POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENTS NOROXYCLOTHEPIN AND OXYCLOTHEPIN; SYNTHESIS OF 8-CHLORO-3-HYDROXY--10-[4-(2-HYDROXYETHYL)PIPERAZINO]- AND -10-[4-(3-HYDROXYPROPYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b,f*]THIEPIN*

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Substitution reactions of 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin with 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine gave the piperazine derivatives *IX* and *X*; their demethylation with boron tribromide led to unfavourable results. New procedure for the synthesis of phenolic amines was elaborated starting with demethylation of 8-chloro-3-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one with pyridine hydrochloride, followed by reduction of the hydroxy ketone *XIII* to the diol *XIV*. Reaction with methanesulfonyl chloride in the presence of triethylamine resulted in the dimethanesulfonic ester *XV* which was treated with 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine. The aliphatic sulfoester group underwent substitution, confirmed by isolation of compound *XII*. The aminolysis afforded phenolic compounds *VII* and *VIII* being potential metabolites of the neuroleptic agents noroxyclothepin (*III*) and oxyclothepin (*IV*). Both phenolic amino alcohols have only very low central depressant and cataleptic activity.

Out of the identified and synthesized metabolites[1,2] of the neuroleptic agent clorothepin (octoclothepin) (*I*, ref.[3]), the highest neuroleptic activity was exhibited by the 3-hydroxy derivative *V* (ref.[4]) being after oral administration significantly less toxic than clorothepin (*I*) and simultaneously approximately twice as active in the tests of ataxia and catalepsy. This fact was a reason for synthesizing a series of further 3-hydroxylated potential metabolites of clorothepin[5]. A surprise in this connection was the finding of a very weak activity of the corresponding potential metabolite of oxyprothepin (*II*, ref.[6]), a further neuroleptic agent of the 10-piperazinodibenzo-[*b,f*]thiepin series, *i.e.* of compound *VI* (ref.[7]). The only explanation was the hypothesis according to which the introduction of two hydroxyl groups into the structure of a neuroleptic of this series brings about such an increase of the hydrophilic char-

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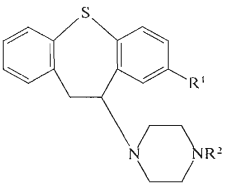
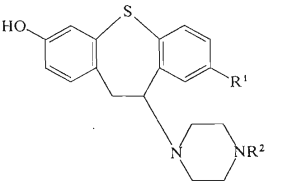
acter of the substance that its molecules are no more able to penetrate through the hydrophobic membranes which results in inactivation. The correctness of this hypothesis was indicated by our experience with some further Ar-dihydroxy and Ar,Ar'--dihydroxy derivatives of this series[8,9]. For getting a conclusive evidence, we carried out the synthesis of the 3-hydroxy derivatives of neuroleptic aminoalcohols noroxyclothepin (*III*, ref.[10–13]) and oxyclothepin (*IV*, ref.[10–12]), *i.e.* of the phenolic amines *VII* and *VIII*, described in the present communication.

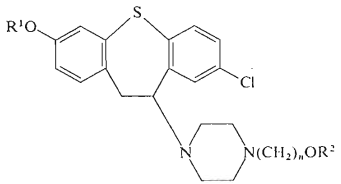


I, $R^1 = Cl$, $R^2 = CH_3$
II, $R^1 = SCH_3$, $R^2 = (CH_2)_3OH$
III, $R^1 = Cl$, $R^2 = (CH_2)_2OH$
IV, $R^1 = Cl$, $R^2 = (CH_2)_3OH$



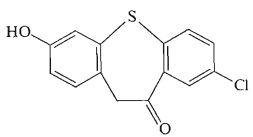
V, $R^1 = Cl$, $R^2 = CH_3$
VI, $R^1 = SCH_3$, $R^2 = (CH_2)_3OH$
VII, $R^1 = Cl$, $R^2 = (CH_2)_2OH$
VIII, $R^1 = Cl$, $R^2 = (CH_2)_3OH$

The first attempt to prepare compounds *VII* and *VIII* proceeded in the same way which was used in the synthesis of most of the phenolic amines of this series[4,5,7–9], consisting in the final stage in demethylation of the corresponding methyl ethers with boron tribromide. The known 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo-[*b*,*f*]thiepin[4] was transformed by substitution reactions with 1-(2-hydroxyethyl)-piperazine and 1-(3-hydroxypropyl)piperazine[14] to the methoxy analogues *IX* and *X* of the desired substances. The products were subjected to treatment with boron tribromide in dichloromethane at room temperature. In the first case (*IX*), the crude reaction product was directly subjected to an alkaline hydrolysis and in addition to a large amount of polymers, the desired product *VII* was obtained in a low yield. In the second case (*X*), the crude product was first decomposed with ethanol and then subjected to alkaline hydrolysis. A large quantity of polymers was formed again and as the only homogeneous product, a small amount of a base was isolated. It is a compound with a free phenolic hydroxyl group which was identified by means of the mass spectrum as the ethyl ether *XI*. Its formation can be explained by ethanolysis of the primarily formed bromoboric ester. In conclusion, the results of these boron tribromide demethylations were completely unsatisfactory and of no use for the preparation of compounds *VII* and *VIII*.

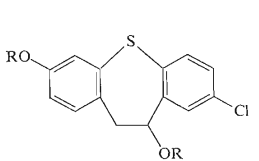


IX, $R^1 = CH_3$, $R^2 = H$, $n = 2$
X, $R^1 = CH_3$, $R^2 = H$, $n = 3$
XI, $R^1 = H$, $R^2 = C_2H_5$, $n = 3$
XII, $R^1 = SO_2CH_3$, $R^2 = H$, $n = 3$

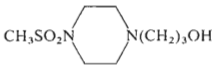
These results induced us to an attempt at finding a new approach to the synthesis of phenolic amines of our series. We started from the known[4] 8-chloro-3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one which could be demethylated in a high yield by heating with pyridine hydrochloride to the hydroxy ketone *XIII*. The following reduction with sodium borohydride in ethanol afforded the diol *XIV*. The crude product, formed by the following treatment with methanesulfonyl chloride in the presence of triethylamine, for which the structure of the dimethanesulfonic ester *XV* was supposed, was subjected to a reaction with 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine[14]. The desired nucleophilic substitution in position 10 takes evidently place and in one case, the 3-(methanesulfonyloxy)-10-[4-(3-hydroxypropyl)piperazino] derivative *XII*, formed as the intermediate, could be isolated. The 3-methanesulfonyloxy group reacts at higher temperature also with an excess of the amine and products of the aminolysis are the free phenol *VIII* on the one hand, and the sulfonamide *XVI* on the other. The phenolic amine *VII* was also prepared in this manner. Both of the title compounds were isolated as crystalline bases containing benzene as the crystal solvent. The tendency of amino alcohols of this type to crystallize in the form of solvates with aromatic hydrocarbons is typical[7]. The bases were characterized by spectra and transformed to crystalline salts.



XIII

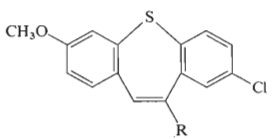


XIV, R = H
XV, R = SO_2CH_3



XVI

A minor less polar component was separated during the isolation of the base *VII* from the crude reaction product by chromatography on alumina; it gave a crystalline maleate. The IR spectrum of the liberated base indicated the presence of methoxyl on the aromatic ring and further of a primary alcohol group; the UV spectrum showed a considerable degree of conjugation, typical for the dibenzo[*b*,*f*]thiepin chromophore. The mass spectrum estimated the composition to be $C_{21}H_{23}ClN_2O_2S$. All of these data identifie the product as the enamine *XVII*. In order to explain its formation, it is necessary to pressume that the used diol *XIV* contained a small quantity of the starting 8-chloro-3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one. The enamine could then result either by a direct reaction with 1-(2-hydroxyethyl)piperazine (methanesulfonic acid formed during the nucleophilic substitution could act as the acid catalyst), or via the primarily formed methanesulfonic enol ester *XVIII*. It is surprising anyway that the enamine *XVII* resisted to the action of 5% hydrochloric acid taking place in the course of the isolation procedure.



XVII, R = N(CH$_2$)$_2$OH

XVIII, R = OSO$_2$CH$_3$

Both title compounds were tested pharmacologically in the form of dihydrochlorides monohydrates (*VII*, VÚFB-14.010; *VIII*, VÚFB-13.762) as potential neuroleptics. They were administered orally to mice and rats and the doses shown were calculated for bases. Compound *VII* has a medium lethal dose in mice (LD_{50}) higher than 1 g/kg; this dose causes lethality of 40% animals. In the rotarod test in mice it shows a very weak effect; ataxia takes place only at a medium effective dose (ED_{50}) of 69 mg/kg. The compound is inactive cataleptically in rats in a dose of 50 mg/kg. Compound *VIII* has the LD_{50} = 940 mg/kg; the medium effective dose bringing about ataxia in mice, ED_{50} = 32 mg/kg; a very weak cataleptic effect in rats was found, ED_{50} = = 67 mg/kg.

The results just shown are in complete agreement with those found for the 3-hydroxy derivative of oxyprothepin[7] as well as for further dihydroxy compounds of this series[8,9]. In this way, it can be considered proven that the introduction of a second hydroxyl group into the molecules of neuroleptic agents of our series brings about an unfavourable shift in the balance between the hydrophobic and hydrophilic moieties of the molecules which are getting too hydrophilic and unable of transport to the sites of action. At this opportunity it should be noted that in the series of neuroleptic 11-piperazinodibenzo[*b,f*]oxazepines and -thiazepines, a similar effect is obtained already by the introduction of one hydroxyl group into the molecule[15]; the cyclic amidine fragment has evidently the function of a second hydrophilic residue. The result is that the amino alcohols of this series are little active and the development of long-acting ester preparation is unlikely.

Compound *VIII* was also tested for antimicrobial activity *in vitro* (Dr L. Langšádl, bacteriological department of this institute); tested microorganisms and minimum inhibitory concentrations in μg/ml are given: *Streptococcus* β-*haemolyticus* 3·12, *Streptococcus faecalis* 100, *Staphylococcus pyogenes aureus* 50, *Pseudomonas aeruginosa* >100, *Escherichia coli* 50, *Proteus vulgaris* >100, *Mycobacterium turberculosis* H37Rv 25, *Saccharomyces pasterianus* 12·5, *Trichophyton mentagrophytes* 25, *Candida albicans* 50, *Aspergillus niger* >50.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected. The samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80MHz) spectrometer, and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

8-Chloro-3-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XIII*)

A solution of 128 g pyridine in 130 ml ethanol was neutralized with 155 ml hydrochloric acid and the solution evaporated completely. 8-Chloro-3-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one[4] (23·0 g) was added to the solid pyridine hydrochloride and the mixture was heated under stirring for 80 min to 200°C. After cooling to 80°C, the mixture was decomposed with 400 ml water and allowed to stand overnight at room temperature. The solid product was filtered, washed with water and crystallized from 70 ml ethanol; 15·8 g (73%), m.p. 200–203°C. Analytical sample, m.p. 203–204°C (ethanol). UV spectrum: λ_{max} 235 nm (log ε 4·38), 262 nm (4·07), 293 nm (3·55), 340 nm (3·60). IR spectrum: 825, 869 (2 adjacent and solitary Ar–H), 1229, 1280, 1298 (ArOH), 1498, 1580, 1607 (Ar), 1659 (ArCOR), 3265 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·88 (s, 1 H, OH), 7·98 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·60 (m, 2 H, 6,7-H_2). 7·33 (d, J = 8·5 Hz, 1 H, 1-H), 7·09 (m, J = 2·0 Hz, 1 H, 4-H), 6·88 (m, J = 8·5; 2·0 Hz, 1 H, 2-H), 4·17 (s, 2 H, $ArCH_2CO$). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·28% H, 12·81% Cl, 11·59% S; found: 60·83% C, 3·40% H, 12·96% Cl, 11·64% S.

8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-3,10-diol (*XIV*)

A solution of 15·8 g *XIII* in 240 ml ethanol was stirred at 72°C and treated dropwise over 15 min with a solution of 2·15 g $NaBH_4$ in 20 ml water containing 0·5 ml 20% NaOH. The mixture was refluxed for 6 h, ethanol was evaporated, the residue decomposed with 150 ml water and extracted with benzene. The extract was evaporated and the solid product (14·3 g, 90%, m.p. 144–147°C) was crystallized from benzene, m.p. 146–148°C. IR spectrum: 820, 859, 868, 886 (2 adjacent and solitary Ar—H), 1 049 (CHOH in the cycle), 1 234 (ArOH), 1 502, 1 582, 1 621 (Ar), 3 150, 3 340 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·52 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·40 (d, J = 8·0 Hz, 1 H, 6-H), 7·15 (mcd, J = 8·0; 3·0 Hz, 1 H, 7-H), 7·00 (d, J = 8·0 Hz, 1 H, 1-H), 6·80 (m, J = 3·0 Hz, 1 H, 4-H), 6·60 (m, J = 8·0; 3·0 Hz, 1 H, 2-H), 5·75 (bd, J = = 5·0 Hz, disappears after D_2O, 1 H, 10-OH), 5·22 (m, after D_2O dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·35 and 3·05 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_{11}$. ClO_2S (278·8) calculated: 60·32% C, 3·98% H, 12·72% Cl, 11·50% S; found: 60·22% C, 3·93% H, 12·65% Cl, 11·31% S.

8-Chloro-10-[4-(2-hydroxyethyl)piperazino]-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*IX*)

A mixture of 15·0 g 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo[*b,f*]-thiepin[4], 20 g 1-(2-hydroxyethyl)piperazine and 20 ml chloroform was refluxed for 6 h. Chloroform was evaporated, the residue decomposed with 50 ml water and extracted with benzene. The extract was washed with 5%NaOH and water and then shaken with an excess of 1·25M-H_2SO_4. The acid aqueous layer was washed with benzene, made alkaline with NH_4OH and the base was extracted with benzene. Processing of the extract gave 14·0 g (72%) oily base. Neutralization with maleic acid in ethanol led to 18·8 g bis(hydrogen maleate), m.p. 138–140°C. Analytical sample, m.p. 138–141°C (ethanol). For $C_{29}H_{33}ClN_2O_{10}S$ (637·1) calculated: 54·67% C, 5·22% H, 5·57% Cl, 4·40% N, 5·03% S; found: 54·83% C, 5·06% H, 5·67% Cl, 4·42% N, 4·98% S. A sample of this salt was decomposed with NH_4OH and the pure base isolated by extraction with ether; oil. ^{1}H-NMR spectrum: δ 7·66 (m, J = 3·0 Hz, 1 H, 9-H), 6·60–7·40 (m, 5 H, remaining Ar—H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·72 (s, 3 H, OCH_3), 3·61 (t, 2 H, CH_2O), 2·88 (s, 1 H, OH), c. 2·60 (m, 10 H, 5 NCH_2).

8-Chloro-10-[4-(3-hydroxypropyl)piperazino]-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*X*)

A mixture of 15·0 g 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin[4], 21 g 1-(3-hydroxypropyl)piperazine[14] and 20 ml chloroform was processed similarly like in the preceding case. There were obtained 14·0 g (70%) oily base. Neutralization with maleic acid in ethanol afforded 17·0 g bis(hydrogen maleate), m.p. 128–131°C. Analytical sample, m.p. 132–134°C (ethanol). IR spectrum: 811, 842, 874 (2 adjacent and solitary Ar—H), 1 070 (CH_2OH), 1 360, 1 505, 1 538, 1 610, 1 628 (COO^- and Ar), 1 715 (COOH), 2 400 (NH^+), 3 428 cm^{-1} (OH). For $C_{30}H_{35}ClN_2$.$O_{10}S$ (651·1) calculated: 55·34% C, 5·42% H, 5·45% Cl, 4·30% N, 4·92% S; found: 55·76% C, 5·54% H, 5·47% Cl, 4·32% N, 4·80% S.

Like in the preceding case, a sample of pure oily base was prepared from the pure salt used for recording the ^{1}H-NMR spectrum: δ 7·66 (m, J = 3·0 Hz, 1 H, 9-H), 6·60–7·40 (m, 5 H, remaining Ar—H), 4·60 (bs, 1 H, OH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·72(s, 3 H, OCH_3), 3·74 (t, 2 H, CH_2O), c. 2·60 (m, 10 H, 5 NCH_2), 1·70 (m, 2 H, CH_2 in the middle of the propane chain).

8-Chloro-3-hydroxy-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*VII*)

A. A stirred solution of 10·0 g *IX* in 40 ml dichloromethane was slowly treated at 10—20°C with a solution of 25·5 g BBr_3 in 20 ml dichloromethane, the mixture was stirred for 5 h at room temperature and allowed to stand overnight. Dichloromethane was evaporated, the residue was treated with 60 ml 20% NaOH and stirred for 3 h. It was then diluted with 30 ml ethanol and stirred for another 3 h. The undissolved polymeric material was filtered off (6·8 g), the filtrate was evaporated, the residue dissolved in dilute hydrochloric acid, a small quantity of undissolved material filtered off and the filtrate was made alkaline with a solution of Na_2CO_3. The separated crude phenolic base was filtered, washed with water and dried; 0·9 g (9%).The characterization of the base is reported under *B*. The base was neutralized with fumaric acid and the obtained fumarate crystallized from acetone, m.p. 225—228°C. For $C_{24}H_{27}ClN_2O_6S$ (507·0) calculated: 56·85% C, 5·37% H, 6·99% Cl, 5·53% N, 6·32% S; found: 56·98% C, 5·65% H, 6·97% Cl, 5·29% N, 6·17% S.

B. A solution of 6·9 g *XIV* and 8·4 g triethylamine in 130 ml dichloromethane was cooled to −10°C and treated under stirring over 1 h with 6·4 g methanesulfonyl chloride. The mixture was stirred for 1 h at 0°C, washed with ice-cold water, 10% hydrochloric acid and 5% $NaHCO_3$ solution, dried with Na_2SO_4 and evaporated. The residue (presumably crude *XV*) was treated with 16·5 g 1-(2-hydroxyethyl)piperazine and the mixture heated for 6 h in a bath of 140°C. After cooling, it was decomposed with water and extracted with dichloromethane. The extract was washed with water and then shaken with an excess of 5% hydrochloric acid. The solution of the hydrochlorides was separated, made alkaline with Na_2CO_3 and the crude product extracted with dichloromethane. Processing of the extract gave 5·6 g mixture of bases which was dissolved in chloroform and chromatographed on a column of 600 g Al_2O_3 (activity II).

Chloroform eluted 0·53 g of the least polar components which were neutralized with maleic acid in acetone. The precipitated maleate was crystallized from acetone, m.p. 144—147°C. It was identified as 8-chloro-10-[4-(2-hydroxyethyl)piperazino]-3-methoxydibenzo[*b,f*]thiepin (*XVII*) bis(hydrogen maleate). Mass spectrum, *m/e* (%): 402·1186 (M^+, corresponds to $C_{21}H_{23}.ClN_2O_2S$, 66), 373 (49), 371 (100), 237 (57), 217 (58), 208 (63), 205 (42), 143 (92), 129 (77). For $C_{29}H_{31}ClN_2O_{10}S$ (635·1) calculated: 54·84% C, 4·92% H, 5·58% Cl, 4·41% N, 5·05% S; found: 54·90% C, 5·07% H, 5·60% Cl, 4·30% N, 5·11% S. A sample of the base, released from the maleate, was used for recording the spectra. UV spectrum: λ_{max} 272 nm (log ε 4·04), infl. 305 nm (3·91). IR spectrum (CS_2): 813, 832, 874 (2 adjacent and solitary Ar-H), 1062 (CH_2OH), 1268, 1301 ($ArOCH_3$), 2750, 2805 (OCH_3, NCH_2), 3400 cm^{-1} (OH).

The chromatography was continued by elution with a mixture of chloroform and ethanol; there were eluted 2·91 g (30%) of the crude base *VII* which crystallized from benzene as a solvate with 1/2 C_6H_6, m.p. 111—113°C. Mass spectrum, *m/e* (%): 390 (M^+ corresponding to $C_{20}H_{23}.ClN_2O_2S$, 13), 359 (15), 317 (14), 261 (52), 233 (42), 226 (48), 129 (50), 102 (51), 100 (100), 99 (60). IR spectrum: 822, 832, 880 (2 adjacent and solitary Ar-H), 1060 (CH_2OH), 1283 (ArOH), 1500, 1580, 1606 (Ar), 2680 (NH^+), 2808 (NCH_2), 3150 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·65 (m, J = 2·5 Hz, 1 H, 9-H), 7·00—7·50 (m, 3 H, 1,6,7-H_3), 6·91 (m, J = = 2·5 Hz, 1 H, 4-H), 6·70 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·50 (t, 2 H, CH_2O), 2·00—3·00 (m, 5 NCH_2 and 2 OH); in $CDCl_3$ the 2 OH appeared as a *bs* at 5·03, disappearing after D_2O. For $C_{20}H_{23}ClN_2O_2S + 1/2\ C_6H_6$ (430·0) calculated: 64·24%C, 6·09% H, 8·25% Cl, 6·52% N, 7·46% S; found: 63·65% C, 6·07% H, 8·30% Cl, 6·49% N, 7·70% S.

The fumarate prepared from the base melted at 211—212°C and we were not able to attain by repeated crystallization from acetone the value given under *A*. For $C_{24}H_{27}ClN_2O_6S$ (507·0)

calculated: 56·85% C, 5·37% H, 6·99% Cl, 5·53% N, 6·32% S; found: 56·82% C, 5·33% H, 7·17% Cl, 5·26% N, 6·31% S.

The dihydrochloride crystallized from a mixture of aqueous ethanol and ether as a monohydrate, m.p. 169–174°C. For $C_{20}H_{27}Cl_3N_2O_3S$ (481·9) calculated: 49·85% C, 5·65% H, 22·07% Cl, 5·81% N, 6·65% S; found: 48·82% C, 5·66% H, 22·04% Cl, 6·20% N, 6·80% S.

8-Chloro-10-[4-(3-ethoxypropyl)piperazino]-3-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XI*)

A solution of 9·3 g *X* in 30 ml dichloromethane was stirred and treated at 10–20°C over 15 min with a solution of 22 g BBr_3 in 20 ml dichloromethane. The mixture was stirred for 5 h at room temperature, allowed to stand overnight, decomposed under cooling with 30 ml ethanol and stirred for 8 h at room temperature. It was then evaporated *in vacuo*, the residue dissolved in 100 ml ethanol, 15 ml 20% NaOH were added and the mixture was refluxed for 6 h. Ethanol was evaporated *in vacuo*, the residue dissolved in water and the undissolved substance removed by filtration. The filtrate was acidified with hydrochloric acid and the precipitated solid was filtered off. The filtrate was washed with benzene and then made alkaline with 20% Na_2CO_3 solution. The separated phenolic base was isolated by extraction with dichloromethane, 1·2 g. Neutralization with fumaric acid in ethanol gave 0·35 g crystalline fumarate, m.p. 117–120°C (acetone). It was identified as the fumarate of the base *XI*. Mass spectrum, *m/e* (%): 432·1640 (M^+ corresponding to $C_{23}H_{29}ClN_2O_2S$, 22), 261 (36), 225 (22), 184 (20), 171 (30), 130 (70), 116 (50), 99 (100). For $C_{27}H_{33}ClN_2O_6S$ (549·1) calculated: 6·46% Cl, 5·10% N, 5·84% S; found: 6·78% Cl, 5·15% N, 5·89% S.

8-Chloro-10-[4-(3-hydroxypropyl)piperazino]-3-(methanesulfonyloxy)-10,11-dihydrodibenzo[*b,f*]thiepin (*XII*)

A solution of 8·36 g *XIV* and 10 g triethylamine in 150 ml dichloromethane was treated at −10°C under stirring with 7·6 g methanesulfonyl chloride, added dropwise over 10 min. The mixture was stirred for 1 h at 0°C, washed with water, 10% HCl and 5% $NaHCO_3$, dried and evaporated. The residue (13·0 g *XV*) was refluxed with 30 ml chloroform and 17·3 g 1-(3-hydroxypropyl) piperazine[14] for 7 h. After cooling, the mixture was diluted with benzene and the solution washed with water. The organic layer was extracted with 10% hydrochloric acid but most of the product proved to be a neutral substance. The acid aqueous layer was made alkaline with 20% NaOH and the basic product isolated by extraction with benzene; 0·3 g base *XII*. Neutralization with maleic acid in acetone gave 0·40 g bis(hydrogen maleate), m.p. 131–132°C (acetone–ether). Mass spectrum, *m/e*: 482 (M^+ corresponding to $C_{22}H_{27}ClN_2O_4S_2$). For $C_{30}H_{35}ClN_2O_{12}S_2$ (715·2) calculated: 50·38% C, 4·93% H, 4·96% Cl, 3·92% N, 8·97%S; found: 50·54%C, 5·14% H, 4·68% Cl, 4·12% N, 9·01% S.

The neutral substance (11·0 g) obtained by evaporation of the benzene layer (considered to be the unchanged *XV* but being in fact the crude 8-chloro-10-ethoxy-3-methanesulfonyloxy-10,11-dihydrodibenzo[*b,f*]thiepin formed from *XV* by the action of ethanol contained in the used chloroform) was heated with 16·0 g 1-(3-hydroxypropyl)piperazime for 7 h to 140°C. Usual processing gave as the only basic and water-insoluble product 0·47 g oil which crystallized from a mixture of benzene and cyclohexane and was identified as 1-(3-hydroxypropyl)-4-(methanesulfonyl)piperazine (*XVI*), m.p. 82–86°C. Mass spectrum, *m/e*: 222 (M^+ corresponding to $C_8H_{18}N_2O_3S$). IR spectrum: 1050 (CH_2OH), 1143, 1172, 1320 (CH_3SO_2NRR'), 3310, 3520 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 4·30 (bs, OH), 3·75 (t, J = 6·0 Hz, 2 H, CH_2O), 3·20 (def. t,

4 H, $CH_2N^4CH_2$), 2·77 (s, 3 H, CH_3SO_2), 2·60 (m, 6 H, remaining 3 NCH_2), 1·75 (m, 2 H, CH_2 in the middle of the propane chain). For $C_8H_{18}N_2O_3S$ (222·3) calculated: 43·22% C, 8·16% H, 12·60% N, 14·42% S; found: 43·63% C, 8·29% H, 12·61% N, 14·23% S.

8-Chloro-3-hydroxy-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIII*)

A solution of 6·9 g *XIV* and 8·4 g triethylamine in 130 ml dichloromethane was treated at −10°C with 6·4 g methanesulfonyl chloride and the obtained crude *XV* was heated with 15·2 g 1-(3-hydroxypropyl)piperazine[14] to 140°C for 6 h. The mixture was processed similarly like in the preparation of *VII* under *B*. There were obtained only 1·9 g (19%) oily base which was soluble in dilute hydrochloric acid as well as in dilute NaOH but insoluble in dilute acetic acid or Na_2CO_3 solution. This base crystallized from a mixture of benzene and cyclohexane as a solvate with 1/2 C_6H_6 and melted at 108—110°C. Mass spectrum, *m/e* (%): 404 (M^+ corresponding to $C_{21}H_{25}$. .ClN_2O_2S, 18), 317 (10), 261 (29), 226 (28), 114 (58), 99 (50), 88 (37), 83 (34), 70 (100). IR spectrum: 806, 832 (Ar-H), 1062 (CH_2OH), 1136, 1380 (Ar—OH), 1500, 1580, 1610 (Ar), 2660 (NH^+), 3160 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·62 (m, J = 2·5 Hz, 1 H, 9-H), 7·39 (d, J = 8·5 Hz, 1 H, 6-H), 7·31 (s, 3 H, 1/2 C_6H_6), 7·15 (m, J = 8·5; 2·5 Hz, 1 H, 7-H), 7·15 (d, J = 8·5 Hz, 1 H, 1-H), 6·90 (m, J = 2·5 Hz, 4-H), 6·70 (m, J = 8·5; 2·5 Hz, 1 H, 2-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·45 (t, J = 7·0 Hz, 2 H, CH_2O), 2·00—3·00 (m, 11 H, 5 NCH_2 and OH), 1·50 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{21}H_{25}ClN_2O_2S$ + 1/2 C_6H_6 (444·0) calculated: 64·92% C, 6·36% H, 7·99% Cl, 6·31% N, 7·22% S; found: 64·72% C, 6·59% H, 7·94% Cl, 6·03% N, 7·20% S.

The dihydrochloride was obtained from an ethanolic solution of the base and hydrogen chloride; it crystallized from aqueous ethanol as a monohydrate, m.p. 172—175°C. For $C_{21}H_{29}$. .$Cl_3N_2O_3S$ (495·9) calculated: 50·86% C, 5·89% H, 21·45% Cl, 5·65% N, 6·47% S; found: 50·22% C, 5·93% H, 21·62% Cl, 5·69% N, 6·33% S.

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