POTENTIAL ANTIPSYCHOTIC AGENTS: 2-CHLORO- AND 2-METHYL-11-(2-PIPERAZINOETHOXY)- -6,11-DIHYDRODIBENZO[*b*,*e*]THIEPINS AND SOME RELATED COMPOUNDS; SYNTHESIS AND PHARMACOLOGY

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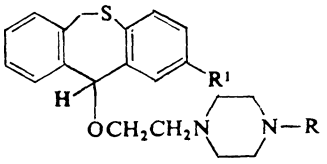
Reactions of 2-chloro- and 2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol with 2-bromoethanol in the presence of sulfuric acid in boiling benzene afforded the 2-bromoethyl ethers *VIa* and *VIb* which were transformed by substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)-piperazine and 1-(ethoxycarbonyl)piperazine to the title compounds. Alkaline hydrolysis of the carbamate *IVa* gave the secondary amine *IIIa*. Treatment of the bromo ether *VIa* with 4-(4-chloro--3-trifluoromethylphenyl)piperidin-4-ol resulted in the piperidine derivative *VIIa*. Substitution reaction of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin with 1-(2-methoxyethyl)piperazine and 1-(2-ethoxyethyl)piperazine led to the amino ethers *VIII* and *IX*. Reaction of 11-chloro-11-phenyl -6,11-dihydrodibenzo[*b*,*e*]thiepin with 2-dimethylaminoethanethiol in dimethylformamide at 90°C gave a mixture of two isomeric bases which was separated to the expected sulfide *X* and the base *XII*, resulting evidently after the rearrangement of the primary carbocation. A similar reaction of 3-dimethylaminopropanethiol afforded a single product of structure *XI*. Out of the compounds prepared, the ether *VIII* was found most interesting: it is little toxic and has significant antireserpine activity in two tests (is considered a potential antidepressant). The ethers *Iab*, *Iab*, *IIIa* and *VIIa* did not reveal the expected neuroleptic activity.

Several aminoalkyl ethers derived from 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol have been prepared some time ago[1-4]; antihistamine activity was their most typical pharmacological effect. Anticholinergic activity was described for the corresponding quaternary salts[5,6]. In the series of the isomeric 10,11-dihydrodibenzo[*b*,*f*]thiepin--10-ol the 2-dimethylaminoethyl ether showed central depressant activity[7] which was increased by the introduction of a neuroleptic substituent to the position 8 (ref.[8,9]) resulting finally in an expressive neuroleptic activity in the case of simultaneous introduction of a piperazine residue into the aliphatic chain[10]. The main purpose of the present investigation was the effort at finding new neuroleptic agents in the series of the basic ethers derived from dibenzo[*b*,*e*]thiepin having in their molecules simultaneously a neuroleptic substituent in the skeleton (atom of chlorine or methyl in position 2) and a piperazine residue in the aliphatic chain. The synthesis of the title compounds *Iab* and *IIab* was, therefore, carried out in the first line.

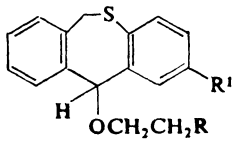
A reaction of 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12] with 2-chloroethanol in the presence of sulfuric acid in boiling benzene afforded in a good yield the 2-chloroethyl ether *Va* whose identity was confirmed by the ^{1}H NMR spectrum. For substitution reactions with amines this chloro derivative was found too little



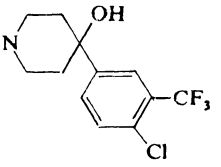
I, R = CH_3
II, R = CH_2CH_2OH
III, R = H
IV, R = $COOC_2H_5$

In formulae *I*–*VII*:
a, R^1 = Cl
b, R^1 = CH_3

reactive which led to the preparation of the 2-bromoethyl ethers *VIa* and *VIb* by similar reactions of 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12] and 2 methyl--6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[13] with 2-bromoethanol. Substitution reactions of these bromo derivatives with 1-methylpiperazine and 1-(2-hydroxyethyl)-piperazine with the use of an excess of these amines proceeded smoothly at 120°C; the obtained bases *Iab* and *IIab* were isolated and purified in the form of hydrogen maleates. In the cases of compounds *Ia* and *IIa*, the treatment of the pure salts with aqueous ammonia resulted in oily bases which were used for recording of the spectra. An attempt at carrying out the reaction of the bromoethyl ether *VIa* with a small



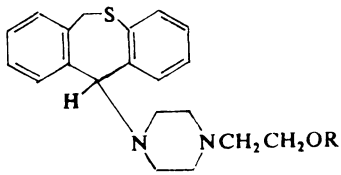
V, R = Cl
VI, R = Br

VII, R = 

excess of 1-methylpiperazine in boiling ethanol in the presence of potassium carbonate afforded the desired amino ether *Ia* in a moderate yield only. The substitution reaction of the 2-bromoethyl ether *VIa* with 1-(ethoxycarbony)piperazine likewise proceeded successfully at 120°C and when using an excess of the amine; compound *IVa* was isolated as hydrogen oxalate. The same product was obtained from 2-chloro-

-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12] which was first transformed by treatment with hydrogen chloride in benzene to 2,11-dichloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[11]. Without having been isolated in pure state, this compound reacted with 1-(ethoxycarbonyl)-4-(2-hydroxyethyl)piperazine[14] in boiling xylene under formation of the base *IVa* in a rather satisfactory yield. Hydrolysis of *IVa* with a concentrated solution of potassium hydroxide in boiling ethanol gave the secondary amine *IIIa*, isolated as hydrogen maleate. A substitution reaction of the bromoethyl ether *VIa* with 4-(4-chloro-3-trifluoromethylphenyl)piperidin-4-ol[15,16] (the basic fragment of the molecule of the neuroleptic agent penfluridol[16–18]) in the presence of potassium carbonate in boiling ethanol resulted in the ether *VIIa*, isolated as hydrogen maleate; its identity was corroborated by spectra of the oily base *VIIa*.

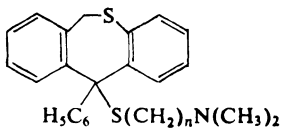
In connection with our previous syntheses of N-substituted 11-piperazino-6,11-dihydrodibenzo[*b*,*e*]thiepins[5,12,19], which disclosed properties of potential antidepressants[20], there were carried out substitution reactions of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[19] with 1-(2-methoxyethyl)piperazine[21] and 1-(2-ethoxyethyl)-piperazine[21] in boiling benzene in the presence of potassium carbonate. Piperazine derivatives *VIII* and *IX* were obtained which were transformed to oxalates for characterization and for pharmacological testing.



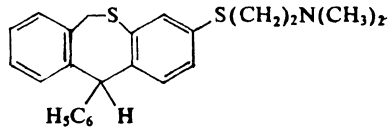
VIII, R = CH_3
IX, R = C_2H_5

In a previous communication[22] we described the investigation of substitution reactions of 11-chloro-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin with nucleophiles and in reactions with amines and with one Grignard reagent we obtained in addition to the expected substitution products also compounds substituted in position 3 of the skeleton which was explained by a "rearrangement" of the primary carbocation. If benzenethiolate was used as the nucleophile, we met with an atypical reaction and no substitution product was obtained at all. Now, we have carried out substitution reactions of 11-chloro-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin[22,23] with 2-dimethylaminoethanethiol[24,25] and 3-dimethylaminopropanethiol[26] in dimethylformamide at 90°C. In the first case there resulted a mixture of approximately same amounts of two bases which were separated by crystallization and by chromatography on silica gel. Analyses and mass spectra determined for the crystalline bases the identical elemental composition $C_{24}H_{25}NS_2$. The higher melting base, whose

hydrochloride crystallized from the acidified mixture as the first product, was identified by means of the ^{1}H NMR and IR spectra as the normal substitution product *X*. The lower melting base presents in the ^{1}H NMR spectrum a signal of the Ar_3CH methine proton at 5·20 ppm with the absence of one aromatic proton (in comparison with the starting compound) and the IR spectrum exhibits in the area of out-of-plane bending of aromatic C—H bonds bands typical for 1,2,4-trisubstituted benzene; on the basis of analogy with the work mentioned[22], the structure of 3-(2-dimethylaminoethylthio)-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XII*) was assigned to the product. In the analogous reaction of 3-dimethylaminopropanethiol[26] the crude product was likewise subjected to chromatography on silica gel. The product appears rather polar because its major part is eluted only with a mixture of chloroform and ethanol. A minor less polar product was identified as 11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[22,23]. Rechromatography of the main product gave a homogeneous base (TLC) affording two hydrochlorides: a high-melting nonsolvated product and a hemihydrate with a double melting point. The released oily base does not present in its ^{1}H NMR spectrum the signal of the Ar_3CH methine proton and in agreement with the IR spectrum the structure of the normal substitution product *XI* is ascribed to it. The mass spectrum, however, indicates a contamination with an Ar-substituted compound similar to the base *XII*.



X, $n = 2$
XI, $n = 3$



XII

The compounds prepared were pharmacologically tested in the form of salts described in the Experimental; the doses given were calculated for the bases. In the testing, the main emphasis was concentrated to the effects of potential psychotropic agents (neuroleptics, antidepressants, tranquillizers); some of the compounds were investigated within a general screening programme. Unless stated otherwise, the compounds were administered orally. Acute toxicity in mice (LD_{50} in mg/kg and the toxic symptoms): *Ia*, 2 000 (high doses elicit convulsions and death occurs within 2 h after the administration); *Ib* 1 500 (a dose of 2 500 mg/kg is lethal for 100% animals perishing in convulsions within 20 min after the administration; a dose of 500 mg/kg brought about only a mild decrease of spotaneous motility for 6 h after the administration and was lethal for 20% animals); *IIb*, 2 000 (a dose of 2 500 mg/kg led to 100% lethality and the animals perish in convulsions in the interval of 10–20 min after the administration which indicates a very rapid absorption);

IIIa, 40 *i.v.* (convulsions and death in a short time after the administration); *VIII*, 531 (a dose of 200 mg/kg lethal for 10%, 500 mg/kg for 90% animals; convulsions); *IX*, 400; *X*, >1 000 (no lethality after this dose). Discoordinating effect in the rotarod test in mice: compounds *Ia*, *IIa*, *IIb* and *VIIa* inactive in a dose of 100 mg/kg; *Ib* inactive at 300 mg/kg; *IIIa* inactive at 8 mg/kg *i.v.*; *IX*, a dose of 40 mg/kg brought about ataxia in 60% animals, 20 mg/kg only in 10%. Central depressant effect manifested by influencing the spontaneous motility of mice in the photo-cell method of Dews, D_{50} in mg/kg; *Ib*, >300; *IIIa*, >8 *i.v.*; *VIII*, >20; *IX*, >50. Thiopental sleeping time potentiation in mice was tested with negative results with compounds *Ib* (300 mg/kg) and *IIIa* (8 mg/kg *i.v.*). Antiamphetamine activity in mice was tested with negative results with compounds *Ia*, *Ib* and *IIb* (300 mg/kg), and *VIII* (50 mg/kg). In the test of catalepsy in rats compound *Ib* was inactive in a dose of 300 mg/kg and compound *IIa* was little active (50 mg/kg, catalepsy in 20% animals). In the test of antagonization of apomorphine stereotypies in rats compounds *Ia*, *IIa*, *IIb* and *VIIa* were inactive in a dose of 40 mg/kg. The rectal temperature of mice was not influenced by the following compounds (doses given): *Ib* (300 mg/kg), *IIIa* (8 mg/kg *i.v.*). Negative findings in the test of anticonvulsant activity in mice towards the electroshock (dose given): *VIII* (100 mg/kg), *IX* (50 mg/kg). Antireserpine activity using the ptosis in mice: compounds *Ia* and *Ib* inactive in doses of 300 mg/kg, *VIII* had significant effect at 25 mg/kg (inactive at 12·5 mg/kg), *IX* and *X* no significant effect at 25 mg/kg. Antireserpine activity using the reserpine ulcer formation in rats: *VIII* had significant effect at 50 mg/kg, *IX* no significant effect at 10 mg/kg, *X* inactive at 50 mg/kg. Antihistamine activity (protection of guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly) was found with compound *IIb*, ED = 5 mg/kg (for mebrophenhydramine as a standard, ED = 1–2·5 mg/kg). Compound *IIIa* at *i.v.* doses of 8 mg/kg elicited brief and deep drops of the blood pressure in normotensive rats and had an antiarrhythmic action in rats toward aconitine (comparable with the effect of quinidine). Compound *VIII* in a dose of 80 mg/kg did not influence the levels of dopamine, homovanillic acid and 5-hydroxyindoleacetic acid in striatum of the rat brain and the level of noradrenaline in the rat hypothalamus.

In conclusion, the potential neuroleptics *Ia*, *Ib*, *IIa*, *IIb*, *IIIa* and *VIIa* did not show the expected pharmacological profile. Out of the potential antidepressants *VIII-X* only compound *VIII* was rather active in the tests for antireserpine activity (intensity comparable to that of imipramine or prothiadene).

The compounds were also tested for antimicrobial activity *in vitro* (the microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *Ia* 100, *IIIa* 25, *VIIa* 12·5, *IX* 100, *X* 50; *Streptococcus faecalis*, *IIIa* 50, *VIIa* 100, *X* 12·5; *Staphylococcus pyogenes aureus*, *Ia* 100, *IIb* 100, *IIIa* 50, *VIIa* 25, *VIII* 50, *IX* 50, *X* 12·5; *Escherichia coli*, *Ia* 100, *IIIa* 100, *VIIa* 50; *Saccharomyces pasterianus*, *VIIa* 50; *Trichophyton mentagrophytes*, *Ib* 50, *IIIa* 50, *VIIa* 50, *VIII* 50, *IX* 50, *X* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block or in a Mettler FP 5 melting point recorder 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 IR spectra (mostly in Nujol) were recorded with Unicam SP 200G and Perkin Elmer 298 spectrophotometers, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Chloro-11-(2-chloroethoxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*Va*)

2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12] (8·8 g) was slowly extracted in a Soxhlet apparatus by the boiling solvent into a refluxing mixture of 150 ml benzene, 4·5 g 2-chloroethanol and 0·6 ml H_2SO_4. After 40 min the extraction and also the reaction were concluded. After cooling the mixture was washed with water, 5% $NaHCO_3$ and water, dried with $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in boiling cyclohexane, the hot solution was filtered and the filtrate allowed to crystallize; 8·6 g (79%), m.p. 104–106°C. Analytical sample, m.p. 107–108°C (cyclohexane). ^{1}H NMR spectrum: δ 7·00–7·50 (m, 8 H, ArH), 5·65 (s, 1 H, Ar_2CH), 4·60 and 4·15 (ABq, J = 14·0 Hz, 1 + 1 H, $ArCH_2S$), *c.* 3·75 (m, 4 H, OCH_2CH_2Cl). For $C_{16}H_{14}Cl_2OS$ (325·3) calculated: 59·08% C, 4·34% H, 21·80% Cl, 9·86% S; found: 59·11% C, 4·26% H, 21·74% Cl, 10·00% S.

11-(2-Bromoethoxy)-2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIa*)

A mixture of 25·0 g 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12], 250 ml benzene, 18·0 g 2-bromoethanol and 1·75 ml H_2SO_4 was stirred and refluxed for 1 h. Similar processing like in the preceding case gave 31·1 g (88%) pure *VIa*, m.p. 90–92°C (benzene–hexane). IR spectrum: 720, 768, 780, 810, 820, 831, 874, 885, 893 (4 and 2 adjacent and solitary Ar—H), 1 100, 1 112, 1 136 (R—O—R′), 1 485, 1 530, 1 576, 3 038, 3 055 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·90 to 7·50 (m, 7 H, ArH), 5·60 (s, 1 H, Ar_2CH), 4·60 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·83 (m, 2 H, CH_2O), 3·52 (m, 2 H, CH_2Br). For $C_{16}H_{14}BrClOS$ (369·7) calculated: 51·98% C, 3·82% H, 21·61% Br, 9·59% Cl, 8·67% S; found: 52·38% C, 3·70% H, 21·38% Br, 9·48% Cl, 8·58% S.

11-(2-Bromoethoxy)-2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIb*)

A mixture of 30·0 g 2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[13], 330 ml benzene, 23·2 g 2-bromoethanol and 3·2 ml H_2SO_4 was processed similarly like in the preceding case; 38·4 g (86%) 6 : 1 solvate with benzene, m.p. 108–110°C (benzene–hexane). Mass spectrum, *m/z*: 348 (M^+ corresponding to $C_{17}H_{17}BrOS$), 225 (M – CH_2CH_2Br, base peak), 192, 178, 165, 149. IR spectrum: 737, 772, 828, 898 (4 and 2 adjacent and solitary Ar—H), 1 122, 1 143, 1 162 (R—O—R′), 1 472, 1 492 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·80–7·40 (m, 7 H, ArH), 5·59 (s, 1 H, Ar_2CH), 4·81 and 3·99 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·82 (m, 2 H, CH_2O), 3·52 (m, 2 H, CH_2Br), 2·38 (s, 3 H, $ArCH_3$). For $C_{17}H_{17}BrOS$ + 1/6 C_6H_6 (362·3) calculated: 59·67% C, 5·01% H, 22·06% Br, 8·85% S; found: 59·83% C, 5·17% H, 21·73% Br, 9·03% S.

2-Chloro-11-[2-(4-methylpiperazino)ethoxy]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*Ia*)

A) A mixture of 5·0 g *VIa* and 5·0 g 1-methylpiperazine was stirred under reflux for 5·5 h in a bath of 120°C. After cooling the mixture was distributed between 30 ml 4% NaOH and 100 ml

chloroform, the organic layer was washed with water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in 25 ml ethanol and the warm solution was treated with a solution of 3·5 g maleic acid in 10 ml ethanol. Standing overnight and filtration gave 7·5 g (89%) bis(hydrogen maleate), m.p. 175–177°C. Analytical sample, m.p. 179–181°C (aqueous methanol). For $C_{29}H_{33}ClN_2O_9S$ (621·1) calculated: 56·08% C, 5·36% H, 5·71% Cl, 4·51% N, 5·16% S; found: 56·12% C, 5·36% H, 5·97% Cl, 4·40% N, 5·23% S.

A sample of the maleate was decomposed with NH_4OH and the oily base was isolated by extraction with ether. IR spectrum: 720, 765, 812, 885 (4 and 2 adjacent and solitary Ar—H), 1 085, 1 100, 1 118, 1 170, 1 286, 1 300 (R—O—R'), 1 460, 1 560, 1 580, 3 000, 3 040 (Ar), 2 780 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·90–7·50 (m, 7 H, ArH), 5·60 (s, 1 H, Ar_2CH), 4·58 and 4·12 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·56 (t, J = 6·0 Hz, 2 H, CH_2O), 2·70 (t, J = = 6·0 Hz, 2 H, CH_2N in aminoethoxy), 2·49 (bs, 8 H, 4 CH_2N of piperazine), 2·25 (s, 3 H, NCH_3).

B) A stirred mixture of 5·0 g *VIa*, 1·5 g 1-methylpiperazine, 2·0 g K_2CO_3 and 4 ml ethanol was refluxed for 3 h. After cooling it was diluted with water and extracted with chloroform. The extract was shaken with 25 ml cold 1 : 4 dilute hydrochloric acid, the solid was filtered off and the filtrate was separated. The aqueous layer was made alkaline with NH_4OH and the base isolated by extraction with ether; 2·4 g (46%). Neutralization with 1·5 g maleic acid in ethanol gave 2·7 g bis(hydrogen maleate), m.p. 179–181°C (aqueous methanol), identical with the product obtained under *A*.

2-Methyl-11-[2-(4-methylpiperazino)ethoxy]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*Ib*)

A mixture of 7·0 g (*VIb* and 7·0 g 1-methylpiperazine was stirred and heated for 4·5 h to 120 to 125°C. After standing overnight the mixture was distributed between chloroform and 1 : 4 diluted NH_4OH, the chloroform layer was washed with water, dried with $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in 70 ml warm ethanol and the solution treated with a solution of 6·5 g maleic acid in 20 ml ethanol; 9·5 g (79%) bis(hydrogen maleate), m.p. 166–169°C. Analytical sample, m.p. 174–175°C (aqueous methanol–acetone). For $C_{30}H_{36}N_2O_9S$ (600·7) calculated: 59·99% C, 6·04% H, 4·67% N, 5·34% S; found: 59·50% C, 6·09% H, 4·98% N, 5·43%S.

1-[2-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)ethyl]-4-(2-hydroxyethyl)piperazine (*IIa*)

A mixture of 5·0 g *VIa* and 5·5 g 1-(2-hydroxyethyl)piperazine was stirred and heated for 5·5 h to 120°C and processed similarly like in the preceding cases (*cf. Ia A*); 8·0 g (91%) bis(hydrogen maleate), m.p. 149–151°C. Analytical sample, m.p. 154–156°C (methanol–ether). For $C_{30}H_{35}$. $.ClN_2O_{10}S$ (651·1) calculated: 55·34% C, 5·42% H, 5·44% Cl, 4·30% N, 4·92% S; found: 55·11%C, 5·51% H, 5·87% Cl, 4·00% N, 5·01% S.

A sample of the maleate was decomposed with NH_4OH and the oily base was isolated by extraction with ether. IR spectrum: 714, 764, 812, 879 (4 and 2 adjacent and solitary Ar—H), 1 055 (CH_2OH), 1 082, 1 113, 1 159 (R—O—R'), 3 300 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90 to 7·50 (m, 7 H, ArH), 5·55 (bs, 1 H, Ar_2CH), 4·50 and 4·10 (ABa, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·60 (t, J = 7·0 Hz, 2 H, CH_2OC), 3·51 (t, J = 7·0 Hz, 2 H, CH_2O of the primary alcohol group), 2·80 (bs, 1 H, OH), 2·60 (t, J = 7·0 Hz, CH_2N in aminoethoxy), 2·50 (t, J = 7·0 Hz, 2 H, CH_2N in hydroxyethylamino), 2·45 (s, 8 H, 4-CH_2N of piperazine).

1-[2-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)ethyl]-4-(2-hydroxyethyl)piperazine (*IIb*)

A reaction of 7·0 g *VIb* and 7·0 g 1-(2-hydroxyethyl)piperazine at 120—125°C for 4·5 h and similar processing like in the preceding case gave 11·4 g (90%) bis(hydrogen maleate), m.p. 150—153°C. Analytical sample, m.p. 153—154°C (aqueous methanol). For $C_{31}H_{38}N_2O_{10}S$ (630·7) calculated: 59·03% C, 6·07% H, 4·44% N, 5·08% S; found: 59·28% C, 6·29% H, 4·44% N, 5·24% S.

2-Chloro-11-[2-(4-ethoxycarbonylpiperazino)ethoxy]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IVa*)

A) A mixture of 10·0 g *VIa* and 13·0 g 1-(ethoxycarbonyl)piperazine was heated for 5·5 h to 120°C. After cooling it was distributed between water and chloroform, the chloorform layer was washed with water and shaken with cool dilute hydrochloric acid. The separated aqueous layer was immediately made alkaline with 20% NaOH and the product was extracted with chloroform. The extract was dried with K_2CO_3 and evaporated *in vacuo* giving 11·2 g (93%) oily *IVa*. Hydrogen oxalate, m.p. 172—173°C (ethanol–ether). For $C_{25}H_{29}ClN_2O_7S$ (537·0) calculated: 55·91% C, 5·44% H, 6·60% Cl, 5·22% N, 5·97% S; found: 55·53% C, 5·54% H, 6·89% Cl, 5·17% N, 5·95% S.

B) A mixture of 5·0 g 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[11,12] and 50 ml benzene was saturated for 1 h with HCl, benzene was evaporated, substituted with 50 ml xylene, 4·0 g 1-ethoxycarbonyl-4-(2-hydroxyethyl)piperazine[14] were added and the mixture was refluxed for 5 h. After cooling the mixture was washed with water, dried with K_2CO_3 and evaporated; 5·7 g (67%) crude oily *IVa*. Neutralization with oxalic acid in ethanol gave the hydrogen oxalate monohydrate, m.p. 167—168°C (96% ethanol). For $C_{25}H_{29}ClN_2O_7S + H_2O$ (555·0) calculated: 54·10% C, 5·63% H, 6·39% Cl, 5·05% N, 5·77% S; found: 53·90% C, 5·55% H, 6·32% Cl, 5·20% N, 5·55% S. Comparison of the product obtained under *A* and *B* by TLC indicated identity. The mixture of the oxalates obtained under *A* and *B* melted without depression.

2-Chloro-11-(2-piperazinoethoxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IIIa*)

A mixture of 9·0 g oily base *IVa*, 15 ml ethanol and 10·0 g KOH was stirred and heated under reflux for 1 h in a bath of 120°C. After cooling the mixture was distributed between water and benzene, from the benzene layer the base was extracted into 100 ml ice-cold 5% hydrochloric acid, the separated aqueous layer was made alkaline with 20% NaOH and the base was extracted with benzene. The extract was dried with K_2CO_3 and evaporated *in vacuo* giving 5·2 g (69%) oily *IIIa*. Neutralization with 3·3 g maleic acid in 40 ml ethanol gave 5·9 g bis(hydrogen maleate), m.p. 147—149°C (ethanol). For $C_{28}H_{35}ClN_2O_9S$ (611·1) calculated: 55·03% C, 5·77% H, 5·80% Cl, 4·58% N, 5·25% S; found: 54·96% C, 5·34% H, 6·00% Cl, 4·42% N, 5·37% S.

1-[2-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)ethyl]-4-(4-chloro-3-trifluoromethylphenyl)piperidin-4-ol (*VIIa*)

A mixture of 4·5 g *VIa*, 3·0 g 4-(4-chloro-3-trifluoromethylphenyl)-4-piperidinol[15,16], 1·7 g K_2CO_3 and 6 ml ethanol was stirred and refluxed for 5 h. After the addition of 15 ml water the mixture was extracted with dichloromethane. The extract was dried with K_2CO_3, filtered with charcoal, the filtrate was evaporated *in vacuo*, the residue dissolved in 15 ml ethanol and the solution was neutralized with a solution of 1·0 g maleic acid in 10 ml ethanol; 5·5 g (75%) hydrogen maleate, m.p. 196—200°C. Analytical sample, m.p. 201—203°C (acetone–ether). For $C_{32}.H_{30}Cl_2F_3NO_6S$ (684·6) calculated: 56·15% C, 4·42% H, 10·36% Cl, 8·33% F, 2·05% N, 4·68%S; found: 56·40% C, 4·68% H, 10·51% Cl, 8·37% F, 2·06% N, 4·83% S.

The oily base, released from the pure salt was used for recording the spectra. IR spectrum: 762, 810, 830, 895 (4 and 2 adjacent and solitary Ar—H), 1 115 (tert C—OH), 1 130, 1 175, 1 315 (Ar—CF_3), 1 570, 1 600 (Ar), 3 380 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·90 (m, 10 H, ArH), 5·62 (s, 1 H, Ar_2CH), 4·45 and 4·16 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·70 (t, J = = 6·5 Hz, 2 H, CH_2O), 2·75 (t, J = 6·5 Hz, CH_2N of aminoethoxy).

11-[4-(2-Methoxyethyl)piperazino]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIII*)

A mixture of 4·9 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[19], 20 ml benzene, 4·1 g 1-(2-methoxyethyl)piperazine[21] and 4·3 g K_2CO_3 was stirred for 1 h at room temperature and then refluxed for 1·5 h. After cooling the solid was filtered off and washed with benzene. The filtrate was washed with water and the base was extracted into 100 ml ice-cold 2·5M-HCl. The aqueous solution was immediately made alkaline with NH_4OH and the base extracted with benzene. Processing of the extract gave 6·1 g (86%) oily *VIII*. Oxalate, m.p. 170—171°C (ethanol). For $C_{23}H_{28}N_2O_5S$ (444·5) calculated: 62·14% C, 6·35% H, 6·30% N, 7·21% S; found: 62·45% C, 6·33% H, 5·93% N, 7·25% S.

11-[4-(2-Ethoxyethyl)piperazino]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IX*)

A similar reaction of 4·9 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[19] with 4·2 g 1-(2-ethoxyethyl)piperazine[21] in 20 ml benzene in the presence of 4·3 g K_2CO_3 gave 5·8 g (79%) oily base which was transformed to the oxalate, m.p. 152—154°C (ethanol). For $C_{24}H_{30}N_2O_5S$ (458·6) calculated: 62·86% C, 6·59% H, 6·11% N, 6·99% S; found: 62·88% C, 6·59% H, 6·09% N, 6·92% S.

11-(2-Dimethylaminoethylthio)-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*)
and 3-(2-Dimethylaminoethylthio)-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XII*)

A solution of 10·0 g freshly prepared 11-chloro-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin[22,23] in 100 ml dimethylformamide was treated with 8·9 g 2-dimethylaminoethanethiol[24,25] and the mixture was heated for 6·5 h to 90°C. After cooling, 2·5 g substance, melting at 242—243°C with decomposition, were filtered off, being evidently di(2-dimethylaminoethyl) disulfide dihydrochloride (lit.[27], m.p. 242—243°C with decomposition). The filtrate was evaporated *in vacuo*, the residue distributed between benzene and water and the benzene layer was shaken with excessive 2M-HCl. The precipitated hydrochloride was filtered after standing overnight and crystallized three times from a mixture of ethanol and ether; 3·40 g *X* hydrochloride hemihydrate, m.p. 203—208°C with decomposition. For $C_{24}H_{26}ClNS_2 + 0{\cdot}5\ H_2O$ (437·1) calculated: 65·95% C, 6·23% H, 8·11% Cl, 3·20% N, 14·67% S; found: 66·22% C, 6·26% H, 8·30% Cl, 3·25% N, 14·50% S.

The base *X* was released by treatment with NH_4OH, isolated by extraction with ether and purified by crystallization from a mixture of cyclohexane and light petroleum, m.p. 138—140°C. Mass spectrum, *m/z* (%): 391·1416 (M^+ corresponding to $C_{24}H_{25}NS_2$, calculated: 391·1425, 0·8%), 287 ($C_{20}H_{15}S$, 9), 254 ($C_{20}H_{14}$, 6), 178 ($C_{14}H_{10}$), 137 (C_7H_7S, 5), 104 ($C_4H_{10}NS$, 8), 58 [$CH_2{=}\overset{+}{N}(CH_3)_2$, 100]. IR spectrum: 704, 745, 750 (4 and 5 adjacent Ar—H), 1 487, 1 577, 1 591, 3 015, 3 042 (Ar), 2 710, 2 765, 2 788, 2 817 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 8·10 (m, 2 H, 1,10-H_2), 7·30—7·80 (m, 11 H, remaining ArH), 3·58 and 3·22 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 1·60—2·50 (m, 4 H, SCH_2CH_2N), 2·08 (s, 6 H, CH_3NCH_3). For $C_{24}H_{25}NS_2$ (391·6) calculated: 73·61% C, 6·44% H, 3·58% N, 16·38% S; found: 73·82% C, 6·57% H, 3·44% N, 16·33% S.

The mother liquors were made alkaline with NH_2OH, the bases were extracted with benzene and the extract was evaporated. The residue (7·3 g) was chromatographed on a column of 200 g

silica gel. Chloroform eluted first further 2·0 g *X*. the total yield being 42%. Continued elution with chloroform gave 4·24 g (35%) crude *XII* which was transformed by treatment with hydrogen chloride in ether to the hydrochloride, m.p. 217–222°C (ethanol–ether). For $C_{24}H_{26}ClNS_2$ (428·1) calculated: 67·34% C, 6·12% H, 8·28% Cl, 3·27% N, 14·98% S; found: 67·24% C, 6·19% H, 8·43% Cl, 3·23% N, 14·83% S.

Pure base *XII* was released similarly like the preceding one and was also purified by crystallization from a mixture of cyclohexane and light petroleum, m.p. 126–128°C. Mass spectrum, *m/z* (%): 391·1416 (M^+ corresponding to $C_{24}H_{25}NS_2$, calculated 391·1429, 0·5%), 58 [$CH_2{=}\overset{+}{N}(CH_3)_2$, 100]. IR spectrum: 700, 714, 762, 810, 841, 856, 875, 891 (5, 4 and 2 adjacent, and solitary Ar—H), 1 490, 1 580, 3 020, 3 048 (Ar), 2 768, 2 780, 2 815 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·80–7·40 (m, 12 H, ArH), 5·20 (s, 1 H, Ar_3CH), 4·10 and 3·08 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·98 (bt, 2 H, CH_2S), 2·50 (bt, 2 H, CH_2N), 2·20 (s, 6 H, CH_3NCH_3). For $C_{24}H_{25}NS_2$ (391·6) calculated: 73·61% C, 6·44% H, 3·58% N, 16·38% S; found: 73·98% C, 6·64% H, 3·48% N, 16·50% S.

11-(3-Dimethylaminopropylthio)-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XI*)

A solution of 10·3 g 11-chloro-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin[22] in 100 ml dimethylformamide was treated with 10·0 g 3-dimethylaminopropanethiol[26] and the mixture was stirred and heated for 6 h to 90°C. The solvent was then evaporated *in vacuo*, the residue was distributed between benzene and water and the benzene layer was washed with excessive 2M-HCl. The acid aqueous solution was made alkaline with NH_4OH, the base (8·7 g) extracted with benzene and chromatographed on 200 g silica gel. Benzene eluted 0·28 g 11-phenyl-6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-ol, m.p. 195–198°C (benzene) (lit.[22], m.p. 204–205°C, comparison by TLC with the authentic sample[22] indicated identity). Continued elution with a mixture of chloroform and ethanol gave 7·50 g (58%) inhomogeneous base which was rechromatographed on 150 g silica gel and then transformed by treatment with HCl in ether to the hydrochloride of *XII*, m.p. 187 to 192°C (ethanol–ether). Mass spectrum, *m/z* (%): 405 (M^+ corresponding to $C_{25}H_{27}NS_2$, 0·3%), 287 (3·5), 254 (11), 118 (100), 58 (39). Contamination by the isomer analogous to *XII* is indicated by fragments with *m/z* 288 and 256. IR spectrum (KBr): 702, 749 (5 and 4 adjacent Ar—H), 1 481, 1 592, 3 010, 3 048 (Ar), 2 400, 2 460, 2 510, 2 560, 2 620, 2 647 cm^{-1} (NH^+). ^1H NMR spectrum: δ *c.* 8·00 (m, 2 H, 1,10-H_2), 7·20 (m, 11 H, remaining ArH), 3·61 and 3·32 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·65 (s and bd, 10 H, CH_3NCH_3, CH_2S and CH_2N), 1·70 (bm, 2 H, CH_2 in the middle of the propane chain). For $C_{25}H_{28}ClNS_2$ (442·1) calculated: 67·92% C, 6·38% H, 8·02% Cl, 3·17% N, 14·51% S; found: 67·39% C, 6·43% H, 7·99% Cl, 3·21% N, 14·20% S.

A different hydrochloride was obtained by crystallization from a mixture of 95% ethanol and ether, m.p. 134–137°C, and after resolidification again at 189°C. It proved to be a hemihydrate. For $C_{25}H_{28}ClNS_2 + 0{\cdot}5\,H_2O$ (451·1) calculated: 66·56% C, 6·48% H, 7·86% Cl, 3·11% N, 14·22% S; found: 66·31% C, 6·62% H, 7·98% Cl, 3·04% N, 13·69% S. Bases released from both hydrochlorides are identical (TLC).

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REFERENCES

1. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
2. Protiva M., Adlerová E., Metyš J. (SPOFA): Belg. 646 051 (Czech. Appl. 04.04.64); Chem. Abstr. *63*, 13 226 (1965); Brit. 1 019 123; Czech. 113 624; Fr. 1 462 172; Ger. Offen. 1 214 245; Austrian 244 982.
3. Metyšová J., Metyš J., Votava Z.: Arzneim.-Forsch. *15*, 524 (1965).
4. Jucker E., Lindenmann A., Gadient F. (Sandoz A. G.): Ger. (East) 55 958 (Swiss Appl. 28.06.65); Fr. 5 770 M; Neth. Appl. 66/8 716; Chem. Abstr. *68*, 48 472 (1968); Swiss 482 719 (Appl. 13.12.68); Chem. Abstr. *72*, 132 568 (1970).
5. Rajšner M., Svátek E., Seidlová V., Adlerová E., Protiva M.: This Journal *34*, 1 278 (1969).
6. Bretz U., Martin U., Mazzoni L.: Progr. Respir. Res. 14 (Asthma), 141 (1980); Chem. Abstr. *94*, 132 231 (1981).
7. Jílek J. O., Seidlová V., Svátek E., Protiva M., Pomykáček J., Šedivý Z.: Monatsh. Chem. *96*, 182 (1965).
8. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
9. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1 895 (1968).
10. Bártl V., Jílek J., Metyšová J., Valchář M., Dlabač A., Wildt S., Protiva M.: This Journal *49*, 1810 (1984).
11. Malen Ch., Danree B., Poignant J. C. (Science Union et Cie. — Société Francaise de Recherche Médicale): Ger. Offen. 2 065 636 (Brit. Appl. 27.03.69); Chem. Abstr. *83*, 9 833 (1975).
12. Bártl V., Svátek E., Dlabač A., Wildt S., Protiva M.: This Journal *49*, 1816 (1984).
13. Rajšner M., Metyš J., Svátek E., Protiva M.: This Journal *34*, 1 015 (1969).
14. Moore T. S., Boyle M., Thorne V. M.: J. Chem. Soc. *1929*, 39.
15. Janssen P. A. J. (Janssen Pharmaceutica N. V.): Brit.. 1 141 664 (Appl. 08.12.65; 23.09.66); Chem. Abstr. *70*, 96 635 (1969).
16. Šindelář K., Rajšner M., Červená I., Valenta M., Jílek J. O., Kakáč B., Holubek J., Svátek E., Mikšík F., Protiva M.: This Journal *38*, 3 879 (1973).
17. Rajšner M., Kopicová Z., Holubek J., Svátek E., Metyš J., Bartošová M., Mikšík F., Protiva M.: This Journal *43*, 1760 (1978).
18. Švestka J., Náhunek K., Češková E.: Acta Fac. Med. Univ. Brunensis *65*, 177 (1979).
19. Seidlová V., Rajšner M., Adlerová E., Protiva M.: Monatsh. Chem. *96*, 650 (1965).
20. Protiva M.: Farmaco, Ed. Sc. (Pavia) *21*, 76 (1966).
21. Polívka Z., Ryska M., Holubek J., Svátek E., Metyš J., Protiva M.: This Journal *48*, 2 395 (1983).
22. Protiva M., Šindelář K., Valenta V., Holubek J., Svátek E., Ryska M., Schlanger J., Urban J., Hrubantová M.: This Journal *47*, 3 094 (1982).
23. Hori M., Kataoka T., Shimizu H., Onogi K.: Yakugaku Zasshi *98*, 1 189 (1978).
24. Clinton R. O., Salvador U. J., Laskowski S. C., Suter C. M.: J. Amer. Chem. Soc. *70*, 950 (1948).
25. Borovička M., Protiva M.: Chem. Listy *48*, 1374 (1954); This Journal *20*, 273 (1955).
26. Andrews K. J. M., Bergel F., Morrison A. L.: J. Chem. Soc. *1953*, 2998.
27. Suzuki T., Imaeda K., Kubota M., Takagi H.: Jap. J. Pharm. Chem. *22*, 464 (1950); Chem. Abstr. *45*, 8 458 (1951).

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