ANALOGUES OF THE NEUROLEPTIC AGENT ISOBUTACLAMOL: STEREOISOMERIC 3*b*,4,5,6,7,9,9a,10-OCTAHYDRO-[1]BENZOTHIEPINO-[2,3,4-*ed*]PYRIDO[2,1-*a*]ISOQUINOLIN-5-OLS AND SOME RELATED COMPOUNDS

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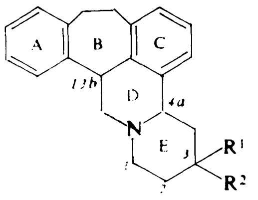
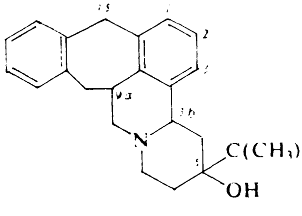
10,11-Dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*XVI*) was reduced with aluminium hydride to the primary amine *XVII* which was formylated with acetic formic anhydride. The formamide derivative *XVIII* was cyclized by the Bischler–Napieralski reaction to the condensed dihydroisoquinoline *XX*. Addition of methyl vinyl ketone to the hydrochloride of compound *XX* at 100°C gave a mixture of the stereoisomeric 3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]-pyrido[2,1-*a*]isoquinolin-5-ones (*XIII*) which was separated by chromatography to the major 3b,9a-*cis* isomer *XIIIb* and the minor 3b,9a-*trans* isomer *XIIIa* to which the configuration was assigned on the basis of analogy. Reactions of both ketones with tert-butylmagnesium chloride and isopropyllithium led to mixtures whose chromatographic separation afforded the tertiary alcohols *XIa*, *XIb*, *XIIa* and *XIIb* mostly in low yields. In most cases the main products were the secondary alcohols *XIV* and apparently also the pinacols *XXIII*, formed by reduction. An attempt at preparing similar [1]benzothiopyrano[2,3,4-*ed*]pyrido[1,2-*a*]isoquinoline derivatives was discontinued because of an anomalous result of cyclization of compound *XXVII*. Compound *XIa*, being a 15-thia analogue of isobutaclamol (*VI*) displayed a high affinity to dopamine receptors in striatum of the rat brain which confirms the correctness of the assignment of relative configuration on $C_{(3b)}$ and $C_{(9a)}$.

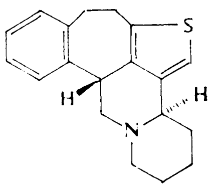
Since 1966 the Ayerst team[1] has been publishing synthetic studies, starting from the knowledge of neurotropic and psychotropic activity of amines derived from the tricyclic dibenzo[*a, d*]cycloheptene system[2], and oriented to such amines in which the amino group is a member of a fourth ring, anelated between positions 4 and 5 of the mentioned system. It was an empirical approach which led to series of interesting compounds[3] subjected to pharmacological screening; some of the products showed properties of potential antidepressants. Only the anelation of the fifth ring, however, led to a substance of promising therapeutic usefulness: it was the experimental anxiolytic agent taclamine (*I*, 4*a*,13b-*trans*) (ref.[4,5]). The pentacyclic ketone *II* was of fundamental importance for further development; it was first prepared as a mixture of stereoisomers[3] which was later separated by chromatography to both racemates[4]. Reactions of the 4a,13b-*trans* racemate with organometallic compounds resulted in a number of tertiary alcohols[6,7] out of which we have to mention butaclamol [*III*, 4*a*,13b-*trans*; 3(OH),13b(H)-*trans*] (ref.[6,8–13]), which showed properties of an antipsychotically active neuroleptic in schizophrenic patients[14,15], further dexclamol (*IV*) (ref.[6,16,17]) and finally deoxybutaclamol (*V*) (ref.[18]). The pharmacologically active racemates of *III* and *IV* were resolved to enantiomers[19], for the active enantiomers the absolute configuration was determined by crystallographic studies[20], and especially in the case of butaclamol (*III*) an almost absolute stereospecificity of the neuroleptic action was established: in behavioural studies in animals[21], in the influence on dopamine metabolism in the rat brain[22] and also in studies of interaction with dopamine receptors in the calf caudate nucleus homogenates using [^{3}H]spiperone as a radioligand[23]. Introduction of an atom of chlorine into some positions of the tricyclic ABC fragment of the structure *III* (which has a dramatic effect on the pharmacological profile in the series of tricyclic neuroleptics[24,25]) did not lead to substances which would be more interesting than the nonsubstituted compound[26,27]. On the other hand, a "rearrangement" of the central ring in the ABC fragment of *III* led to a neuroleptically highly active substance *VI*, called isobutaclamol[28,29], which likewise displayed a high degree of stereoselectivity of action[23]. The thiophene analogue of taclamine *VII* (ref.[30–33]) is being also denoted as a pharmacologically interesting substance. The empirically oriented studies attained finally at important conclusions on the mechanism of neuroleptic action[19] and led to attempts at mapping the dopamine receptor[28,34–36].



I, $R^1 = R^2 = H$
II, $CR^1R^2 = CO$
III, $R^1 = C(CH_3)_3$, $R^2 = OH$
IV, $R^1 = CH(CH_3)_2$, $R^2 = OH$
V, $R^1 = C(CH_3)_3$, $R^2 = H$

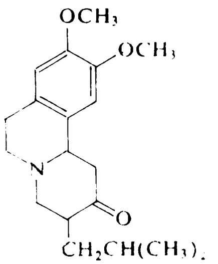


VI

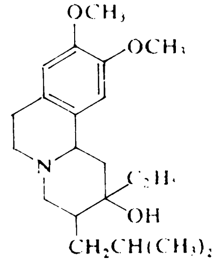


VII

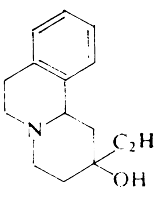
The tricyclic CDE fragment of butaclamol (*III*) and of related compounds, including the position of substituents in the alicyclic ring, shows a striking similarity with structures of the tranquillizers and mild neuroleptics of the series of 2- and 2,3-substituted 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizines[37] as demonstrated by structures of tetrabenazine (*VIII*) (ref.[38–42]), compound *IX* (ref.[43,44]) and finally of the most simple substance *X* (ref.[45–48]). This structural relation in connection with attempts at classification of the neuroleptic agents resulted in considering butaclamol and analogues as a subgroup of the benzo[*a*]quinolizine series of neuroleptics[49], similarly like some derivatives of 8*H*-dibenzo[*a*, *g*]quinolizine and especially its 5,6,13,13a-tetrahydro derivative (berbine). In contradiction to this conception is the theory of the Canadian authors[19] on the mechanism of action of the butaclamol group compounds according to which the phenylethylamine fragment with the aromatic ring A of the skeleton is important for the interaction of the butaclamol molecule with the dopamine receptor; this ring, indeed, is absent in the series of benzo[*a*]quinolizine derivatives. On the other hand, the high degree of activity of isobutaclamol (*VI*) (ref.[23,28,29]), in whose molecule the ring A is a part of a 3-phenylpropylamine fragment (not corresponding to the dopamine molecule), is also controversial from the view-point of the mentioned theory; the Canadian authors[28], however, have a plausible explanation for this discrepancy.



VIII



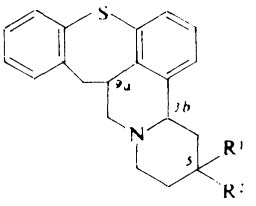
IX



X

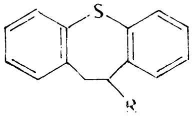
In connection with our pharmaco-chemical studies in the series of dibenzo[*b*, *f*]thiepin derivatives[50] we selected as the main object of the present communication the description of synthesis of the ABC-dibenzo[*b*, *f*]thiepin analogue of isobutaclamol (*VI*), *i.e.* of compound *XIa* which may be called 15-thiaisobutaclamol. The molecule of this compound contains the pentacyclic skeleton of [1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinoline which has not been described so far. In our synthesis we used reactions analogous to those elaborated for the syntheses of butaclamol (*III*) (ref.[1,3,4,6]) and isobutaclamol (*VI*) (ref.[28]), so far as it was possible. The starting compound was the recently described[51] 10,11-dihydrodibenzo[*b*, *f*]thiepin-10-carbonitrile (*XVI*) which was reduced with aluminium hydride, prepared *in situ* by a reaction of lithium aluminium hydride with aluminium chloride in ether (method[52,53]). The oily 10,11-dihydrodibenzo[*b*, *f*]thiepin-10-methylamine (*XVII*) was obtained in a high yield .For transformation to the formamide derivative *XVIII* a reaction of the amine *XVII* with acetic formic anhydride (ref.[54]) was used. The desired amide *XVIII* was obtained in a yield of about 70%. Chromatography of the mother liquors on alumina led to the isolation of a small amount of a somewhat less polar substance which was identified as the acetamido derivative *XIX*. Formylation is thus not the only reaction taking place in acylation of amines with acetic formic anhydride; acetylation appears also in a small extent.

For the following cyclization of the formamido derivative *XVIII* by the Bischler–Napieralski reaction[55], polyphosphoric acid at 160–170°C was used as the reagent. A mixture was formed which was separated by chromatography on alumina and some fractions were rechromatographed on silica gel. In this way, the oily 12,12a-dihydro-



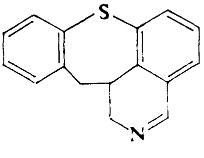
a, 3b, 9a-*trans*
b, 3b, 9a-*cis*

XI, $R^1 = C(CH_3)_3$, $R^2 = OH$
XII, $R^1 = CH(CH_3)_2$, $R^2 = OH$
XIII, $CR^1R^2 = CO$
XIV, $R^1 = H$, $R^2 = OH$
XV, $R^1 = R^2 = OC_2H_5$

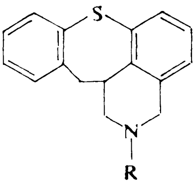


XVI, $R = CN$
XVII, $R = CH_2NH_2$
XVIII, $R = CH_2NHCHO$
XIX, $R = CH_2NHCOCH_3$

-1*H*-[1]benzothiepino[2,3,4-*ed*]isoquinoline (*XX*) was obtained, which afforded a crystalline hydrochloride and whose identity was corroborated by spectra. Reduction of this hydrochloride with sodium borohydride in methanol resulted in 2,3,12, 12a-tetrahydro derivative *XXI*, again an oily base affording a crystalline hydrogen maleate. Methylation of compound *XXI* by the Eschweiler–Clarke method[56,57] gave the N-methyl derivative *XXII* which also was isolated as a crystalline hydrogen maleate. The last two compounds (*XXI*, *XXII*) were prepared for a more general pharmacological screening.



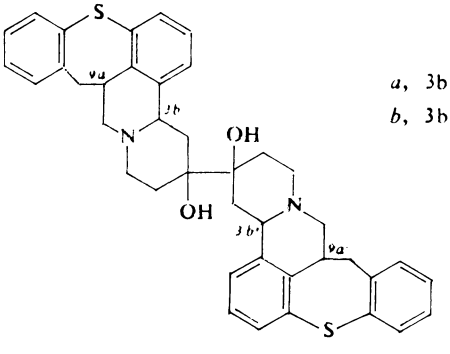
XX



XXI, $R = H$
XXII, $R = CH_3$

Similarly like in the studies of the Canadian authors[3,4,28], a cycloaddition reaction of the hydrochloride of the Schiff base *XX* with methyl vinyl ketone was used for anelation of the fifth ring. This reaction[58–60], is considered the most useful method for preparing 3,4,6,7-tetrahydrobenzo[*a*]quinolizin-2(1*H*-)ones[61]. Similarly like in the cited cases[3,4,28], a mixture of two racemic pentacyclic ketones *XIII* was obtained and separated by chromatography on silica gel. A mixture of benzene and chloroform eluted first the higher melting racemate (*b*), which was followed in the same eluent by the lower melting racemate (*a*). The racemate *b* is the slightly prevailing product (46%) whereas racemate *a* was obtained in a somewhat lesser amount (29%). The recorded spectra of both isomers did not contribute in any way to elucidating the configuration.Only on the basis of analogy to the elution sequence of the stereoisomeric pentacyclic ketones with known configuration[4,28], we assigned to our racemate *a* the 3b,9a-*trans* configuration and to the racemate *b* the 3b,9a-*cis* configuration. This assumption was confirmed in principle by the biological activity of one of the final products as described in the following part of this paper. In further work 3b,9a-*trans*-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido-[2,1-*a*]isoquinolin-5-one (*XIIIa*) as well as its *cis*-isomer *XIIIb* were used.

The final steps were reactions of ketones *XIIIa* and *XIIIb* with tert-butylmagnesium chloride [62] on the one hand, and with isopropyllithium[63] on the other. The mentioned Grignard reagent was prepared by a reaction of tert-butyl chloride[64] with magnesium in ether. The reaction with ketone *XIIIa* was carried out in a mixture of ether and benzene first at room temperature and then at the boiling point of the mixture. After decomposition of the mixture with a solution of ammonium chloride, an inhomogeneous product was obtained which was chromatographed on a column of silica gel. Chloroform eluted as the main and the least polar product a homogeneous crystalline base with the elemental composition $C_{24}H_{29}NOS$ (mass spectrum) and analysis corresponding to an ethanol solvate (the presence of ethanol was proven by the IR and ^1H NMR spectra). Treatment with hydrogen chloride in ether and crystallization from ethanol afforded the hydrochloride crystallizing as a hemihydrate. All experimental data indicate that we are dealing here with the desired tertiary alcohol *XIa* to which on the basis of its biological activity and on the basis of analogy with butaclamol[6] and isobutaclamol[28,29] a configuration on $C_{(5)}$ is ascribed as corresponding to the relation 5(OH),9a(H)-*trans*. The continued chromatography with use of ethyl acetate as eluent gave a small amount of a high-melting base which needed for recording of the mass spectrum a much higher temperature as with the preceding product and even then it was not possible to register the molecular ion. The main fragment has the composition $C_{20}H_{18}NOS$ (m/z 320). According to the IR spectrum, the compound is a tertiary alcohol; the structure of the pinacol *XXIIIa* was ascribed to it. The reduction of ketones by Grignard reagents to pinacols is indeed less common but it was decribed[65]. Acetone and finally ethanol eluted a small quantity of the most polar component of the mixture which was isolated as the crystalline hydrochloride. On the basis of spectra (especially of the mass spectrum) and analysis it is possible to assign to it rather rigorously the structure of the secondary alcohol *XIVa* (configuration on $C_{(5)}$ unknown), *i.e.* of a further product of reduction of the ketone *XIIIa* by the Grignard reagent. Reductions of this type are a common phenomenon[66].



a, 3b,9a-*trans*; 3b', 9a'-*trans*
b, 3b,9a-*cis*; 3b', 9a'-*cis*

XXIII

A reaction of the isomeric ketone *XIIIb* with tert-butylmagnesium chloride was carried out similarly and gave likewise a mixture which had to be separated by chromatography on silica gel. Chloroform eluted as the least polar component about 4% of the starting ketone *XIIIb*. The same solvent eluted then an oily base (about 15%) which afforded a crystalline hydrochloride. According to the IR spectrum, we are dealing here with a tertiary alcohol and the mass spectrum, indicating inhomogeneity of the sample, settled for one of the molecular ions the composition $C_{24}H_{29}NOS$ (m/z 379). The substance consists evidently in major part either of one of the stereoisomers *XIb* or of the mixture of both racemates *XIb*. The mass spectrum, however, registered also the molecular ion with elemental composition $C_{24}H_{29}NO_2S$ (m/z 395) with characteristic fragments with m/z 350 and 320. This indicates the presence of the ketal *XVb* (in the form of the hydrochloride) formed from the unreacted ketone *XIIIb*, contained in the first chromatographic fractions, by reaction with hydrogen chloride and ethanol from which the substance was crystallized. This assumption was confirmed by comparison with the properties of the homogeneous ketal *XVb*, obtained in one of the next experiments. As a further product there was eluted with ethyl acetate a high-melting base, affording the mass spectrum only at temperatures above 250°C, similarly like the corresponding product in the last experiment. The main fragment is again the ion with m/z 320 ($C_{20}H_{18}NOS$) and the product is considered to be the pinacol *XXXIIIb*. In agreement with that is the band at 1 139 cm^{-1} in the IR spectrum, ascribed to a tertiary alcohol group. Finally, from the mother liquor after the preceding product there was isolated in a considerable amount (25%) a further crystalline base which on the basis of the IR spectrum (band at 1 065 cm^{-1}) and the ^1H NMR spectrum (signal of the proton on the carbon atom carrying the hydroxyl group at 4·10 ppm) must be a secondary alcohol. The mass spectrum proved the elemental composition $C_{20}H_{21}NOS$ and the analysis (the mass spectrum too) indicates the solvation with benzene. We are thus dealing here with the secondary alcohol *XIVb*, *i.e.* again with a product of reduction of the starting compound. With a mixture of ether and benzene it affords a high-melting hydrochloride with unequivocal analysis.

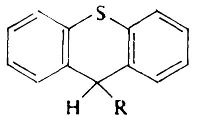
The overall material balance shows that in this case the desired tertiary alcohol *XIb* is only a minor product and the predominating reaction is the reduction to the secondary alcohol *XIVb* and to the pinacol *XXIIIb*. It has to be explained by the fact that tert-butylmagnesium chloride was used instead of tert-butyllithium which was used by the Canadian authors[6,28].

In continuing the work we attempted to synthesize the 15-thia analogues of the unknown isodexclamol, *i.e.* the stereoisomeric tertiary isopropyl carbinols *XIIa* and *XIIb*. Isopropyl chloride[67] was transformed to isopropyllithium by refluxing with lithium in pentane and the reagent was subjected to a reaction with the ketone *XIIIa* in a mixture of pentane and benzene. The mixture obtained was separated by chromatography similarly like in the preceding cases. The starting ketone was not found in the mixture at all and the reduction was considerably put down (it is in general rather uncommon in reactions of organolithium compounds but it has already been described[68]). An oily base was eluted with chloroform as the first product giving a crystalline hydrochloride. By means of spectra it was characterized as the minor stereoisomer of the tertiary alcohol *XIIa*. The mass spectrum exhibits the expected molecular ion with m/z 365 (corresponding to the composition $C_{23}H_{27}NOS$) being simultaneously the base peak. The analysis of the hydrochloride corresponds to a hemihydrate. The main product is then eluted with ethyl acetate. It is a further oily base affording likewise a crystalline hydrochloride, differing clearly from the preceding one. The mass spectrum is very similar to that of the preceding compound and corroborates its identification as the major stereoisomer of the tertiary alcohol *XIIa*; the analysis of the hydrochloride is in full agreement. Both stereoisomeric alcohols *XIIa* are very closely similar by their polarity. As the most polar product there was eluted by a mixture of ethyl acetate and acetone in a yield of about 20% an oily aminoalcohol affording a crystalline hydrochloride. The mass spectrum estimated the composition as $C_{20}H_{21}NOS$ and the analysis of the hydrochloride is in full agreement. The mass spectrum is practically identical with the spectrum of the already mentioned secondary alcohol *XIVa* and there is not much difference in the melting points of the hydrochlorides; both compounds are probably identical. The most interesting fact is that we are dealing here with a rigorously identified product of reduction of a ketone by an organolithium compound.

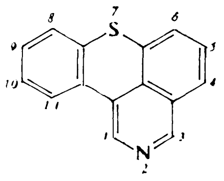
Finally, the reaction of the ketone *XIIIb* with isopropyllithium was carried out similarly. On chromatography of the mixture obtained there were first recovered some 5% of the starting ketone by elution with chloroform. The following chloroform fraction contained already the desired product *XIIb* but the ketone *XIIIb* was still present in a considerable amount; an attempt at preparing the hydrochloride and its crystallization from ethanol led to the formation of the hydrochloride of the ketal *XVb*, identified by means of the mass spectrum (molecular ion with m/z 395 and the composition $C_{24}H_{29}NO_2S$, an abundant fragment $C_{22}H_{23}NOS$ corresponding to an easy thermic cleavage of ethanol). Still with chloroform there was eluted the main product (an oily base affording a crystalline hydrochloride) which was identified by means of the mass spectrum as the tertiary alcohol *XIIb*; the spectrum is very similar to those of the stereoisomeric alcohols *XIIa*. Finally, ethyl acetate eluted about 35% of a crystalline base which is the secondary alcohol *XIVb*. According to the IR spectrum it is identical with the corresponding compound obtained in the tert-butyl series which, however, appeared to be a solvate with benzene; there is almost no difference in the melting points of both products.

A further synthetic experiment was aimed at the synthesis of analogues of butaclamol (*III*) in whose molecule the CH_2CH_2 bridge in the ring B would be substituted by an atom of sulfur. The basic ABC tricycle is the thioxanthene and our experiments started from thioxanthene derivatives. Thioxanthene-9-carbonitrile (*XXIV*) (ref.[69]) was reduced with aluminium hydride (similarly like in the preceding series) to thioxanthene-9-methylamine (*XXV*). The compound was prepared as base as well as the described hydrochloride[70] (the analysis of our product indicated that we had a hemihydrate). The isolated neutral by-product of the reduction reaction (some 10%) was identified as thioxanthene (*XXVI*) (ref.[71,72]). Its formation is explained by a reductive decyanation of the starting nitrile *XXIV* being of a similar type like the hydrogenolysis of halogeno derivatives with the hydride reagents. Attempts at preparing the amine *XXV* by the method described in the literature[70], *i.e.* by the Schmidt reaction from thioxanthene-9-acetic acid[72,73] (treatment with thionyl chloride followed by a reaction of the crude product with sodium azide and the final hydrolysis with boiling hydrochloric acid), were unsuccessful and the starting thioxanthene-9-acetic acid was recovered. Acylation of the amine *XXV* with acetic formic anhydride afforded smoothly the formamide derivative *XXVII*, which was subjected to treatment with polyphosphoric acid either at 160 or at 180°C (similarly like in the preceding part of this communication) in order to achieve a cyclization in the sense of the Bischler–Napieralski reaction. When working at 160°C we recovered 15–20% of the starting compound and the hydrochloride of the product was obtained in a yield of 60% (per conversion). Raising the temperature to 180°C resulted in complete disappearing of the starting compound but the yield on the hydrochloride of the product was lower than given for the preceding experiment. The mass spectrum of this hydrochloride determined for the corresponding base the elemental composition $C_{15}H_9NS$ (m/z 235) which is two hydrogen atoms less than expected for the desired condensed dihydroisoquinoline, *i.e.* the normal product of the Bischler–Napieralski reaction. From the hydrochloride the crystalline base was released and identified by UV, ^{1}H NMR and mass spectra as pyrido[3,4,5-*kl*]thioxanthene (*XXVIII*). The primarily formed dihydro derivative is evidently spontaneously dehydrogenated (by air oxygen or by the oxidative effect of polyphosphoric acid[74]). This unexpected reaction was the reason for discontinuation of our synthetic experiment.

Compounds *XIa*, *XIVb*, *XXI* and *XXII* were tested in the form of salts described in the Experimental; the compounds were administered orally and the doses (in mg/kg) were calculated for the bases. Compound *XIa* in a dose of 200 mg/kg is nontoxic for mice. In a dose of 5 mg/kg it brings about a very strong increase of the homovanillic acid (HVA) level in the rat brain striatum which is a manifestation of an important influence on the dopamine metabolism, typical for neuroleptics.



XXIV, R = CN
XXV, R = CH_2NH_2
XXVI, R = H
XXVII, R = CH_2NHCHO



XXVIII

In the interval of 3 h after the administration an increase of HVA concentration to 527% of the control value was noted. At this dose, there is no significant difference with butaclamol [*III*, 4a,13b-*trans*; 3 (OH), 13b (H)-*trans*] increasing the HVA level in the same dose to 644%. In lower doses butaclamol proved to be significantly more active than our substance: 0·5 mg/kg of compound *XIa* increases HVA to 254% (butaclamol to 659%); 0·1 mg/kg *XIa* to 131% (butaclamol to 306%). The analgesic activity of compound *XIa* in the peritoneal test in rats is expressed by the ED_{50} value 13·2 mg/kg (for butaclamol, ED_{50} = 4·0 mg/kg). Compound *XIVb* belonging to the 3b,9a-*cis* series and lacking the alkyl substituent on $C_{(5)}$ showed in the biochemical test only an indication of effect: a dose of 5 mg/kg increases the HVA level in the rat striatum only to 157% of the control value.

Compound *XXI* in an orientation test of acute toxicity in mice was administered in doses of 200 mg/kg (lethal for 10% animals) and 500 mg/kg (lethal for 100% animals). In the test of electroshock in mice it has anticonvulsant effect; D_{50} = 43 mg/kg. Compound *XXII* in a dose of 200 mg/kg is nontoxic for mice, a dose of 500 mg/kg is lethal for 60% animals. In the electroshock test it is less active than the preceding compound; a dose of 100 mg/kg has protective effect only in 40% mice. Both compounds in a dose of 80 mg/kg influences neither levels of dopamine, HVA and 5-hydroxyindole-3-acetic acid in the rat striatum (in the interval of 3 h after the administration), nor the noradrenaline level in the rat hypothalamus. In a dose of 50 mg/kg they do not show antiapomorphine effects in rats and in a dose of 20 mg/kg they do not influence the motility of mice in the photo-cell method of Dews. In a dose of 50 mg/kg they have significant antireserpine effect in the test of ptosis in mice; a lower dose of 25 mg/kg is ineffective. They show antimicrobial activity toward some microorganisms (the minimum inhibitory concentrations in μg/ml given, unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *XXI* 50; *Streptococcus faecalis*, *XXI* 50, *XXII* 100; *Staphylococcus pyogenes aureus*, *XXI* 25, *XXII* 100; *Escherichia* *coli*, *XXI* 50; *Proteus vulgaris*, *XXI* 50; *Saccharomyces pasterianus*, *XXI* 50; *Trichophyton mentagrophytes*, *XXI* 50, *XXII* 25.

EXPERIMENTAL

The melting points of analytical samples were determined in a Mettler FP-5 melting point recorder. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectrum (in methanol) was recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) were recorded with a Perkin Elmer 298 spectrophotometer, the ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the spectrometers MCH 1320 and/or Varian MAT 44S. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

10,11-Dihydrodibenzo[*b*,*f*]thiepin-10-methylamine (*XVII*)

A stirred suspension of 3·8 g $LiAlH_4$ in 100 ml ether was treated dropwise over 5 min under nitrogen with a solution of 10 g $AlCl_3$ in 100 ml ether, the mixture was stirred for 10 min and a solution of 11·85 g *XVI* (ref.[51]) in a mixture of 100 ml ether and 40 ml tetrahydrofuran was added over 20 min. It was refluxed for 3 h, after cooling decomposed with water and 150 ml 3M-H_2SO_4, the aqueous solution was made alkaline with 20% NaOH and the product was extracted with a mixture of benzene and chloroform. The extract was filtered, dried and evaporated; 11·8 g (98%) homogeneous oily *XVII*. Neutralization of a sample with HCl in ether gave the hydrochloride, m.p. 220·5—223°C (ethanol–ether). For $C_{15}H_{16}ClNS$ (277·8) calculated: 64·85% C, 5·81% H, 12·76% Cl, 5·04% N, 11·54% S; found: 64·66% C, 5·87% H, 12·90% Cl, 5·15% N, 11·55% S.

Thioxanthene-9-methylamine (*XXV*)

A stirred suspension of 38·8 g $LiAlH_4$ in 900 ml ether was treated under cooling with a solution of 111 g $AlCl_3$ in 900 ml ether over 30 min under nitrogen. A solution of 122 g *XXIV* (ref.[69]) in 370 ml tetrahydrofuran was then added over 30 min and the mixture was refluxed for 3 h. After cooling it was decomposed by a slow addition of 160 ml water and 1·6 l 3M-H_2SO_4. The precipitated solid was filtered, combined with the aqueous layer of the filtrate and the suspension was made alkaline with 20% NaOH. The base was isolated by extraction with chloroform; 110 g (89%) oil which slowly crystallized, m.p. 56·5—58°C (hexane). ^{1}H NMR spectrum: δ 7·10—7·50 (m, 8 H, ArH), 4·00 (t, $J = 7{\cdot}0$ Hz, 1 H, Ar_2CH), 2·96 (d, $J = 7{\cdot}0$ Hz, 2 H, CH_2N), 1·00 (s, 2 H, NH_2). For $C_{14}H_{13}NS$ (227·3) calculated: 73·97% C, 5·76% H, 6·16% N, 14·11% S; found: 74·09% C, 5·88% H, 6·09% N, 14·01% S.

Hydrochloride hemihydrate, m.p. 242—244 and the rest unsharply 257—270°C with decomposition (2-propanol). For $C_{14}H_{14}ClNS + 0{\cdot}5\,H_2O$ (272·8) calculated: 61·64% C, 5·54% H, 13·00% Cl, 5·14% N, 11·75% S; found: 61·75% C, 5·62% H, 12·86% Cl, 4·98% N, 12·00% S. Literature[70], m.p. of the nonsolvated hydrochloride 258—260°C (the compound was prepared differently).

The organic layer after the separation of the basic product with dilute H_2SO_4 was washed with water, dried with $MgSO_4$ and evaporated. The residue gave by crystallization from 50 ml benzene 6·20 g (6%) thioxanthene (*XXVI*), m.p. 129—130°C. The analysis confirmed the composition $C_{13}H_{10}S$ and a direct comparison with an authentic sample (m.p. 128—129°C) (ref.[71,72]) by TLC and mixed melting point determination confirmed the identity.

N-(10,11-Dihydrodibenzo[*b*,*f*]thiepin-10-ylmethyl)formamide (*XVIII*)

A mixture of 39·4 g acetic anhydride and 17·8 g 100% formic acid was stirred for 2 h at 60°C and allowed to stand for 48 h. *XVII* (36·4 g) was added, the mixture was stirred for 7 h at room temperature and allowed to stand overnight. It was then poured into a mixture of 350 g ice and water, the mixture was neutralized with 10% NaOH and the product was extracted with a mixture of ether and benzene. The extract was dried (K_2CO_3) and evaporated. The residue crystallized after mixing with 70 ml ether; 29·4 g (72%), m.p. 89—93°C. Analytical sample, m.p. 93—96°C (benzene–light petroleum). IR spectrum: 760 (4 adjacent Ar—H), 1 520, 1 647 (RNHCHO), 3 020 (Ar), 3 255 cm^{-1} (NH). ^1H NMR spectrum: δ 8·08 (d, $J = 2·0$ Hz, 1 H, CHO), 6·90—7·50 (m, 8 H, ArH), 5·86 (bs, 1 H, NH), 3·00—4·00 (m, 5 H, $ArCH_2CHAr$ and CH_2N). For $C_{16}H_{15}NOS$ (269·4) calculated: 71·34% C, 5·61% H, 5·20% N, 11·90% S; found: 71·52% C, 5·69% H, 4·90% N, 11·91% S.

The mother liquors from four similar experiments (from 121 g *XVII*) were combined, evaporated *in vacuo*, the residue (26·5 g) was dissolved in 20 ml benzene and chromatographed on a column of 650 g neutral Al_2O_3 (activity II). Benzene and a 1 : 1 mixture of benzene and chloroform eluted first 4·61 g (3%) N-(10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ylmethyl)acetamide (*XIX*), m.p. 127—128°C (benzene–light petroleum). IR spectrum: 750 (4 adjacent Ar—H), 1 551, 1·647 (RNHCOR′), 3 060 (Ar), 3 295 cm^{-1} (NH). ^1H NMR spectrum: δ 6·90—7·60 (m, 8 H, ArH), 5·80 (bt, 1 H, NH), 3·00—4·00 (m, 5 H, $ArCH_2CHAr$ and CH_2N), 1·95 (s, 3 H, $COCH_3$). For $C_{17}H_{17}NOS$ (283·1) calculated: 72·05% C, 6·05% H, 4·94% N, 11·31% S; found: 71·93% C, 6·16% H, 4·59% N, 11·25% S. Chloroform eluted then 19·1 g *XVIII*, m.p. 92—96°C (ether) which raises the yield on this compound to 82%.

N-(9-Thioxanthenylmethyl)formamide (*XXVII*)

A mixture of 58·7 g acetic anhydride and 26·5 g 100% formic acid was stirred for 2 h at 60°C, cooled to room temperature, 51·0 g *XXV* were added and the mixture was stirred for 20 h at room temperature. It was then poured into 500 g mixture of ice and water, neutralized with 20% NaOH and extracted with a 1 : 1 mixture of benzene and ether. The extract was dried with K_2CO_3 and evaporated. The residue was crystallized from 300 ml benzene; 47·3 g, m.p. 122—129°C. Processing of the mother liquor gave further 6·1 g product, the total yield being 53·4 g (93%). Analytical sample, m.p. 130—131°C (benzene). IR spectrum: 730, 750 (4 adjacent Ar—H), 1 560, 1·648 (RNHCHO), 1 571 (Ar), 3 010, 3 195, 3 230 cm^{-1} (NH). ^1H NMR spectrum: δ 8·04 (d, $J =$ $= 1·5$ Hz, 1 H, CHO), 7·10—7·50 (m, 8 H, ArH), 5·60 (bm, 1 H, NH), 4·31 (t, $J = 7·0$ Hz, 1 H, Ar_2CH), 3·48 (bt, 2 H, CH_2N). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·95% C, 5·29% H, 5·47% N, 12·45% S.

12,12a-Dihydro-1*H*-[1]benzothiepino[2,3,4-*ed*]isoquinoline (*XX*)

A mixture of 400 g polyphosphoric acid and 33·2 g *XVIII* was stirred and heated to 160—170°C for 4 h. After cooling it was poured on ice, made alkaline with a solution of 430 g NaOH in 500 ml water and extracted with chloroform. The extract was dried with K_2CO_3, evaporated and the inhomogeneous residue (30·3 g) was chromatographed on a column of 1 kg neutral Al_2O_3 (activity II). Elution with benzene removed 0·5 g of the least polar impurities and a mixture of benzene and chloroform eluted 10·5 g homogeneous oily base *XX*. Elution with ethanol gave finally 13·3 g mixture of *XX* with two further components. This mixture was rechromatographed on 400 g silica gel and gave by elution with chloroform further 3·66 g homogeneous *XX*. Both fractions of the base were combined and transformed by treatment with HCl in ether to the hydrochloride; 12·6 g (36%), m.p. 223—225°C, and a small part 280°C (ethanol). Mass spectrum, *m/z*: 251 (M^+ corresponding to $C_{16}H_{13}NS$, 100%), 250. IR spectrum: 751, 784 (4 and 3 adjacent Ar—H), 1 515, 1 565, 1 585, 3 010 (Ar), 1 675 (C=NH$^+$), 2 510 cm^{-1} (NH^+). For $C_{16}H_{14}ClNS$ (287·8) calculated: 66·77% C, 4·90% H, 12·32% Cl, 4·87% N, 11·14% S; found: 66·64% C, 4·94% H, 12·34% Cl, 4·62% N, 11·09% S.

Pyrido[3,4,5-*kl*]thioxanthene (*XXVIII*)

A mixture of 55 g polyphosphoric acid and 4·35 g *XXVII* was stirred and heated to 160°C for 4 h. After cooling it was poured into 200 g mixture of ice and water, it was made alkaline with 20% NaOH and extracted with chlorform. The extract was dried with K_2CO_3, evaporated, the residue was dissolved in ether and the solution treated with a slight excess of HCl in ether. The oily hydrochloride was separated and processing of the organic layer led to recovery of 0·82 g starting *XXVII* (m.p. 125—128°C). The hydrochloride was crystallized from a mixture of ethanol and ether; 2·40 g (49%), m.p. 219—223°C. The analysis indicates a monohydrate. Mass spectrum, *m/z*: 235 (M^+ corresponding to $C_{15}H_9NS$, 100%). For $C_{15}H_{10}ClNS + H_2O$ (289·8) calculated: 62·17% C, 4·17% H, 12·24% Cl, 4·83% N, 11·07% S; found: 62·37% C, 5·00% H, 12·38% Cl, 4·80% N, 11·20% S.

The hydrochoride was decomposed with 10% NaOH and the base was isolated by extraction with chloroform; m.p. 149—150°C (benzene-hexane). Mass spectrum, *m/z* (%): 235 (M^+ corresponding to $C_{15}H_9NS$, 100%), 208 (24), 203 (15), 190, 163, 118, 104. UV spectrum: λ_{max} 226 nm (log ε 4·49), 239 nm (4·44), 273 nm (3·89), 281 nm (3·89), 302·5 nm (3·80), 324 nm (3·75), 370 nm (3·78), 397 nm (3·83). ^1H NMR spectrum: δ 8·85 (d, $J = 3·5$ Hz, 2 H, 1, 3-H_2), 7·00—8·00 (m, 7 H, remaining ArH). For $C_{15}H_9NS$ (235·3) calculated: 5·95% N, 13·63% S; found: 5·76% N, 13.59% S.

2,3,12,12a-Tetrahydro-1*H*-[1]benzothiepino[2,3,4-*ed*]isoquinoline (*XXI*)

XX.HCl (1·44 g) was dissolved in 50 ml methanol and the stirred solution was slowly treated with 0·4 g $NaBH_4$. The mixture was stirred for 6 h at room temperature, allowed to stand for 48 h and evaporated *in vacuo*. The residue was decomposed with 5 ml water and extracted with benzene, the extract was filtered, dried and evaporated. The residue was neutralized with a solution of maleic acid in ether; 1·8 g (97%) hydrogen maleate, m.p. 163—164°C (acetone-ethanol). For $C_{20}H_{19}NO_4S$ (369·4) calculated: 65·02% C, 5·18% H, 3·79% N, 8·68% S; found: 64·96% C, 5·19% H, 3·44% N, 8·87% S.

2-Methy-2,3,12,12a-tetrahydro-1*H*-[1]benzothepino[2,3,4-*ed*]isoquinoline (*XXII*)

A mixture of 3·9 g *XXI* (released from the pure hydrogen maleate), 6 ml 35% formaldehyde and 5 ml 98% formic acid was heated for 9 h in a bath of 120°C. Hydrochloric acid (2·5 ml) was added, the solution was washed with ether, the aqueous layer was made alkaline with aqueous NH_3 and the base was extracted with benzene. The extract was dried with K_2CO_3 and evaporated *in vacuo*. The residue was neutralized with maleic acid in ether; 5·37 g (91%) hydrogen maleate, m.p. 167 to 168°C (acetone-ethanol). For $C_{21}H_{21}NO_4S$ (383·5) calculated: 65·78% C, 5·52% H, 3·65% N, 8·36% S; found: 65·84% C, 5·66% H, 3·33% N, 8·56% S.

A sample of the hydrogen maleate was decomposed with aqueous NH_3 and the base was isolated by extraction with ether, oil. ^1H NMR spectrum: δ 6·80—7·60 (m, 7 H, ArH), 2·50—4·10 (m, 7 H, $ArCH_2CHAr$ and 2 CH_2N), 2·44 (s, 3 H, NCH_3).

3b,4,5,6,7,9,9a,10-Octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ones (*XIII*)

A mixture of 13·1 g *XX*.HCl and 100 ml methyl vinyl ketone was heated for 2 h under reflux in a bath maintained at 100°C, after cooling the mixture was diluted with ether and the solid was filtered. It was then treated with 10% NaOH and the mixture of bases was extracted with chloroform. The residue obtained by evaporation of the extract was chromatographed on a column of 400 g silica gel (Silpearl). Benzene eluted 0·18 g least polar component which was discarded. A mixture of benzene and chloroform eluted then 6·75 g (46%) homogeneous racemate *b* (3b,9a-*cis*-*XIII*) which was crystallized from a mixture of benzene and light petroleum, m.p. 166—171°C. Analytical sample, m.p. 169—172°C (benzene–hexane). IR spectrum: 705, 750, 790 (4 and 3 adjacent Ar—H), 1 555, 3 055 (Ar), 1 710 (CO), 2 750 cm^{-1} (CH_2N). ^1H NMR spectrum: δ 6·80 to 7·50 (m, ArH), 2·00—4·40 (m, CH_2 and CH groups). For $C_{20}H_{19}NOS$ (321·4) calculated: 74·73% C, 5·96% H, 4·36% N, 9·98% S; found: 74·95% C, 6·07% H, 3·96% N, 10·14% S.

After an intermediate fraction which was a mixture of both stereoisomers, the same mixture of solvents eluted 4·2 g (29%) homogeneous racemate *a* (3b,9a-*trans*-*XIII*) which crystallized from a mixture of benzene and light petroleum and melted at 156—162°C. Analytical sample, m.p. 161·5—163°C (benzene–hexane). IR spectrum: 700, 715, 752, 790 (4 and 3 adjacent Ar—H), 1 558, 1 588 (Ar), 1 704 cm^{-1} (CO). ^1H NMR spectrum: δ 6·80—7·50 (m, ArH), 2·00—4·20 (m, CH_2 and CH groups). For $C_{20}H_{19}NOS$ (321·4) calculated: 74·73% C, 5·96% H, 4·36% N, 9·98% S; found: 75·11% C, 6·04% H, 4·03% N, 9·98% S.

3b,9a-*trans*-5-tert-Butyl-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ol (*XIa*)

A mixture of 4·9 g Mg and 20 ml ether was treated with 0·5 g tert-butyl chloride[64] and further 18·5 g tert-butyl chloride in 100 ml ether were added to the stirred mixture over 6·5 h. The mixture was stirred for another 15 min and treated dropwise with a solution of 3·95 g *XIIIa* in 60 ml benzene over 2 min. It was stirred for 30 min, allowed to stand overnight, refluxed for 4 h, diluted with 100 ml benzene and decomposed with 150 ml 20% NH_4Cl. The organic layer was dried with K_2CO_3 and evaporated. The residue was chromatographed on 200 g silica gel. Chloroform eluted 3·31 g (71%) homogeneous *XIa* which crystallized from ethanol as a solvate with ethanol, m.p. 98—108·5°C. Mass spectrum, *m/z* (%): 379 (M^+ corresponding to $C_{24}H_{29}NOS$, 47%), 322 (100, $C_{20}H_{20}NOS$), 304 (36, $C_{20}H_{18}NS$), 278 (48, $C_{18}H_{15}NS$), 256 (17, $C_{17}H_{22}NO$). IR spectrum: 756, 800 (4 and 3 adjacent Ar—H), 1 043 (CH_2OH of ethanol), 1 130, 1 147 (R_3C—OH), 1 561, 1 590, 3 043, 3 060 (Ar), 3 350, 3 395 cm^{-1} (OH). ^1HNMR spectrum: δ 6·90—7·50 (m, 7 H, ArH), 1·00—4·00 (m, CH_2 and CH groups), 0·90 [s, 9 H, $C(CH_3)_3$]. For $C_{24}H_{29}NOS$ + C_2H_6O (425·6) calculated: 73·37% C, 8·29% H, 3·29% N, 7·53% S; found: 73·19% C, 8·53% H, 3·11% N, 7·45% S.

Hydrochloride hemihydrate, m.p. 255—260°C with decomposition (ethanol). For $C_{24}H_{30}Cl.NOS$ + 0·5 H_2O (425·0) calculated: 67·82% C, 7·35% H, 8·34% Cl, 3·29% N, 7·55% S; found: 68·23% C, 7·50% H, 8·29% Cl, 2·77% N, 7·80% S.

Continuation of the chromatography by elution with ethyl acetate gave 0·38 g (10%) crystalline compound melting at 220—222°C with decomposition (ethanol or chloroform–benzene) which is considered to be bi(3b,9a-*trans*-5-hydroxy-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-yl) (*XXIIIa*). Mass spectrum, *m/z*: 320 ($C_{20}H_{18}NOS$, 100%), 278, 250. IR spectrum: 759, 783 (4 and 3 adjacent Ar—H), 1 110, 1 125 (R_3C—OH), 1 563, 3 060 (Ar), 2 765, 2 815 (CH_2—N), 3 140 cm^{-1} (OH). For $C_{40}H_{40}N_2O_2S_2$ (644·9) calculated: 74·50% C, 6·25% H, 4·34% N, 9·95% S; found: 74·22% C, 6·34% H, 3·99% N, 10·02% S.

The chromatography was concluded by elution with acetone and finally with ethanol; 0·52 g (13%) homogeneous oil, identified as 3b,9a-*trans*-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino-[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ol (*XIVa*). Hydrochloride, m.p. 233—240°C with decomposition (ethanol–ether). Mass spectrum. *m/z* (%): 323 (M^+ corresponding to $C_{20}H_{21}NOS$, 100%), 322 (78, $C_{20}H_{20}NOS$), 306 (27, $C_{20}H_{20}NS$), 278 (32), 251 (27), 250 (32), 200 (21). IR spectrum: 708, 758, 801 (4 and 3 adjacent Ar—H), 1 073 (CHOH in a ring), 2 470, 2 590, 2 630 (NH^+), 3 310 cm^{-1} (OH). For $C_{20}H_{22}ClNOS$ (359·9) calculated: 66·74% C, 6·16% H, 9·85% Cl, 3·89% N, 8·91% S; found: 66·25% C, 6·34% H, 9·63% Cl, 3·46% N, 8·77% S.

3b,9a-*cis*-5-tert-Butyl-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]-isoquinolin-5-ol (*XIb*)

Tert-butylmagnesium chloride was prepared from 19·0 g tert-butyl chloride[64] and 4·86 g Mg in 125 ml ether similarly like in the preceding case. It was treated with a solution of 6·4 g *XIIIb* in a mixture of 100 ml ether and 100 ml benzene, the mixture was refluxed for 4·5 h, allowed to stand overnight and decomposed with 100 ml 20% NH_4Cl. Processing of the organic layer gave 6·7 g mixture which was chromatographed on 200 g silica gel. The first to be eluted with chloroform was the starting *XIIIb* (0·25 g, m.p. 168—172°C). It was followed by 1·02 g (14%) oily *IXb*, contaminated by some starting *XIIIb*. Transformation to the hydrochloride and crystallization from ethanol led to conversion of *XIIIb* to the ketal *XVb* which was shown by the mass spectrum. *XIb* hydrochloride hemihydrate (with some *XVb*.HCl), m.p. 175·5—178·5°C with decomposition and after resolidification again 243—258°C. Mass spectrum, *m/z* (%): 379 (M^+ corresponding to $C_{24}H_{29}NOS$, 4%), 395 (M^+ corresponding to $C_{24}H_{29}NO_2S$, 3%); the fragments correspond rather to *XVb* than to *XIb*: 365 ($C_{22}H_{23}NO_2S$), 350 (34, $C_{22}H_{24}NOS$), 320 (100, $C_{20}H_{18}NOS$). IR spectrum: 750, 774, 800 (4 and 3 adjacent Ar—H), 1 055 (C—O—C—O—C), 1 123, 1 133 (R_3C—OH), 1 477, 1 565, 1 582, 3 060 (Ar), 2 550 (NH^+), 3 340 cm^{-1} (OH). For $C_{24}H_{30}ClNOS + 0·5\ H_2O$ (425·0) calculated: 67·82% C, 7·35% H, 8·34% Cl, 3·30% N, 7·54% S; found: 67·59% C, 7·29% H, 8·23% Cl, 3·01% N, 7·50% S.

Ethyl acetate eluted 3·48 g mixture which gave by crystallization from a mixture of benzene and ether 0·78 g (12%) bi(3b,9a-*cis*-5-hydroxy-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino-[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-yl) (*XXIIIb*), m.p. 243—247°C with decomposition (chloroform–ether). Mass spectrum, *m/z* (%): 320 (100, $C_{20}H_{18}NOS$). IR spectrum: 745, 750, 792 (4 and 3 adjacent Ar—H), 1 065 (C—N), 1 139 (R_3C—OH), 1 560, 3 045, 3 060 (Ar), 2 752, 2 809 (CH_2—N), 3 275 cm^{-1} (OH). For $C_{40}H_{40}N_2O_2S_2$ (644·9) calculated: 74·50% C, 6·25% H, 4·34% N, 9·95% S; found: 73·56% C, 6·24% H, 4·05% N, 9·80% S.

From the mother liquor after *XXIIIb* there were obtained by evaporation and crystallization from a mixture of benzene and light petroleum 1·77 g (25%) 3b,9a-*cis*-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ol (*XIVb*), crystallizing as a 3 : 1 benzene solvate, m.p. 151—154·5°C with first changes at 122—125°C. Mass spectrum, *m/z* (%): 323 (M^+ corresponding to $C_{20}H_{21}NOS$, 100%), 322 (73), 306 (26), 278 (28), 251 (19), 250 (24), 200 (19). IR spectrum: 680, 752, 790 (4 and 3 adjacent Ar—H), 1 065 (CHOH in a ring), 1 562, 3 065 (Ar), 2 750 (CH_2—N) 3 210 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·50 (ArH), 4·10 (bm, 1 H, CH—O), 1·20—4·00 (CH_2 and CH groups). For $C_{20}H_{21}NOS + 1/3\ C_6H_6$ (349·5) calculated: 75·61% C, 6·63% H, 4·01% N, 9·18% S; found: 75·55% C, 6·83% H, 3·85% N, 9·39% S.

Hydrochloride, m.p. 235—250°C with decomposition (ethanol). For $C_{20}H_{22}ClNOS$ (359·9) calculated: 66·74% C, 6·16% H, 9·85% Cl, 3·89% N, 8·91% S; found: 66·70% C, 6·25% H 9·78% Cl, 3·55% N, 9·00% S.

3b,9a-*trans*-5-Isopropyl-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]-isoquinolin-5-ols (*XIIa*)

A boilinng mixture of 2·0 g Li and 100 ml pentane was treated dropwise under nitrogen with a solution of 11·3 g isopropyl chloride[67] in 100 ml pentane over 1 h. The mixture was refluxed for 2 h, undissolved Li was separated by decantation and the solution of isopropyllithium was treated with a solution of 2·3 g *XIIIa* in 50 ml benzene. The mixture was refluxed for 1 h, allowed to stand for 3 days at room temperature, diluted with benzene and decomposed with water. The organic layer was evaporated and the residue chromatographed on 60 g silica gel. Chloroform eluted 0·42 g (16%) oily base identified as the minor stereoisomer of *XIIa*. It was transformed by treatment with HCl in ether to the hydrochloride which crystallized from a mixture of acetone and 96% ethanol as a hemihydrate, m.p. 216—218·5°C. Mass spectrum, *m/z* (%): 365 (M^+ corresponding to $C_{23}H_{27}NOS$, 100%), 364 (57), 348 (10), 332 (10), 322 (90, $C_{20}H_{20}NOS$), 304 (38, $C_{20}H_{18}NS$), 278 (78, $C_{18}H_{15}NS$), 250 (44, $C_{16}H_{12}NS$), 242 (36). For $C_{23}H_{28}ClNOS + 0·5\,H_2O$ (411·0) calculated: 67·21% C, 7·11% H, 8·63% Cl, 3·41% N, 7·80% S; found: 67·30% C, 6·91% H, 9·03% Cl, 3·18% N, 7·88% S.

Chromatography was continued by elution with ethyl acetate; 1·04 g (40%) oily base identified as the major stereoisomer of *XII*a. The hydrochloride crystallized from a mixture of acetone and ethanol and melted at 240—245°C with decomposition. Mass spectrum. *m/z* (%): 365 (M^+ corresponding to $C_{23}H_{27}NOS$, 100%), 364 (56), 348 (10), 332 (10), 322 (80, $C_{20}H_{20}NOS$), 304 (38, $C_{20}H_{18}NS$), 278 (72, $C_{18}H_{15}NS$), 250 (38, $C_{16}H_{12}NS$), 242 (35). For $C_{23}H_{28}ClNOS$ (402·0) calculated: 68·72% C, 7·02% H, 8·82% Cl, 3·48% N, 7·98% S; found: 68·46% C, 7·04% H, 8·89% Cl, 3·24% N, 7·95% S.

A mixture of ethyl acetate and acetone eluted 0·42 g (18%) oily 3b,9a-*trans*-3b,4,5,6,7,9,9a,10--octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ol (*XIVa*). Hydrochloride, m.p. 242—248°C with decomposition (acetone–ethanol). Mass spectrum, *m/z*: 323·1316 (M^+ corresponding to $C_{20}H_{21}NOS$, calculated 323·1344), 322, 306, 290, 278, 265, 221, 200. IR spectrum: 765, 790, 800 (4 and 3 adjacent Ar—H), 1 080 (CHOH in a ring), 1 115 (C—N), 1 515, 1 520, 3 048 (Ar), 2 460 (NH^+), 3 350 cm^{-1} (OH). For $C_{20}H_{22}ClNOS$ (359·9) calculated: 66·74% C, 6·16% H, 9·85% Cl, 3·84% N, 8·91% S; found: 66·60% C, 6·33% H, 9·88% Cl, 3·65% N, 9·08% S.

3b,9a-*cis*-5-Isopropyl-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]pyrido[2,1-*a*]isoquinolin-5-ol (*XIIb*)

Isopropyllithium was prepared from 2·0 g Li and 11·3 g isopropyl chloride[67] in 200 ml pentane similarly like in the preceding case and was treated with a solution of 5·65 g *XIIIb* in 150 ml benzene and 200 ml light petroleum. The mixture was refluxed for 1 h, allowed to stand overnight and decomposed with water. The organic layer was evaporated and the residue was chromatographed on 200 g silica gel. Chloroform eluted first 0·31 g starting *XIIIb* (m.p. 164—169°C) and then 1·21 g mixture of *XIIIb* and *XIIb* which was transformed to the hydrochloride and crystallized from ethanol. The product was 3b,9a-*cis*-5,5-diethoxy-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino]2,3,4-*ed*]pyrido[2,1-*a*]isoquinoline (*XVb*) hydrochloride, m.p. 179—183°C with decomposition (ethanol–acetone). Mass spectrum, *m/z*: 395 (M^+ corresponding to $C_{24}H_{29}NO_2S$), 350, 349 ($C_{22}H_{23}NOS$), 320 ($C_{20}H_{18}NOS$). For $C_{24}H_{30}ClNO_2S$ (432·0) calculated: 66·72% C, 7·00% H, 8·21% Cl, 3·24% N, 7·42% S; found: 65·84% C, 6·90% H, 8·39% Cl, 2·99% N, 7·76% S.

Still with chloroform 1·80 g (28%) oily *XIIb* were eluted; hydrochloride, m.p. 205—215°C with decomposition (acetone). Mass spectrum, *m/z* (%): 365 (M^+ corresponding to $C_{23}H_{27}NOS$, 100%), 364 (54), 349 (9), 332 (10), 322 (66, $C_{20}H_{20}NOS$) 304 (38, $C_{20}H_{18}NS$), 278 (68, $C_{18}H_{15}NS$), 250 (41, $C_{16}H_{12}NS$), 242 (30). For $C_{23}H_{28}ClNOS$ (402·0) calculated: 8·82% Cl, 3·48% N, 7·98% S; found: 9·08% Cl, 3·18% N, 7·86% S.

The chromatography was accomplished by elution with ethyl acetate; 2·07 g (36%) base, m.p. 144—150°C, identified as 3b,9a-*cis*-3b,4,5,6,7,9,9a,10-octahydro-[1]benzothiepino[2,3,4-*ed*]-pyrido[2,1-*a*]isoquinolin-5-ol (*XIVb*) being identical with the corresponding product in the tert-butyl series. Analytical sample, m.p. 153—155°C (benzene). IR spectrum (KBr): 750, 789 (4 and 3 adjacent Ar—H), 1 063 (CHOH in a cycle), 1 474, 1 559, 1 588, 3 055 (Ar), 2 740, 2 795 (CH_2—N), 3 230, 3 410 cm^{-1} (OH). For $C_{20}H_{21}NOS$ (323·4) calculated: 74·28% C, 6·55% H, 4·33% N; found: 74·83% C, 6·73% H, 3·71% N.

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REFERENCES

1. Humber L. G., Davis M. A., Thomas R. A., Otson R., Watson J. R.: J. Heterocycl. Chem. *3*, 247 (1966).
2. Protiva M.: Farmaco, Ed. Sc. *21*, 76 (1966).
3. Humber L. G., Davis M. A., Beaulieu G., Charest M.-P.: Can. J. Chem. *46*, 2981 (1968).
4. Bruderlein F. T., Humber L. G., Pelz K.: Can. J. Chem. *52*, 2119 (1974).
5. Pugsley T. A., Lippmann W.: Arch. Int. Pharmacodyn. Ther. *213*, 73 (1975).
6. Bruderlein F. T., Humber L. G., Voith K.: J. Med. Chem. *18*, 185 (1975).
7. Voith K., Bruderlein F. T., Humber L. G.: J. Med. Chem. *21*, 694 (1978).
8. Humber L. G., Bruderlein F.: 167th Amer. Chem. Soc. Natl. Meeting, Los Angeles, Apr. 1974; Abstr., MEDI 5.
9. Voith K.: 167th Amer. Chem. Soc. Natl. Meeting, Los Angeles, Apr. 1974; Abstr., MEDI 6.
10. Humber L., Bruderlein F., Voith K.: 4th Int. Symp. Med. Chem., Noordwijkerhout (Neth.), Sept. 1974; Abstr. p. 77.
11. Voith K., Herr F.: Psychopharmacologia *42*, 11 (1975).
12. Humber L. G. in the book: *Chronicles of Drug Discovery* (J. S. Bindra, D. Lednicer, Eds) 1, 61. Wiley, New York 1982.
13. Castañer J., Chatterjee S. S.: Drugs Future *1*, 171 (1976); *3* ,328 (1978); *4*, 302 (1979); *8*, 360 (1983).
14. Clark M. L., Paredes A., Costiloe J. P., Wood F.: J. Clin. Pharmacol. *17*, 529 (1977).
15. Nestoros J. N., Lehmann H. E., Ban T. A.: Int. Pharmacopsychiat. *13*, 138 (1978); Ringdoc *15*, 39 856 (1978).
16. Pugsley T. A., Lippmann W.: Naunyn Schmiedeberg's Arch. Pharmacol. *295*, 117 (1976).
17. Castañer J., Paton D. M.: Drugs Future *1*, 366 (1976); *2*, 557 (1977).
18. Fortier S., Przybylska M., Humber L. G.: Can. J. Chem. *58*, 1444 (1980).
19. Humber L. G., Bruderlein F. T., Voith K.: Mol. Pharmacol. *11*, 833 (1975).
20. Bird P. H., Bruderlein F. T., Humber L. G.: Can. J. Chem. *54*, 2715 (1976).
21. Voith K., Cummings J. R.: Can. J. Physiol. Pharmacol. *54*, 551 (1976); Chem. Abstr. *85*, 153 926 (1976).
22. Lippmann W., Pugsley T., Merker J.: Life Sci. *16*, 213 (1975).
23. Seeman P., Westman K., Protiva M., Jílek J., Jain P. C., Saxena A. K., Anand N., Humber L., Philipp A.: Eur. J. Pharmacol. *56*, 247 (1979).
24. Protiva M.: Drugs Today *12*, 151 (1976).

25. Schmutz J., Picard C. W. in the book: *Handbook Experimental Pharmacology*, Vol. 55/I. *Psychotropic Agents* (F. Hoffmeister, G. Stille, Eds), p. 3. Springer, Berlin—Heidelberg—New York 1980.
26. Humber L. G., Sideridis N., Asselin A. A., Bruderlein F. T., Voith K.: J. Med. Chem. *21*, 1225 (1978).
27. Pugsley T. A., Lippmann W.: J. Pharm. Pharmacol. *31*, 47 (1979).
28. Philipp A. H., Humber L. G., Voith K.: J. Med. Chem. *22*, 768 (1979).
29. Humber L. G., Philipp A. H., Voith K., Pugsley T., Lippmann W., Ahmer F. R., Przybylska M.: J. Med. Chem. *22*, 899 (1979).
30. Arribas E., Elguero J., Sarriá E., Tomé M. P. F., Vega S.: 7th Int. Symp. Med. Chem., Torremolinos, Sept. 1980; Abstr. P 171.
31. Arribas E., Elguero J., Vega S.: 8th Int. Congr. Heterocycl. Chem., Graz, Aug. 1981; Abstr. p. 254.
32. Benito C., Tome M. P. F., Guisado E., Rio J. del, Vega S.: J. Pharmacol. (Paris) *13*, 94 (1982); Ringdoc *19*, 22 721 (1982).
33. Vega S., Rio J. del: Drugs Future *8*, 30 (1983).
34. Humber L. G., Bruderlein F. T., Philipp A. H., Götz M., Voith K.: J. Med. Chem. *22*, 761 (1979).
35. Humber L. G., Philipp A. H., Bruderlein F. T., Götz M., Voith K.: 177th Amer. Chem. Soc. Natl. Meeting; Abstr. Pt. 1, COMP 28 (1979); Ringdoc *16*, 34 001 (1979).
36. Humber L. G.: 7th Int. Symp. Med. Chem., Torremolinos, Sept. 1980; Abstr. p. E-2.
37. Kaiser C., Setler P. E. in the book: *Burger's Medicinal Chemistry*, 4th Ed. (M. E. Wolff, Ed.). Part III, p. 935. Wiley, New York 1981.
38. Brossi A., Lindlar H., Walter M., Schnider O.: Helv. Chim. Acta *41*, 119 (1958).
39. Osbond J. M.: J. Chem. Soc. *1961*, 4711.
40. Pletscher A.: Science *126*, 507 (1957).
41. Pletscher A., Besendorf H., Bächtold H. P.: Arch. Exp. Path. Pharmakol. *232* 499, (1958).
42. Leusen I., Lacroix E., Demeester G.: Arch. Int. Pharmacodyn. Ther. *119*, 225 (1959).
43. Brossi A., Bruderer H., Da Prada M., Steiner F. A., Pletscher A.: Arzneim.-Forsch. *15*, 670 (1965).
44. Colpaert F. C., Lenaerts F. M., Niemegeers C. J. E., Janssen P. A. J.: Arch. Int. Pharmacodyn. Ther. *215*, 40 (1975).
45. Merck E., AG.: Neth Appl. 65/8468 (Ger. Appl. 25.07.64); Chem. Abstr. *64*, 19 572 (1966).
46. Merck E., AG.: Neth. Appl. 66/2640 (Ger. Appl. 17.03.65); Chem. Abstr. *66*, 65 406 (1967).
47. Dietsch P., Albrecht F., Mönikes H. J. in the book: *Psychopharmacology, Sexual Disorders and Drug Abuse.* Proc. Symp. at the VIIIth Congr. C.I.N.P. (Copenhagen, Aug. 1972), p. 171. North-Holland/Avicenum, Amsterdam—Prague 1973.
48. Goncalves N.: 9th Congr. C.I.N.P., Paris, July 1974; J. Pharmacol. (Paris) *5*, Suppl. *2*, 38 (1974).
49. Protiva M.: *Pokroky ve farmacii* 2, p. 141. Avicenum, Prague 1980.
50. Protiva M.: Lectures Heterocycl. Chem. *4*, S-1 (1978).
51. Šindelář K., Holubek J., Ryska M., Svátek E., Urban J., Grimová J., Červená I., Hrubantová M., Protiva M.: This Journal *48*, 1187 (1983).
52. Fieser L. F., Fieser M.: *Reagents for Organic Synthesis* 1, p. 595. Wiley, New York 1967.
53. Nystrom R. F.: J. Amer. Chem. Soc. *77*, 2544 (1955).
54. Huffman C. W.: J. Org. Chem. *23*, 727 (1958).
55. Whaley W. M., Govindachari T. R.: Org. Reactions *6*, 74 (1951).
56. Clarke H. T., Gillespie H. B., Weisshaus S. Z.: J. Amer. Chem. Soc. *55*, 5671 (1933).
57. Moore M. L.: Org. Reactions *5*, 301 (1949).

58. Brossi A., Chopard-dit-Jean L. H., Würsch J., Schnider O.: Helv. Chim. Acta *43*, 583 (1960).
59. Beke D., Szántay C.: Chem. Ber. *95*, 2132 (1962).
60. Szántay C., Rohály J.: Chem. Ber. *98*, 557 (1965).
61. Popp F. D., Watts R. F.: Heterocycles *6*, 1189 (1977).
62. Puntambeker S. V., Zoellner E. A.: Org. Syn., Coll. Vol. *1*, 524 (1932).
63. Gilman H., Moore F. W., Baine O.: J. Amer. Chem. Soc. *63*, 2479 (1941).
64. Norris J. F., Olmsted A. W.: Org. Syn., Coll. Vol. *1*, 144 (1932).
65. Theilacker W., Wessel M. L.: Justus Liebigs Ann. Chem. *594*, 229 (1955).
66. Bláha K. in the book: *Preparativní reakce v organické chemii.* VI. *Reakce organokovových činidel* (M. Hudlický, Ed.), p. 563. Nakladatelství ČSAV, Prague 1961.
67. Norris J. F., Taylor H. B.: J. Amer. Chem. Soc. *46*, 756 (1924).
68. Greenhalgh C. W., Henbest H. B., Jones E. R. H.: J. Chem. Soc. *1951*, 1190.
69. Muren J. F.: J. Med. Chem. *13*, 140 (1970).
70. Winter W., Thiel M., Stach K., Schaumann W., Ribbentrop A. (C. F. Boehringer u. Soehne GmbH): S. African 67/7695 (Ger. Appl. 23.12.66); Chem. Abstr. *70*, 68 202 (1969).
71. Graebe C., Schulthess O.: Justus Liebigs Ann. Chem. *263*, 1 (1891); Ber. Deut. Chem. Ges. *24*, R 390 (1891).
72. Jílek J. O., Holubek J., Svátek E., Ryska M., Pomykáček J., Protiva M.: This Journal *44*, 2124 (1979).
73. Jones R. G., Soper Q. F., Behrens O. K., Corse J. W.: J. Amer. Chem. Soc. *70*, 2843 (1948).
74. Wenham A. J. M., Whitehurst J. S.: J. Chem. Soc. *1956*, 3857.

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