11-(3-[4-(2-HYDROXYETHYL)PIPERAZINO]PROPYLIDENE)-6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN, ITS 2-CHLORO DERIVATIVE AND SOME RELATED COMPOUNDS AS POTENTIAL ANTIPSYCHOTIC AGENTS; SYNTHESIS AND PHARMACOLOGY

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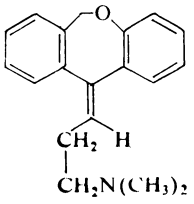
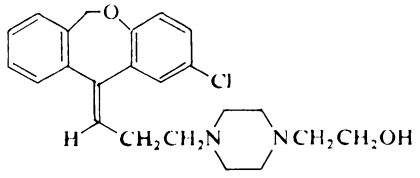
Substitution reactions of (*E*)-11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIIIa*) and its 2-chloro derivative *VIIIb* with 1-(2-hydroxyethyl)piperazine gave the title compounds *IIIa* and *IIIb* which afforded by treatment with acetic anhydride, decanoyl chloride and 3,4,5-trimethoxybenzoyl chloride the esters *IVab*—*VIab*. Reduction of the olefinic compounds *IIIa* and *IIIb* with hydroiodic acid resulted in the saturated amines *IXa* and *IXb*. The piperazine derivative *X* was obtained by a substitution reaction of 2,11-dichloro-6,11-dihydrodibenzo[*b*,*e*]thiepin with 1-(2-hydroxyethyl)piperazine. The amino alcohols *IIIa* and *IIIb*, as well as their acetates and 3,4,5-trimethoxybenzoates, are almost devoid of the CNS effects. The decanoates *Va* and *Vb* have not the properties of the depot antipsychotics (neither antidepressants, nor neuroleptics). The saturated amino alcohol *IXa* showed some antihistamine, spasmolytic and adrenolytic effects.

The molecules of tricyclic antidepressants and tricyclic neuroleptics show in many cases a striking similarity: The main parts of their structures may be the same tricyclic systems with a basic side chain connected to the central ring. Relatively small structural changes may result in a reversal of the antidepressant activity into a neuroleptic one and *vice versa*. Systems lacking substituents in the external rings are typical for tricyclic antidepressants and are mostly combined with an aliphatic side chain terminated by a dimethylamino or even better by a methylamino group[1]. Molecules of the neuroleptic agents, on the other hand, are typical by the presence of a "neuroleptic substituent" in a position, corresponding to the position of the chlorine atom in chlorpromazine, and their side chains often contain a piperazine or a piperidine residue[2,3]. A transition of an antidepressant to a neuroleptic agent may be demonstrated by the pair of the psychotropic agents doxepin *I* (ref.[4,5]) and pinoxepin *II* (ref.[6–8]). The antidepressant doxepin (*I*) lacks any substitution in the aromatic nuclei and contains an aliphatic side chain terminated by a dimethylamino group. The neuroleptic pinoxepin *II*, on the other hand, has the atom of chlorine in the typical position as the "neuroleptic substituent" and contains in the side

chain a hydroxyethylpiperazine fragment. A further difference consists in the geometrical isomerism on the ethene double bond. While doxepin *I* is a mixture of approximately 80% of the (*E*)-isomer and 20% (*Z*)-isomer (the difference in the antidepressant activity of both geometrical isomers is not important) (ref.[4,5]), pinoxepin *II* is the pure (*Z*)-isomer and its (*E*)-isomer is neuroleptically inactive[6] (we are dealing here evidently with a similar dependence of the neuroleptic activity on the geometrical isomerism like in the series of analogous thioxanthene derivatives[9-11]; for the explanation *cf.* [12]). With transitions from the structural field of antidepressant activity into the field of the neuroleptic one we have recently met in series of tricyclic substances containing two chalcogen atoms in the central seven-membered ring[13-17].



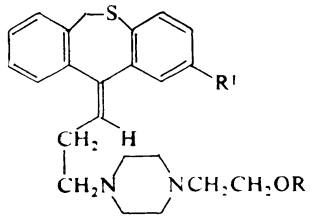
I



II

The object of the present communication is a pharmacochemical study in the series of dibenzo[*b*,*e*]thiepin derivatives coming out from the relation of compounds *I* and *II*. The antidepressant agent prothiadene is a dibenzo[*b*,*e*]thiepin analogue of compound *I*; it is an almost homogeneous (*E*)-isomer[18]. The patents[19] describe the N-(2-hydroxyethyl)piperazine analogue *IIIa* of prothiadene which was obtained by a substitution reaction of the bromo compound *VIIIa* with 1-(2-hydroxyethyl)-piperazine. A comparison of melting points of *VIIIa* (ref.[19]) and of a product prepared by our group[20] by a reaction of the cyclopropyl carbinol *VIIa* with a solution of hydrogen bromide in acetic acid, indicates the identity of both substances. With regard to the fact that by means of the IR spectrum it was possible to assign the (*E*)-configuration to our product[20], the same configuration evidently belongs also to the described – but very poorly characterized – piperazine derivative *IIIa* (ref.[19]). We have now, likewise, carried out the substitution reaction of the (*E*)-derivative *VIIIa* (ref.[20]) with excessive 1-(2-hydroxyethyl) piperazine and obtained in a good yield the crude piperazine derivative *IIIa* which afforded a crystalline bis(hydrogen maleate). Decomposition of this salt with aqueous ammonia released the base *IIIa* whose homogeneity was proven by thin-layer chromatography and by the ^{1}H NMR spectrum. The out-of-plane vibrations of the aromatic C—H bonds in the IR spectrum indicate for it the (*E*)-configuration (a satelite band at 782 to 783 cm^{-1}, which is typical for the (Z)-series, is missing, ref.[18]). By reaction of the amino alcohol *IIIa* with a mixture of acetic anhydride and acetic acid at room

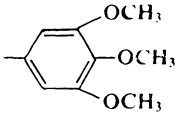
temperature there was prepared the acetate *IVa*. Reactions of compound *IIIa* with decanoyl chloride[21] and 3,4,5-trimethoxybenzoyl chloride[22] gave the esters *Va* and *VIa*. All the three esters were oily and were transformed to maleates. The (*E*)-configuration is supposed for them without further proofs. Decomposition of the maleate of the ester *Va* afforded the pure base whose solution in Miglyol^R (*cf.*[23]) was used for intramuscular administration. The ester *Va* represents our further attempt at developing an intramuscular depot antidepressant[23,24].



III, R = H

IV, R = $COCH_3$

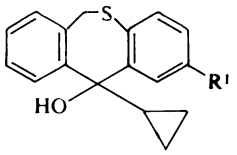
V, R = $CO(CH_2)_8CH_3$

VI, R = 

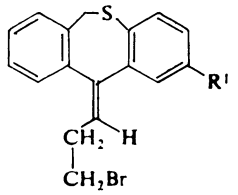
In formulae *III*–*IX*: *a*, R^1 = H; *b*, R^1 = Cl.

For approaching to the structure *II*, we carried out a similar synthetic work in the series of 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin. Cyclopropyl bromide[25] was converted in tetrahydrofuran to the Grignard reagent[20] which was subjected to treatment with 2-chlorodibenzo[*b*,*e*]thiepin-11(6*H*)-one[26–29]. The cyclopropyl carbinol *VIIb* was obtained and reacted with a solution of hydrogen bromide in acetic acid at room temperature to give derivative *VIIIb* (analogy, *cf.*[20]). The IR spectrum of this substance shows a strong band at 883 cm^{-1} of the solitary C—H in position 1 of the skeleton which corresponds to the typical band at 873 cm^{-1} of the (*E*)-isomer in the analogous 2-methyl series[30]. The (*E*)-configuration is thus assigned to compound *VIIIb* and to all unsaturated substances of the *b* series. Similarly like in the series *a*, a substitution reaction of compound *VIIIb* with 1-(2-hydroxyethyl)piperazine was carried out and resulted in the amino alcohol *IIIb*. By decomposition of the recrystallized maleate the crystalline base was released and its IR spectrum indicates, likewise, the (*E*)-configuration. Similar esterification reactions like in series *a* led to the acetate *IVb*, decanoate *Vb* and 3,4-trimethoxybenzoate *VIb* (3,4,5-trimethoxybenzoyl chloride[31] was prepared from 3,4,5-trimethoxybenzoic acid[32] by treatment with thionyl chloride). All the three esters were prepared in the form of crystalline maleates. The IR spectra of the released bases *IVb* and *Vb* were recorded and confirmed their belonging to the (*E*)-series. In the case of the

decanoate *Vb* the base was again used for preparing a solution in Miglyol[R] for intramuscular administration because in this case it was possible to expect for this compound properties either of a depot antidepressant or of a depot neuroleptic. Of course, a principal difference between the neuroleptic pinoxepin *II* and our substances *IIIb* – *VIb* consisted in the different configuration on the double bond.

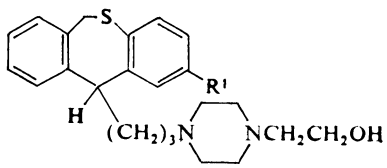


VII



VIII

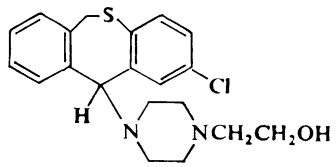
In previous communications[33,34] we described the reduction of 11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol, some of its halogeno derivativtives and also 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin[34] with hydroiodic acid under various conditions to the corresponding 11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepins. Now, we have subjected the amino alcohols *IIIa* and *IIIb* to a similar reduction and used to this end a boiling mixture of 55% hydroiodic acid and acetic acid in the presence of red phosphorus. Mass and ^{1}H NMR spectra of the obtained crude bases indicated that the reactions result in very inhomogeneous products. Their neutralization with maleic acid afforded in low yields maleates of expected dihydro compounds *IXa* and *IXb*. In the case of the chloro derivative *IXb* the base released from the crystalline maleate proved to be a mixture of two compounds (TLC). It was separated by chromatography on a column of aluminium oxide. The main fraction gave a crystalline maleate affording satisfactory analytical data and the product is thus considered to be the dihydro compound *IXb*. The used method of reducing the olefinic amines of type of compounds *IIIa* and *IIIb* deserves, however, further attention.



IX

A reduction of 2-chlorodibenzo[*b*,*e*]thiepin-11(6*H*)-one[26–29] with sodium borohydride in ethanol[35] gave in an almost theoretical yield 2-chloro-6,11-dihydrodibenzo-[*b*,*e*]thiepin-11-ol (the melting point 162 – 164°C found is higher than the literature[35]

value, *viz.* 158–160°C) which was transformed by boiling with thionyl chloride in a yield of 60% to 2,11-dichloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[35]. A substitution reaction of this compound with excessive 1-(2-hydroxyethyl)piperazine in chloroform afforded the oily amino alcohol *X* which gave a crystalline malcate. The product obtained is a member of the series including 11-(4-methylpiperazino)-6,11-dihydrodibenzo[*b*,*e*]thiepin[34], 11-(4-methylpiperazine)-6,11-dihydrodibenzo[*b*,*e*]oxepin[36] and 11-(4-methylpiperazino)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5,5-dioxide[37], which exhibited partly a considerable antireserpine activity[36,38], combined in one case with a relatively strong central depressant effect[34,38].



X

Compounds *IIIa*, *IIIb*, *Va* and *Vb* were evaluated as potential thymoleptics, and neuroleptics, respectively. The first two compounds were administered orally in the form of bis(hydrogen maleates); the doses given were calculated for the bases. Acute toxicity in mice, LD_{50}: *IIIa*, 740 mg/kg; *IIIb*, >800 mg/kg. Discoordination activity in the rotarod test in mice, ED_{50}: *IIIa*, 120 mg/kg; *IIIb*, 103 mg/kg. Central depressant activity (influencing the spontaneous motility of mice) in the photo-cell method of Dews, D_{50} : *IIIa*, >100 mg/kg; *IIIb*, 100 mg/kg. In the test of Ther in mice both compounds were inactive sedatively in a dose of 100 mg/kg. In the same dose they were inactive in the test of catalepsy in rats and in the test of reserpine ptosis antagonization in mice. In the test of inhibition of the ulcerogenic effect of reserpine both compounds were inactive in a dose of 50 mg/kg. Compound *IIIa* in a dose of 25 mg/kg does not affect significantly the reserpine hypothermia in mice. Compounds *Va* and *Vb* were administered intramuscularly in the form of 2·5% (*Va*) or 5% (*Vb*) solutions in Miglyol^{R}. Compound *Va* until the dose of 200 mg/kg did not cause lethality in mice. A dose of 100 mg/kg did not influence the reserpine ptosis in mice in the intervals of 2 and 10 h after the administration. A dose of 50 mg/kg did not affect the formation of reserpine ulcers in rats. In a dose of 100 mg/kg the compound is inactive towards the convulsant effect of electroshock in mice. Compound *Vb* in doses of 25 and 50 mg/kg did not show efficacy in tests of catalepsy and of the apomorphine stereotypies in rats. It can be concluded that compounds *IIIa* and *IIIb* did show properties neither of oral thymoleptics nor of neuroleptics; with compound *IIIb* it is possible to justify that by the unfavourable configuration on the double bond. The only effect proven is a mild tranquillizing action (including discoordinating effect) which is higher with the chlorinated com-

pound *IIIb*. Compound *Va* did not show properties of a depot thymoleptic; it is not surprising because of the fact that even the starting amino alcohol had no thymoleptic activity upon oral administration. Compound *Vb* is not a depot neuroleptic which has a similar reason like in the preceding case.

Compounds *IVa*, *IVb*, *VIa*, *VIb* and *IXa* were evaluated in the form of maleates by methods of the general pharmacological screening. In the first line values of acute toxicity in mice (LD_{50}), the way of administration and doses (D) used in the screening are given (doses in mg/kg): *IVa*, 30, *i.v.*, 6; *IVb*, >2 500, *p.o.*, 300; *VIa*, >2 500, *p.o.*, 300; *VIb*, >2 500, *p.o.*, 300; *IXa*, 70, *i.v.*, 14. In doses D all compounds were inactive in the rotarod test in mice, in the test of thiopental sleeping time potentiation in mice, affecting the spontaneous motility in mice, catalepsy in rats, antiapomorphine and antireserpine efficacy in mice. They thus show the character neither of thymoleptics nor of neuroleptics. Toxic doses higher than D brought about a reduced activity and ataxia in mice, with chlorinated compounds (*IVb*, *VIb*) ptosis was observed; the highest toxic doses elicited convulsions. Compound *IXa* in the dose D effected brief and deep drops of the blood pressure in normotensive rats and lowered the pressor response after a standard dose of adrenaline to less than 50% of the control value (adrenolytic effect). In concentrations of 1–10 μg/ml it reduced the barium chloride contractions of the isolated rat duodenum by 50% (papaverine-like spasmolytic effect). It had a mild antihistamine effect: a dose of 5 mg/kg *s.c.* protected 50% of guinea-pigs from the lethal effect of 5 mg/kg histamine, administered intrajugularly.

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml unless they exceed 100 μg/ml are given): *Streptococcus* β-*haemolyticus*, *IIIa* 100, *IIIb* 25, *IVb* 50; *Streptococcus faecalis*, *IIIb* 50, *IVb* 100; *Staphylococcus pyogenes aureus*, *IIIb* 50, *IVb* 100; *Escherichia coli*, *IIIb* 50, *IVb* 50; *Mycobacterium tuberculosis* H37Rv, *IIIb* 100, *IVb* 50; *Trichophyton mentagrophytes*, *IIIb* 50, *IVb* 25.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C or at room temperature. The UV spectrum (in methanol) was recorded with a Unicam SP 8000 spectrophotometer, IR spectra were recorded with a Unicam SP 200G spectrophotometer and ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromarography on silica gel (Silufol).

2-Chloro-11-cyclopropyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VIIb*)

Grignard reagent[20] was prepared by a reaction of 4·7 g Mg and 25·0 g cyclopropyl bromide[25] in 100 ml tetrahydrofuran. The reagent was cooled, stirred and treated at room temperature with a warm solution of 25·0 g 2-chlorodibenzo[*b*,*e*]thiepin-11(6*H*)-one[27] in 100 ml tetrahydrofuran, added dropwise over 1 h. The mixture was refluxed for 1 h, cooled with ice and decom-

posed under stirring by a slow addition of 135 ml saturated NH_4Cl solution. The mixture was extracted with ether, the extract was washed with saturated NaCl solution, dried with Na_2SO_4 evaporated; 26·7 g (92%), m.p. 124–127°C. Analytical sample, m.p. 129–131°C (benzene–light petroleum). IR spectrum (Nujol): 744, 769, 810 (Ar—H), 1 110 (tert-C—OH), 3 025, 3 050 (Ar), 3 470 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90–7·80 (m, 7 H, ArH), 5·00 and 4·08 (ABq, J = = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·30 (bs, 1 H, OH), 1·90 (m, 1 H, CH of cyclopropyl), 0·40 to 1·00 (m, 4 H, CH_2CH_2 of cyclopropyl). For $C_{17}H_{15}ClOS$ (302·8) calculated: 67·43% C, 4·99% H, 11·71% Cl, 10·59% S; found: 67·86% C, 5·12% H, 11·95% Cl, 10·32% S.

(*E*)-11-(3-Bromopropylidene)-2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIIIb*)

A stirred solution of 10·0 g *VIIb* in 170 ml acetic acid was treated dropwise at 10–15°C over 30 min with 85 ml of a 15% solution of HBr in acetic acid. The mixture was allowed to stand for 24 h at room temperature, filtered with charcoal, diluted with 200 ml water and extracted with benzene. The extract was washed with water. dried with $MgSO_4$ and evaporated. The residue crystallized after the addition of cyclohexane; 9·0 g (75%), m.p. 95–100°C. Analytical sample, m.p. 109 to 111°C (cyclohexane–hexane). IR spectrum (KBr): 760, 815, 860 (4 and 2 adjacent and solitary Ar—H), 1 486, 3 028 cm^{-1} (Ar); in CS_2: 762, 781, 807, *883* cm^{-1} (Ar—H). ^1H NMR spectrum: δ 6·70–7·40 (m, 7 H, ArH), 5·91 (t, J = 7·0 Hz, 1 H, C=CH), 4·91 and 3·38 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·39 (t, J = 6·0 Hz, 2 H, CH_2Br), 2·55 (m, 2 H, CH_2 in the middle of propylidene). For $C_{17}H_{14}BrClS$ (365·7) calculated: 55·83% C, 3·86% H, 21·85% Br, 9·69% Cl, 8·77% S; found: 56·09% C, 4·08% H, 21·76% Br, 9·66% Cl, 8·52% S.

(*E*)-1-[3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-4-(2-hydroxyethyl)piperazine (*IIIa*)

A mixture of 25·0 g *VIIIa* (ref.[20]), 34·0 g 1-(2-hydroxyethyl)piperazine and 65 ml chloroform was stirred and refluxed for 3 h. The mixture was diluted with 100 ml chloroform, filtered with charcoal, the filtrate was washed with water and then extracted with a solution of 25 ml hydrochloric acid in 175 ml water. The aqueous layer was filtered with charcoal, the filtrate was made alkaline with NH_4OH and the product extracted with dichloromethane. The extract was dried with K_2CO_3 and evaporated. The oily residue was dissolved in 150 ml ethanol and the solution was treated with a solution of 16·8 g maleic acid in 60 ml ethanol. Standing and cooling led to crystallization of 28·2 g (61%) bis(hydrogen maleate), m.p. 154–155°C. Analytical sample, m.p. 155–156°C (ethanol). For $C_{31}H_{36}N_2O_9S$ (612·7) calculated: 60·77% C, 5·92% H, 4·57% N, 5·23% S; found: 60·61% C, 5·82% H, 4·48% N, 5·30% S.

A sample of the salt was decomposed with NH_4OH and the pure oily base was isolated by extraction with ether. IR spectrum (CS_2): 709, 749, 763 (4 adjacent Ar—H), 1 063, 3 540 cm^{-1} (CH_2OH). ^1H NMR spectrum: δ 6·90–7·40 (m, ArH), 5·90 (t, J = 7·0 Hz, 1 H, C=CH), 4·95 and 3·31 (ABq, J = 14·0 Hz, 1 + 1 H, $ArCH_2S$), 3·58 (bt, J = 6·0 Hz, 2 H, CH_2O), 2·75 (bs, 1 H, OH), *c.* 2·40 (m, remaining 7 CH_2).

(*E*)-1-[3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-4-(2-hydroxyethyl)piperazine (*IIIb*)

A mixture of 5·0 g *VIIIb*, 6·0 g 1-(2-hydroxyethyl)piperazine and 10 ml chloroform was stirred and refluxed for 3 h. The mixture was processed similarly like in the preceding case; 5·2 g (59%) bis(hydrogen maleate), m.p. 163–165°C. Analytical sample, m.p. 165–166°C (ethanol–ether). For $C_{31}H_{35}ClN_2O_9S$ (647·1) calculated: 57·54% C, 5·45% H, 5·48% Cl, 4·33% N, 4·95% S; found: 57·88% C, 5·59% H, 5·62% Cl, 4·04% N, 5·14% S.

Treatment of 5·0 g maleate with NH_4OH and extraction with chloroform gave 3·0 g crystalline base *IIIb*, m.p. 121–122°C (benzene–light petroleum). UV spectrum: λ_{max} 231 nm (log ε 4·34), 272 nm (4·02), 311 nm (3·41). IR spectrum (CS_2): 719, 763, 809, **880** (4 and 2 adjacent and solitary Ar–H), 1 063, 3 530 cm^{-1} (CH_2OH). ^1H NMR spectrum: δ 6·80–7·40 (m, 7 H, ArH), 5·95 (t, J = 7·0 Hz, 1 H, C=CH), 4·93 and 3·35 (ABq, J = 14·0 Hz, 1 + 1 H, $ArCH_2S$), 3·58 (bt, J = 6·0 Hz, 2 H, CH_2O), 2·90 (bs, 1 H, OH), *c* 2·40 (m, remaining 7 CH_2). For $C_{23}H_{27}ClN_2OS$ (415·0) calculated: 66·57% C, 6·56% H, 8·54% Cl, 6·75% N, 7·73% S; found: 66·39% C, 6·52% H, 8·60% Cl, 6·63% N, 7·86% S.

Neutralization of the base with methanesulfonic acid in ethanol gave the dimethanesulfonate, m.p. 206–208°C (ethanol–ether). For $C_{25}H_{35}ClN_2O_7S_3$ (607·2) calculated: 49·45% C, 5·81% H, 5·84% Cl, 4·61% N, 15·84% S; found: 48·98% C, 5·86% H, 6·10% Cl, 4·57% N, 15·54% S.

(*E*)-1-[3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-4-(2-acetoxyethyl)piperazine (*IVa*)

A mixture of 5·0 g *IIIa*, 7·0 ml acetic anhydride and 50 ml acetic acid was allowed to stand for 24 h at room temperature, it was then diluted with water, made alkaline with NH_4OH and extracted with benzene. The extract was dried with K_2CO_3, evaporated, the residue was dissolved in 25 ml ethanol and the solution neutralized with a solution of 32 g maleic acid in 10 ml ethanol; 8·2 g (95%) bis(hydrogen maleate), m.p. 176–178°C. Analytical sample, m.p. 182–183°C (ethanol). For $C_{33}H_{38}N_2O_{10}S$ (654·7) calculated: 60·54% C, 5·85% H, 4·28% N, 4·90% S; found: 60·85% C, 5·93% H, 4·41% N, 4·71% S.

(*E*)-1-[3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-4-(2-acetoxyethyl)-piperazine (*IVb*)

A mixture of 4·2 g *IIIb*, 5·0 ml acetic anhydride and 15 ml acetic acid was allowed to stand at room temperature for 48 h and then heated for 2 h to 100°C. A similar processing like in the preceding case gave 5·6 g (80%) bis(hydrogen maleate), m.p. 190–192°C. Analytical sample, m.p. 192–193°C (ethanol). For $C_{33}H_{37}ClN_2O_{10}S$ (689·2) calculated: 57·51% C, 5·41% H, 5·14% Cl, 4·06% N, 4·65% S; found: 57·55% C, 5·65% H, 5·22% Cl, 4·19% N, 4·55% S.

A sample of the pure maleate was decomposed with NH_4OH and the oily base was isolated by extraction with ether. IR spectrum (CS_2): 718, 760, 808, **875** (4 and 2 adjacent and solitary Ar–H), 1 110, 1 160, 1 235, **1 742** cm^{-1} (RCOOR').

(*E*)-1-[3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-
-4-(2-decanoyloxyethyl)piperazine (*Va*)

A mixture of 5·0 g *IIIa*, 5·1 g decanoyl chloride[21], 8 ml chloroform and 25 ml benzene was allowed to stand at room temperature for 24 h and then refluxed for 3 h. After cooling the mixture was distributed between dilute NH_4OH and benzene, the benzene layer was dried with K_2CO_3 and evaporated. The residue was neutralized with 3·2 g maleic acid in 35 ml ethanol; 8·9 g (88%) bis (hydrogen maleate), m.p. 168–169°C (ethanol). For $C_{41}H_{54}N_2O_{10}S$ (767·0) calculated: 64·21% C, 7·10% H, 3·65% N, 4·18% S; found: 63·99% C, 6·96% H, 3·67% N, 4·42% S.

(*E*)-1-[3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-
-4-(2-decanoyloxyethyl)piperazine (*Vb*)

A mixture of 4·2 g *IIIb*, 3·9 g decanoyl chloride[21], 6 ml chloroform and 20 ml benzene was processed similarly like in the preceding case. There were obtained 6·5 g (80%) bis(hydrogen

maleate), m.p. 178—179°C (ethanol). For $C_{41}H_{53}ClN_2O_{10}S$ (801·4) calculated: 61·45% C, 6·67% H, 4·42% Cl, 3·50% N, 4·00% S; found: 61·56% C, 6·84% H, 4·42% Cl, 3·53% N, 4·03% S.

The homogeneous oily base was released from a sample of the salt and used for recording the IR spectrum (CS_2): 715, 762, 898, **874** (4 and 2 adjacent and solitary Ar—H), 1 105, 1 160, **1 738** cm^{-1} (RCOOR').

(*E*)-1-[3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-
-4-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]piperazine (*VIa*)

A mixture of 5·0 g *IIIa*, 6·1 g 3,4,5-trimethoxybenzoyl chloride[22], 25 ml benzene and 10 ml chloroform was allowed to stand at room temperature for 36 h. It was then distributed between dilute NH_4OH and benzene, the benzene layer was washed with a saturated NH_4Cl solution, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was treated with 3·2 g maleic acid in 35 ml ethanol; 9·5 g (90%) bis(hydrogen maleate), m.p. 149—151°C. Analytical sample, m.p. 153—154°C (ethanol). For $C_{41}H_{46}N_2O_{13}S$ (806·9) calculated: 61·03% C, 5·75% H, 3·47% N, 3·97% S; found: 61·04% C, 5·61% H, 3·13% N, 3·97% S.

(*E*)-1-[3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-
-4-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]piperazine (*VIb*)

A mixture of 3·1 g 3,4,5-trimethoxybenzoic acid[32], 25 ml benzene and 3·0 ml $SOCl_2$ was refluxed for 6 h and evaporated *in vacuo*. The residue was dissolved in 30 ml benzene and the evaporation was repeated. There were then added 3·0 g *IIIb*, 15 ml benzene and 5 ml chloroform and the mixture was processed similarly like in the preceding case; 4·7 g (80%) bis(hydrogen maleate), m.p. 168—169°C (ethanol). For $C_{41}H_{45}ClN_2O_{13}S$ (841·3) calculated: 58·53% C, 5·39% H, 4·21% Cl, 3·33% N, 3·81% S; found: 58·05% C, 5·30% H, 4·52% Cl, 3·28% N, 4·00% S.

1-[3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)propyl]
4-(2-hydroxyethyl)piperazine (*IXa*)

A mixture of 5·0 g *IIIa*, 15 ml acetic acid, 15 ml 55% HI and 2·0 g red P was refluxed for 5 h. After cooling the mixture was filtered, the filtrate diluted with water and extracted with benzene. The extract was washed with water, with a solution of Na_2CO_3 and water, dried with K_2CO_3 and evaporated under reduced pressure. The very inhomogeneous residue (TLC, ^1H NMR spectrum) was dissolved in 25 ml ethanol and the solution was treated with 3·0 g maleic acid in 15 ml ethanol. After standing overnight the precipitated bis(hydrogen maleate) was filtered; 2·4 g (30%), m.p. 143—146°C. Analytical sample, m.p. 145—146·5°C (ethanol). For $C_{31}H_{38}$·N_2O_9S (434·6) calculated: 60·57% C, 6·23% H, 4·56% N, 5·22% S; found: 60·34% C, 6·01% H, 4·42% N, 5·29% S.

1-[3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)propyl]-
-4-(2-hydroxyethyl)piperazine (*IXb*)

A mixture of 13·5 g *IIIb*, 60 ml acetic acid, 42 ml 55% HI and 5·6 g red P was stirred and refluxed for 5 h. After standing overnight it was filtered, the filtrate was diluted with water, made alkaline with 20% NaOH and extracted with chloroform. The extract was washed with water and evaporated. The residue was treated with 8·0 g maleic acid in 45 ml ethanol and the precipitated maleate was crystallized from water, m.p. 162—164°C. The base, released from a sample of the maleate, proved to be a mixture of at least two components. The whole quantity of the maleate was decomposed with NH_4OH, the base isolated by extraction with chloroform and chromato-

graphed on a column of 150 g neutral Al_2O_3 (activity II). There were obtained by elution with benzene 4·5 g (33%) homogeneous base which afforded 4·8 g bis(hydrogen maleate), m.p. 182 to 184°C (80% aqueous ethanol). For $C_{31}H_{37}ClN_2O_9S$ (649·2) calculated: 57·36% C, 5·75% H, 5·46% Cl, 4·32% N, 4·94% S; found: 57·33% C, 5·57% H, 5·21% Cl, 3·74% N, 5·01% S.

1-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4-(2-hydroxyethyl)piperazine (*X*)

A mixture of 5·6 g 2,11-dichloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[35] with 15 ml chloroform was stirred and treated with 5·2 g 1-(2-hydroxyethyl)piperazine. An exothermic reaction took place (spontaneous heating and transitional formation of a clear solution). The mixture was stirred for 40 min without heating and then for 1 h at 70—75°C under reflux. After cooling it was distributed between water and chloroform, the chloroform layer was dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in ethanol and the solution was treated with a solution of HCl in ether. The oily hydrochloride formed was separated by decantation, washed with ether, decomposed with NH_4OH and the purified base was isolated by extraction with ether. The extract was dried with K_2CO_3, filtered with charcoal and evaporated; 5·6 g (75%) oily base. Neutralization with maleic acid in ethanol gave only 3·2 g hygroscopic maleate, m.p. 168—170°C (ethanol–ether). For $C_{24}H_{27}ClN_2O_5S$ (491·0) calculated: 58·71% C, 5·54% H, 7·22% Cl, 5·71% N, 6·53% S; found: 58·78% C, 5·54% H, 7·45% Cl, 5·72% N, 6·73% S.

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