NONCATALEPTIC NEUROLEPTIC AGENTS: 2-(4-(2-(2-CHLORO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN-10-YLOXY)-ETHYL)PIPERAZINE-1-YL)ETHANOL AND SOME RELATED COMPOUNDS

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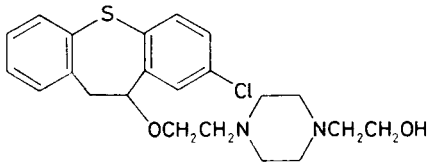
Dedicated to the memory of Dr Karel Bláha.

10-(2-Bromoethoxy)-2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*X*), prepared by two methods, was subjected to substitution reactions with 2-(1-piperazinyl)ethanol, 3-(1-piperazinyl)propanol, 1-methylpiperazine, 3-(1-piperazinyl)propionamide, piperazine, and 1-(ethoxycarbonyl)piperazine and gave the title compounds *II*–*VII*. The alcohol *II* was esterified by treatment with acid chlorides to compounds *VIII* and *IX*. Compounds *II*, *V*, and *VIII* proved to be noncataleptic neuroleptic agents and *II* (clopithepin, VÚFB-17 076) was selected for preclinical studies.

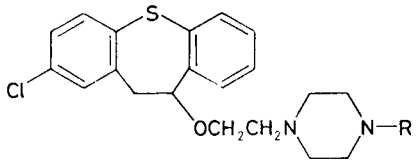
In a previous communication[1] compound *I* and two analogues were described as neuroleptic agents with low toxicity, rather strong central depressant, antiapomorphine, and antidopaminergic activity, relatively mild cataleptic effects and very low peripheral adrenolytic efficacy. We have now attempted to eliminate the cataleptic activity by using the "clozapine trick" (ref.[2]), i.e. by shifting the "neuroleptic substituent" (atom of chlorine) from position 8 into the quasi-symmetrical position 2 similarly as in a series of previous investigations[3–7]. In this way, the title compound *II* as well as its analogues *III*–*VI* and esters *VIII* and *IX* were designed and the present paper deals with their synthesis and pharmacological properties.

The synthesis started from 2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol which is available in six steps from 1,4-dichlorobenzene[8,9]. The first step was the transformation of this alcohol to the 2-bromoethyl ether *X* by treatment with 2-bromoethanol in the presence of boron trifluoride etherate (analogy[1]). A different method for preparing *X* consists in reaction of 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]-thiepin[9] with 2-bromoethanol in the presence of potassium carbonate at room temperature. Carrying out this reaction without potassium carbonate at 100°C resulted in elimination of hydrogen chloride and *XI* (refs[9,10]) was the only product to be isolated. Compound *X* is oily and it was not possible to purify it by distillation without decomposition which led to the necessity of using the crude product for the

next reaction (for analysis the compound was chromatographed and obtained in homogeneous form).

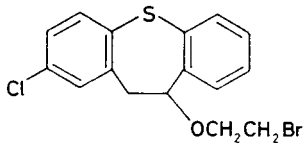


I

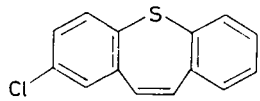


II, R = CH_2CH_2OH
III, R = $(CH_2)_3OH$
IV, R = CH_3
V, R = $CH_2CH_2CONH_2$
VI, R = H
VII, R = $COOC_2H_5$
VIII, R = $CH_2CH_2OCOCH_3$
IX, R = $(CH_2)_2OCO(CH_2)_8CH_3$

Substitution reaction of crude *X* with 2-(1-piperazinyl)ethanol in dimethylformamide at 90–100°C in the presence of potassium carbonate gave the oily base *II* in high yield. It was characterized by spectra and by a series of salts (succinate, bis(hydrogen maleate), dimethanesulfonate, and dihydrochloride). Similar substitution reactions of *X* with 3-(1-piperazinyl)propanol[11], 1-methylpiperazine, and 3-(1-piperazinyl)propionamide[7,12] resulted in oily bases *III*, *IV*, and *V* which were transformed to succinates. Homogeneous bases, released from the purified succinates, were used for recording the spectra.



X



XI

The further target was the secondary amine *VI* and it was anticipated that it could be obtained via *VII*. Similar substitution reaction of *X* with 1-(ethoxycarbonyl)-piperazine like in the preceding cases gave the oily *VII* which was characterized

as hydrochloride. Hydrolysis of *VII* with boiling ethanolic potassium hydroxide, however, led to a complete cleavage of the molecule and only *XI* was obtained. It was thus necessary to use the substitution reaction of *X* with piperazine. It led to a mixture which was separated by chromatography on silica gel. The first to be eluted was probably the stereoisomeric mixture of the corresponding doubly alkylated piperazines which was not characterized. It was followed by the wanted *VI* which was identified by the mass spectrum and transformed to the succinate and dihydrochloride. Treatment of *II* with acetyl chloride and decanoyl chloride[13] in benzene or chloroform at various temperatures afforded the esters *VIII* and *IX* which were transformed to salts and characterized by the ^{1}H NMR spectra of bases, released from the homogeneous salts.

Compounds *II*–*V*, *VI*, *VIII*, and *IX* were pharmacologically tested as potential neuroleptic agents; with the exception of *IX* they were administered orally in the form of succinates (the doses given were calculated per bases). The basic data are assembled in Table I: *a*) Acute toxicities in mice are expressed in the usual LD_{50} values (toxic symptoms were sedation and then convulsions). *b*) Influence on the spontaneous locomotor activity of mice was followed by the photo-cell method of Dews; the medium inhibitory doses D_{50} are given. *c*) In the test of catalepsy in rats, the medium effective doses ED_{50} were higher in all cases than 50 mg/kg. *d*) The same situation was found in attempts to determine the activity against apomorphine-induced stereotypies in rats. *e*) Affinity to dopamine D-2 receptors in striatum of the rat brain was evaluated by the inhibition of binding of 0·5 nM [^{3}H]spiperone as the ligand (medium inhibitory concentrations IC_{50} in nM are given). *f*) Antidopaminergic activity in vivo was evaluated by the influence on the turnover and metabolism of dopamine in rat brain striatum, i.e. on the concentration of homovanillic acid (HVA) as the main dopamine metabolite and on the concentration of dopamine (DA) itself (% of HVA and DA are given in comparison with the control which is 100% in both lines). For comparison, the recently announced noncataleptic neuroleptic agent VÚFB-15 496 ("cloflumide") (refs[7,14]) and clozapine[2] as the prototype of noncataleptic neuroleptics were included. The data in the Table I show that all new compounds are less toxic than cloflumide and clozapine, all of them have significantly lower sedative activity than the standards, all are noncataleptic and free of the antiapomorphine effect in doses of 50 mg/kg similarly as cloflumide and clozapine, all of them have lower affinity to dopamine D-2 receptors than cloflumide but *II*, *IV*, *V*, and *VIII* have slightly higher affinity than clozapine, the antidopaminergic action in vivo of *II* is lower than that of cloflumide but higher than that of clozapine.

The most interesting member of the new series, which was selected for preclinical testing as a noncataleptic neuroleptic agent, is compound *II* (succinate VÚFB-17 076, "clopithepin"). In addition to the data given in Table I the following has to be stated. Acute toxicity in mice on intravenous adminstration, LD_{50} = 65·4 mg/kg. Inco-

TABLE I

Pharmacological properties of 1-(2-(2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)ethyl)piperazines (oral administration, doses in mg/kg)

Compound	Acute toxicity LD_{50}	Inhibition of locomotor. activity, D_{50}	Catalepsy ED_{50}	Apomorphine stereotypies ED_{50}	[^{3}H]Spiperone inhibition IC_{50} in nM	Antidopaminerg. in vivo 80 mg/kg	
						% HVA	% DA
II	346	15·7	>50[b]	>50[b]	212·3	504	82
III	618	>10[a]	>50[b]	>50[b]	349·8	64	71
IV	401	>10[a]	>50[b]	>50[b]	263·7	96	60
V	667	>10[a]	>50[b]	>50[b]	230·7	308	38
VI	509	>10[a]	>50[b]	>50[b]	1 000	80	85
VIII	691	>10[a]	>50[b]	>50[b]	219·5	244	56
Cloflumide	336	1·05	>50[b]	>50[b]	49·7	647	—
Clozapine	199	4·0	>50[b]	>50[b]	288·5	349	74

[a] At this dose the locomotor activity was mildly but significantly decreased; [b] at this dose completely inactive.

ordinating effect in the rotarod test in mice, ED_{50} = 44 mg/kg p.o. This is much lower than with cloflumide (2·0) or with thioridazine[15,16] (14·6). Some cataleptic action was found only in the dose of 100 mg/kg p.o. (catalepsy in 40% of the rats); thioridazine, used for comparison, has the same effect already in the dose of 50 mg/kg p.o. With catalepsy, brought about by perphenazine, *II* showed indication of procataleptogenic action starting with the dose of 20 mg/kg p.o. In the test of apomorphine-induced climbing in mice[17], PD_{50} = 23·5 mg/kg p.o. (for cloflumide 2·9, clozapine 13·1). Influence on apomorphine-induced emesis in dogs: *II* was administered in doses of 5, 10, and 20 mg/kg p.o. and the effect was evaluated in intervals of 4, 24, and 48 h; the emetic effect was inhibited only in the interval of 4 h starting with the dose of 10 mg/kg. In addition to the data on the antidopamineric action of *II* in vivo (cf. Table I) it has to be stated that the threshold dose, which significantly increases the HVA concentration in the rat striatum is 20 mg/kg p.o., in tuberculum olfactorium 10 mg/kg. The affinity of *II* to dopamine D-1 receptors in rat striatum is very low. The adrenolytic action and influence on the cardiovascular parameters: the peripheral adrenolytic effect in mice is very low; only in the dose of 100 mg/kg p.o. *II* blocked the lethal effect of adrenaline in 20% of the animals. In monkeys (*Maccacus rhesus*) oral doses of 10 mg/kg did not influence the blood pressure and the heartbeat frequency; the behaviour of the animals was not altered. Anticholinergic action in vivo could not be proven: in the dose of 30 mg/kg i.p. *II* did not influence the oxotremorine-induced tremor in mice (clozapine was active, ED_{50} = 3·5 mg/kg i.p.). The central anticholinergic action in vitro was found to be very low: inhibition of binding of [^{3}H]quinuclidinyl benzilate in the rat brain is characterized by the IC_{50} = 4 149 nM (for clozapine 72·1 and atropine 3·38 nM). Compound *II* is a weak inhibitor of reuptake of serotonin and noradrenaline in the rat brain.

In conclusion, clopithepin (VÚFB-17 076, *II* succinate) is an interesting atypical neuroleptic agent with clear antidopaminergic activity in vivo and with a high affinity to dopamine D-2 receptors in the brain in vitro. It has a very low central depressant activity in mice, is practically free of the cataleptogenic effect, does not influence the apomorphine stereotypies in rats, and only mildly inhibits the apomorphine climbing in mice. Its adrenolytic action in mice is very low and in the dose used it does not influence the blood pressure and heartbeat frequency in monkeys. Its anticholinergic action in vivo and in vitro is insignificant.

Clopithepin decanoate (*IX*) was considered a potential noncataleptic depot neuroleptic. Its testing in the form of a solution containing 375 mg of *IX* in 1 ml "Miglyol 812" is under way. It was administered intramuscularly in the dose of 600 mg/kg to rats (males) and concentrations of HVA and DA in striatum were determined in the intervals of 24 h and 3 days after the administration. No significant influence was found (increase of HVA to 169% in 24 h).

Compounds *II* – *VI* and *VIII* were also screened for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 128 μg/ml): *Streptococcus β-haemolyticus*, *II* 50, *III* 16, *IV* 8, *V* 16, *VI* 8, *VIII* 16; *Streptococcus faecalis*, *II* 12·5, *III* 16, *IV* 16, *V* 32, *VI* 8, *VIII* 32; *Staphylococcus pyogenes aureus*, *II* 25, *III* 16, *IV* 16, *V* 32, *VI* 8, *VIII* 16; *Pseudomonas aeruginosa*, *III* 64, *IV* 64, *V* 64, *VI* 64, *VIII* 64; *Escherichia coli*, *IV* 64, *V* 64, *VI* 32; *Proteus vulgaris*, *II* 50, *III* 128, *IV* 128, *V* 128, *VI* 32, *VIII* 128; *Saccharomyces pasterianus*, *IV* 25, *VI* 50, *VIII* 50; *Trichophyton mentagrophytes*, *II* 12·5, *III* 12·5, *IV* 25, *VI* 50, *VIII* 12·5.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3, δ, J in Hz) with a Tesla BS 487 C (80 MHz) spectrometer, and the mass spectra (m/z, composition and/or %) with MCH 1 320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

10-(2-Bromoethoxy)-2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*X*)

A) A solution of 6·0 g 2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol[9] in 60 ml benzene was cooled to 12–14°C, treated under stirring with 4·5 g 2-bromoethanol, and then dropwise over 1·5 h with 3·4 g $BF_3.O(C_2H_5)_2$. The stirring at 12–14°C was continued for 1 h and the mixture was decomposed by a slow addition of 30 ml water. After 15 min stirring the benzene layer was separated, washed with water, dried with K_2CO_3, and evaporated under reduced pressure. The residue (8·2 g) was the crude oily *X* containing 95% of the desired substance and could be used for the next step in this state; the yield was thus 7·8 g (92%). A sample of this product was chromatographed on silica gel. Elution with light petroleum containing 10% of benzene removed the less polar components. Elution with a 7 : 3 mixture of light petroleum and benzene afforded then the homogeneous *X*. The residue, obtained by complete removal of the solvents by evaporation in vacuo, was used for recording the spectrum and for analysis. ^1H NMR spectrum: 3·20 to 4·00 m, 6 H ($ArCH_2$ and OCH_2CH_2Br); 5·40 dd, 1 H (Ar—CH—O, J = 8·0; 4·0); 6·90–7·60 m, 7 H (7 ArH). For $C_{16}H_{14}BrClOS$ (369·7) calculated: 51·98% C, 3·82% H, 21·62% Br, 9·59% Cl, 8·67% S; found: 52·14% C, 3·85% H, 21·51% Br, 9·58% Cl, 8·57% S.

B) A mixture of 22·0 g 2-bromoethanol, 5·0 g K_2CO_3, and 5·0 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[9] was stirred for 16 h at 20–22°C. The mixture was then diluted with 10 ml dichloromethane and refluxed under stirring for 3 h. After cooling, 20 ml dichloromethane were added, the solid was filtered off, and washed with dichloromethane. Volatile components were removed by evaporation in vacuo and the oily residue was dissolved in 100 ml toluene, the solution was washed with water and evaporated; 6·2 g (95%) crude *X* of similar quality like under *A*). The identity of both products was proven by TLC and by comparison of physical properties (d 1·40; n_D^{20} 1·625).

2-(4-(2-(2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yloxy)-ethyl)piperazine-1-yl)ethanol (*II*)

A solution of 7·5 g *X* in 30 ml dimethylformamide was stirred and treated with 3·5 g 2-(1-piperazinyl)ethanol and 3·75 g K_2CO_3. The mixture was stirred for 1 h at room temperature and then for 6 h at 90—92°C (bath temperature 95—100°C). After standing overnight the mixture was diluted with 65 ml water and extracted with 100 ml toluene. The extract was washed with water, filtered with active carbon, and from the filtrate the base was transferred to the aqueous layer by shaking with a solution of 5 ml methanesulfonic acid in 75 ml water. The aqueous solution of the methanesulfonate was filtered again with active carbon, the filtrate was made alkaline with 12 ml NH_4OH, and the released base was isolated by extraction with toluene; 7·4 g of 97% *II* (yield 85%). This oily base resisted to all attempts at its crystallization.

Succinate, m.p. 103—105°C (acetone). For $C_{26}H_{33}ClN_2O_6S$ (537·1) calculated: 58·14% C, 6·19% H, 6·60% Cl, 5·22% N, 5·97% S; found: 57·88% C, 6·20% H, 6·75% Cl, 5·10% N, 6·12% S.

Bis(hydrogen maleate), m.p. 165—166°C (aqueous ethanol). For $C_{30}H_{35}ClN_2O_{10}S$ (651·1) calculated: 55·34% C, 5·42% H, 5·45% Cl, 4·30% N, 4·92% S; found: 55·71% C, 5·59% H, 5·45% Cl, 4·15% N, 5·19% S.

Dimethanesulfonate, m.p. 160—162°C (ethanol–ether). For $C_{24}H_{35}ClN_2O_8S_3$ (611·2) calculated: 47·16% C, 5·77% H, 5·80% Cl, 4·58% N, 15·74% S; found: 46·65% C, 5·92% H, 5·88% Cl, 4·41% N, 15·79% S.

Dihydrochloride, m.p. 175—176°C (aqueous ethanol). Mass spectrum (CI): 419 (M^+, $C_{22}H_{27}.ClN_2O_2S$); EI: 387 (0·5), 244 (30), 209 (25), 176 (5), 143 (100), 128 (15), 112 (15), 100 (42), 70 (70), 42 (60). IR spectrum: 758, 813, 870 (4 and 2 adjacent, and solitary Ar—H); 1 067 (CH_2OH); 1 091 (R—O—R′); 1 560, 1 580, 3 050 (Ar); 2 410, 2 510, 2 630 (NH^+); 3 310 (OH). For $C_{22}H_{29}.Cl_3N_2O_2S$ (491·9) calculated: 53·71% C, 5·94% H, 21·62% Cl, 5·70% N, 6·52% S; found: 53·82% C, 5·99% H, 21·48% Cl, 5·49% N, 6·46% S.

The base was released from the dihydrochloride with NH_4OH, isolated by extraction with ether, and used for recording the spectra. IR spectrum (film): 759, 812, 877 (4 and 2 adjacent, and solitary Ar—H); 1 055 (CH_2OH); 1 096, 1 109 (R—O—R′); 1 550, 1 562, 1 580, 3 055 (Ar); 3 400 (OH). ^{1}H NMR spectrum: 2·55 m, 12 H (6 CH_2N); 3·10 bs, 1 H (OH); 3·20—3·80 m, 6 H (2 CH_2O and $ArCH_2$); 5·30 dd, 1 H (Ar—CH—O, J = 8·0; 4·0); 6·80—7·60 m, 7 H (7 ArH).

3-(4-(2-(2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yloxy)--ethyl)piperazine-1-yl)propanol (*III*)

Similar reaction of 15·0 g *X*, 7·2 g 3-(1-piperazinyl)propanol[11], and 5·0 g K_2CO_3 in 60 ml dimethylformamide gave 15·7 g (86%) oily III which was transformed to succinates by neutralization with succinic acid in acetone.

Succinate monohydrate, m.p. 76—77°C (acetone). Mass spectrum: 432 (M^+, $C_{23}H_{29}ClN_2O_2S$, 0·1), 387 (0·1), 359 (0·1), 262 (0·3), 245 (7), 210 (7), 187 (2), 178 (2), 172 (20), 157 (40), 127 (100), 70 (40). For $C_{27}H_{35}ClN_2O_6S + H_2O$ (569·1) calculated: 56·98% C, 6·55% H, 6·23% Cl, 4·92% N, 5·63% S; found: 57·04% C, 6·44% H, 6·79% Cl, 4·92% N, 5·82% S.

Bis(hydrogen succinate), m.p. 71—72°C (acetone). For $C_{31}H_{41}ClN_2O_{10}S$ (669·2) calculated: 55·64% C, 6·18% H, 5·30% Cl, 4·19% N, 4·79% S; found: 55·73% C, 6·23% H, 5·64% Cl, 4·20% N, 4·87% S.

The base was released from the succinate with NH_4OH, isolated by extraction with ether, and used for recording the ^1H NMR spectrum: 1·68 m, 2 H (N—C—CH_2—C—O); 2·52 bs, 8 H (4 CH_2N of piperazine); 2·60 t, 4 H (2 CH_2N in positions 1 and 4 of piperazine, J = 7·0); c. 3·30 m, 2 H ($ArCH_2$); 3·65 t, 2 H (CH_2O in hydroxypropyl, J = 7·0); 3·70 t, 2 H (OCH_2—C—N, J = 7·0); 3·90 bs, 1 H (OH); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80—7·60 m, 7 H (7 ArH).

1-(2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)ethyl)-4-methylpiperazine (*IV*)

Similar reaction of 15·0 g *X*, 5·0 g 1-methylpiperazine, and 5·0 g K_2CO_3 in 60 ml dimethylformamide gave 14·2 g (90%) oily *IV* which was neutralized with succinic acid in aqueous acetone to give the bis(hydrogen succinate), m.p. 116—117°C (aqueous acetone). UV spectrum: 269 (4·40). IR spectrum: 735, 752, 810, 885 (4 and 2 adjacent, and solitary Ar—H); 1 182, 1 315, 1 725 (COOH); 1 620 (COO^-); 2 450 (NH^+). For $C_{29}H_{37}ClN_2O_9S$ (625·1) calculated: 55·71% C, 5·97% H, 5·67% Cl, 4·48% N, 5·13% S; found: 55·55% C, 5·96% H, 5·96% Cl, 4·73% N, 5·30% S.

The released base was used for recroding the ^1H NMR spectrum: 2·20 s, 3 H (NCH_3); 2·48 bs, 8 H (4 CH_2N of piperazine); 2·58 t, 2 H (remaining CH_2N, J = 7·0); c. 3·30 m, 2 H ($ArCH_2$); 3·64 t, 2 H (CH_2O, J = 7·0); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80—7·60 m, 7 H (7 ArH).

3-(4-(2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)-ethyl)piperazine-1-yl)propionamide (*V*)

Similar reaction of 16·0 g *X*, 6·8 g 3-(1-piperazinyl)propionamide[7], and 5·5 g K_2CO_3 in 60 ml dimethylformamide gave 18·0 g (93%) oily *V*. Neutralization with succinic acid in acetone gave the bis(hydrogen succinate), m.p. 100—103°C (acetone). For $C_{31}H_{40}ClN_3O_{10}S$ (682·2) calculated: 54·58% C, 5·91% H, 5·20% Cl, 6·16% N, 4·70% S; found: 54·66% C, 6·11% H, 5·67% Cl, 6·31% N, 5·02% S.

^1H NMR spectrum of the released base: 2·00—2·80 m, 14 H ($CH_2N(CH_2CH_2)_2NCH_2CH_2CO$); c. 3·20 m, 2 H ($ArCH_2$); 3·65 t, 2 H ($CH_2O$, J = 7·0); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 5·90 bs and 7·98 bs, 1 + 1 H ($CONH_2$); 6·80—7·60 m, 7 H (7 ArH).

1-(2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)ethyl)piperazine (*VI*)

A solution of 13·7 g piperazine in 45 ml dimethylformamide was treated with 5·5 g K_2CO_3 and over 30 min a solution of 15·0 g *X* in 15 ml dimethylformamide was added dropwise. The mixture was heated for 6 h to 100°C, cooled, and distributed between 150 ml water and 150 ml benzene. The benzene layer was washed with water and the bases were transferred into the aqueous layer by shaking with 150 ml 10% methanesulfonic acid. The obtained solution of the methanesulfonates was made alkaline with 30 ml NH_4OH. The released bases were isolated by extraction with benzene, the extract was evaporated, and the inhomogeneous residue (13·7 g) was chromatographed on a column of silica gel (Kieselgel 40). Elution with chloroform and chloroform with 10% ethanol removed the less polar components (8·0 g). The oily base *VI* (5·7 g, 38%) was obtained by elution with chloroform saturated with NH_3 (shaken with NH_4OH).

Dihydrochloride monohydrate, m.p. 152—154°C (ethanol–ether). Mass spectrum, CI: 376 ($(M + H)^+$, $C_{20}H_{23}ClN_2OS$), 245 (100), 131, 113, 99; EI: 245 ($C_{14}H_{10}ClS$), 210 ($C_{14}H_{10}S$), 165 ($C_{13}H_9$), 114 ($C_6H_{14}N_2$), 99 ($C_5H_{11}N_2$), 86, 70, 56, 44. For $C_{20}H_{25}Cl_3N_2OS + H_2O$ (465·9) calculated: 51·56% C, 5·84% H, 22·83% Cl, 6·01% N, 6·88% S; found: 50·93% C, 5·60% H, 23·26% Cl, 5·64% N, 7·06% S.

Succinate, m.p. 149–150°C (ethanol). For $C_{24}H_{29}ClN_2O_5S$ (493·0) calculated: 58·47% C, 5·93% H, 7·19% Cl, 5·68% N, 6·50% S; found: 58·45% C, 6·02% H, 7·52% Cl, 5·70% N, 6·73% S.

^{1}H NMR spectrum of the base released from the succinate: 2·40 m, 5 H ($CH_2N^1CH_2$ of piperazine and NH); 2·58 t, 2 H (CH_2N in the chain, J = 7·0); 2·95 m, 4 H ($CH_2N^4CH_2$ of piperazine); c. 3·20 m, 2 H ($ArCH_2$); 3·65 t, 2 H (CH_2O, J = 7·0); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80–7·60 m, 7 H (7 ArH).

1-(2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)-ethyl)-4-(ethoxycarbonyl)piperazine (*VII*)

Similar reaction of 15·0 g *X*, 12·6 g 1-(ethoxycarbonyl)piperazine, and 5·5 g K_2CO_3 in 60 ml dimethylformamide like in the preparation of *II* (8 h, 100°C) gave 17·6 g (97%) of oily *VII*. Neutralization with HCl in ether gave the hydrochloride, m.p. 148–150°C (ethanol–ether). For $C_{23}H_{28}Cl_2N_2O_3S$ (483·4) calculated: 57·14% C, 5·84% H, 14·67% Cl, 5·80% N, 6·63% S; found: 56·96% C, 5·96% H, 15·06% Cl, 5·73% N, 6·72% S.

The base was released from the hydrochloride and used for recording the spectra. IR spectrum (film): 760, 812, 875 (4 and 2 adjacent, and solitary Ar—H); 1 100 (ROR'); 1 243 (C—O in COOR); 1 465, 1 580, 3 035 (Ar); 1 700 (NCOOR); 2 805 (CH_2—N). ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3, J = 7·0); 2·40 m, 4 H ($CH_2N^1CH_2$ of piperazine); 2·60 t, 2 H (CH_2N in the chain, J = 7·0); 3·40 m, 6 H ($CH_2N^4CH_2$ of piperazine and $ArCH_2$); 3·65 t, 2 H (CH_2O, J = 7·0); 4·10 q, 2 H ($COOCH_2$, J = 7·0); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80–7·60 m, 7 H (7 ArH).

2-Chlorodibenzo[*b*,*f*]thiepin (*XI*)

A) A mixture of 1·4 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[9] and 3·75 g 2-bromoethanol was heated for 3 h to 100°C. After cooling the mixture was dissolved in 50 ml benzene, the solution was washed with 5% $NaHCO_3$ and water, dried, and evaporated. The crystalline residue (1·2 g) was crystallized from 3 ml cyclohexane; 1·0 g (82%) of *XI*, m.p. 75–76°C. In admixture with authentic *XI* (ref.[10]) there was no depression of melting point; comparison by TLC confirmed also the identity.

B) A mixture of 15·0 g *VII*, 7·5 g 85% KOH, and 15 ml ethanol was stirred and refluxed (bath temperature 125°C) for 6 h. Ethanol was evaporated, the residue was distributed between 100 ml water and 100 ml benzene, the benzene layer was washed with a dilute solution of methanesulfonic acid, dried, and evaporated; 6·7 g (82%) of *XI*, m.p. 76–77°C (cyclohexane). The product proved identical with that obtained under *A*.

2-(4-(2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yloxy)-ethyl)piperazine-1-yl)ethyl Acetate (*VIII*)

A stirred solution of 10·5 g *II* in 50 ml benzene was treated over 20 min with 11·0 g acetyl chloride, added dropwise. The mixture was stirred for 6 h at 60°C, after cooling the thick suspension was distributed between 100 ml water and 100 ml benzene, the mixture was shaken with 30 ml NH_4OH, the benzene layer was washed with water, dried, and evaporated; 10·6 g (91%) of homogeneous *VIII* (glassy solid). It was transformed to the salts.

Bis(hydrogen maleate), m.p. 171–172°C (aqueous acetone). For $C_{32}H_{37}ClN_2O_{11}S$ (693·2) calculated: 55·44% C, 5·38% H, 5·12% Cl, 4·04% N, 4·63% S; found: 55·39% C, 5·47% H, 5·43% Cl, 4·09% N, 4·87% S.

Bis(hydrogen succinate), m.p. 97–98°C (aqueous acetone). IR spectrum: 740, 812, 888 (4 and 2 adjacent, and solitary Ar—H); 1 070, 1 110 (R—O—R'); 1 175, 1 299 (C—O in COOR and COOH); 1 580, 3 020, 3 050 (Ar); 1 720 (COOH); 1 745 (COOR); 2 390 (NH^+). For $C_{32}H_{41}Cl.N_2O_{11}S$ (697·2) calculated: 55·13% C, 5·93% H, 5·08% Cl, 4·02% N, 4·60% S; found: 55·12% C, 6·08% H, 5·40% Cl, 4·30% N, 4·79% S.

^{1}H NMR spectrum of the base released from the succinate: 2·00 s, 3 H (CH_3CO); 2·52 s, 8 H (4 CH_2N of piperazine); 2·58 t, 4 H (2 CH_2N in the chains, J = 7·0); c. 3·30 m, 2 H ($ArCH_2$); 3·62 t, 2 H (OCH_2, J = 7·0); 4·14 t, 2 H ($COOCH_2$, J = 7·0); 5·33 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80–7·60 m, 7 H (7 ArH).

2-(4-(2-(2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yloxy)-
-ethyl)piperazine-1-yl)ethyl Decanoate (*IX*)

A) A solution of 10·0 g *II* in 40 ml benzene was treated under stirring with a solution of 6·9 g decanoyl chloride[13] in 30 ml benzene, the mixture was refluxed for 8 h, after cooling shaken with 80 ml benzene, 100 ml water, and 10 ml NH_4OH, the emulsion formed was separated by centrifuging, the benzene layer was dried, and evaporated; 11·0 g (80%) of *IX*. Neutralization of 2·1 g of this product with 0·90 g maleic acid in acetone gave 2·75 g of bis(hydrogen maleate), m.p. 165°C (aqueous acetone). Mass spectrum (EI and CI): 572 (M^+, $C_{32}H_{45}ClN_2O_3S$, under 0·1), 401 ($C_{22}H_{26}ClN_2OS$, 1), 387 (1), 312 (3), 297 (32), 245 (22), 210 (11), 199 (14), 156 (8), 140 (36), 125 (88), 112 ($C_6H_{12}N_3$, 100). For $C_{40}H_{53}ClN_2O_{11}S$ (805·4) calculated: 59·65% C, 6·63% H, 4·40% Cl, 3·48% N, 3·98% S; found: 59·61% C, 6·81% H, 4·66% Cl, 3·75% N, 4·04% S.

The base for pharmacological testing and for recording the spectrum was released from the maleate with dilute NH_4OH and isolated by extraction with benzene. ^{1}H NMR spectrum: 0·82 def. t, 3 H (CH_3); 1·25 bs, 12 H (6 CH_2 in positions 3–8 of decanoyl); 1·55 bm, 2 H (CH_2 in position 9 of decanoyl); 2·22 t, 2 H (CH_2 in position 2 of decanoyl); 2·51 s, 8 H (4 CH_2N of piperazine); 2·58 t, 4 H (2 CH_2N in the chains, J = 7·0); c. 3·30 m, 2 H ($ArCH_2$); 3·65 t, 2 H (OCH_2, J = 7·0); 4·15 t, 2 H ($COOCH_2$, J = 7·0); 5·30 dd, 1 H (Ar—CH—O, J = 4·0; 8·0); 6·80–7·60 m, 7 H (7 ArH).

B) A stirred solution of 14·6 g *II* in 50 ml chloroform was treated over 20 min with a solution of 10·0 g decanoyl chloride[13] in 30 ml chloroform. The mixture was stirred for 2 h at room temperature and refluxed for 4 h. After cooling the clear solution was diluted with 50 ml chloroform and shaken with 100 ml water and 15 ml NH_4OH. The separation proceeded much better than in the preceding case. The chloroform layer was dried and evaporated; 21·0 g (90%) of almost homogeneous *IX*. Neutralization with 8·8 g maleic acid in 350 ml acetone gave 23·8 g bis(hydrogen maleate), m.p. 158–159°C. Recrystallization from a mixture of 1·5 l acetone and 25 ml water gave 18·0 g, m.p. 163–165°C. Treatment with 30 ml NH_4OH in 150 ml water and extraction with benzene gave 12·5 g (63%) homogeneous *IX* which was used for pharmacological testing.

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