Only the fluoro derivatives *Va* and *VIa* showed a clear cataleptic activity in rats. The other compounds are very little active in this line and the iodo derivative *VId* was found to be completely inactive in a high oral dose, but it revealed an intensive antidopaminergic action in biochemical tests. By its pharmacological profile it resembles the known noncataleptic neuroleptic agent clozapine.

In our studies of neuroleptics of the 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin series we used in two cases the isopropyl group as the „neuroleptic" substituent in position 8. The first case[1] were the 8-isopropyl derivatives *I* and *II* which had a high degree of cataleptic and discoordinating activity, and the second case was the 3-fluoro-8-isopropyl derivative *III* („isofloxythepin") which showed in addition to a high intensity of these effects also an important prolongation of their duration after the oral administration[2-4]. On the other hand, in the search after noncataleptic agents of this series among the 2-substituted 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins[5-9] only the 2-halogeno derivatives[7] manifested the desired properties and the 2-chloro compound *IV* („docloxythepin") (ref.[10-15]) was found a noncataleptic neuroleptic of a similar type like clozapine[16]. The purpose of the present investigation was to establish the influence of a combination of isopropyl

* Part CLXXXVII in the series Neurotropic and Psychotropic Agents; Part CLXXXVI: This Journal *48*, 2977 (1983).

in position 8 with a halogen atom in position 2 upon the pharmacological properties. We expected that the isopropyl in position 8 will determine the antidopaminergic character of the compounds, whereas the role of the halogen atom in position 2 was to attenuate the cataleptic activity which is in a clear connection with the unwanted side effects of the neuroleptic agents. For attaining the goal mentioned we have synthesized the title 2-halogeno-8-isopropyl derivatives *Vabc* and *VIa–d* and have studied their pharmacological and biochemical properties.



I, R = CH_3, $R^1 = R^2 = H$, $R^3 = CH(CH_3)_2$
II, R = $(CH_2)_3OH$, $R^1 = R^2 = H$, $R^3 = CH(CH_3)_2$
III, R = $(CH_2)_2OH$, $R^1 = H$, $R^2 = F$, $R^3 = CH(CH_3)_2$
IV, R = $(CH_2)_2OH$, $R^1 = Cl$, $R^2 = R^3 = H$

The synthesis of compounds *Vabc* and *VIa–d* was carried out by procedures described[1,7] for perathiepin derivatives. In the case of the fluoro, chloro and bromo derivatives the synthesis started from 5-halogeno-2-(4-isopropylphenylthio)benzoic acids *VIIabc* and proceeded *via* intermediates *VIIIabc–XIVabc*. In the case of the iodo derivative *VId*, the synthesis entered this scheme only in the stage of the ketone *XIId*. The final products were obtained by substitution reactions of the chloro derivatives *XIVa–d* with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in boiling chloroform. In order to separate the resulting bases from the simultaneously formed neutral products (elimination products) it was not possible to use the usual extraction of bases into dilute hydrochloric acid because the hydrochlorides are insoluble in water and partly soluble in organic solvents. For this reason, the crude products were separated by chromatography either on silica gel (method *A*) or on alumina (method *B*); the elimination products were removed in the first fractions as the least polar components; they were formed in small amounts and we did not try to isolate them and characterize. The desired bases were obtained in high yields and characterized by spectra. For pharmacological testing they were transformed into crystalline methanesulfonates. All final products *V* and *VI* are assembled in Table I with the usual experimental data. The Experimental describes only the preparation of *Va* (method *A*) and *VIc* (method *B*).

In the individual series the syntheses proceeded in the following way: In series *a* (fluoro derivatives) the starting 5-fluoro-2-iodobenzoic acid was prepared from 5-fluoro-2-nitrotoluene[17] by a procedure elaborated earlier[18]. We modified the pre-

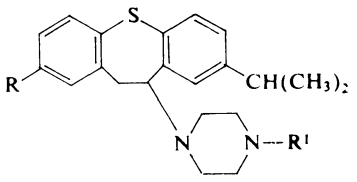
TABLE I

2-Halogeno-8-isopropyl-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins and their dimethanesulfonates

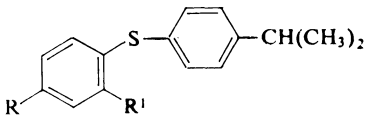
Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% N	% S	% Hal
Va	*A*[a] (90)	108—111 (cyclohexane–benzene)	$C_{22}H_{27}FN_2S$ (370·5)	71·31 71·25	7·35 7·32	7·56 7·12	8·65 8·80	5·13 5·41
Va-2 MS[b,c]	—	182—185; 201—203 (ethanol–ether)	$C_{24}H_{35}FN_2O_6S_3 + H_2O$ (580·8)	49·64 49·79	6·42 6·20	4·82 4·80	16·56 16·73	3·27 3·65
Vb	*A* (87)	107—110[d] (hexane)	$C_{22}H_{27}ClN_2S$ (387·0)	68·28 68·47	7·03 7·22	7·24 7·13	8·29 8·35	9·16 9·34
Vb-2 MS[b,c]	—	213—215[e] (ethanol–ether)	$C_{24}H_{35}ClN_2O_6S_3 + H_2O$ (597·2)	48·26 48·48	6·25 6·02	4·69 4·89	16·10 15·65	5·94 6·20
Vc	*A* (86)	122—123[f] (hexane)	$C_{22}H_{27}BrN_2S$ (431·5)	61·24 61·33	6·31 6·39	6·49 6·69	7·43 7·55	18·52 18·65
Vc-2 MS[b,g]	—	140—145; 206—208 (ethanol)	$C_{24}H_{35}BrN_2O_6S_3 + 0{\cdot}5\ H_2O$ (632·7)	45·56 45·66	5·74 5·61	4·43 4·76	15·21 15·18	12·63 13·10
VIa	*A* (71)	75—88[h] (cyclohexane)	—	—	—	—	—	—
VIa-2 MS[b]	—	206—207 (ethanol–ether)	$C_{25}H_{37}FN_2O_7S_3$ (592·8)	50·65 50·65	6·29 6·42	4·73 4·76	16·23 16·08	3·21 3·45
VIb-2 MS[b,g]	*B* (80)	178—179[i] (ethanol)	$C_{25}H_{37}ClN_2O_7S_3 + 0{\cdot}5\ H_2O$ (618·3)	48·57 48·10	6·20 6·02	4·53 4·46	15·56 15·70	5·74 5·92

VIc[j]	*B*[a]	79—82	$C_{23}H_{29}BrN_2OS$	61·34	6·80	5·72	6·55	16·32
	(86)	(benzene–cyclohexane)	+ 1/3 C_6H_{12}	61·33	6·89	5·41	6·88	16·74
			(489·5)					
VIc-2 MS[b,g]	—	175—177	$C_{25}H_{37}BrN_2O_7S_3$	45·31	5·78	4·23	14·52	12·06
		(ethanol–ether)	+ 0·5 H_2O	45·11	5·68	4·06	14·63	12·23
			(662·8)					
VId-2 MS[b,g]	*B*	182—184[k]	$C_{25}H_{37}IN_2O_7S_3$	42·31	5·40	3·95	13·56	16·91
	(67)	(ethanol–ether)	+ 0·5 H_2O	42·23	5·33	3·57	13·71	16·57
			(709·8)					

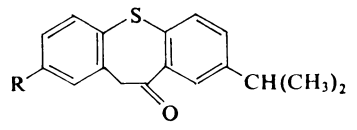
[a] See Experimental. [b] Dimethanesulfonate. [c] Monohydrate. [d] ^{1}H NMR spectrum: δ 6·80—7·60 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2$·.CHAr), 2·85 (m, 1 H, ArCH of isopropyl), 2·65 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·43 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·26 (s, 3 H, NCH_3), 1·23 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). [e] With decomposition. [f] ^{1}H NMR spectrum: δ 6·80—7·50 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·85 (m, 1 H, ArCH of isopropyl), 2·65 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (m, 3 H, NCH_3), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). [g] Hemihydrate. [h] A nonstoichiometric solvate with cyclohexane which was used for recording the spectra. IR spectrum: 819, 872 (2 adjacent and solitary Ar—H), 1·059 (CH_2OH), 1 580, 1 599, 3 045 (Ar), 2 700, 2 763 (CH_2—N), 3 180, 3 380 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·60—7·60 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 6·0 Hz, 2 H, CH_2O), 3·15 (s, 1 H, OH), 2·85 (m, 1 H, ArCH of isopropyl), *c.* 2·60 (m, 10 H, 5 CH_2N), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). [i] The pure oily base was released from the salt with NH_4OH, isolated by extraction with ether and used for recording the spectra. IR spectrum (KBr): 820, 827, 880 (2 adjacent and solitary Ar—H), 1 065, 1 097 (CH_2OH), 1 562, 1 580 (Ar), 2 760, 2 815 (CH_2—N), 3 450 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·80—7·60 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, J = 7·0 Hz, 2 H, CH_2O), 2·80 (bs, 1 H, ArCH of isopropyl), *c.* 2·60 (m, 11 H, 5 CH_2N and OH), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). [j] A 3 : 1 solvate with cyclohexane. [k] Mass spectrum, m/z (formula and %): 508 (M^+ corresponding to $C_{23}H_{29}IN_2OS$, low intensity), 378 ($C_{17}H_{15}IS$, 55), 345 ($C_{17}H_{14}I$, 6), 330 ($C_{16}H_{11}I$, 9), 251 ($C_{17}H_{15}S$, 100), 236 ($C_{16}H_{12}S$, 46), 221 ($C_{15}H_9S$, 9), 218 ($C_{17}H_{14}$, 9), 209 ($C_{14}H_9S$, 30), 208 ($C_{14}H_8S$, 30), 203 ($C_{16}H_{11}$, 38), 202 ($C_{16}H_{10}$, 32). IR spectrum (KBr): 812, 830, 885 (2 adjacent and solitary Ar—H), 1 039, 1 193, 1 203 (SO_3H), 1 050, 1 058 (CH_2OH), 2 558 (NH^+), 3 400 cm^{-1} (OH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·10—8·00 (m, 6 H, ArH), 4·75 (bm, 1 H, Ar——CH—N), 3·00—4·00 (m, 14 H, $ArCH_2$, 5 CH_2N, CH_2O), 2·90 (m, 1 H, ArCH of isopropyl), 2·58 (s, 6 H, 2 CH_3SO_3), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl).



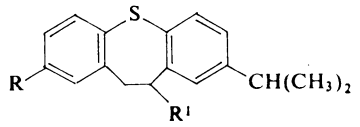
V, $R^1 = CH_3$
VI, $R^1 = CH_2CH_2OH$



VII, $R^1 = COOH$
VIII, $R^1 = CH_2OH$
IX, $R^1 = CH_2Cl$
X, $R^1 = CH_2CN$
XI, $R^1 = CH_2COOH$



XII

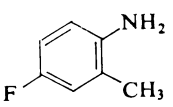


XIII, $R^1 = OH$
XIV, $R^1 = Cl$

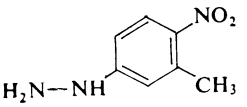
In formulae *V*—*XIV*: *a*, R = F; *b*, R = Cl; *c*, R = Br; *d*, R = I; *e*, R = NO_2; *f*, R = NH_2

paration of the first intermediate, *i.e.* 2-amino-5-fluorotoluene (*XV*), obtained earlier by catalytic hydrogenation of the mentioned nitro compound[18]. Now, the reduction was carried out in an almost theoretical yield with iron in boiling dilute hydrochloric acid. An attempt at reducing 5-fluoro-2-nitrotoluene with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and charcoal[19] did not lead to the amine *XV*; there proceeded a substitution reaction in which the very reactive fluorine atom was replaced with the hydrazine residue and 3-methyl-4-nitrophenylhydrazine (*XVI*) was obtained. 5-Fluoro-2-iodobenzoic acid[18] was subjected to a reaction with 4-isopropylthiophenol[1] in a boiling aqueous potassium hydroxide solution in the presence of copper and the acid *VIIa* was obtained in an almost theoretical yield. It was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate in a mixture of benzene and toluene and gave in a high the alcohol *VIIIa*. The following treatment with thionyl chloride in boiling benzene led to the substituted benzyl chloride *IXa*. The treatment of *IXa* with potassium cyanide was carried out in a boiling mixture of ethanol ,water and tetrahydrofuran; a homogeneous nitrile *Xa* was obtained in a high yield. Its hydrolysis to the acid *XIa* was carried out with a boiling potassium hydroxide solution in aqueous ethanol. The following cyclization to the ketone *XIIa* proceeded by heating with polyphosphoric acid to 150–155°C; the desired product was obtained in a yield of 76%. Reduction of this ketone with sodium borohydride in a boiling mixture of ethanol and tetrahydrofuran afforded the secondary alcohol *XIIIa* which was transformed by treatment with hydrogen chloride

in benzene at room temperature and in the presence of calcium chloride to 10-chloro--2-fluoro-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVa*).



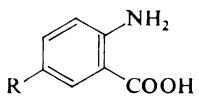
XV



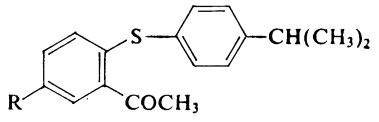
XVI

The series *b* (chloro derivatives) started from 2-amino-5-chlorobenzoic acid (*XVII*) which is accessible by chlorination of anthranilic acid with sulfuryl chloride in ether[20,21]. Now, it has also been obtained by hydrogenation of 5-chloro-2-nitrobenzoic acid on a palladium/charcoal catalyst. This reaction proved unreliable because when processing a larger batch, the consumption of hydrogen did not stop, hydrogenolysis of the chlorine atom took place and anthranilic acid hydrochloride[22,23] was the product (treatment of a sample with triethylamine in water gave anthranilic acid[24]). Transformation of the acid *XVII* to 5-chloro-2-iodobenzoic acid used the procedure described earlier[25] and further processing to the substituted benzyl chloride *IXb* proceeded *via* intermediates *VIIb* and *VIIIb* similarly like in series *a*. Compound *IXb* was processed by a reaction with sodium cyanide in dimethylformamide at 110°C. An inhomogeneous product (the crude nitrile *Xb*) was formed which decomposed in an attempt at its distillation and was, therefore. subjected without characterization to the alkaline hydrolysis; the acid *XIb* was obtained in a moderate yield. Further two attempts at preparing the acid *XIb* by alternative methods did not lead to useful results. In the first one there was the intention to use the Willgerodt reaction in the Kindler's modification[26–29]. Heating of 2,5-dichloroacetophenone[29] with 4-isopropylthiophenol[1], potassium carbonate and copper to 140–150°C gave 53% of the ketone *XIX*; its reaction with sulfur and boiling morpholine gave an oily mixture of the corresponding thiomorpholide and oxothiomorpholide which could not be separated by chromatography and the work along this line was discontinued. In the second attempt, 5-chloro-3*H*-benzo[*b*]thiophen-2-one[29] was transformed by alkaline hydrolysis to 2-(5-chloro-2-mercaptophenyl)acetic acid (*XXI*) which could be considered a potential intermediate in the synthesis of the acid *XIb* but which was not used to this end. Cyclization of the acid *XIb* to the ketone *XIIb* was carried out again with polyphosphpric acid by heating to 155–160°C. The following reduction to the alcohol *XIIIb* used sodium borohydride in boiling ethanol and the transformation to the chloro derivative *XIVb* proceeded similarly like in series *a*.

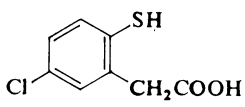
In series *c* (bromo derivatives) the starting 5-bromoanthranilic acid (*XVIII*) was obtained by bromination of anthranilic acid[30] and was transformed to 5-bromo--2-iodobenzoic acid (*XXII*) by diazotization and the following reaction of the diazo-



XVII, R = Cl
XVIII, R = Br



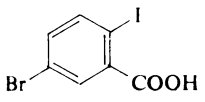
XIX, R = Cl
XX, R = Br



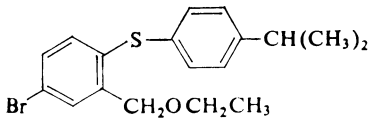
XXI

nium chloride solution with potassium iodide in the presence of sulfuric acid (analogy[31]); the preparation of compound *XXII* was described so far only by bromination of 2-iodobenzoic acid[32,33]. Conversion of the acid *XXII* to the acid *VIIc* was carried out similarly like in series *a*. Difficulties appeared in the stage of the reduction of the acid *VIIc* to the alcohol *VIIIc*. When using a milder modification like in series *a*, *i.e.* reducing with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene at room temperature, an inhomogeneous oily product with a low content of bromine was obtained: the unwanted hydrogenolysis proceeded in a great extent. A better experience was made with the reaction of the acid in tetrahydrofuran with diborane, formed *in situ*, *i.e.* by a reaction of sodium borohydride with boron trifluoride etherate. The course of the reaction was influenced by the insolubility of the sodium salt of the acid *VIIc* in the reaction medium and in a low yield there was obtained the inhomogeneous alcohol *VIIIc*. For this reason, the reduction of the acid *VIIc* in tetrahydrofuran was carried out with diborane, formed separately by a reaction of sodium borohydride with boron trifluoride etherate in bis(2-methoxyethyl) ether (diglyme) and introduced into the reaction mixture with a stream of nitrogen[34]. In this way, the homogeneous alcohol *VIIIc* was obtained in a yield of 80%. As a further favourable alternative a different procedure was used in which the acid *VIIc* was first esterified with methanol and hydrogen chloride and the methyl ester formed – without being isolated in pure state and characterized – was reduced with lithium borohydride in tetrahydrofuran; the alcohol *VIIIc* was obtained in a yield of 82%. Its conversion to the chloride *IXc* was carried out similarly like in series *a*. For the following transformation of the chloride *IXc* to the nitrile *Xc* in a small batch there was used potassium cyanide in dimethylformamide at 90–110°C and distillation gave the homogeneous product. In a larger batch the reaction with potassium cyanide was carried out in a boiling mixture of tetrahydrofuran, ethanol and water, the crude product was purified by chromatography on silica gel and was used without distillation for the next step. Whilst the hydrolysis of the distilled nitrile *Xc* with boiling potassium hydroxide solution in aqueous ethanol afforded smoothly the pure acid *XIc*, the use of the undistilled nitrile necessitated the introduction of chromatography of the crude product on silica gel or at least the processing of the mother liquors by this separation technique. As the least polar product, a neutral oil was isolated and identified by means of analysis and spectra as the substituted benzyl ethyl ether *XXIII*. Its formation by a solvolytic reaction of the chloride *IXc* with etha-

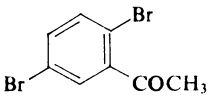
nol, which was present in the reaction mixtures, is evident. Likewise in the case of the acid *XIc* it was the intention to use the Willgerodt reaction in Kindler's modification[26-29]. For this reason, 2,5-dibromoacetophenone (*XXIV*) (ref.[35-37]) was prepared by the Friedel–Crafts reaction of 1,4-dibromobenzene with acetyl chloride and aluminium chloride by using an analogy of our procedure for preparing 2,5-dichloroacetophenone[29]; compound *XXIV* was obtained as the higher melting crystal modification[35]. Its reaction with 4-isopropylthiophenol[1] and potassium carbonate in the presence of copper and a small quantity of ethanol gave an inhomogeneous oil (the crude ketone *XX*) which afforded the corresponding crystalline semicarbazone but the attempt at its using in the Willgerodt reaction did not lead to the homogeneous thiomorpholide. The acid *XIc* was then cyclised similarly like in series a but it was necessary to purify the crude ketone *XIIc* by chromatography on silica gel. Reduction to the alcohol *XIIIc* was carried out similarly like in series *b* and transformation to the chloro derivative *XIVc* like in series *a*.



XXII



XXIII



XXIV

In series *d* (iodo derivatives) we used a similar approach like in the preceding cases of syntheses of iodo derivatives within the perathiepin series[7,38,39]. A reaction of 2-(2-chloro-5-nitrophenyl)acetic acid[8] with 4-isopropylthiophenol[1] in a boiling aqueous solution of potassium hydroxide in the presence of copper afforded in a moderate yield the acid *XIe* which was reduced with hydrazine in ethanol in the presence of ferric chloride to the amino acid *XIf*. This acid was cyclized with polyphosphoric acid at 130°C giving in a good yield the amino ketone *XIIf*, which was transformed to the iodo ketone *XIId* by diazotization and the following reaction of the diazonium salt solution with potassium iodide (analogies, *cf.*[7,38,39]). The last two steps, *i.e.* the preparation of intermediates *XIIId* and *XIVd*, were carried out similarly like in series *c*.

The methanesulfonates of compounds *Vabc* and *VIa–d* were evaluated by a series of pharmacological tests on oral administration; all doses given are in mg/kg and

were calculated for the bases. With the evaluated compounds the acute toxicity in mice (LD_{50} values) was determined, further the discoordinating activity in the rotarod test in mice (ED_{50} values) and the influence on the spontaneous locomotor activity of mice by the photo-cell method of Dews. In the last case the results are expressed on the one hand as medium effective doses (ED_{50}) inhibiting the locomotor activity to 50% of the control value, and on the other hand as percent of inhibition of locomotor activity (control 100%) after a constant dose of 5 mg/kg in two time intervals (after 1 h and 3 h after the administration). Further results relate to the test of catalepsy in rats where only for a part of compounds it was possible to estimate the medium effective doses ED_{50} for the other compounds the administered dose and the percent of cataleptic animals are given (the testing was carried out on groups by 10 animals). The antiapomorphine activity in rats is expressed as the percent of stereotypies (chewing) and agitation after an oral dose of 50 mg/kg (apomorphine was administered intravenously in a dose of 1·25 mg/kg), for controls both of these parameters equal 100%. All results are assembled in Table II; values with the sign$^+$ are of statistical significance (Student's t-test, $p < 0{\cdot}05$ was considered to be significant).

With the noncataleptic or almost noncataleptic compounds the evaluation of the influence on the dopamine metabolism in the rat striatum was carried out where the main interest was devoted to the increase of the level of homovanillic acid (HVA) as the main dopamine metabolite in the interval of 3 h after the administration. Two doses were used and the results are expressed as percent of HVA with the control (100%). After a dose of 10 mg/kg the following results were obtained: *Vc*, 126; *VIc*, 124; *VId*, 173; these results were not statistically significant. After a dose of 80 mg/kg: *Vc*, 268$^+$; *VIc* 231$^+$; *VId*, 266$^+$. It is apparent that these results are significant. For the most interesting compound *VId* (from the view point of the combination of findings in the pharmacological tests and the test just described) the threshold dose increasing the HVA concentration with statistical significance was determined. ED = 20 mg/kg. This compound is thus more active than clozapine[16] which is not yet active in this dose. With a somewhat different methodical arrangement compound *VIb* was also evaluated in this test (this compound, however, is clearly cataleptic). It was evaluated in the dose range of 5 – 80 mg/kg *p.o.* in the 3 h interval and the influence on the levels of HVA, 5-hydroxyindole-3-acetic acid (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and dopamine (DA) in the rat striatum was followed. The compound is active starting from the dose of 20 mg/kg: there comes to a significant increase of the HVA and DOPAC levels and to the decrease of the DA level; the concentration of 5-HIAA was not influenced in the whole dose range. The increase of the HVA and DOPAC levels lasted partly for 24 h after the administration. After a dose of 80 mg/kg an increase of the HVA level to 426% took place and the DA level was decreased by 15% (at the border of significance). These and the pharmacological findings show that it is not possible to consider

TABLE II

Pharmacological properties of compounds *Vabc* and *VIa—d* (oral administration)

Test	*Va*	*Vb*	*Vc*	*VIa*	*VIb*	*VIc*	*VId*
Acute toxicity							
LD_{50}, mg/kg	99·8	92·8	124·9	121·1	185	137·4	100—200[a]
Rotarod							
ED_{50}, mg/kg	2·3	2·3	2·2	5·0	5·0[b]	4·6	7·2
Locomotor activity							
ED_{50}, mg/kg	3·2	3·1	3·8	3·5	[c]	5·7	[c]
5 mg/kg, 1 h, %	49·8$^+$	27·3$^+$	44·5$^+$	23·3$^+$	[c]	71·7$^+$	105·8
5 mg/kg, 3 h, %	17·5$^+$	10·2$^+$	25·9$^+$	16·3$^+$	[c]	44·9$^+$	84·8
Cataleptic activity							
ED_{50}[d], mg/kg	14·1	>50 (40)	>50 (30)	7·6	5—10[e]	>100 (30)	>100 (0)
Antiapomorphine activity							
50 mg/kg, chewing, %	61·1$^+$	97·7	100	100	[f]	100	100
50 mg/kg, agitation, %	32·2$^+$	78·2$^+$	84·7$^+$	82·3$^+$	[f]	91·8	96·5

[a] A dose of 100 mg/kg was lethal for 20% animals, a dose of 200 mg/kg for 60% animals. [b] A dose of 20 mg/kg showed protracted discoordinating effect: ataxia appeared in 30% animals in 24 h after the administration. [c] Was not determined. [d] In parentheses percent of cataleptic animals after the dose given. [e] Maximum effect in 4·5—6·5 h after the administration. [f] Significant effect starting from a dose of 5 mg/kg *p.o* given 3 h before apomorphine, or 40 mg/kg *p.o.* administered 1 h before apomorphine. Doses of 40 and 80 mg/kg are still effective in 24 h after the administration.

compound *VIb* a noncataleptic neuroleptic agent but rather a neuroleptic with protracted actions.

With the most interesting compound *VId*, the affinity to dopamine binding sites in the rat striatum was evaluated by means of estimating the displaced [^{3}H]piperone, bound to the receptors. The IC_{50} value means the concentration of the compound which displaces 50% of the radioactive ligand. For compound *VId*, IC_{50} = 1 067 nmol l^{-1}. For compound *VIb*, IC_{50} = 831 nmol l^{-1}. Both compounds are comparable in this test with clozapine[16] whose IC_{50} = 1 174 nmol l^{-1}.

From the point of view of structure–activity relations it is interesting that the introduction of the atom of iodine and partly of bromine into position 2 of the molecules of the present series leads to an important suppression of the cataleptic action without decreasing the antidopaminergic activity. A similar finding – so far as the cataleptic efficacy is concerned – was made earlier[7] in the analogous series of the 2-halogeno derivatives lacking the "neuroleptic" substituent in position 8 (in the present case isopropyl): whilst the fluoro derivative was clearly cataleptic and the chloro derivative showed an indication of effect, the bromo and iodo compound were cataleptically inactive. The opposite situation appears when the halogen atoms are located in position 8 where they have the function of the "neuroleptic" substituents: out of the 8-halogeno compounds the 8-iodo derivatives have the most intensive cataleptic activity[38,39]. At any rate, 10-[4-(2-hydroxyethyl)piperazino]--2-iodo-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VId*) represents a very interesting noncataleptic potential neuroleptic agent which resembles clozapine[16] by its activity profile.

Compounds *V* and *VI* were also tested for the antimicrobial activity *in vitro* (Dr V. Holá, bacteriological department of this institute) and revealed partly a noteworthy activity. The microorganisms used, formula numbers of the compounds tested and the minimum inhibitory concentrations (in μg/ml) unless they exceed 100 μg/ml are given: *Streptococcus* β-*haemolyticus*, *Va* 6·2, *Vb* 2·5, *Vc* 5, *VIa* 6·2, *VIb* 12·5, *VIc* 3·1; *Streptococcus faecalis*, *Va* 12·5, *Vb* 5, *Vc* 6·2, *VIa* 12·5, *VIb* 12·5, *VIc* 6·2; *Staphylococcus pyogenes aureus*, *Va* 2·5, *Vb* 2·5, *Vc* 2·5, *VIa* 5, *VIb* 6·2, *VIc* 2·5; *Proteus vulgaris*, *Va* 100; *Saccharomyces pasterianus*, *Va* 25, *Vb* 25, *Vc* 25, *VIa* 50, *VIb* 25, *VIc* 25; *Trichophyton mentagrophytes*, *Va* 12·5, *Vb* 6·2, *Vc* 12·5, *VIa* 6·2, *VIb* 25, *VIc* 6·2; *Candida albicans*, *Vb* 50, *Vc* 50, *VIc* 50; *Aspergillus niger*, *Vb* 50, *Vc* 50, *VIa* 50, *VIb* 50, *VIc* 50.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Univam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with Unicam SP 200G and Perkin–Elmer 298 spectrophotometers, the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with MCH-1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Amino-5-fluorotoluene (*XV*)

5-Fluoro-2-nitrotoluene[17] (111 g) was added dropwise over 2 h to a boiling mixture of 1 080 ml water, 21·6 g hydrochloric acid and 215·3 g Fe. The mixture was stirred and refluxed for 2 h, cooled, made alkaline with a solution of 20 g NaOH in 80 ml water and the product was distilled with steam. The 2·5 l distillate were extracted with ether, the extract was dried with K_2CO_3 and distilled; 87·3 g (97%), b.p. 93–94°C/2·3 kPa. Lit.[18], b.p. 100–102°C/3·3 kPa.

3-Methyl-4-nitrophenylhydrazine (*XVI*)

A solution of 201 g 5-fluoro-2-nitrotoluene[17] in 1 400 ml ethanol was treated with 150 g 100% $N_2H_4.H_2O$, 24 g charcoal and a solution of 6·4 g $FeCl_3$ in 60 ml ethanol and the mixture was stirred and refluxed for 10 h. It was filtered, the filtrate cooled by standing overnight and the product was filtered; 123 g (51%), m.p. 135–136°C. Analytical sample, m.p. 137–138°C (ethanol). UV spectrum: λ_{max} 237 nm (log ε 3·82), 382 nm (4·17). IR spectrum: 812, 860, 870 (2 adjacent and solitary Ar—H), 1 365, 1 515 ($ArNO_2$), 1 575 (Ar), 1 610, 1 633 (ArNH), 3 300, 3 330 cm^{-1} (NH_2, NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·10 (bs, 1 H, NH), 7·98 (d, J = 8·0 Hz, 1 H, 5-H), 6·68 (m, 2 H, 2,6-H_2), 4·35 (bs, 2 H, NH_2), 2·55 (s, 3 H, CH_3). For $C_7H_9N_3O_2$ (167·2) calculated: 50·29% C, 5·43% H, 25·14% N; found: 50·17% C, 5·50% H, 24·74% N.

2-Amino-5-chlorobenzoic Acid (*XVII*)

A) A solution of 50 g 5-chloro-2-nitrobenzoic acid in 150 ml methanol was treated with 1·5 g Pd catalyst on charcoal and hydrogenated with shaking under normal conditions (room temperature, atmospheric pressure). The consumption of hydrogen corresponded to the theory after 2 h and stopped. After filtration the solution was evaporated giving 42·6 g (100%) *XVII*, m.p. 209–212°C. Lit.[21], m.p. 210–212°C.

B) A solution of 396 g 5-chloro-2-nitrobenzoic acid in 1·5 l methanol was similarly hydrogenated over a catalyst consisting in 3·0 g Pd on 40 g C. The consumption of hydrogen proceeded slowly during 80 h when it stopped. Similar processing gave 341 g (100%) product, m.p. 160 to 167°C. After recrystallization from methanol the m.p. was 164–167°C and the product was identified as anthranilic acid hydrochloride. For $C_7H_8ClNO_2$ (173·6) calculated: 48·43% C, 4·65% H, 20·42% Cl, 8·07% N; found: 48·21% C, 4·63% H, 19·99% Cl, 8·00% N. Lit.[22,23], m.p. 191, and 193–194°C, respectively. A sample of the product was dissolved in water and the solution was treated with several drops of triethylamine; the precipitated product was identified as anthranilic acid, m.p. 144–146°C, Lit.[24], m.p. 147°C.

5-Chloro-2-(4-isopropylphenylthio)acetophenone (*XIX*)

A mixture of 38 g 2,5-dichloroacetophenone[29], 32 g 4-isopropylthiophenol[1], 48 g K_2CO_3 and 2 g Cu was stirred and heated for 1 h to 140–150°C (bath temperature). After cooling the thick mixture was diluted with 100 ml benzene and after dissolving the organic components, the inorganic salts and copper were filtered off and washed with 50 ml benzene. The filtrate was dried with $MgSO_4$ and evaporated under reduced pressure. The solid residue was crystallized from methanol; 32·5 (53%), m.p. 74–76°C. Analytical sample, m.p. 77–78°C (methanol). UV spectrum: λ_{max} 272 nm (log ε 4·01), 345 nm (3·63). IR spectrum: 820, 830, 880 (2 adjacent and solitary Ar—H), 1 673 cm^{-1} (ArCOR). For $C_{17}H_{17}ClOS$ (304·8) calculated: 66·98% C, 5·62% H, 11·63% Cl, 10·52% S; found: 66·76% C, 5·68% H, 11·92% Cl, 10·96% S.

2-(5-Chloro-5-mercaptophenyl)acetic Acid (*XXI*)

5-Chloro-3*H*-benzo[*b*]thiophen-2-one[29] (16·5 g) was refluxed with a solution of 11·8 g KOH in 50 ml water for 10 h. After cooling the solution was acidified with dilute hydrochloric acid; 9·6 g (53%), m.p. 101·5–103°C. Analytical sample, m.p. 103·5–104·5°C (benzene–light petroleum). IR spectrum: 803, 874, 899 (2 adjacent and solitary Ar—H), 1 232 (C—O in COOH), 1 587, 3 020 (Ar), 1 715 (R—COOH), 2 553 (SH), infl. 3 160 cm^{-1} (OH in COOH). For $C_8H_7ClO_2S$ (202·7) calculated: 47·41% C, 3·48% H, 17·90% Cl, 15·82% S; found: 47·38% C, 3·50% H, 17·66% Cl, 15·70% S.

5-Bromo-2-iodobenzoic Acid (*XXII*)

A solution of 39·1 g *XVIII* (ref.[30]), 15·4 g $NaNO_2$ and 9·1 g NaOH in 550 ml water was added dropwise over 1·5 h to a stirred and cooled solution of 64 ml hydrochloric acid in 90 ml water at 0°C. The stirring at 0°C was continued for 30 min and the formed suspension of the diazonium salt was added over 20 min to a stirred solution of 45·3 g KI and 11 ml H_2SO_4 in 75 ml water at 35–40°C. It was then heated to 90°C, stirred for 30 min at this temperature and the free iodine was removed by distillation with steam. The mixture was stirred and cooled, the crude product was filtered and washed with water. It was dissolved under stirring in 50 ml 40% NaOH, the polymeric components were separated by decantation and the clear solution was acidified with 15% hydrochloric acid. The product was extracted with ether, the extract was dried with $MgSO_4$ and evaporated. The residue was crystallized from 50% aqueous ethanol; 44·5 g (75%), m.p. 153–158°C. Analytical sample, m.p. 160–161°C (aqueous ethanol). IR spectrum: 818, 890, 900 (2 adjacent and solitary Ar—H), 922, 1 248, 1 292 (C—O in COOH), 1 546, 1 568, 3 080, 3 090 (Ar), 1 673, 1 702 (ArCOOH), 2 530, 2 640, infl. 3 100 cm^{-1} (COOH). Lit.[32], m.p. 157·5–158°C.

2,5-Dibromoacetophenone (*XXIV*)

Acetyl chloride (58·9 g) was added over 2 min to a mixture of 118 g 1,4-dibromobenzene and 167 g $AlCl_3$, the mixture was stirred, heated over 20 min to 120°C and kept for 2 h at this temperature. After cooling to 90°C it was poured into a stirred mixture of 435 ml hydrochloric acid, 690 g ice and 200 ml water. The product was extracted with chloroform, the extract was washed with water, 200 ml 10% Na_2CO_3 and water, dried with Na_2SO_4–$MgSO_4$ and evaporated under reduced pressure. The residue was distilled; 119·3 g (86%), b.p. 101–103°C/40 Pa, m.p. 57 to 59°C. Analytical sample, m.p. 59–60°C (hexane). For $C_8H_6Br_2O$ (277·9) calculated: 34·57% C, 2·18% H, 57·50% Br; found: 34·74% C, 2·17% H, 57·08% Br. We are evidently dealing here with the higher melting crystal modification because the literature gives the melting point values of 40–41 and 41°C on the one hand[36,37], and 60°C on the other[35].

5-Bromo-2-(4-isopropylphenylthio)acetophenone (*XX*)

A mixture of 111·4 g *XXIII*, 67 g 4-isopropylthiophenol[1], 83 g K_2CO_3, 1·6 g Cu and 20 ml ethanol was stirred and heated under reflux (bath temperature 140–150°C) for 3 h. After cooling the mixture was diluted with 500 ml benzene, filtered, the filtrate was washed with 10% NaOH and with water, dried with K_2CO_3 and evaporated under reduced pressure; 121 g (86%) inhomogeneous oil. A sample was distilled; b.p. 155–160°C/27 Pa. This product afforded a semicarbazone, m.p. 218–221°C (ethanol). UV spectrum: λ_{max} 254 nm (log ε 4·38), inflexes at 274 nm (4·23) and 325 nm (3·41). IR spectrum: 816, 821, 831, 872 (2 adjacent and solitary Ar—H), 1 580 (Ar and CONH), 1 616 (Ar—C=N), 1 705 (NHCONH$_2$), 3 070 (Ar), 3 210, 3 440 cm^{-1} (NH_2). For $C_{18}H_{20}BrN_3OS$ (406·4) calculated: 53·21% C, 4·96% H, 19·66% Br, 10·34% N, 7·89% S; found: 53·34% C, 5·07% H, 19·66% Br, 10·36% N, 7·77% S.

5-Fluoro-2-(4-isopropylphenylthio)benzoic Acid (*VIIa*)

4-Isopropylthiophenol[1] (57 g) was added to a solution of 68 g KOH in 380 ml water and after 15 min stirring at 60°C there were added 93·1 g 5-fluoro-2-iodobenzoic acid[18] and 2·0 g Cu. The mixture was stirred and refluxed for 6 h, filtered while hot, the filtrate was cooled and acidified with hydrochloric acid. The product was extracted with ethyl acetate, the extract was washed with water, dried with Na_2SO_4–$MgSO_4$, stirred with charcoal for 2 h and filtered. The filtrate was evaporated under reduced pressure, the residue was crystallized from a mixture of 100 ml benzene and 150 ml hexane. The yield (including the second crop obtained by processing of the mother liquor) was 97·8 g (96%), m.p. 138—140°C. Analytical sample, m.p. 139—140·5°C (benzene–hexane). UV spectrum: λ_{max} 223 nm (log ε 4·37), 253 nm (3·94), 329 nm (3·56), infl. 275 nm (3·67). IR spectrum (KBr): 822, 884 (2 adjacent and solitary Ar—H), 915, 1 250, 1 690, 3 070 (ArCOOH), 1 567, 1 600 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·70 (bs, 1 H, COOH), 7·84 (dd, J_{H-F} = 9·0 Hz; J_{H-H} = 3·0 Hz, 1 H, 6-H), 7·50 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of isopropylphenyl), 7·30 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of isopropylphenyl), *c.* 6·90 (m, 2 H, 3,4-H_2), 3·00 (m, 1 H, ArCH), 1·35 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{16}H_{15}FO_2S$ (290·4) calculated: 66·19% C, 5·21% H, 6·54% F, 11·04% S; found: 66·98% C, 5·25% H, 6·68% F, 10·83% S.

5-Chloro-2-(4-isopropylphenylthio)benzoic Acid (*VIIb*)

Was prepared similarly like *VIIa* from 46·2 g 5-chloro-2-iodobenzoic acid[25], 27·2 g 4-isopropylthiophenol[1], 1·75 g Cu and 32 g KOH in 310 ml water; 46·2 g (92%), m.p. 163—166°C. Analytical sample, m.p. 164—167°C (benzene–hexane). Mass spectrum, *m/z* (%): 306 (M^+ corresponding to $C_{16}H_{15}ClO_2S$, 70%) 293, 292, 291 (100), 273, 257, 121 (22), 119, 91, 77. For $C_{16}H_{15}ClO_2S$ (306·7) calculated: 62·64% C, 4·93% H; found: 62·64% C, 4·88% H.

5-Bromo-2-(4-isopropylphenylthio)benzoic Acid (*VIIc*)

Was prepared similarly like *VIIa* from 44·5 g *XXII*, 20·8 g 4-isopropylthiophenol[1], 3·1 g Cu and 27 g KOH in 310 ml water; 20·6 g (43%), m.p. 167—170°C. Analytical sample, m.p. 171°C (aqueous ethanol). UV spectrum: λ_{max} 220 nm (log ε 4·47), 263 nm (4·09), 330 nm (3·68). IR spectrum: 819, 834, 897 (2 adjacent and solitary Ar—H), 920, 1 250 (C—O in COOH), 1 490, 1 546 (Ar), 1 680 (ArCOOH), 2 540, 2 600, 2 670, 2 710, infl. 3 200 cm^{-1} (COOH). For $C_{16}H_{15}$·BrO_2S (351·3) calculated: 54·71% C, 4·30% H, 22·75% Br, 9·12% S; found: 54·29% C, 4·35% H, 22·99% Br, 9·09% S.

5-Fluoro-2-(4-isopropylphenylthio)benzyl Alcohol (*VIIIa*)

A solution of 87·1 g *VIIa* in 580 ml benzene was stirred and treated over 75 min with 270 ml 50% solution of sodium dihydridobis(2-methoxyethoxy)aluminate in toluene. The temperature rose spontaneously to 40°C and the mixture was stirred for 3 h. It was then decomposed by a slow addition of 480 ml 10% NaOH and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layers were washed with water, dried with K_2CO_3 and distilled; 71·0 g (86%), b.p. 165—167°C/27 Pa. IR spectrum (film): 820, 871 (2 adjacent and solitary Ar—H), 1 031 (CH_2OH), 1 490, 1 580, 1 600, 3 015, 3 065 (Ar), 3 340 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70—7·40 (m, 3 H, 3,4,6-H_3), 7·09 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 4·81 (d, J = 5·5 Hz, 2 H, $ArCH_2$), 2·88 (m, 1 H, ArCH), 2·38 (bt, J = 5·5 Hz, 1 H, OH), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{16}H_{17}FOS$ (276·4) calculated: 69·53% C, 6·20% H, 6·88% F, 11·60% S; found: 69·85% C, 6·36% H, 6·79% F, 11·64% S.

5-Chloro-2-(4-isopropylphenylthio)benzyl Alcohol (*VIIIb*)

The reduction of 99·4 g *VIIb* in 640 ml benzene with 300 ml 50% solution of sodium dihydridobis-(2-methoxyethoxy)aluminate in toluene was carried out similarly like in the preceding case. The crude product (101·6) g) was dissolved in 100 ml benzene and the solution was filtered through a 25 cm column (diameter of 2·5 cm) of silica gel; 95·0 g (*c.* 100%) almost homogeneous oil were eluted with benzene. This product was used for further work. A sample was distilled, b.p. 177°C/40 Pa. IR spectrum (film): 822, 876 (2 adjacent and solitary Ar—H), 1 017, 1 039, 1 060 (CH_2OH), 1 363, 1 383 [$CH(CH_3)_2$]. 1 492, 1 557, 1 580, 1 594, 3 030 (Ar), 3 310 cm^{-1} (OH). For $C_{16}H_{17}ClOS$ (292·8) calculated: 12·11% Cl, 10·95% S; found: 11·72% Cl, 10·91% S.

5-Bromo-2-(4-isopropylphenylthio)benzyl Alcohol (*VIIIc*)

A) B_2H_6 was developed by treating a solution of 9·0 ml BF_3 etherate in 20 ml diglyme dropwise with a solution of 1·4 g $NaBH_4$ in 20 ml diglyme over 2 h and it was introduced together with nitrogen into a solution of 7·0 g *VIIc* in 50 ml tetrahydrofuran. The introduction of nitrogen was continued for further 2 h, the mixture was allowed to stand overnight, refluxed for 1 h, cooled and decomposed under stirring by a slow addition of 10 ml water. It was diluted with 50 ml benzene, the precipitated solid was filtered off, the aqueous layer of the filtrate was separated and the organic layer was evaporated *in vacuo*. The residue was dissolved in 50 ml benzene, the solution was washed with 5% NaOH, dried with K_2CO_3 and distilled; 5·4 g (80%), b.p. 80°C/40 Pa, m.p. 44—45°C (light petroleum). IR spectrum: 817, 828, 887 (2 adjacent and solitary Ar—H), 1 016, 1 058 (CH_2OH), 1 486, 1 580, 3 010, 3 030, 3 060 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum: δ 7·59 (d, J = 2·5 Hz, 1 H, 6-H), 7·29 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 7·10 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 7·03 (d, J = 8·0 Hz, 1 H, 3-H), 4·70 (d, J = 6·0 Hz, after ^2H_2O s, 2 H, $ArCH_2O$), 3·81 (m, 1 H, ArCH), 2·18 (t, J = 6·0 Hz, disappears after ^2H_2O, 1 H, OH), 1·20 (d, J = 6·0 Hz, 6 H, 2 CH_3). For $C_{16}H_{17}BrOS$ (337·3) calculated: 56·97% C, 5·08% H, 23·70% Br, 9·51% S; found: 57·01% C, 5·08% H, 24·00% Br, 9·47% S.

B) A mixture of 20·5 g *VIIc* and 100 ml methanol was saturated with gaseous HCl and then refluxed for 2 h. After cooling it was diluted with 300 ml water and the methyl ester of *VIIc* was extracted with ether. The extract was washed with 10% Na_2CO_3 and water, dried with $MgSO_4$ and evaporated. The residue (18·3 g) was dissolved in 35 ml tetrahydrofuran and the solution was added dropwise over 1·5 h to a refluxing mixture of 2·5 g $LiBH_4$ and 35 ml tetrahydrofuran. It was then stirred and refluxed for 6 h, allowed to stand overnight, cooled with ice and decomposed over 2 h under stirring by a slow addition of 23 ml 3M-HCl. It was diluted with 350 ml water and extracted with ether. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue (16·1 g, 82%) crystallized on standing, m.p. 43—44°C, identical with the product described under *A*.

5-Fluoro-2-(4-isopropylphenylthio)benzyl Chloride (*IXa*)

A refluxing and stirred solution of 68·2 g *VIIIa* in 185 ml benzene was treated dropwise over 30 min with 46·2 g $SOCl_2$ and the mixture was stirred and refluxed for 90 min. It was then evaporated *in vacuo*, the residue was diluted with 50 ml benzene and the evaporation was repeated. The residue was dissolved in 150 ml benzene and the solution was filtered through a column of 180 g silica gel. Benzene eluted 70·0 g (91%) homogeneous oil which was used for further work. A sample was distilled, b.p. 148—150°C/40 Pa. For $C_{16}H_{16}ClFS$ (294·8) calculated: 65·18% C, 5·47% H, 12·03% Cl, 6·44% F, 10·88% S; found: 65·66% C, 5·61% H, 11·92% Cl, 6·57% F, 10·88% S.

5-Chloro-2-(4-isopropylphenylthio)benzyl Chloride (*IXb*)

The reaction of 89·2 g *VIIIb* with 57·2 g $SOCl_2$ in 230 ml benzene was carried out similarly like in the preceding case. The residue after evaporation of benzene and $SOCl_2$ was dissolved in 300 ml benzene, the solution was washed with 5% Na_2CO_3 and water, dried with $MgSO_4$ and filtered through a 15 cm column of silica gel (diameter of 3 cm). Elution with benzene gave 86·8 g (92%) oily product which is almost homogeneous and which was used for further work. A sample for analysis was distilled, b.p. 168—169°C/40 Pa. ^{1}H NMR spectrum: δ 7·49 (bs, 1 H, 6-H), 7·20 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 7·15 (m, 2 H, 2,3-H_2), 4·21 (s, 2 H, $ArCH_2Cl$), 2·90 (m, 1 H, ArCH), 1·26 (d, J = 6·0 Hz, 6 H, 2 CH_3). For $C_{16}H_{16}Cl_2S$ (311·3) calculated: 61·74% C, 5·18% H, 10·30% S; found: 61·78% C, 5·47% H, 10·12% S.

5-Bromo-2-(4-isopropylphenylthio)benzyl Chloride (*IXc*)

A refluxing solution of 16·1 g *VIIIc* in 30 ml benzene was treated over 30 min with 10 g $SOCl_2$ and the mixture was stirred and refluxed for 3 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in 50 ml benzene and the solution was filtered through a column of 30 g silica gel (Silpearl). The product was eluted with benzene and the filtrate was distilled; 16·2 g (95%), b.p. 180—185°C/60 Pa. Analytical sample, b.p. 172°C/50 Pa. ^{1}H NMR spectrum: δ 7·58 (d, J = 2·5 Hz, 1 H, 6-H), 7·25 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 7·19 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 7·00 (d, J = 8·0 Hz, 1 H, 3-H), 4·70 (s, 2 H, $ArCH_2Cl$), 2·88 (m, 1 H, ArCH), 1·21 (d, J = 6·0 Hz, 6 H, 2 CH_3). For $C_{16}H_{16}BrClS$ (355·7) calculated: 54·02% C, 4·53% H, 22·47% Br, 9·97% Cl, 9·01% S; found: 54·31% C, 4·51% H, 22·77% Br, 10·10% Cl, 8·93% S.

5-Fluoro-2-(4-isopropylphenylthio)phenylacetonitrile (*Xa*)

A solution of 42 g *IXa* in 100 ml ethanol was treated with a solution of 17·5 g KCN in 30 ml water, 60 ml tetrahydrofuran were added and the solution was refluxed for 5 h under stirring. It was allowed to stand overnight, evaporated *in vacuo*, the residue was diluted with 30 ml water and extracted with benzene. The extract was washed with water, dried with Na_2SO_4–$MgSO_4$, filtered through a 1 cm layer of silica gel, and evaporated *in vacuo*; 38·9 g (96%) almost homogeneous oil which was used for further work. A sample for analysis was distilled; b.p. 166°C/27 Pa (signs of decomposition). IR spectrum (film): 820, 860 (2 adjacent and solitary Ar—H), 1 490, 1 580, 1 600, 3 020, 3 068 (Ar), 2 248 cm^{-1} (R—CN). ^{1}H NMR spectrum: δ 6·80—7·60 (m, 3 H, 3,4,6-H_3), 7·18 and 7·00 (ABq, J = 8·5 Hz, 2 + 2 H, 2,3,5,6-H_4 of isopropylphenyl), 3·88 (s, 2 H, $ArCH_2CN$), 2·89 (m, 1 H, ArCH), 1·27 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{16}FNS$ (285·4) calculated: 6·66% F, 4·91% N, 11·24% S; found: 6·75% F, 4·45% N, 10·92% S.

5-Bromo-2-(4-isopropylphenylthio)phenylacetonitrile (*Xc*)

A) A mixture of 2·2 g *IXc*, 6·0 ml dimethylformamide and 0·55 g KCN was stirred and heated for 8 h to 90—110°C (bath temperature). The solvent was evaporated *in vacuo*, the residue was diluted with 50 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and distilled; 1·40 g (65%), b.p. 182°C/50 Pa. IR spectrum: 825, 885 (2 adjacent and solitary Ar—H), 1 465, 1 492, 1 552, 1 580, 1 600, 3 020, 3 060, 3 075 (Ar), 2 255 cm^{-1} (R—CN). ^{1}H NMR spectrum: δ 7·60 (d, J = 2·0 Hz, 1 H, 6-H), 7·31 (q, J = 8·0; 2·0 Hz, 1 H, 4-H), 7·10 (d, J = 8·0 Hz, 1 H, 3-H), 7·10 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 3·75 (s, 2 H, $ArCH_2CN$), 2·80 (m, 1 H, ArCH), 1·20 (d, 6 H, 2 CH_3). For $C_{17}H_{16}BrNS$ (346·3) calculated: 58·96% C, 4·66% H, 23·08% Br, 4·04% N, 9·26% S; found: 59·33% C, 4·63% H, 23·50% Br, 3·66% N, 9·25% S.

B) The reaction of 16·2 g *IXc* in 30 ml ethanol with 4·75 g KCN in 8 ml water in the presence of 30 ml tetrahydrofuran was carried out similarly like in the preparation of *Xa*. The crude product obtained (15·5 g) was chromatographed on a column of 50 g silica gel. Elution with benzene recovered first 0·5 g starting *IXc* and gave then 14·2 g (90%) homogeneous oily *Xc* which was used for further work.

2-[5-Fluoro-2-(4-isopropylphenylthio)phenyl]acetic Acid (*XIa*)

A solution of 13·8 g *Xa* in 30 ml ethanol was treated with a solution of 13 g KOH in 15 ml water and the mixture was stirred and refluxed for 6 h. After standing overnight it was diluted with 100 ml water, acidified with 20 ml hydrochloric acid and extracted with benzene. The extract was washed with water, dried with Na_2SO_4–$MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from a mixture of 15 ml cyclohexane and 15 ml hexane; 12·2 g (83%), m.p. 91—92·5°C. Analytical sample, m.p. 92—93° (cyclohexane). IR spectrum (KBr): 820, 825, 871 (2 adjacent and solitary Ar—H), 936, 1 226, 1 239, 1 272 (C—O of COOH), 1 492, 1 580, 1 602 (Ar), 1 705 (R—COOH), infl. 3 100 cm^{-1} (COOH). ^1H NMR spectrum: δ 11·40 (bs, 1 H, COOH), 6·80—7·50 (m, 3 H, 3,4,6-H_3), 7·09 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 3·88 (s, 2 H, $ArCH_2CO$), 2·85 (m, 1 H, ArCH), 1·23 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{17}FO_2S$ (304·4) calculated: 67·08% C, 5·63% H, 6·24% F, 10·54% S; found: 67·65% C, 5·69% H, 6·26% F, 10·75% S.

2-[5-Chloro-2-(4-isopropylphenylthio)phenyl]acetic Acid (*XIb*)

A mixture of 83 g *IXb*, 200 ml dimethylformamide and 39 g NaCN was stirred and heated for 10 h to 110°C. It was evaporated *in vacuo*, the residue was diluted with water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$, filtered through a column of 70 g neutral Al_2O_3 (activity II), the column was washed with benzene and the filtrates were evaporated under reduced pressure. The residue (70·4 g) was considered the crude nitrile *Xb* and was processed without purification and characterization. It was dissolved in 210 ml ethanol, the solution was treated with 57 g KOH in 130 ml water and the mixture was stirred and refluxed for 6 h. Ethanol was evaporated under reduced pressure, the residue was diluted with water, acidified with hydrochloric acid and extracted with dichloromethane. The extract was dried with Na_2SO_4 and evaporated. The inhomogeneous residue was dissolved in benzene and the solution was chromatographed on a column of 800 g silica gel. Benzene and benzene containing 10% chloroform eluted the neutral components* and chloroform eluted 29·9 g (40%) *XIb*, m.p. 85—87°C (hexane). IR spectrum: 815, 833, 870, 897 (2 adjacent and solitary Ar—H), 920, 1240 (C—O of COOH), 1 485, 1 580 (Ar), 1 708 (R—COOH), 2 525, 2 610, 2 695, infl. 3 100 cm^{-1}

* *Added in proof*: Rechromatography of the neutral fraction on silica gel and elution with chloroform gave 2·1 g substance melting at 107—110°C (benzene–hexane) which was identified as 2,3-bis[5-chloro-2-(4-isopropylphenylthio)phenyl]propionamide. Mass spectrum, *m/z* (%): 593 (M^+ corresponding to $C_{33}H_{33}Cl_2NOS_2$, 9 %), 442 (21), 397 (7), 318 (10), 273 (34), 233 (100), 231 (50), 198 (45). IR spectrum (KBr): 818, 830, 880 (2 adjacent and solitary Ar—H), 1 490, 1 510, 1 576, 1 600 (Ar), 1 680 ($CONH_2$), 3 230, 3 300, 3 480 cm^{-1} (NH_2). ^1H NMR spectrum: δ 6·90—7·80 (m, 14 H, ArH), 5·85 and 5·15 (2 bs, 1 + 1 H, $CONH_2$), 3·68 (t, J = = 8·0 Hz, 1 H, Ar—CH—CO), 3·60 and 3·12 (2 dd, J = 14·0; 8·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·90 (m, 2 H, 2 ArCH of two isopropylphenyls), 1·25 and 1·22 (2 d, J = 7·0 Hz, 12 H, 4 CH_3 of two isopropyls). For $C_{33}H_{33}Cl_2NOS_2$ (594·7) calculated: 66·65% C, 5·59% H, 11·93% Cl, 2·36% N, 10·78% S; found: 66·85% C, 5·69% H, 11·80% Cl, 2·21% N, 10·79% S.

(COOH). ^{1}H NMR spectrum: δ 10·95 (bs, 1 H, COOH), *c.* 7·20 (m, 3 H, 3,4,6-H_3), 7·12 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 3·88 (s, 2 H, $ArCH_2CO$), 2·82 (m, 1 H, ArCH), 1·24 (d, J = = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{17}ClO_2S$ (320·9) calculated: 63·64% C, 5·34% H, 11·05% Cl, 10·00% S; found: 63·81% C, 5·35% H, 11·01% Cl, 10·23% S.

2-[5-Bromo-2-(4-isopropylphenylthio)phenyl]acetic Acid (*XIc*)

A) The distilled nitrile *Xc* (0·80 g) was hydrolyzed by refluxing with 1·0 g KOH in 5 ml ethanol and 1 ml water for 4 h. Ethanol was evaporated, the residue was diluted with 10 ml water, the solution was acidified with hydrochloric acid and extracted with benzene. Processing of the extract gave 0·85 g (100%) *XIc*, m.p. 106—107°C (benzene–light petroleum). IR spectrum: 829, 893 (2 adjacent and solitary Ar—H), 910, 1 268, 1 282, 1 300 (C—O of COOH), 1 485, 1 573 (Ar), 1 700 (R—COOH), infl. 3 100 cm^{-1} (OH of COOH). ^{1}H NMR spectrum: δ 11·30 (bs, 1 H, COOH), 7·00—7·50 (m, 7 H, ArH), 3·80 (s, 2 H, $ArCH_2CO$). 2·80 (m, 1 H, ArCH), 1·21 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{17}BrO_2S$ (365·3) calculated: 55·89% C, 4·69% H, 21·88% Br, 8·78% S; found: 56·36% C, 4·90% H, 22·22% Br, 8·82% S.

B) The undistilled nitrile *Xc* (14·0 g) was similarly hydrolyzed with 10·7 g KOH in 12 ml water and 25 ml ethanol (refluxing for 6 h). The mixture was evaporated *in vacuo*, the residue was diluted with 100 ml water, acidified with hydrochloric acid and extracted with dichloromethane. Processing of the extract gave 14·7 g inhomogeneous product which was dissolved in 8 ml warm benzene, the solution was diluted with 25 ml hexane and inoculated with a crystal obtained under *A*; 8·2 g *XIc*, m.p. 105—107°C. The mother liquor was evaporated and chromatographed on a column of 100 g silica gel. Elution with benzene gave in the most polar fractions further 1·9 g *XIc*, the total yield being 10·1 g (68%).

The least polar fraction from the just mentioned chromatography (3·0 g) consisted of a neutral oily substance, b.p. 163—164°C/10 Pa, which was identified to be 5-bromo-2-(4-isopropylphenylthio)benzyl ethyl ether (*XXIII*). IR spectrum: 824, 886, 890 (2 adjacent and solitary Ar—H), 1 114 (R—O—R'), 1 462, 1 495, 1 553, 1 580, 1 600, 3 000, 3 050 cm^{-1} (Ar). ^{1}H NMR spectrum δ 7·60 (d, J = 2·5 Hz, 1 H, 6-H), 7·25 (q, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·12 (s, 4 H, 2,3,5,6-H_4 of isopropylphenyl), 7·00 (d, J = 8·5 Hz, 1 H, 3-H), 4·55 (s, 2 H, $ArCH_2O$), 3·58 (q, J = 7·0 Hz, 2 H, CH_2O of ethoxyl), 2·85 (m, 1 H, Ar CH), 1·22 (t, J = 7·0 Hz, 3 H, CH_3 of ethoxyl), 1·19 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{18}H_{21}BrOS$ (365·3) calculated: 59·17% C, 5·79% H, 21·88% Br, 8·78% S; found: 60·00% C, 5·92% H, 22·60% Br, 8·37% S.

2-[2-(4-Isopropylphenylthio)-5-nitrophenyl]acetic Acid (*XIe*)

A mixture of 108 g KOH in 1 l water, 131 g 2-(2-chloro-5-nitrophenyl)acetic acid[8], 102 g 4-isopropylthiophenol[1] and 7·2 g Cu was refluxed under stirring for 8 h, filtered and the cooled filtrate was acidified with hydrochloric acid. The solid was filtered, washed with water and dissolved in 2 l dichloromethane. The solution was washed with water, dried with Na_2SO_4, filtered and evaporated. The residue was crystallized from a mixture of benzene and hexane; 93·3 g (46%), m.p. 144—145°C. Analytical sample, m.p. 144·5—146·5°C (aqueous ethanol). UV spectrum: λ_{max} 223 nm (log ε 4·31), 253 nm (3·94), 340 nm (4·09). IR spectrum: 830, 889 (2 adjacent and solitary Ar—H), 930, 1 236 (C—O in COOH), 1 337, 1 504 ($ArNO_2$), 1 574, 1 600 (Ar), 1 710 (R—COOH), 2 543, 2 625, 2 728, infl. 3 200 cm^{-1} (COOH). ^{1}H NMR spectrum: δ 11·05 (bs, 1 H, COOH), 8·09 (d, J = 2·5 Hz, 1 H, 6-H), 7·92 (dd, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·40 and 7·21 (ABq, J = 8·5 Hz, 2 + 2 H, 2,3,5,6-H_4 of isopropylphenyl), 6·98 (d, J = 8·5 Hz, 1 H, 3-H), 3·95 (s, 2 H, $ArCH_2CO$), 2·95 (m, 1 H, ArCH), 1·30 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{17}$·.NO_4S (331·4) calculated: 61·62% C, 5·17% H, 4·23% N, 9·68% S; found: 61·71% C, 5·11% H, 4·50% N, 9·70% S.

2-[5-Amino-2-(4-isopropylphenylthio)phenyl]acetic Acid (*XIf*)

A solution of 93·3 g *XIe* in 250 ml ethanol was treated successively with 13 g charcoal, 184 ml 30% $N_2H_4.H_2O$ and over 30 min with a solution of 3·6 g $FeCl_3$ in 60 ml ethanol under stirring. The mixture was refluxed for 8 h, filtered and the filtrate was evaporated under reduced pressure. The residue was diluted with 500 ml water, acidified with acetic acid and the precipitated solid was extracted with chloroform. The extract was dried with Na_2SO_4 and evaporated. The residue was heated with 200 ml hexane and the crystalline product was filtered after cooling; 63·0 g (75%), m.p. 140–142·5°C. Analytical sample, m.p. 144–146°C (chloroform–hexane). IR spectrum: 820, 858 (2 adjacent and solitary Ar—H), 980, 1 220, 1 292 (C—O of COOH), 1 492, 1 576, 1 600, 3 020, 3 040, 3 070 (Ar), 1 620 ($ArNH_2$). 1 700 (R—COOH), 3 190, 3 280, 3 367 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·30–7·30 (m, 7 H, ArH), 3·52 (s, 2 H, $ArCH_2CO$), 2·80 (m, 1 H, ArCH), 1·15 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{19}NO_2S$ (301·4) calculated: 67·74% C, 6·35% H, 4·65% N, 10·64% S; found: 67·80% C, 6·39% H, 4·46% N, 10·77% S.

2-Fluoro-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIa*)

Polyphosphoric acid was prepared from 154 ml 85% H_3PO_4 and 227 g P_2O_5 by heating to 155°C for 2 h. *XIa* (31·2 g) was added under stirring and the mixture was heated for 4·5 h to 150 to 155°C. After cooling it was poured into 500 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with Na_2SO_4–$MgSO_4$ and filtered through a column of 50 g silica gel which was washed with benzene. The filtrate was evaporated under reduced pressure and the residue was crystallized from a mixture of 20 ml cyclohexane and 5 ml hexane; 22·2 g (76%), m.p. 79–81°C. Analytical sample, m.p. 80–81·5°C (cyclohexane–hexane). UV spectrum: λ_{max} 241 nm (log ε 4·29), 335 nm (3·57), infl. 260 nm (4·07). IR spectrum (KBr): 811, 829, 881 (2 adjacent and solitary Ar—H), 1 583, 1 598, 3 055 (Ar), 1 675 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·02 (d, J = 2·0 Hz, 1 H, 9-H), 7·58 (dd, J_{H-H} = 8·0 Hz; J_{H-F} = 5·0 Hz, 1 H, 4-H), 8·53 (d, J = 8·0 Hz, 1 H, 6-H), 7·28 (dd, J = 8·0; 2·0 Hz, 1 H, 7-H), 7·15 (dd, J_{H-H} = = 2·5 Hz; J_{H-F} = 8·0 Hz, 1H, 1-H), 6·87 (dt, J_{H-H} = 2·5; 8·0 Hz; J_{H-F} = 8·0 Hz, 1 H, 3-H), 4·39 (s, 2 H, $ArCH_2CO$), 2·90 (m, 1 H, ArCH), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{15}FOS$ (286·4) calculated: 71·30% C, 5·28% H, 6·63% F, 11·20% S; found: 71·46% C, 5·35% H, 6·76% F, 11·50% S.

2-Chloro-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIb*)

Polyphosphoric acid was prepared similarly like in the preceding case from 75 ml 85% H_3PO_4 and 112 g P_2O_5 and was used to cyclize 16·0 g *XIb* at 155°C for 4 h. Similar processing gave 14·6 g crude product. Crystallization from 15 ml cyclohexane and processing of the mother liquor gave 11·3 g (75%) product melting at 77–79°C. Analytical sample, m.p. 78–80°C (cyclohexane). UV spectrum: λ_{max} 234 nm (log ε 4·40), 337 nm (3·62), infl. 260 nm (4·07). IR spectrum: 810, 820, 900 (2 adjacent and solitary Ar-H), 1 675 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·09 (d, J = 2·0 Hz, 1 H, 9-H), 7·53 (d, J = 8·0 Hz, 1 H, 4-H), 7·51 (d, J = 8·0 Hz, 1 H, 6-H), 7·42 (d, J = 2·0 Hz, 1 H, 1-H), 7·29 (q, J = 8·0; 2·0 Hz, 1 H, 7-H), 7·11 (q, J = 8·0; 2·0 Hz, 1 H, 3-H), 4·32 (s, 2 H, $ArCH_2CO$), 2·88 (m, 1 H, ArCH), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{15}ClOS$ (302·8) calculated: 67·43% C, 5·00% H, 11·71% Cl, 10·59% S; found: 67·70% C, 5·12% H, 11·55% Cl, 10·44% S.

2-Bromo-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIc*)

XIc (7·8 g) was cyclized with polyphosphoric acid (from 32 g 85% H_3PO_4 and 47 g P_2O_5) at 150°C for 4·5 h similarly like in the preceding cases. After cooling to 80°C it was decomposed with 300 g ice and water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with Na_2SO_4–$MgSO_4$ and evaporated. The residue was chromatographed on a column of 80 g silical gel. Elution with benzene gave 6·3 g (85%) *XIIc*,m.p. 95—97°C (cyclohexane). UV spectrum: λ_{max} 240 nm (log ε 4·49), 335 nm (3·59), infl. 265 nm (4·04). IR spectrum (KBr): 830, 883 (2 adjacent and solitary Ar—H), 1 571, 1 591, 3 063 (Ar), 1 670 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·10 (d, J = 2·0 Hz, 1 H, 9-H), 7·20—7·70 (m, 5 H, 1,3,4,6,7-H_5), 4·39 (s, 2 H, $ArCH_2CO$), 2·98(m, 1 H, ArCH), 1·30 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{15}BrOS$ (347·3) calculated: 58·80% C, 4·35% H, 23·01% Br, 9·23% S; found: 59·25% C, 4·50% H, 23·34% Br, 9·34% S.

2-Amino-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIf*)

XIf (55·2 g) was cyclized with polyphosphoric acid (from 185 ml 85% H_3PO_4 and 370 g P_2O_5) by heating to 125—130°C for 2 h. After cooling to 80°C it was decomposed with 3 kg ice and water, the precipitated product was filtered with suction and suspended in 1·5 l 5% Na_2CO_3. The suspension was stirred for 1·5 h at room temperature, the solid was filtered, washed with water and dried. It was then dissolved in 1·5 l chloroform, the undissolved part was filtered off and the filtrate was evaporated. The residue was dissolved in 250 ml benzene and chromatographed on 300 g neutral Al_2O_3 (activity II). The first benzene eluate (1·5 g) was discarded and the following 46·5 g crude product were crystallized from a mixture of 50 ml benzene and 40 ml cyclohexane; 36·1 g (70%), m.p. 148—151°C. Analytical sample, m.p. 150—152°C (benzene–cyclohexane). UV spectrum: λ_{max} 264 nm (log ε 4·31), 351 nm (3·50). IR spectrum: 825, 840, 846, 869 (2 adjacent and solitary Ar—H), 1 565, 1 596 (Ar), 1 620 ($ArNH_2$), 1 660 (ArCO), 3 208, 3 340, 3 460 cm^{-1} (NH_2). ^1H NMR spectrum: δ 8·02 (d, J = 2·5 Hz, 1 H, 9-H), 7·10 to 7·50 (m, 3 H, 3,6,7-H_3), 6·70 (d, J = 2·5 Hz, 1 H, 1-H), 6·40 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 4·24 (s, 2 H, $ArCH_2CO$), 3·80 (bs, 2 H, NH_2), 2·88 (m, 1 H, ArCH), 1·21 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}NOS$ (283·4) calculated: 72·05% C, 6·05% H, 4·94% N, 11·32% S; found: 72·67% C, 6·40% H, 4·44% N, 11·05% S.

2-Iodo-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIId*)

A mixture of 10·6 g *XIIf*, 135 ml water and 34 ml hydrochloric acid (suspension of the hydrochloride) was stirred and diazotized at 0°C with a solution of 2·8 g $NaNO_2$ in 6 ml water over 30 min. The mixture was stirred for 2 h at 0°C and treated dropwise at the same temperature with a solution of 11·3 g KI and 1·1 g *I* in 17 ml water. The temperature was then raised to 20°C and the mixture was stirred for 1 h. After standing overnight at room temperature it was extracted with benzene. The extract was washed with 5% NaOH, 5% $Na_2S_2O_3$ and water, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a column of 300 g silica gel. The first benzene eluates were discarded and the following 4·5 g were purified by distillation *in vacuo*; 4·2 g (28%), b.p. 220°C/13 Pa, m.p. 105—106°C (cyclohexane). UV spectrum: λ_{max} 240 nm (log ε 4·55), 335 nm (3·79), infl. 265 nm (4·10). IR spectrum (KBr): 830, 880 (2 adjacent and solitary Ar—H), 1 567, 1 590, 3 050 (Ar), 1 670 cm^{-1} (ArCO). ^1H NMR spectrum: δ 8·10 (d, J = 2·0 Hz, 1 H, 9-H), 7·80 (d, J = 2·0 Hz, 1 H, 1-H), 7·20—7·60 (m, 4 H, 3,4,6,7-H_4), 4·35 (s, 2 H, $ArCH_2CO$), 2·98 (m, 1 H, ArCH), 1·30 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{15}IOS$ (394·3) calculated: 51·79% C, 3·84% H, 32·19% I, 8·13% S; found: 52·13% C, 3·91% H, 31·45% I, 8·30% S.

2-Fluoro-8-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIIIa*)

A suspension of 21·3 g *XIIa* in 300 ml ethanol was heated to 50°C, the addition of 20 ml tetrahydrofuran brought about a complete dissolution of the ketone and the stirred solution was slowly treated with 3·4 g $NaBH_4$. The mixture was refluxed for 15 min, cooled to 20°C, treated with 50 ml water and the volatile solvents were evaporated *in vacuo*. The residue was diluted with 300 ml water and the product was extracted with benzene. The extract was washed with water, dried with Na_2SO_4–$MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from a mixture of 25 ml benzene and 75 ml hexane; 19·8 g (92%), m.p. 111·5—113°C. Analytical sample, m.p. 112—113·5°C (benzene–hexane). IR spectrum (KBr): 815, 875 (2 adjacent and solitary Ar-H), 1 470, 1 580, 1 597 (Ar), 3 390 cm^{-1} (OH). ^1H NMR spectrum: δ 6·60—7·60 (m, 6 H, ArH), 5·22 (bd, 1 H, Ar—CH—O), 3·70 and 3·29 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·85 (m, 1 H, ArCH), 2·60 (bd, 1 H, OH), 1·22 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}FOS$ (288·4) calculated: 70·80% C, 5·94% H, 6·59% F, 11·12% S; found: 70·78% C, 6·00% H, 6·76% F, 11·29% S.

2-Chloro-8-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIIIb*)

A solution of 8·5 g *XIIb* in 160 ml ethanol was stirred and treated at 50°C with 1·6 g $NaBH_4$ over 10 min. The mixture was refluxed for 30 min, cooled, diluted with 150 ml water and extracted with chloroform. Processing of the extract gave 9·3 g crude product which was dissolved in 25 ml boiling cyclohexane and the solution was allowed to crystallize; 8·3 g (97%), m.p. 87—89°C. IR spectrum: 815, 825, 890 (2 adjacent and solitary Ar—H), 1 092 (CHOH), 3 330, 3 400 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·50 (m, 6 H, ArH), 5·30 (bm, 1 H, Ar—CH—O), 3·69 and 3·29 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·80 (m, 1 H, ArCH), 2·17 (bd, 1 H, OH), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}ClOS$ (304·9) calculated: 66·98% C, 5·62% H, 11·63% Cl, 10·52% S; found: 66·96% C, 5·70% H, 11·42% Cl, 10·38% S.

2-Bromo-8-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIIIc*)

A solution of 8·25 g *XIIc* in 135 ml ethanol was reduced with 1·35 g $NaBH_4$ similarly like in the preceding case. The mixture was evaporated under reduced pressure, the residue was diluted with 150 ml water and extracted with chloroform. Processing of the extract gave the crude product which was purified by chromatography on 100 g silica gel. Elution with benzene containing 20% chloroform gave 8·0 g (96%) *XIIIc*, m.p. 58—61°C (cyclohexane). IR spectrum (KBr): 810, 820, 890 (2 adjacent and solitary Ar—H), 1 060 (CHOH), 1 572, 1 595 (Ar), 3 270 cm^{-1} (OH). ^1H NMR soectrum: δ 6·90—7·40 (m, 6 H, ArH), 5·28 (bm, 1 H, Ar—CH—O), 3·68 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·90 (m, 1 H, ArCH), 2·30 (bd, 1 H, OH), 1·24 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}BrOS$ (349·3) calculated: 58·46% C, 4·91% H, 22·88% Br, 9·18% S; found: 59·09% C, 5·18% H, 22·35% Br, 9·05% S.

2-Iodo-8-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIIId*)

A solution of 4·65 g *XIId* in 70 ml ethanol was reduced with 0·67 g $NaBH_4$ similarly like in the preceding case. A similar processing gave 2·9 g (62%) *XIIId*, m.p. 72—75°C (cyclohexane). IR spectrum (KBr): 811, 825, 890 (2 adjacent and solitary Ar—H), 1 059 (CHOH), 1 568, 1 595 (Ar), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·70 (m, 6 H, ArH), 5·30 (bm, 1 H, Ar—CH—O), 3·69 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·90 (m, 1 H, ArCH), 2·20 (bs, 1 H, OH), 1·24 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}IOS$ (396·3) calculated: 51·52% C, 4·32% H, 8·09% S; found: 52·02% C, 4·58% H, 8·04% S.

10-Chloro-2-fluoro-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVa*)

Powdered $CaCl_2$ (7·0 g) was added to a solution of 18·8 g *XIIIa* in 190 ml benzene and the suspension was saturated for 4 h with HCl. After standing overnight the mixture was filtered, the filtrate evaporated under reduced pressure and the residue crystallized from 25 ml hexane; 17·3 g (87%) *XIVa*, m.p. 86·5–88·5°C (hexane with a small amount of benzene). ^{1}H NMR spectrum: δ 6·80 to 7·60 (m, 6 H, ArH), 5·78 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·02 and 3·65 (2 dd, J = 14·0; 4·0 and 14·0; 4·0 Hz, 1 + 1 H, $ArCH_2$), 2·86 (m, 1 H, ArCH), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{16}ClFS$ (306·8) calculated: 66·55% C, 5·26% H, 11·55% Cl, 6·19% F, 10·45% S; found: 66·68% C, 5·30% H, 11·60% Cl, 6·47% F, 10·32% S.

2,10-Dichloro-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVb*)

A similar reaction of 10·4 g *XIIIb* in 105 ml benzene with HCl in the presence of 3·7 g $CaCl_2$ gave 7·4 g (67%) product, m.p. 91–92°C (cyclohexane). ^{1}H NMR spectrum: δ 6·90–7·50 (m, 6 H, ArH), 5·76 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·98 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·80 (m, 1 H, ArCH), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{16}Cl_2S$ (323·3) calculated: 63·16% C, 4·99% H, 21·93% Cl, 9·92% S; found: 63·33% C, 5·01% H, 22·09% Cl, 9·50% S.

2-Bromo-10-chloro-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVc*)

Prepared similarly from 9·0 g *XIIIc* and HCl in 90 ml benzene in the presence of 3·0 g $CaCl_2$; 7·9 g (83%), m.p. 94–96°C (benzene–hexane). ^{1}H NMR spectrum: δ 6·90–7·50 (m, 6 H, ArH), 5·78 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·98 and 3·62 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·88 (m, 1 H, ArCH), 1·24 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{16}$·BrClS (367·8) calculated: 55·52% C, 4·39% H, 21·73% Br, 9·64% Cl, 8·72% S; found: 55·90% C, 4·39% H, 22·25% Br, 9·84% Cl, 8·89% S.

10-Chloro-2-iodo-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVd*)

Prepared similarly from 2·6 g *XIIId* and HCl in 25 ml benzene in the presence of 1·0 g $CaCl_2$; 2·4 g (88%), m.p. 100–101°C (benzene–hexane). IR spectrum (KBr): 825_1 829, 889 (2 adjacent and solitary Ar—H), 1 550, 1 568 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·90–7·60 (m, 6 H, ArH), 5·75 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·58 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·84 (m, 1 H, ArCH), 1·22 (d, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{17}H_{16}$·.ClIS (414·8) calculated: 49·23% C, 3·89% H, 8·55% Cl, 30·60% I, 7·73% S; found: 49·67% C, 3·94% H, 8·40% Cl, 30·34% I, 7·85% S.

2-Fluoro-8-isopropyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Va*) (Method *A*)

A mixture of 10·3 g *XIVa*, 10·1 g 1-methylpiperazine and 12 ml chloroform was stirred and refluxed for 7 h. After cooling it was shaken with 100 ml 5% NH_4OH and extracted with dichloromethane. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of 80 g silica gel. Benzene eluted 1·2 g of the neutral components. The product (11·1 g, 90%) was then eluted with chloroform and crystallized from a mixture of cyclohexane and benzene, m.p. 109–111°C. IR spectrum: 820, 825, 871 (2 adjacent and solitary Ar—H), 1 580, 1 599, 3 010, 3 050, 3 080 (Ar), 2 730, 2 755, 2 780 cm^{-1} (N—CH_2, N—CH_3). ^{1}H NMR spectrum: δ 6·60–7·60 (m, 6 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$),

2·80 (m, 1 H, ArCH of isopropyl), 2·68 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·42 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3), 1·20 (d, $J = 7·0$ Hz, 6 H,2 CH_3 of isopropyl). Neutralization with methanesulfonic acid in 96% ethanol and addition of ether gave the dimethanesulfonate monohydrate, m.p. 182—185 and after resolidification 201—203°C (ethanol–ether). The analyses are in Table I.

2-Bromo-10-[4-(2-hydroxyethyl)piperazino]-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIc*) (Method *B*)

A stirred mixture of 5·0 g *XIVc*, 4·4 g 1-(2-hydroxyethyl)piperazine and 5 ml chloroform was refluxed for 6 h. After cooling it was shaken with 50 ml 5% NH_4OH and extracted with dichloromethane. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of 180 g neutral Al_2O_3 (activity II). Elution with benzene separated 1·0 g neutral oil. The product was eluted with chloroform and crystallized from a mixture of cyclohexane and benzene as a 3 : 1 solvate with cyclohexane; 5·7 g (86%), m.p. 79—82°C. Mass spectrum, *m/z* (%): 460 (M^+ corresponding to $C_{23}H_{29}BrN_2OS$, below 1%), 331 (14), 210 (15), 142 (15), 129 (51), 127 (33), 116 (15), 115 (14), 102 (72), 100 (100), 58 (29), 56 (41). IR spectrum (KBr): 810, 824, 888 (2 adjacent and solitary Ar—H), 1 079 (CH_2OH), 1 552, 1 572, 1 595 (Ar), 2 810 (CH_2—N), 3 420 cm^{-1} (OH). ^1H NMR spectrum: δ 6·80—7·50 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, $J = 6·0$ Hz, 2 H, CH_2O), 2·90 (s, 1 H, OH), 2·85 (m, 1 H, ArCH of isopropyl), c. 2·60 (m, 10 H, 5 CH_2N), 1·43 (s, 4 H, 2 CH_2 of cyclohexane), 1·21 (d, $J = 7·0$ Hz, 6 H, 2 CH_3 of isopropyl). Neutralization of the base with methanesulfonic acid in ethanol and addition of ether gave the dimethanesulfonate hemihydrate, m.p. 175—177°C (ethanol–ether). Analyses are in Table I.

Dr K. Šindelář, Mr Z. Prošek, Mr Z. Šedivý, Mr D. Půček and Mr J. Pomykáček participated in the preparation of intermediates. The authors are indebted to Dr M. Ryska and Mrs A. Hrádková (Physico-chemical department of this institute) for a part of the spectral data. The analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech a Mrs J. Kropáčová (Analytical department of this institute).

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Translated by the author (M. P.).