# 8-CHLORO AND 8-METHYLTHIO DERIVATIVES OF 10-PIPERAZINO--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS; NEW COMPOUNDS AND NEW PROCEDURES*

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The resolution of racemic clorothepin (*Ia*) was repeated and the water-soluble methanesulfonates of (*S*)(+)-clorothepin and (*R*)(−)-clorothepin were prepared which were used in recent studies of the stereoselectivity of action of this neuroleptic agent. Alkylation of the secondary amine *VIa* with 2-chloroethyl decanoate resulted in noroxyclothepin decanoate *IVa* whose basically catalyzed ethanolysis afforded smoothly the amino alcohol *IIa*. Reactions of amines *VIa* and *VIb* with 1,2-butene oxide gave the amino alcohols *VIIab*. Alkylation of the amine *VIa* with 5-bromopentan-2-one and the following reduction of the amino ketone *IXa* formed gave the amino alcohol *VIIIa*. Amino alcohols *IIa* and *IIIb* were transformed by treatment with thionyl chloride to the chloroalkylamines *Xa* and *Xb* which were used for the synthesis of mandelates *XIIa*, *XIIIb* and benzilates *XIVa*, *XVb* derived from noroxyclothepin *IIa* and oxyprothepin *IIIb*. A substitution reaction of 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin with 1,4-diazabicyclo[4,3,0]nonane led to the clorothepin analogue *XVI*. From 2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one *XVII via* the 11-bromo derivative *XVIII* the amino ketone *XIX* was prepared. While its reduction with sodium borohydride gave the *cis*-amino alcohol *XXI*, the reduction with diborane gave the *trans*--amino alcohol *XXII*. The pharmacological properties of the new piperazine derivatives are described; some of them showed a high degree of neuroleptic activity of various profile.

In the group of tricyclic neuroleptics of the 10-piperazino-10,11-dihydrodibenzo-[*b*,*f*]thiepin series[1−4] the greatest practical utility was found for the 8-chloro and 8-methylthio derivatives. Out of the 8-chloro compounds, clorothepin (octoclothepin, *Ia*) (refs[5−9]) found its place in the therapy of schizophrenic psychoses, and noroxyclothepin (*IIa*) (refs[10,11]) and its decanoate *IVa* (refs[12−14]) were the objects of experimental studies. An extraordinary attention was paid to the basic representative of the 8-methylthio derivatives, *i.e.* to methiothepin (*Ib*) (refs[15,16]) as an experimental neuroleptic, and oxyprothepin (*IIIb*) (refs[10,17−19]) and oxyprothepin decanoate (*Vb*) (refs[12,20,21]) after successful clinical trials were released to practical use in the therapy of psychoses (the former as an oral, the latter as a depot antipsychotic agent). The experimental work in this series of compounds, proceeding for a long time, leads to the synthesis of new analogues and to new procedures which are reported in this communication.

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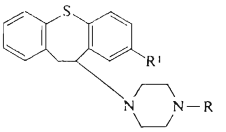
In one of the preceding communications[7] we described the resolution of the racemic clorothepin (*Ia*) to enantiomers which were placed at disposal in the form of maleates for pharmacological testing. On the basis of the almost equal discoordinating effect of both enantiomers and an incorrect interpretation of the results in the test of catalepsy we concluded erroneously that the neuroleptic action of clorothepin (*Ia*) is not stereoselective. Swiss authors[22] carried out a crystallographic and difractometric study of (±)- and (+)-clorothepin, they described the preferred conformation of the dextro rotatory form and the absolute configuration at $C_{(10)}$ as *S*. They published then[23] the finding of stereoselectivity of the neuroleptic effects of clorothepin in the test of catalepsy in rats and further in the tests of antiapomorphine and antiamphetamine action: in the racemic clorothepin the (*S*)(+)-enantiomer is the active component. Shortly thereafter we did confirm this finding[24] and had to correct our previous statement with regard to the result in the test of catalepsy; neither in the discoordinating effect, nor in the acute toxicity any significant differences between the enantiomers could be found. These results led to recommendation of clinical testing of both enantiomers of clorothepin (*Ia*) which was carried out by the Náhunek's team[25–30], which was joined by Hrbek[31,32]. It was found that the (*S*)(+)-enantiomer is antipsychotically more potent and brings about more extrapyramidal reactions. The (*R*)(−)-enantiomer, however, is not completely inactive which indicated that the stereoselectivity of the clorothepin effects has only a certain limited degree.

More recently we repeated the resolution of the racemic clorothepin and the optically active bases were transformed to the monomethanesulfonates which are well water-soluble. These substances were evaluated *in vitro* from the view-point of their affinity to brain dopamine receptors on the one hand using crude homogenates of caudate nucleus from calf brains with [$^3$H]-spiperone as the radioactive ligand[33], and with preparations of the rat-brain striatal membranes with [$^3$H]-haloperidol[34] on the other. In both cases the expected higher affinity of *S*(+)-clorothepin to the receptors was confirmed but it was only about 10 fold of that of (*R*)(−)-clorothepin. This finding is in agreement with the mentioned clinical findings but is at variance with the data given for the pair of enantiomers of butaclamol[35] where the (+)-enantiomer has about 3 000 fold activity than the (−)-enantiomer[33]. This contradiction could be explained by a relative flexibility of the clorothepin molecule which is thus able to a certain adjustment to the shape and binding sites positions of the receptor; on the other hand the molecule of butaclamol is completely rigid. The stereoselectivity of the action of clorothepin (*Ia*) was the object of many discussions and reflections about the mechanism of interactions of the molecules of neuroleptics with the dopamine receptors[36–43].

Noroxyclothepin decanoate *IVa* was obtained until now only by the reaction of the amino alcohol *IIa* with decanoyl chloride[12]. Now it has been prepared by alkylation of 2-chloro-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIa*) (ref.[10]) with



*a*, $R^1 = Cl$
*b*, $R^1 = SCH_3$

*I*, $R = CH_3$
*II*, $R = CH_2CH_2OH$
*III*, $R = (CH_2)_3OH$
*IV*, $R = (CH_2)_2OCO(CH_2)_8CH_3$
*V*, $R = (CH_2)_3OCO(CH_2)_8CH_3$
*VI*, $R = H$
*VII*, $R = CH_2CHCH_2CH_3$ (OH)
*VIII*, $R = (CH_2)_3CHCH_3$ (OH)
*IX*, $R = (CH_2)_3COCH_3$

*X*, $R = CH_2CH_2Cl$
*XI*, $R = (CH_2)_3Cl$
*XII*, $R = (CH_2)_2OCOCHC_6H_5$ (OH)
*XIII*, $R = (CH_2)_3OCOCHC_6H_5$ (OH)
*XIV*, $R = (CH_2)_2OCOC(C_6H_5)_2$ (OH)
*XV*, $R = (CH_2)_3OCOC(C_6H_5)_2$ (OH)

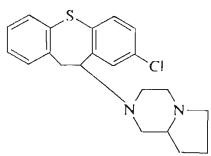
2-chloroethyl decanoate[44] in boiling toluene in the presence of triethylamine. By heating with ethanol in the presence of a small amount of sodium ethoxide the ester *IVa* undergoes quantitatively ethanolysis (re-esterification) under the formation of the amino alcohol *IIa* (ref.[10]). Out of the amino alcohols corresponding to clorothepin (*Ia*) there were prepared until now the 2-hydroxyethyl (*IIa*) (ref.[10]), 2-hydroxypropyl[45], 3-hydroxypropyl (*IIIa*) (ref.[10]), 3-hydroxybutyl[10], 4-hydroxybutyl[10], 3-hydroxy-2-methylpropyl[45] and 2,3-dihydroxypropyl analogue[45]; these compounds altogether showed a high degree of neuroleptic activity. Now, two further types of amino alcohols have been prepared. Reactions of the secondary amines *VIa* and *VIb* (ref.[10]) with 1,2-butene oxide in boiling methanol gave mixtures of stereoisomeric 2-hydroxybutyl derivatives *VIIa* and *VIIb*. In the former case the base crystallized and repeated crystallization led to a pure racemate; for pharmacological tests there was prepared on the one hand the methanesulfonate of this homogeneous base, and the methanesulfonate of the mixture of racemates on the other. In the latter case (*VIIb*) the base did not crystallize and only the methanesulfonate of the mixture of racemates could be handed over to the testing. With regard to the fact, that for the N-(4-hydroxypentyl) analogue of the neuroleptic "loxapine" a very important dissociation of the antiapomorphine and cataleptic activities was described[46] (*cf.* also[47]), we have now prepared the N-(4-hydroxypentyl) analogue *VIIIa* of clorothepin. Compound *VIa* (ref.[10]) was alkylated with 5-bromopentan-2-one[48] in boiling acetone in the presence of potassium carbonate and the resulting oily 4-oxopentyl derivative *IXa* (characterized as the hydrogen maleate) was reduced with sodium borohydride in aqueous ethanol (method similar like[46]). There resulted a glassy

base *VIIIa*, evidently a mixture of stereoisomers, which was transformed – without attempts at their separation – to the bis(hydrogen maleate) for pharmacological testing.

The amino alcohols *IIa* and *IIIb* (ref.[10]) were treated with thionyl chloride in benzene or chloroform in the presence of pyridine and the N-(2-chloroethyl) derivative *Xa* and N-(3-chloropropyl) derivative *XIb* were obtained. Both bases were prepared in pure state by chromatography of the crude products on aluminium oxide. The base *Xa* is crystalline and affords the maleate and methanesulfonate. The base *XIb* remained oily even after chromatography but afforded without difficulty similar crystalline salts like the preceding base. Compounds *Xa* and *XIb* were prepared as intermediates for further work but their pharmacological interest could also be expected. As alkylating analogues of the potent neuroleptics they could form by interactions with the dopamine receptors more stable products than usual for normal agonists and antagonists and they could thus be irreversible blockers of the receptors. Similar cases are known in the groups of α-adrenolytics[49] and antihistamine agents[50]; N-(2-chloroethyl)norapomorphine has recently been described as an irreversible antagonist of the dopamine receptors[51] and similar properties have been claimed for the N-(2-chloroethyl) analogue of the neuroleptic agent flupenthixol[52] already in the time when the present communication has been prepared for publication. Our substances *Xa* and *XIb* have been prepared and tested six years ago when the methods of evaluating the binding of compounds to the dopamine receptors did not exist yet. We used them for the synthesis of esters *XIIa*, *XIIIb*, *XIVa* and *XVb*, whose structure were designed on the basis of a hypothesis according to which the muscarinic anticholinergic activity of the neuroleptics could suppress their extrapyramidal effects[53]. Such properties were proven to a certain degree for clozapine and it was one way how to explain the absence of extrapyramidal side effects after this neuroleptic agent[54,55]. Our esters were designed as basic esters in which the amino alcohol components are the neuroleptically effective noroxyclothepin (*IIa*) and oxyprothepin (*IIIb*) and the acid components are mandelic and benzilic acids which are typical components of molecules of the anticholinergics and parasympatholytic antispamodics[56]. 3-Quinuclidyl benzilate (QB) (ref.[57]) is the best example in this connection, the highly potent and psychotomimetic anticholinergic agent, whose [$^3$H]-analogue is used as a radioligand for the investigation of the binding to the acetylcholine receptors in the brain[58]. The esters *XIIa*–*XVb* were prepared by reactions of compounds *Xa* and *XIb* with the potassium salts of mandelic and benzilic acids in boiling 2-propanol. The (±)-mandelic acid used introduces a second center of chirality to the molecules; the esters *XIIa* and *XIIIb* are thus mixtures of stereoisomers. In spite of that the base of the ester *XIIIb* crystallized and is apparently homogeneous (it is also indicated by the well differentiated $^1$H NMR spectrum). On the contrary the base *XIIa* remained oily even after having been released from the crystalline maleate. With esters *XIVa* and *XVb* there are no reasons

for inhomogeneity; both bases, however, are glassy without showing tendency to crystallization, both afforded crystalline maleates and methanesulfonates.

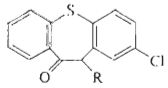
In the molecule of the neuroleptic agent azabutyrone (azabuperone) (ref.[59]) the bicyclic piperazine system of octahydropyrolo[1,2-*a*]pyrazine (1,4-diazabicyclo[4,3,0]nonane) found use as the basic component. By a substitution reaction of 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[5] with octahydropyrrolo[1,2-*a*]-pyrazine[60] compound *XVI* was obtained having again two centres of chirality. The base could be induced to crystallize but the badly differentiated $^1$H NMR spectrum indicates that our product was not completely homogeneous. The same is shown by the amorphous character of the methanesulfonate which was prepared for testing.



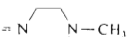

*XVI*

A further part of this paper deals with the incompletely solved problem of the 10-hydroxy derivatives of clorothepin, *i.e.* 2-chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ols. The preparation of one of these compounds was described in patents[61] by reduction of the corresponding ketone *XIX* (ref.[62]) with lithium aluminium hydride in tetrahydrofuran. The product was incompletely characterized and the question of its stereochemistry remained open. In this line the situation is the same like with 11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin--10-ol, prepared by our group[63]. In the meantime, however, we were able to prepare and identify both stereoisomeric 8-chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ols[64]. For this reason we have now attempted to use a similar way for the synthesis of both stereoisomeric 10-hydroxy derivatives of clorothepin (*XXI*, *XXII*). A reaction of 2-chlorodibenzo[*b*,*f*]thiepin-10(10*H*)-one (*XVII*) (ref.[65]) with bromine in chloroform at room temperature gave the bromo ketone *XVIII*. In patents[62] this compound was mentioned as the starting material but its preparation and characterization were not described. The substitution reaction with 1-methylpiperazine in 2-butanone at 50°C led to a semi-solid basic product, obtained in a yield of about 70%, which was considered the amino ketone *XIX* and was used without further purification. In addition there was obtained a yellow neutral product in a yield of 9% which was identified as 2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin--10,11-dione (*XX*) (ref.[64]). We met with a similar disproportionation reaction earlier and attempted at its explanation[63,64]. The patents[62] do not mention this side reaction and describe the amino ketone *XIX* as a crystalline compound melting

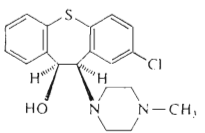
at 167–170°C, and 174–177°C, respectively. By repeated crystallization from ethanol we also were able to obtain a crystalline product melting at 175–180°C, but the substance undergoes evidently during crystallization decomposition and further quantities of the diketone *XX* are formed which led us to its using in crude state. The reduction of ketone *XIX* was carried out with sodium borohydride in aqueous dioxane on the one hand, and with diborane, generated by treatment of sodium borohydride with boron trifluoride etherate in tetrahydrofuran on the other. In both cases crystalline bases were obtained which differed only slightly in the melting points (similar like that given in patents[61] for the product obtained by reduction with lithium aluminium hydride) but differing significantly by their $^1$H NMR spectra. On the basis of these spectra it was possible to assign the *cis*-configuration (*XXI*) to the product of reduction with sodium borohydride and the *trans*-configuration (*XXII*) to the product of reduction with diborane. These results are thus precisely analogous like in the cases of the mentioned position isomers[64]. Both isomers afforded crystalline fumarates which greatly differ: while the *cis*-amino alcohol *XXI* behaves like a monobasic substance and affords a hemi-fumarate, the *trans*-amino alcohol *XXII* gives a neutral fumarate and shows thus properties of a dibasic substance. The tendency to protonation on the piperazine $N^1$ is decreased with the *cis*-derivative *XXI* probably due to steric hindrance or intramolecular hydrogen bonding.



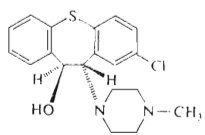
*XVII*, R = H
*XVIII*, R = Br



*XIX*, R = N—CH$_3$
*XX*, R = =O



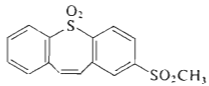
*XXI*



*XXII*

The following work to be described was in connection with the chemistry and synthesis of the methylthio derivatives methiothepin (*Ib*) and oxyprothepin (*IIIb*). Oxidation of compound *Ib* with excessive hydrogen peroxide in boiling acetic acid

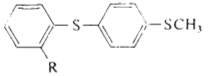
gave 2-(methylsulfonyl)dibenzo[*b*,*f*]thiepin 5,5-dioxide (*XXIII*), *i.e.* a complete oxidation on both sulfur atoms and the elimination of methylpiperazine took place. The last mentioned reaction is probably the result of the Cope elimination[66,67]. A similar reaction course was observed heretofore with the oxidation of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[63].



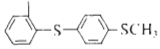

*XXIII*

The common starting compound for the syntheses of substances *Ib* and *IIIb* is the acid *XXIV* (ref.[15]) whose reduction to the alcohol *XXV* was described until now only with lithium aluminium hydride[15] or with sodium dihydridobis(2-methoxyethoxy)aluminate[68,69]. We attempted to use to this end a method which was successful in the case of reduction of 2-iodobenzoic acid to 2-iodobenzyl alcohol[70]: by treatment of the acid *XXIV* with ethyl chloroformate in dioxane the mixed anhydride of this acid with monoethyl carbonate was formed and reduced *in situ* with sodium borohydride. Some 5% of the starting acid were recovered and a mixture of at least four neutral products was obtained in which the presence of the alcohol *XXV* could qualitatively be proven (thin-layer chromatography). The only crystalline product, which was obtained in a yield of 5%, was identified as the anhydride *XXVI*. Its identity was deduced from the mass spectrum and analysis, confirmed by the IR and $^1$H NMR spectra and further by alkaline hydrolysis leading to the acid *XXIV* (ref.[15]). The same reaction was then carried out in the presence of triethylamine (in the step of mixed anhydride formation); a more homogeneous product was obtained which was chromatographed on aluminium oxide and afforded some 50% of a little polar crystalline compound which was identified as the ethyl ester *XXVII*. We already met with the formation of ethyl esters in reactions of carboxylic acids with ethyl chloroformate in the presence of triethylamine[71–73]; we are evidently dealing here with a general reaction and we suppose that the ethyl esters are formed by decomposition of the unstable mixed anhydrides by cleavage of carbon dioxide. While the transformation of the alcohol *XXV* to the chloride *XXVIII* by treatment with thionyl chloride (*cf.*[15]) in benzene or chloroform proceeds with a yield of about 70% and the oily product obtained is difficultly to be induced to crystallize, a similar reaction carried out in light petroleum (b.p. 60–70°C) yields 90% of the crystalline chloride *XXVIII*. For the following reaction with sodium cyanide dimethylformamide (without heating or at 100°C) is a better reaction medium than ethanol[15]; the crude nitrile *XXIX* is formed in an almost theoretical yield and its alkaline hydrolysis affords 93% of the acid *XXX* (ref.[15]). From the neutral product after the hydrolysis

two compounds were isolated whose identity indicates that the crude nitrile contains a small amount of the unchanged chloride *XXVIII* and further a small amount of a product of alkylation of the nitrile *XXIX* with the chloride *XXVIII*, *i.e.* of compound *XXXI* (*cf.*[74]). The oily neutral product afforded by distillation first the ether *XXXII* (analysis and the $^1$H NMR spectrum), apparently product of ethanolysis of the chloride *XXVIII* during the final treatment of the crude nitrile *XXIX* with ethanolic potassium hydroxide. When continued, the distillation showed signs of decomposition and from the distillation residue a crystalline substance was isolated which was identified as the stilbene derivative *XXXIII* (mass spectrum and analysis), apparently resulting from the thermic decomposition of compound *XXXI* (the sterically hindered nitrile resisted to the hydrolysis) with hydrogen cyanide elimination.

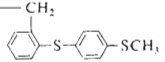


*XXIV*, R = COOH
*XXV*, R = $CH_2OH$
*XXVI*, R = $CO-O-CO$

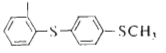


*XXVII*, R = $COOC_2H_5$
*XXVIII*, R = $CH_2Cl$
*XXIX*, R = $CH_2CN$

*XXX*, R = $CH_2COOH$
*XXXI*, R = $CH(CN)-CH_2$

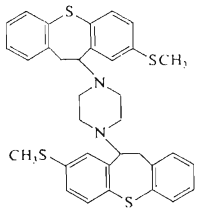


*XXXII*, R = $CH_2OC_2H_5$
*XXXIII*, R = $CH=CH$

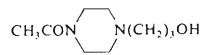


During purification of a larger batch of the base *IIIb* (ref.[10]) by crystallization from ethanol there was separated by filtration about 1% of an insoluble compound whose melting point indicated that it could be the stereoisomer A of the disubstituted piperazine *XXXV*, obtained previously[75] by the substitution reaction of 11-chloro-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin with piperazine. The analysis and the mass spectrum confirmed the expected composition but the mass spectrum resembles that of the stereoisomer B which was isolated[75] in the form of maleate from the crude substance *IIIb* previously. 1-(3-Hydroxypropyl)piperazine[76] used in the synthesis of compound *IIIb* contains some piperazine which reacts with 11-chloro-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin under the formation of both possible stereoisomers of compound *XXXIV*; the fact that previously[75] the stereoisomer B and now the stereoisomer A was isolated is probably a matter of chance. The small difference in the mass spectrum has to be explained by the difference of conditions during the registration of the spectrum. 1-Acetyl-4-(3-hydroxypropyl)-piperazine (*XXXV*) was synthesized as a potential intermediate of the preparation

of 1-(3-hydroxypropyl)piperazine by a reaction of 1-acetylpiperazine hydrochloride[77,78] with 3-chloropropanol in boiling ethanol in the presence of potassium carbonate.




*XXXIV*




*XXXV*

The compounds prepared were pharmacologically evaluated as potential neuroleptics and administered orally. The results in the tests of acute toxicity in mice ($LD_{50}$), of the discoordinating activity on the rotarod in mice ($ED_{50}$) and of the cataleptic activity in rats ($ED_{50}$) are summarised in Table I. The Table includes clorothepin (*Ia*) and chlorpromazine for comparison.

Comparison of the homogeneous *VIIa* with the mixture of stereosiomers indicates that the second component in the mixture is more active than the isolated pure *VIIa*. In general, the amino alcohols *VIIa*, *VIIb* and *VIIIa* are quite potent neuroleptics. The expected dissociation of the antiapomorphine and cataleptic activity of compound *VIIIa* could not be confirmed; the antiapomorphine activity in rats towards the stereotypies, $D_{50}$ = 4·1 mg/kg *p.o.*, toward the agitation, $D_{50}$ = 3·2 mg/kg *p.o.* (for clorothepin 4·1 and 4·5 mg/kg). It is apparent that the active doses in both tests are almost the same. Compound *Xa* was also tested on intravenous administration: $LD_{50}$ = 75 mg/kg; a dose of 15 mg/kg brought about brief and deep drops of the blood pressure in normotensive rats and the compound blocked significantly the pressoric response after adrenaline (ED = 0·5 mg/kg). Higher doses than 15 mg/kg inhibit the activity and reactivity of mice, bring about ataxia, tremor and convulsions. With the esters *XIIa*, *XIIIb*, *XIVa* and *XVb* the antagonism of tremor produced in mice by oxotremorine was evaluated as an indication of a potential antiparkinsonic effect[79]: *XIIa* showed in a dose of 40 mg/kg *p.o.* a significant effect (higher than 10 mg/kg of trihexyphenidyl), *XIIIb* was effective in doses above 40 mg/kg, *XIVa* in a dose of 40 mg/kg was equipotent with 10 mg/kg of trihexyphenidyl, *XVb* was ineffective in a dose of 10 mg/kg. Compound *XIIIb* enhanced significantly the homovanillic acid level in homogenates of the rat brain and behaves thus like a typical neuroleptic agent (Dr M. Valchář, Department of pharmacology

of this institute). Compound *XIVa* did not show the antiapomorphine effect in rats in doses of 50 and 100 mg/kg *p.o.* Compound *XVI* (stereoisomeric mixture) proved rather potent neuroleptic. The stereoisomeric amino alcohols *XXI* and *XXII* are tranquillizers which are almost free of the neuroleptic component. The *cis*-isomer *XXI* is significantly less toxic than the *trans*-isomer *XXII*.

The compounds were also tested for antimicrobial activity *in vitro*; the used microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *VIIa* 25, *VIIb* 25, *VIIIa* 50, *Xa* 25, *XXI* 100, *XXII* 50; *Streptococcus faecalis*, *VIIIa* 50, *Xa* 50; *Staphylococcus pyogenes aureus*, *VIIa* 25, *VIIb* 25, *VIIIa* 25, *Xa* 12·5, *XIIa* 50, *XXII* 50; *Escherichia coli*, *VIIIa* 25, *XIIIb* 100, *XXI* 100, *XXII* 100; *Mycobacterium tuberculosis* H37Rv, *VIIa* 12·5, *VIIb* 12·5, *Xa* 25, *XIb* 25, *XIIa* 12·5, *XIIIb* 12·5; *Saccharomyces pasterianus*, *Xa* 50, *XIIIb* 50; *Trichophyton mentagrophytes*, *VIIa* 50, *VIIb* 50, *VIIIa* 50, *Xa* 25, *XIb* 50, *XIIIb* 50, *XIVa* 50, *XVb* 50, *XXI* 25, *XXII* 50.

TABLE I

Pharmacological properties of 8-chloro and 8-methylthio derivatives of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins (Oral administration, doses in mg/kg, numbers in parentheses are percent of animals responding to the dose given)

| Compound[a] | Acute toxicity $LD_{50}$ | Ataxia (rotarod) $ED_{50}$[b] | Catalepsy $ED_{50}$ |
|---|---|---|---|
| *VIIa*[c] | 112 | 3·2[d] | 9·0 |
| *VIIa*[e] | 133 | 2·0 | 8·0 |
| *VIIb* | 62 | 5·3 | 8·5 |
| *VIIIa* | 173 | 3·1 | 3·2 |
| *Xa* | 115 | 3·0 | 26·0 |
| *XIb* | 190 | 3·9 | 23·5 |
| *XIIa* | 420 | 10·5 | 23·0 |
| *XIIIb* | 530 | 11·0 | 6·7 |
| *XIVa* | >400 (0) | >100 (10) | >200 (10) |
| *XVb* | 530 | 78 | 22·0 |
| *XVI* | 34[f] | 0·45[f] | 3·6[g] |
| *XXI* | 321 | 5·4 | > 50 (20) |
| *XXII* | 144 | 5·4 | > 50 (0) |
| *Ia* (ref.[6,8]) | 78 | 2·2 | 4·3 |
| Chlorpromazine | 198 | 8·2 | 16·0 |

[a] The compounds were tested in the form of salts described in the Experimental; the doses were calculated for bases. [b] The data given refer to the maximum activity in the interval of 3—4 h after the administration. [c] One homogeneous racemate. — [d] On *i.v.* administration, $ED_{50}$ = = 0·46 mg/kg. [e] Mixture of two racemates. [f] Intravenous administration. [g] Intraperitoneal administration.

## EXPERIMENTAL

The melting points of analytical preparations were determined in a Mettler FP-5 melting point recorder; the samples were dried at about 60 Pa over $P_2O_5$ at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, $^1$H NMR spectra (in $C^2HCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with Varian MAT 44S and MCH 1 320 spectrometers. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol). Preparative column chromatographic separations were carried out on neutral $Al_2O_3$ (activity II).

(*S*)(+)-2-Chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*)

(*S*)(+)-*Ia* (ref.[7]) (3·0 g) was neutralized with 0·84 g methanesulfonic acid in acetone; 3·4 g monomethanesulfonate monohydrate, m.p. 123—124°C (acetone), $[\alpha]_D^{20}$ +31·0° (1% solution in methanol). For $C_{20}H_{25}ClN_2O_3S_2 + H_2O$ (459·0) calculated: 52·33% C, 5·92% H, 7·72% Cl, 6·10% N, 13·97% S; found: 52·65% C, 5·72% H, 7·88% Cl, 6·18% N, 13·74% S.

(*R*)(−)-2-Chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*)

(*R*)(−)-*Ia* (ref.[7]) (2·4 g) was neutralized with 0·67 g methanesulfonic acid in a mixture of trichloroethylene and ethanol; 2·0 g monomethanesulfonate monohydrate, m.p. 125—126°C (acetone), $[\alpha]_D^{20}$ −31·0° (1% solution in methanol). For $C_{20}H_{25}ClN_2O_3S_2 + H_2O$ (459·0) calculated: 52·33% C, 5·92% H, 7·72% Cl, 6·10% N, 13·97% S; found: 52·47% C, 5·78% H, 7·72% Cl, 6·24% N, 14·04% S.

2-Chloro-11-[4-(2-decanoyloxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVa*)

A mixture of 5·2 g *VIa* (ref.[10]), 10·5 g 2-chloroethyl decanoate[44], 40 ml toluene and 4·5 g triethylamine was refluxed for 30 h with stirring. After cooling the precipitated solid was filtered off and the residue (13·9 g) was chromatographed on 220 g $Al_2O_3$. Benzene eluted first 8·9 g starting 2-chloroethyl decanoate and then 1·50 g (19%) oily *IVa*. Bis(hydrogen maleate), m.p. 149—150°C (acetone). Lit.[12], m.p. 150—151°C.

2-Chloro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIa*)

A solution of 100 g *IVa* (ref.[12]) in 400 ml ethanol was treated with a solution of 3·0 g Na in 500 ml ethanol. The mixture was refluxed for 4 h, treated with 50 ml water and evaporated under reduced pressure. The residue was dissolved in 700 ml benzene and the solution was shaken with 500 ml 3M-HCl. The precipitated hydrochloride was filtered and added to the aqueous layer of the filtrate, the suspension was made alkaline with $NH_4OH$ and the product was extracted with chloroform. Without drying the extract was evaporated *in vacuo*; 72·4 g (almost theoretical yield) hemihydrate of *IIa*, m.p. 102—107°C (aqueous ethanol), Lit.[10], m.p. 103—105°C.

2-Chloro-11-[4-(2-hydroxybutyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIa*)

A solution of 8·3 g *VIa* (ref.[10]) in 25 ml methanol was treated with 4·4 g 1,2-butene oxide and the mixture was refluxed for 5 h. Evaporation *in vacuo* gave 10·1 g (100%) mixture of stereoisomers which was repeatedly crystallized from ethanol until the constant melting point was reached;

3·1 g, m.p. 129–131°C. IR spectrum: 750, 809, 830, 888 (4 and 2 adjacent and solitary Ar—H), 1 106 (CHOH), 1 549, 1 573, 3 052, 3 065 (Ar), 3 220 and infl. 3 360 $cm^{-1}$ (OH). $^1H$ NMR spectrum: $\delta$ 7·66 (d, $J$ = 2·0 Hz, 1 H, 1-H), 7·48 (q, 1 H, 6-H), 7·30 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·80–7·30 (m, 4 H, remaining ArH), 3·00–4·00 (m, 4 H, $ArCH_2CHAr$ and CH—O), 2·10–2·80 (m, 10 H, 5 $NCH_2$), 2·30 (s, 1 H, OH), 1·40 (m, 2 H, $CH_2$ in butyl adjacent to methyl), 0·98 (t, 3 H, $CH_3$). For $C_{22}H_{27}ClN_2OS$ (403·0) calculated: 65·57% C, 6·75% H, 8·80% Cl, 6·95% N, 7·96% S; found: 65·45% C, 6·70% H, 8·70% Cl, 6·96% N, 7·82% S.

*Monomethanesulfonate hemihydrate*, m.p. 177–179°C (aqueous ethanol–ether). For $C_{23}H_{31}ClN_2O_4S_2 + 0{\cdot}5\ H_2O$ (508·1) calculated: 54·37% C, 6·34% H, 6·97% Cl, 5·51% N, 12·61% S; found: 54·20% C, 6·59% H, 7·04% Cl, 5·67% N, 12·46% S.

The mother liquors after the crystallization of the base were combined and evaporated giving 4·20 g mixture of stereoisomeric bases, m.p. 99–102°C (ethanol). For $C_{22}H_{27}ClN_2OS$ (403·0) calculated: 65·57% C, 6·75% H, 8·80% Cl, 6·95% N, 7·96% S; found: 65·85% C, 6·75% H, 8·81% Cl, 6·84% N, 8·11% S. Neutralization with methanesulfonic acid gave 4·0 g mixture of monomethanesulfonates, m.p. 155–167°C (ethanol–ether), which was used for pharmacological testing.

11-[4-(2-Hydroxybutyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIb*)

A mixture of 6·0 g *VIb* (ref.[10]), 20 ml methanol and 3·15 g 1,2-butene oxide was refluxed for 5 h and evaporated under reduced pressure; 7·3 g (100%) oily mixture of stereoisomeric *VIIb*.

*Maleate*, m.p. 133–135°C (acetone–ether). For $C_{27}H_{34}N_2O_5S_2$ (530·7) calculated: 61·10% C, 6·46% H, 5·28% N, 12·08% S; found: 61·06% C, 6·66% H, 5·30% N, 12·21% S.

The oily base (4·05 g) which was obtained from the crystalline maleate by treatment with $NH_4OH$ and extraction with benzene, was neutralized with methanesulfonic acid (1·0 g) to give 3·1 g monomethanesulfonate, m.p. 140–143°C (ethanol–ether). For $C_{24}H_{34}N_2O_4S_3$ (510·7) calculated: 56·44% C, 6·71% H, 5·49% N, 18·83% S; found: 55·98% C, 6·74% H, 5·37% N, 18·65% S.

2-Chloro-11-[4-(4-oxopentyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IXa*)

A mixture of 9·96 g *VIa* (ref.[10]), 100 ml acetone, 7·5 g $K_2CO_3$ and 6·5 g 5-bromo-2-pentanone[48] was stirred and refluxed for 8 h, the solid was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in 100 ml benzene, the solution washed with 10% $NH_4OH$, dried with $K_2CO_3$ and evaporated; 8·6 g (69%) oily *IXa*. Neutralization with maleic acid in acetone gave the bis(hydrogen maleate), m.p. 150–151°C (ethanol). IR spectrum: 731, 742, 820, 869 (4 and 2 adjacent and solitary Ar—H), 1 222, 1 352 ($COO^-$), 1 485, 1 550 (Ar and $COO^-$), 1 720 (CO), 2 172, 2 280, 2 380 $cm^{-1}$ ($NH^+$). For $C_{31}H_{35}ClN_2O_9S$ (647·1) calculated: 57·53% C, 5·45% H, 5·48% Cl, 4·33% N, 4·95% S; found: 57·72% C, 5·46% H, 5·69% Cl, 4·41% N, 5·17% S.

2-Chloro-11-[4-(4-hydroxypentyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIIa*)

A solution of 6·0 g *IXa* in 50 ml ethanol was added dropwise to a stirred solution of 1·8 g $NaBH_4$ in 50 ml 90% ethanol containing 0·3 ml 10% NaOH at 30–35°C. The mixture was stirred at room temperature for 3 h and slowly treated with 30 ml acetone. After standing overnight the solid was filtered off and the filtrate was evaporated *in vacuo*. The filtered solid was added to the residue, the mixture was treated with 100 ml 5% NaOH and extracted with benzene. The extract

was washed with water, dried with $K_2CO_3$ and evaporated; 5·50 g (91%) glassy mixture of stereoisomeric bases *VIIIa*. IR spectrum: 749, 807, 827, 876 (4 and 2 adjacent and solitary Ar—H), 1 102, 1 123, 1 146 (CHOH), 1 472, 1 500, 1 571, 3 003, 3 025, 3 035 (Ar), 3 350 $cm^{-1}$ (OH). $^1H$ NMR spectrum: $\delta$ 7·65 (d, $J$ = 2·5 Hz, 1 H, 1-H), 6·80—7·50 (m, 6 H, remaining Ar—H), 5·80 (bs, 1 H, OH), 3·00—4·00 (m, 4 H, $ArCH_2CHAr$ and CH—O), 1·40—2·65 (m, 14 H, 5 $NCH_2$ and $CH_2CH_2$ of the side chain), 1·15 (d, $J$ = 6·0 Hz, 3 H, $CH_3$).

*Bis(hydrogen maleate)*, m.p. 142—143°C with decomposition (ethanol). For $C_{31}H_{37}ClN_2O_9S$ (649·2) calculated: 57·35% C, 5·75% H, 5·46% Cl, 4·32% N, 4·94% S; found: 57·34% C, 5·65% H, 5·72% Cl, 4·30% N, 5·12% S.

2-Chloro-11-[4-(2-chloroethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Xa*)

A solution of 30·0 g *IIa* hemihydrate (ref.[10]) and 12·5 g pyridine in 250 ml benzene was stirred and slowly treated at 10°C with 16·4 g $SOCl_2$. The mixture was stirred for 2 h at room temperature, decomposed with 250 ml water and made alkaline with 5% NaOH. The product was extracted with benzene, the extract was washed with water and then shaken with an excess of 3M-HCl. The precipitated hydrochloride was filtered and added to the aqueous layer of the filtrate, the suspension was made alkaline with 10% NaOH and the product extracted with benzene. Evaporation of the extract gave 29·5 g crude product which was dissolved in 50 ml benzene and the solution was chromatographed on a column of 120 g $Al_2O_3$. Elution with benzene gave 24·4 g (79%) homogeneous *Xa*, which crystallized on standing, m.p. 105—106°C (cyclohexane). $^1H$ NMR spectrum: $\delta$ 7·60 (d, $J$ = 3·0 Hz, 1 H, 1-H), 7·40 (q, 1 H, 6-H), 7·28 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·80—7·20 (m, 4 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·52 (t, $J$ = 7·0 Hz, 2 H, $CH_2Cl$), 3·65 (t, $J$ = 7·0 Hz. 2 H, $NCH_2$ in the chain), 2·55 (m, 8 H, 4 $NCH_2$ of piperazine). For $C_{20}H_{22}Cl_2N_2S$ (393·4) calculated: 61·06% C, 5·64% H, 18·03% Cl, 7·12% N, 8·15% S; found: 61·08% C, 6·41% H, 18·28% Cl, 6·80% N, 8·23% S.

*Maleate*, m.p. 151—153°C (ethanol). For $C_{24}H_{26}Cl_2N_2O_4S$ (509·5) calculated: 56·58% C, 5·14% H, 13·92% Cl, 5·50% N, 6·29% S; found: 56·55% C, 5·18% H, 13·92% Cl, 5·42% N, 6·52% S.

*Monomethanesulfonate*, m.p. 168—169°C (ethanol–ether). For $C_{21}H_{26}Cl_2N_2O_3S_2$ (489·5) calculated: 51·53% C, 5·35% H, 14·49% Cl, 5·72% N, 13·10% S; found: 51·68% C, 5·40% H, 14·55% Cl, 6·04% N, 12·11% S.

11-[4-(3-Chloropropyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIb*)

A solution of 20 g *IIIb* (ref.[10]) and 8 ml pyridine in 200 ml chloroform was stirred and treated dropwise without cooling with 24 g $SOCl_2$ (maximum temperature of 40—45°C). It was allowed to stand overnight, decomposed with 200 ml 10% NaOH under cooling with ice-cold water and then made strongly alkaline with 35% NaOH. The chloroform layer was separated and evaporated under reduced pressure. The residue was dissolved in 250 ml benzene, the solution was shaken with 200 ml 3M-HCl, the precipitated hydrochloride was filtered, suspended in water, the suspension was made alkaline with 15% NaOH and the base was extracted with benzene. The extract was evaporated and the residue was chromatographed on a column of 500 g $Al_2O_3$. Benzene eluted 13·5 g (65%) homogeneous oily *XIb*.

*Maleate*, m.p. 162—164°C (aqueous ethanol). For $C_{26}H_{31}ClN_2O_4S_2$ (535·1) calculated: 58·36% C, 5·84% H, 6·62% Cl, 5·24% N, 11·98% S; found: 58·32% C, 6·12% H, 6·76% Cl, 5·48% N, 11·89% S.

*Dimethanesulfonate*, m.p. 160–163 °C (acetone). For $C_{24}H_{35}ClN_2O_6S_4$ (611·3) calculated: 47·16% C, 5·77% H, 5·80% Cl, 4·58% N, 20·98% S; found: 46·67% C, 6·03% H, 5·60% Cl, 4·57% N, 20·77% S.

2-Chloro-11-[4-(2-mandeloyloxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIa*)

A solution of 30 g (±)-mandelic acid in 80 ml methanol and of 13·0 g 85% KOH in 20 ml water was evaporated *in vacuo*, the residue (potassium (±)-mandelate) was dried and powdered; 39 g.

A solution of 3·14 g potassium mandelate and 6·50 g *Xa* in 90 ml 2-propanol was refluxed for 7 h and, after cooling, the mixture was diluted with 90 ml benzene. After standing overnight the precipitated KCl was filtered off and the filtrate was evaporated *in vacuo*; 8·40 g (100%) oily *XIIa*.

*Bis(hydrogen maleate)*, m.p. 121–123°C (acetone-ether). For $C_{36}H_{37}ClN_2O_{11}S$ (741·2) calculated: 58·34% C, 5·03% H, 4·78% Cl, 3·78% N, 4·33% S; found: 58·13% C, 5·06% H, 4·89% Cl, 3·86% N, 4·58% S.

*Monomethanesulfonate*: A solution of 7·0 g oily *XIIa* in 10 ml acetone was neutralized with 1·26 g methanesulfonic acid and the solution was induced to crystallize by treatment with ether; 3·5 g, m.p. 186–189°C (90% ethanol-ether). IR spectrum (KBr): 700, 746, 770, 805 (Ar–H), 1 105 (CHOH), 1 038, 1 170, 1 220 ($SO_3H$), 1 755 (RCOOR'), 2 640 ($NH^+$), 3 335 $cm^{-1}$ (OH). $^1H$ NMR spectrum ($C^2H_3SOC^2H_3$): $\delta$ 7·00–7·50 (m, 12 H, ArH), 5·13 (s, 1 H, CO–CH–O), 2·40–4·40 (m, remaining $CH_2$ and CH groups), 2·30 (s, 3 H, $CH_3SO_3^-$). For $C_{29}H_{33}ClN_2O_6S_2$ (605·2) calculated: 57·56% C, 5·50% H, 5·86% Cl, 4·63% N, 10·50% S; found: 57·57% C, 5·62% H, 5·94% Cl, 4·60% N, 10·70% S.

11-[4-(3-Mandeloyloxypropyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIb*)

A solution of 3·0 g potassium mandelate and 6·6 g *XIb* in 90 ml 2-propanol was refluxed for 7 h, allowed to stand overnight, KCl was filtered off and the filtrate was evaporated *in vacuo*; 7·7 g (91%) *XIIIb*, m.p. 116–119°C. After two crystallizations from 85% ethanol the constant melting point of 120–121°C was reached. The substance is evidently one of the two possible racemates. IR spectrum: 712, 749, 775, 820, 900 (5, 4 and 2 adjacent and solitary Ar–H), 1 130 (CHOH), 1 475, 1 586 (Ar), 1 740, 1 765 (RCOOR'), 3 150 $cm^{-1}$ (=O···HO). $^1H$ NMR spectrum: $\delta$ 6·80–7·70 (m, 12 H, ArH), 5·16 (s, 1 H, CO–CH–O), 4·20 (t, $J$ = 6·0 Hz, 2 H, $CH_2O$), 3·90 (s, 1 H, OH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (s, 3 H, $SCH_3$), 2·30 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·18 (t, $J$ = 6·0 Hz, 2 H, $NCH_2$ in the chain), 1·80 (m, 2 H, $CH_2$ in the middle of the propane residue). For $C_{30}H_{34}N_2O_3S_2$ (534·7) calculated: 67·38% C, 6·41% H, 5·24% N, 11·99% S; found: 67·67% C, 6·49% H, 5·24% N, 11·63% S.

*Maleate*, m.p. 137–139°C (ethanol). For $C_{34}H_{38}N_2O_7S_2$ (650·8) calculated: 62·75% C, 5·88% H, 4·31% N, 9·85% S; found: 62·83% C, 5·96% H, 4·46% N, 10·18% S.

11-[4-(2-Benziloyloxyethyl)piperazino]-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVa*)

A solution of 30 g benzilic acid in 90 ml methanol was mixed with a solution of 25 g 85% KOH in 25 ml water. The crystalline potassium benzilate was filtered, washed with methanol and dried; 28·5 g.

A mixture of 5·10 g *Xa*, 3·45 g potassium benzilate and 90 ml 2-propanol was refluxed for 7 h, diluted with 90 ml benzene, KCl was filtered off, and the filtrate was evaporated *in vacuo*; 7·7 g (100%) glassy *XIVa*. $^1$H NMR spectrum: $\delta$ 6·90—7·70 (m, 17 H, ArH), 4·35 (t, 2 H, $CH_2O$), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·10—2·70 (m, 10 H, 5 $NCH_2$).

*Maleate*, m.p. 180—182°C (aqueous ethanol). For $C_{38}H_{37}ClN_2O_7S$ (701·3) calculated: 65·09% C, 5·32% H, 5·06% Cl, 3·99% N, 4·57% S; found: 65·03% C, 5·52% H, 5·04% Cl, 3·97% N, 4·60% S.

*Monomethanesulfonate*, m.p. 139—141°C (acetone). For $C_{35}H_{37}ClN_2O_6S_2$ (681·3) calculated: 61·71% C, 5·48% H, 5·20% Cl, 4·11% N, 9·41% S; found: 61·51% C, 5·50% H, 5·00% Cl, 4·09% N, 9·40% S.

11-[4-(3-Benziloyloxypropyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVb*)

Was prepared similarly like *XIVa* from 6·4 g *XIb* and 4·0 g potassium benzilate in 90 ml 2-propanol; 9·2 g (98%) glassy *XIVb*. $^1$H NMR spectrum ($C^2H_3SOC^2H_3$): $\delta$ 7·21 (s, 10 H, 2 $C_6H_5$), 6·80—7·60 (m, 7 H, remaining ArH), 6·50 (s, disappears after $^2H_2O$, 1 H, OH), 4·10 (def. t, 2 H, $CH_2O$), 2·30 (s, 3 H, $SCH_3$), 1·60 (m, 2 H, $CH_2$ in the middle of the propane chain), 1·80 to 3·90 (m, 13 H, remaining $CH_2$ and CH groups).

*Maleate*, m.p. 94—97° with decomposition (acetone). For $C_{40}H_{42}N_2O_7S_2$ (726·9) calculated: 66·09% C, 5·82% H, 3·85% N, 8·82% S; found: 66·21% C, 5·78% H, 3·96% N, 8·87% S.

*Monomethanesulfonate*, m.p. 185—186°C (acetone). For $C_{37}H_{42}N_2O_6S_3$ (707·0) calculated: 62·86% C, 5·99% H, 3·96% N, 13·60% S; found: 62·66% C, 6·16% H, 3·99% N, 13·62% S.

2-Chloro-11-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVI*)

A mixture of 2·8 g 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[5], 1·9 g octahydropyrrolo-[1,2-*a*]pyrazine (1,4-diazabicyclo[4,3,0]nonane) (ref.[60]) and 4 ml chloroform was refluxed for 7 h and evaporated *in vacuo*. The residue was treated with 30 ml water, 5 ml $NH_4OH$ and extracted with benzene. The extract was shaken with 10 ml 3M-HCl, the precipitated hydrochloride was filtered, washed with benzene and suspended in 50 ml water. The suspension was made alkaline with 10 ml $NH_4OH$ and the base was isolated by extraction with benzene; 2·55 g (69%) glassy product which was crystallized from ethanol, m.p. 145—150°C. $^1$H NMR spectrum: $\delta$ 7·62 (d, $J$ = 2·0 Hz, 1 H, 1-H), 7·50 (m, 1 H, 6-H), 7·21 (d, $J$ = 8·5 Hz, 1 H, 4 H), *c.* 7·15 (m, 3 H, 7,8,9-$H_3$), 6·95 (q, $J$ = 8·5; 2·0 Hz, 1 H, 3-H), 1·30—4·00 (m, 16 H, remaining $CH_2$ and CH groups). For $C_{21}H_{23}ClN_2S$ (370·9) calculated: 68·00% C, 6·25% H, 9·56% Cl, 7·55% N, 8·46% S; found: 68·17% C, 6·52% H, 9·67% Cl, 7·08% N, 8·80% S.

Neutralization of the base (700 mg) with 180 mg methanesulfonic acid in 3 ml ethanol and evaporation of the solution gave 880 mg amorphous methanesulfonate (mixture of stereoisomers) which was well water-soluble and was used for pharmacological testing. All attempts at inducing the crystallization failed.

11-Bromo-2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIII*)

A stirred solution of 60 g *XVII* (ref.[65]) in 300 ml chloroform was treated dropwise with a solution

of 36·7 g Br in 100 ml chloroform, added over 2 h at room temperature. The mixture was stirred for additional 30 min, washed with water, dried with $MgSO_4$ and evaporated under reduced pressure; 77·5 g (99%), m.p. 140–142°C. Analytical sample, m.p. 144·5–145°C (benzene). UV spectrum: $\lambda_{max}$ 231 nm (log $\varepsilon$ 4·35), 327 nm (3·61), infl. at 260 nm (3·97). IR spectrum: 753, 821, 901 (4 and 2 adjacent and solitary Ar–H), 1 550, 1 580 (Ar), 1 690 $cm^{-1}$ (ArCO). $^1H$ NMR spectrum: $\delta$ 8·12 (m, 1 H, 9-H), 7·79 (d, $J$ = 2·5 Hz, 1 H, 1-H), 7·20–7·60 (m, 3 H, 6,7,8-$H_3$), 7·50 (d, $J$ = 8·0 Hz, 1 H, 4-H), 7·11 (q, $J$ = 8·0; 2·5 Hz, 1 H, 3-H), 6·65 (s, 1 H, Ar—CHBr—CO). For $C_{14}H_8BrClOS$ (339·6) calculated: 49·51% C, 2·37% H, 23·53% Br, 10·44% Cl, 9·44% S; found: 49·76% C, 2·37% H, 23·63% Br, 10·49% Cl, 9·58% S.

2-Chloro-11-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIX*)

A mixture of 132·7 g *XVIII*, 88·5 g 1-methylpiperazine and 1 350 ml 2-butanone was stirred for 2 h at 52°C and allowed to stand overnight. 1-Methylpiperazine hydrobromide was filtered off, the filtrate evaporated under reduced pressure, the residue treated with 1 l : 1 diluted $NH_4OH$ and the mixture extracted with warm benzene. The extract was shaken with 1·5 l 10% HCl and the benzene layer was washed with water, dried and evaporated; 9·8 g (9%) 2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10,11-dione (*XX*), m.p. 168–172°C (benzene). Lit.[64], m.p. 169–171°C.

The acid aqueous layer was made alkaline with 1 : 1 dilute $NH_4OH$, the base was extracted with warm benzene, the extract was dried with $MgSO_4$ and evaporated *in vacuo*; 99·1 g (71%) semi-solid *XIX* which was used without purification for the reduction experiments. A sample was repeatedly crystallized from ethanol, m.p. 175–180°C. Lit.[62], m.p. 167–170°C, and 174 to 177°C, respectively.

*cis*-2-Chloro-11-(4-methylpiperazino)-10,11-dihydro-dibenzo[*b*,*f*]thiepin-10-ol (*XXI*)

A mixture of 27·2 g *XVIII*, 40 ml 1-methylpiperazine and 120 ml dioxane was stirred for 3 h at room temperature and refluxed for 1 h. After cooling the solid was filtered off, the filtrate was treated with a solution of 5·2 g $NaBH_4$ in 20 ml water containing 2 drops of 20% NaOH and the mixture was refluxed for 1·5 h. Dioxane was evaporated under reduced pressure, the residue was treated with 50 ml water and extracted with benzene. The extract was shaken with 200 ml 10% hydrochloric acid, the precipitated hydrochloride was filtered and combined with the aqueous layer of the filtrate. The suspension was made alkaline with 1 : 1 diluted $NH_4OH$ and the base was extracted with benzene.

Processing of the extract gave 21·4 g (74%) crude *XXI*, m.p. 190–197°C. Analytical sample, m.p. 200·5–201·5°C (benzene–ethanol). IR spectrum: 769, 800, 820, 890 (4 and 2 adjacent and solitary Ar—H), 1 083 (CHOH), 1 556, 1 561, 1 572, 1 590, 3 030 (Ar), 2 675, 2 790, 3 060 $cm^{-1}$ (OH···N). $^1H$ NMR spectrum ($C^2H_3SOC^2H_3$): $\delta$ 7·10–7·80 (m, 7 H, ArH), 5·60 (d, $J$ = 4·0 Hz, disappears after $^2H_2O$, 1 H, OH), 5·31 (bd, after $^2H_2O$ s, 1 H, Ar—CH—O), 4·29 (s, 1 H, Ar—CH—N), 2·50 and 2·20 (2 bm, 8 H, 4 $NCH_2$ of piperazine), 2·05 (s, 3 H, $NCH_3$). For $C_{19}H_{21}ClN_2OS$ (360·9) calculated: 63·23% C, 5·87% H, 9·82% Cl, 7·76% N, 8·88% S; found: 63·54% C, 5·95% H, 10·14% Cl, 7·84% N, 9·10% S. Lit.[61] gave a m.p. of 196–201°C for the product of reduction of *XIX* with $LiAlH_4$ without reporting the spectra and without attempting to assign the configuration.

*Hemifumarate*, m.p. 233·5–235·5°C (ethanol). For $C_{19}H_{21}ClN_2OS + 0·5\ C_4H_4O_4$ (418·9) calculated: 60·20% C, 5·53% H, 8·46% Cl, 6·69% N, 7·66% S; found: 59·67% C, 5·48% H, 8·64% Cl, 6·41% N, 7·62% S.

*trans*-2-Chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XXII*)

A solution of 99·1 g crude *XIX* in 1 l tetrahydrofuran was treated under nitrogen with 25 g $NaBH_4$ and the stirred mixture was treated over 20 min with 124 g $BF_3.2(C_2H_5)_2O$, added dropwise. The mixture was stirred for 4 h at room temperature, allowed to stand overnight, decomposed under stirring with 550 ml 5% HCl, added dropwise, made alkaline with $NH_4OH$ and extracted with benzene (3 × 500 ml). Drying of the extract ($MgSO_4$) and evaporation under reduced pressure gave 58·9 g (59%) crude base, m.p. 195–198 °C. Analytical sample, m.p. 203–203·5 °C (benzene–ethanol). IR spectrum: 750, 800, 810, 880 (4 and 2 adjacent and solitary Ar—H), 1 100 (CHOH), 1 600, 3 020, 3 038 (Ar), 2 665, 2 705, 3 100 $cm^{-1}$ (OH···N). $^1H$ NMR spectrum ($C^2H_3SOC^2H_3$): $\delta$ 7·00–7·80 (m, 7 H, ArH), 5·80 (bd, $J$ = 8·0 Hz, after $^2H_2O$ d, 1 H, Ar—CH—O), 5·30 (d, $J$ = 4·0 Hz, disappears after $^2H_2O$, 1 H, OH), 3·75 (d, $J$ = 8·0 Hz, 1 H, Ar—CH—N), *c.* 3·50 (m, 8 H, 4 $NCH_2$ of piperazine), 2·12 (s, 3 H, $NCH_3$). For $C_{19}H_{21}Cl.N_2OS$ (360·9) calculated: 63·23% C, 5·87% H, 9·82% Cl, 7·76% N, 8·88% S; found: 63·42% C, 5·85% H, 10·05% Cl, 7·67% N, 8·61% S.

*Fumarate*, m.p. 212·5–215 °C (ethanol). For $C_{23}H_{25}ClN_2O_5S$ (477·0) calculated: 57·91% C, 5·28% H, 7·43% Cl, 5·87% N, 6·72% S; found: 57·63% C, 5·30% H, 7·28% Cl, 5·63% N, 6·48% S.

2-Methylsulfonyldibenzo[*b*,*f*]thiepin-5,5-dioxide (*XXIII*)

A solution of 2·0 g *Ib* (ref.[15]) in 30 ml acetic acid was stirred and treated dropwise over 5 min with 15 ml 30% $H_2O_2$. It was stirred for 3 h at room temperature and refluxed for 6 h. After cooling it was diluted with 90 ml water, the precipitated solid was filtered, dissolved in 100 ml boiling benzene, the solution was washed with 3M-HCl, 1 : 2 dilute $NH_4OH$ and water, dried with $K_2CO_3$ and evaporated; 0·90 g (50%) crude product which was crystallized from ethyl acetate, m.p. 165–169°C. UV spectrum: $\lambda_{max}$ 229·5 nm (log $\varepsilon$ 4·54), 302 nm (3·96), infl. at 267 nm (3·82). IR spectrum: 760, 800, 882, 899 (4 and 2 adjacent and solitary Ar—H), 1 150, 1 305 ($SO_2$), 1 540, 1 559, 1 589, 3 034, 3 060 $cm^{-1}$ (Ar). $^1H$ NMR spectrum ($C^2H_3SOC^2H_3$): $\delta$ 7·50 to 8·50 (m, 9 H, ArH and CH=CH), 3·35 (s, 3 H, $SO_2CH_3$). For $C_{15}H_{12}O_4S_2$ (320·4) calculated: 56·23% C, 3·78% H, 20·01% S; found: 55·80% C, 3·53% H, 19·78% S.

2-(4-Methylthiophenylthio)benzoic Acid Anhydride (*XXVI*)

A mixture of 50 g *XXIV* (ref.[15]) with 150 ml dioxane was stirred and treated with 21·5 g ethyl chloroformate. The mixture was refluxed for 5 h, cooled to 40°C and treated over 2 h with 15 g $NaBH_4$. It was stirred for 1 h at 40–50°C and refluxed for 1·5 h. After standing overnight it was decomposed under stirring with 100 ml water, added dropwise, and after stirring for 30 min at room temperature it was extracted with 400 ml chloroform. The extract was washed with 150 ml 10% $Na_2CO_3$ (acidification of the washing led to recovery of 2·7 g acid *XXIV*), dried with $CaCl_2$ and evaporated. The residue (35 g mixture of at least four neutral compounds containing also the alcohol *XXV*) was dissolved in 70 ml benzene, the solution was filtered with charcoal and allowed to crystallize; 3·0 g (6%) solid melting at 148–152°C; analytical sample, m.p. 160–162°C (acetone). It was identified as *XXVI*. Mass spectrum, *m/z* (%): 534 ($M^+$ corresponding to $C_{28}H_{22}O_3S_4$, 30%), 276 (45), 259 (100), 212 (52), 184 (40). UV spectrum (saturated solution in methanol): $\lambda_{max}$ 271 and 340 nm. IR spectrum: 745, 752, 810, 820 (4 and 2 adjacent Ar—H), 1 110, 1 120, 1 210, *1 775* (RCOOCOR), 1 575, 1 590, 3 085 $cm^{-1}$ (Ar). $^1H$ NMR spectrum: $\delta$ 8·13 (dd, $J$ = 2·0; 8·0 Hz, 2 H, 6,6′-$H_2$ in the benzoic acid residues), 7·50 (d, $J$ = 8·5 Hz, 4 H, 2,6,2′,6′-$H_4$ in the methylthiophenyl residues), 7·30 (d, $J$ = 8·5 Hz, 4 H, 3,5,3′,5′-$H_4$ in the methylthiophenyl

residues), *c.* 7·25 (m, 4 H, 4,5,4′,5′-$H_4$ in the benzoic acid residues), 6·88 (dd, $J$ = 2·0; 8·0 Hz, 2 H, 3,3′-$H_2$ in the benzoic acid residues), 2·53 (s, 6 H, 2 $SCH_3$). For $C_{28}H_{22}O_3S_4$ (534·7) calculated: 62·89% C, 4·15% H, 23·98% S; found: 62·78% C, 4·26% H, 23·45% S.

*XXVI* (2·0 g) was stirred and heated for 1 h with 20 ml 10% KOH to 100°C. The solution obtained was acidified with hydrochloric acid, the precipitated product was filtered (1·5 g) and crystallized from ethanol, m.p. 197 C. Lit.[15] gave for pure *XXIV* the m.p. of 197—199°C.

Ethyl 2-(4-Methylthiophenylthio)benzoate (*XXVII*)

*XXIV* (ref.[15]) (50 g) was dissolved in 200 ml dioxane at 70°C, 20 g triethylamine were added at 40—50°C and the mixture was treated with 21·5 g ethyl chloroformate. It was refluxed for 5 h, cooled to 40—50°C and treated slowly under stirring with 15 g $NaBH_4$. The stirring at 40 to 50°C was continued for 1 h and the mixture was refluxed for 2 h. After cooling it was decomposed by a slow addition of 400 ml water and extracted with chloroform. The extract was washed with 150 ml 10% $Na_2CO_3$, dried with $CaCl_2$, filtered and evaporated. The residue was dissolved in benzene and chromatographed on a column of 1 kg $Al_2O_3$. Benzene eluted as the least polar fraction 26·5 g (48%) *XXVII*, m.p. 85—87°C (cyclohexane). UV spectrum: $\lambda_{max}$ 268 nm (log $\varepsilon$ 4·23), inflexes at 285 nm (4·12), 320 nm (3·80). IR spectrum: 735, 810 (4 and 2 adjacent Ar—H), 1 245, 1 265, *1 700* (ArCOOR), 1 560, 1 575, 1 585, 3 043, 3 072 $cm^{-1}$ (Ar). $^1H$ NMR spectrum: $\delta$ 7·98 (m, 1 H, 6-H), 7·43 and 7·22 (ABq, $J$ = 8·5 Hz, 4 H, 1,4-$C_6H_4$), *c.* 7·15 (m, 2 H, 4,5-$H_2$), 6·78 (m, 1 H, 3-H), 4·39 (q, $J$ = 7·0 Hz, 2 H, $OCH_2$), 2·48 (s, 3 H, $SCH_3$), 1·40 (t, $J$ = 7·0 Hz, 3 H, $CH_3$ of ethyl). For $C_{16}H_{16}O_2S_2$ (304·4) calculated: 63·13% C, 5·30% H, 21·06% S; found: 63·18% C, 5·41% H, 20·84% S.

2-(4-Methylthiophenylthio)benzyl Chloride (*XXVIII*)

A mixture of 124 g *XXV* (ref.[68,69]) and 300 ml benzine (b.p. 60—70°C) was heated to 50°C and treated under stirring over 1 h with 76 g $SOCl_2$ (temperature at 56—60°C). The stirring was continued at 65°C for 30 min, the mixture was cooled to 50°C and the solution was decanted from the black polymers on the walls. The clear solution was then cooled and stirred for 2 h at 10°C and the product was filtered; 120 g (90%), m.p. 52—56°C. This product was sufficiently pure for the next step. Lit.[15], m.p. 59—61°C.

2-[2-(4-Methylthiophenylthio)phenyl]acetic Acid (*XXX*)

A stirred solution of 65 g *XXVIII* in 175 ml dimethylformamide was treated with 24·5 g NaCN. The mixture was stirred for 45 min without heating and for 5 h at 100°C. Dimethylformamide was evaporated *in vacuo*, the residue was treated with 200 ml water and extracted with benzene. The extract was filtered and evaporated under reduced pressure giving 60·4 g (97%) crude 2-(4-methylthiophenylthio)phenylacetonitrile (*XXIX*). It was dissolved in 360 ml ethanol, the solution was treated with a solution of 55 g KOH in 65 ml water and the mixture was stirred and refluxed for 6 h. Ethanol was evaporated, the residue was dissolved in 400 ml water and the solution washed with 250 ml benzene. The aqueous solution was acidified with 150 ml 1 : 1 dilute hydrochloric acid, the acid layer was decanted from the separated oily product which crystallized after treatment with 500 ml cold water; 59·9 g (93%) crude *XXX* which could be used directly for the next step[15], m.p. 108—113°C. Lit.[15], m.p. 117—119°C.

The benzene washings containing neutral by-products were dried and distilled. A small quantity of a homogeneous oil was obtained, b.p. 150—155°C/13 Pa. The substance was shown to be 2-(4-methylthiophenylthio)benzyl ethyl ether (*XXXII*). $^1H$ NMR spectrum: $\delta$ 7·00—7·70 (m, 8 H,

ArH), 4·61 (s, 2 H, $ArCH_2O$), 3·58 (q, $J$ = 7·0 Hz, 2 H, $OCH_2$ in ethoxyl), 2·48 (s, 3 H, $SCH_3$), 1·28 (t, $J$ = 7·0 Hz, 3 H, $CH_3$ in ethoxyl). For $C_{16}H_{18}OS_2$ (290·4) calculated: 66·16% C, 6·24% H, 22·08% S; found: 66·48% C, 6·36% H, 21·74% S.

Continued distillation proceeded with signs of decomposition. It was discontinued and the residue was treated with a small quantity of benzene. The precipitated solid was recrystallized from benzene; 70 mg 2,2'-bis(4-methylthiophenylthio)stilbene (*XXXIII*), solvate with 0·5 molecule of benzene, m.p. 179–181°C. Mass spectrum, *m/z* (%): 488·0785 ($M^+$ corresponding to $C_{28}H_{24}S_4$, calculated 488·0762, 45%), 364·0437 ($C_{21}H_{16}S_3$, 15), 333 ($C_{21}H_{17}S_2$, 100), 284·0646 ($C_{20}H_{12}S$, 41), 243·0283 ($C_{14}H_{11}S_2$, 78), 240 (56), 197·0415 ($C_{13}H_9S$, 43), 155 ($C_7H_7S_2$, 83). For $C_{28}H_{24}S_4 + 0{\cdot}5\ C_6H_6$ (527·8) calculated: 70·54% C, 5·16% H, 24·30% S; found: 70·77% C, 5·14% H, 24.10% S.

1,4-Bis(2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)-piperazine (*XXXIV*)

Crude base *IIIb* (ref.[10]) (500 g) was purified by crystallization from 1 800 ml ethanol. The mixture was heated to dissolve the base but a small quantity remained undissolved and was filtered off; 6·0 g, m.p. 273–278°C. It was purified by recrystallization from a large volume of xylene, m.p. 281–283°C. The compound was shown to be the stereoisomer A of *XXXIV* (*cf.*[75]). Mass spectrum, *m/z* (elemental composition): 598·1578 ($M^+$ corresponding to $C_{34}H_{34}N_2S_4$, calculated 598·1593), 475 ($C_{27}H_{27}N_2S_3$), 341 ($C_{19}H_{21}N_2S_2$), 314 ($C_{18}H_{20}NS_2$), 299 ($C_{17}H_{17}NS_2$), 257 ($C_{15}H_{13}S_2$, base peak), 210 ($C_{14}H_{10}S$). For $C_{34}H_{34}N_2S_4$ (598·9) calculated: 68·19% C, 5·72% H, 4·68% N, 21·41% S; found: 68·08% C, 5·77% H, 5·02% N, 21·10% S. Lit.[75], m.p. 276–278°C.

1-Acetyl-4-(3-hydroxypropyl)piperazine (*XXV*)

A solution of 16·4 g 1-acetylpiperazine hydrochloride (m.p. 161–163°C) (ref.[77,78]) in 100 ml warm ethanol was treated with 14·0 g 3-chloropropanol and 28·0 g $K_2CO_3$ and the mixture was stirred and refluxed for 12 h. After cooling the salts were filtered off and washed with ethanol, and the filtrate was evaporated under reduced pressure. The residue (18·6 g crude oily *XXXV*) was dissolved in 40 ml ethanol and the solution was treated with a slight excess of a solution of HCl in ether. The precipitated crude hydrochloride was crystallized from ethanol; 12 g (54%), m.p. 160–163°C. Analytical sample, m.p. 164–165°C (ethanol). For $C_9H_{19}ClN_2O_2$ (222·7) calculated: 48·53% C, 8·60% H, 15·92% Cl, 12·59% N; found: 48·67% C, 8·71% H, 16·02% Cl, 12·38% N.

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