THE 3-HYDROXY DERIVATIVE OF THE NEUROLEPTIC OXYPROTHEPIN AND SOME OTHER 3,8-DISUBSTITUTED 10-PIPERAZINODIBENZO[*b,f*]THIEPIN DERIVATIVES*

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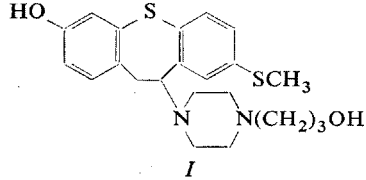
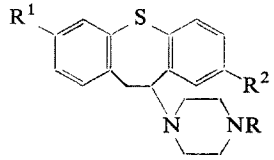
3-Methoxy-8-methylthio (*XIa*), 3-chloro-8-fluoro (*XIb*) and 3,8-dichloro derivative (*XIc*) of dibenzo[*b,f*]thiepin-10(11*H*)-one were synthesized in five steps from acids *VIa*, *VIb* and *VIc*. Two further steps resulted in the chloro derivatives *XIIIa*—*XIIIc*. Substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine led to 3,8-disubstituted 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins *IIb*, *IIc*, *IIIb* and *IVa*. Reaction of ketone *XIb* with 1-methylpiperazine and titanium tetrachloride led to enamine *V*. The methoxy derivative *IVa* was demethylated with boron tribromide to *I* which is a 3-hydroxy derivative and a potential metabolite of the neuroleptic "oxyprothepin".

Similarly to the chlorpromazine series, where the most interesting hydroxylated metabolite was found to be the 7-hydroxy derivative of chlorpromazine (for references see[1,2]), the analogously derived 3-hydroxy derivative of octoclothepin is of interest not only as a metabolite of octoclothepin but also as a highly effective neuroleptic of relatively low toxicity[1]. These properties have stimulated the synthesis of the analogous hydroxy derivative *I*, derived from another potent neuroleptic of the 10-piperazinodibenzo[*b,f*]thiepin series, 10-[4-(3-hydroxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin ("oxyprothepin", ref.[2-4]). An intermediate product of this synthesis was the corresponding methoxy derivative *IVa*. At the same time, the preparation of four other 3,8-disubstituted 10-piperazinodibenzo-[*b,f*]thiepins *IIb*, *IIc*, *IIIb* and *V* was described.

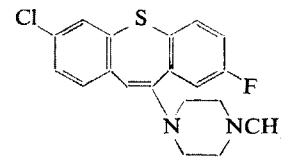


I

* Part XCII in the series Neurotropic and Psychotropic Agents; Part XCI: This Journal *40*, 3519 (1975).

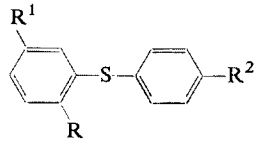


II, R = CH_3
III, R = $(CH_2)_2OH$
IV, R = $(CH_2)_3OH$

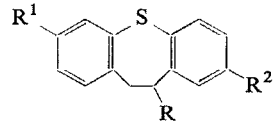


V

In the synthesis of the above compounds, conventional procedures with *VIabc* to *XIIIabc* as intermediates were used. In series a the starting compounds were 2-iodo--4-methoxybenzoic acid[1] and 4-(methylthio)thiophenol[5]. In series *b* and *c*, it was 2-bromo-4-chlorobenzoic acid which was obtained from 4-amino-2-bromotoluene[6]. Diazotization and Sandmeyer's reaction yielded 2-bromo-4-chlorotoluene (for another preparation procedure see[7]) which was oxidized to 2-bromo-4-chlorobenzoic acid with potassium permanganate (for other preparation procedures see[7-9]). The thiol component used in series *b* was 4-fluorothiophenol[10], in series *c* 4-chlorothiophenol[11]. In series a the reaction of the iodo acid with the thiol was done in boiling aqueous potassium hydroxide in the presence of copper, giving rise to acid *VIa*. Acids *VIb* and *VIc* were obtained by a reaction of the above components in boiling dimethylformamide again in the presence of potassium hydroxide and copper. Acid *VIa* was reduced to alcohol *VIIa* either with lithium tetrahydridoaluminate in ether, or with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene. Acids *VIb* and *VIc* were reduced to alcohols *VIIb* and *VIIc* with diborane, generated in the reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran. Transformation of alcohols *VII* to chlorides *VIII* was done with thionyl chloride in benzene or chloroform in the presence of an equivalent of pyridine. In a further step, chlorides *VIII* were converted to nitriles *IX* by treatment with sodium cyanide in dimethylformamide or dimethyl sulfoxide. When using dimethyl formamide as the medium, the reaction proceeds at a sufficient rate even at room temperature; on the other hand, heating of the reaction mixture results in the formation of by-products



VI, R = COOH
VII, R = CH_2OH
VIII, R = CH_2Cl
IX, R = CH_2CN
X, R = CH_2COOH

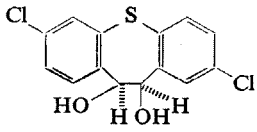


XI, R = =O
XII, R = OH
XIII, R = Cl

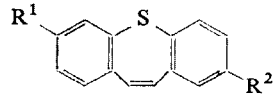
and in a low yield of the desired *IXc*. To hydrolyze the nitriles *IX* to the acids *X*, a boiling aqueous–ethanolic solution of potassium hydroxide was used.

Acids *X* were cyclized to derivatives of dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIabc*) by treatment with polyphosphoric acid. In series *a*, we worked in the presence of boiling toluene to achieve gentler reaction conditions and to prevent any O- and S-demethylation; in series *b* and *c*, the cyclization was done without solvent at 125–135°C. The ketones obtained were reduced to alcohols *XII* with sodium borohydride in aqueous ethanol, aqueous dioxane or in a mixture of these solvents. In the case of reduction of ketone *XIc*, the alcohol *XIIc* was accompanied by a small amount of more polar and less benzene-soluble 2,7-dichloro-10,11-dihydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIV*). Its proton magnetic resonance spectrum shows it to possess a *cis*-configuration, the structure being supported by its mass spectrum. A similar type of by-product, the formation of which must be ascribed to a contaminant of the starting ketone, was encountered before[12]. Alcohols *XII* were converted to chlorides *XIII* by treatment with hydrogen chloride in benzene, chloroform or a mixture of the two.

Chlorides *XIII* were then subjected to substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine[13] in boiling chloroform. The main products obtained were the bases *IIb*, *IIc*, *IIIb* and *IVa*. In a smaller extent, one may observe elimination reactions, their products being dibenzo[*b*,*f*]thiepins *XV*; compounds *XVb* and *XVc* were isolated and characterized in a pure state. Reaction of the ketone *XIb* with 1-methylpiperazine and titanium tetrachloride in boiling benzene led to enamine *V*. The methoxy derivative *IVa* was demethylated with boron tribromide in chloroform at room temperature (see[1]). The phenolic amine obtained (*I*) was identified with the aid of its mass spectrum as a solvate with toluene, the source of the solvent being ethanol denatured with toluene which was used for recrystallization of the crude product. If pure ethanol in a mixture with benzene was used for recrystallization, the resulting solvate was with benzene. To characterize base *I*, IR and PMR spectra were used, both of them bearing out the presence of the phenolic hydroxyl and excluding the possibility of S-demethylation accompanying the O-demethylation. Phenolic base *I* behaves like a univalent base,



XIV



XV

In formulae *II*–*IV*, *VI*–*XIII*, *XV*: *a*; $R^1 = OCH_3$, $R^2 = SCH_3$; *b*; $R^1 = Cl$, $R^2 = F$; *c*; $R^1 = R^2 = Cl$

yielding crystalline salts with oxalic and fumaric acid, the salt containing 1 molecule of acid and 2 molecules of base *I*.

It was reported recently[14] that one of the phenolic metabolites of oxyprothepin, obtained from the glucuronide fraction of the urine of patients treated with the neuroleptic, shows an R_F value identical with that of our synthetic product *I*.

The piperazine derivatives prepared were evaluated pharmacologically using oral administration and with respect to the expected central depressant and neuroleptic activity; the effects were partly followed also from the viewpoint of the possible prolongation of their duration. The results are summarized in the usual manner in Table I including as standards the 3-hydroxy derivative of octoclothepin[1] and the 3-fluoro derivative of octoclothepin[10]. The table shows values of acute toxicity in

TABLE I

Pharmacological Properties of the Compounds Prepared on Oral Administration (mg/kg)[a]

Compound[a]	Code No VÚFB-	Acute toxicity LD_{50}	Rotating rod		Locomotor activity		Catalepsy ED_{50}[f]	Antiapomorphine[g] activity %	
			ED_{50} max.[b]	24 h[c]	D_{50}[d]	24 h[e]		chewing	agitation
I	10·680	400	16·0		10·7	+	65	52+	53+
IIb	10·566	166	5·2	5/10	1·2	—	>50[h]	100	86
IIc	10·573	380	8·4	8/10	2·9	+	30	51+	56+
IIIb	10·564						>50[i]		
IVa	10·563	220	45	4/10	6·8	—	>50[i]	41+	36+
V	10·571						<50[j]		
3-HO-OCT[k]		350	0·84				2·4		
3-F-OCT[m]		28·5	0·8	9/10			3·8		

[a] The compounds were evaluated in the form of salts described in the experimental part; the values given were calculated for bases. [b] The mean effective dose in the time of maximal effect (1—2 h after administration). [c] The number of animals from the group showing ataxia in maximal extent 24 h after administration. [d] The dose reducing the locomotor activity 1 h after administration to 50% (in comparison with the control being 100%). [e] Affecting the locomotor activity 24 h after administration of the substance: + means that a significant inhibition is still apparent, — means that the effect disappeared. [f] The mean effective doses in the test of catalepsy in rats. [g] The compounds were administered in a dose of 40 mg/kg 4 h before apomorphine; the values are % of the apomorphine activity (evaluated by the two usual parameters, *i.e.* chewing and agitation) of the control group being 100%; + means statistical significance of the values. [h] The dose given produced catalepsy in 30% of animals. [i] The dose given produced catalepsy in 40% of animals. [j] The dose given produced catalepsy in 70% of animals; after 24 h 20% of the animals are still in the state of catalepsy; further testing of the compound was stopped because of the instability of the used aqueous solutions of the methanesulfonate. [k] 3-Hydroxy derivative of octoclothepin[1]. [m] 3-Fluoro derivative of octoclothepin[10].

mice (LD_{50}), further the mean effective doses producing ataxia in the rota-rod test in mice, doses decreasing the locomotor activity of mice in the photo-cell method to 50%, the mean effective doses in the test of catalepsy in rats, and finally values of the antiapomorphine activity in rats with respect to the inhibition of the apomorphine-induced chewing and agitation, expressed in % of the respective activity of the control group being 100%.

The Table shows that the compounds prepared – when compared with the standards – are of low central depressant, as well as cataleptic activity. Especially the low activity of the 3-hydroxy derivative of oxyprothepin (*I*) in comparison with the high activity of the 3-hydroxy derivative of octoclothepin[1] was a surprize. The metabolic 3-hydroxylation of the compounds of our series cannot thus generally be considered a bioactivation process; the pharmacodynamic activity of the hydroxylated metabolite is evidently influenced by the character of the substituent in position 8, and probably even more by the character of the substituent on the piperazine N^4. Compound *I* – in comparison with the 3-hydroxy derivative of octoclothepin[1] – must be substantially more polar which may negatively influence in a decisive extent its transport to the receptor. The effect of interchanging the atoms of chlorine and fluorine in the molecule of the 3-fluoro derivative of octoclothepin[10] resulting in compound *IIb* is also striking. This compound is indeed more than 5 times less toxic than 3-fluorooctoclothepin but at the same time more than 5 times less active sedatively and almost inactive in the test of catalepsy; it is interesting that its sedative effect preserves some degree of protraction. It is rather active in the test of inhibition of the locomotor activity but inactive in the test of apomorphine antagonism. The importance of the atom of chlorine in position 8 for the neuroleptic character of the substance is demonstrated by compound *IIc*, the 3,8-dichloro derivative: it has a distinct cataleptic and a rather high antiapomorphine activity. The antiapomorphine effects of the new compounds do not show signs of protraction; they disappeared within 24 hours in all cases.

The salts of the piperazine derivatives were also tested by Dr J. Turinová and Dr A. Čapek (Bacteriological department of this institute) for antimicrobial activity in tests *in vitro* toward a standard set of microorganisms. They were found to possess a broad activity spectrum as reported several times in this series. The individual microorganisms and the minimum inhibitory concentrations of the compounds in μg/ml are shown: *Streptococcus β-haemolyticus*, *IIb* 25, *IIc* 10, *IIIb* 25, *IVa* 50, *V* 20; *Streptococcus faecalis*, *IIb* 25, *IIc* 10, *IIIb* 25, *IVa* 50, *V* 20; *Staphylococcus pyogenes aureus*, *I* 50, *IIb* 25, *IIc* 10, *IIIb* 25, *IVa* 50, *V* 50; *Pseudomonas aeruginosa*, *IIc* 100, *V* 100; *Escherichia coli*, *IIc* 100, *V* 100; *Proteus vulgaris*, *V* 100; *Mycobacterium tuberculosis* H37Rv, *I* 25, *IIb* 6·25, *IIc* 6·25, *IIIb* 6·25; *IVa* 12·5, *V* 100; *Saccharomyces pasterianus*, *IIb* 50, *IIc* 50, *IIIb* 25, *IVa* 100, *V* 25; *Trichophyton mentagrophytes*, *I* 100, *IIb* 25, *IIc* 25, *IIIb* 25, *IVa* 25, *V* 12·5; *Candida albicans*, *IIb* 100, *IIc* 50, *IIIb* 100, *IVa* 100, *V* 25; *Aspergillus niger*, *IIb* 50, *IIc* 25, *IIIb* 100, *IVa* 50, *V* 25.

During the printing of this paper, the text of three patent applications[15–17] was published, of which the first one[15] described the synthesis of our substance *IIb*, the second one[16] the synthesis

of our compound *IVa*, and the third one[17] the whole sequence of intermediates leading to chlorides *XIIIa* and *XIIIb*. Whereas the last application[17] bears some marks of originality (new types of side chains on the piperazine N^4), the first two[15,16] are by their topic, as well as the used synthetic methods completely dependent on our previous work in the series. Most of the descriptions of preparations are without experimental details, all lack data on the yields. The products are not characterized by analyses and spectra; the melting points given are practically in all cases lower than our values. Substances *VIIa*, *VIIIa*, *VIIIb*, *IXa* and *IXb* are characterized as "brown", "dark brown" or "black" oils. The final products (*IIb*, *IVa*) were prepared in the form of other salts than described in this paper which makes a comparison impossible.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 0·5 Torr over phosphorus pentoxide at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) or in a Tesla BC 487 (80 MHz) spectrometer, the mass spectra in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of silica gel.

2-Bromo-4-chlorotoluene

A mixture of 580 g 4-amino-2-bromotoluene hydrochloride[6] and 1 200 ml concentrated hydrochloric acid was cooled by addition of 1 kg ice and then, under external cooling and stirring, a solution of 193 g $NaNO_2$ in 500 ml water was added dropwise at 0—5°C. The mixture was stirred at that temperature for 1 h and the solution of diazonium chloride obtained was poured at 0°C to a solution of 407 g CuCl in 1 200 ml hydrochloric acid. After standing overnight, the lower phase was separated, the upper one extracted with benzene which contained the separated lower phase. The benzene solution was washed with H_2SO_4 and water, dried with $MgSO_4$ and distilled: 401 g (79%), b.p. 105—106°C/17 Torr. Ref.[7] reports a b.p. of 112—114°C/12 Torr for a product obtained in a different way.

2-Bromo-4-chlorobenzoic Acid

A mixture of 47·7 g 2-bromo-4-chlorotoluene with a solution of 106 g $KMnO_4$ in 3 l water was refluxed under stirring for 7 h. After standing overnight, 50 ml ethanol was added for removing the excess of $KMnO_4$, the nonreacted starting compound was removed by steam distillation (recovery of 13·6 g), MnO_2 was filtered off and the filtrate was acidified with hydrochloric acid. On the following day, filtration, washing with water and drying yielded 23·5 g (60% perconversion) product melting at 159—160°C. For a product prepared in other ways, ref.[7—9] report m.p. of 154—155°C.

4-Methoxy-2-(4-methylthiophenylthio)benzoic Acid (*VIa*)

4-(Methylthio)thiophenol[5] (34 g) was added in parts to a solution of 28·5 g 85% KOH in 270 ml water; this was followed after a while of stirring with 60 g 2-iodo-4-methoxybenzoic acid[1] and 1·0 g Cu ("molecular") and the mixture was refluxed for 7 h under stirring. The hot mixture was diluted with 250 ml boiling water and the copper was filtered while hot. The warm filtrate, from which a poorly soluble potassium salt of the product precipitates on standing,

was made acid with hydrochloric acid. After standing overnight, the precipitated acid was filtered, washed with water and dried; 57 g (87%), m.p. 210–212°C. Recrystallization from ethanol yielded a pure compound, melting at 211–213°C. IR spectrum: 817, 885 (2 adjacent and solitary Ar—H), 932 (COOH), 1029, 1239 ($ArOCH_3$), 1330 (COOH), 1549, 1576, 1594 (Ar), 1661 (ArCOOH), 2400–3100 cm^{-1} (COOH). For $C_{15}H_{14}O_3S_2$ (306·4) calculated: 58·80% C, 4·61% H, 20·93% S: found: 58·85% C, 4·71% H, 20·68% S.

4-Chloro-2-(4-fluorophenylthio)benzoic Acid (*VIb*)

A mixture of 500 ml dimethylformamide, 88·3 g 2-bromo-4-chlorobenzoic acid, 49 g 4-fluorothiophenol[10], 43·7 g KOH and 4 g Cu was refluxed under stirring for 16 h in an atmosphere of nitrogen. The solvent was evaporated *in vacuo*, the residue was diluted with 600 ml hot water, the solution was filtered and the filtrate acidified with hydrochloric acid. The crude product was filtered, dried and recrystallized from benzene; 49·0 g (46%), m.p. 211–214°C; analytical product melted at 216–218°C (benzene). For $C_{13}H_8ClFO_2S$ (282·7) calculated: 55·23% C, 2·85% H, 12·54% Cl, 6·72% F, 11·34% S; found: 55·48% C, 3·01% H, 12·74% Cl, 6·57% F, 11·07% S.

4-Chloro-2-(4-chlorophenylthio)benzoic Acid (*VIc*)

Like in the preceding case, 75 g 2-bromo-4-chlorobenzoic acid and 43 g 4-chlorothiophenol[11] yielded 38·6 g (40%) product melting at 194–204°C. Recrystallization from a mixture of benzene and ethanol yielded a pure compound melting at 207–208·5°C. The compound could not be analyzed (it could not be weighed accurately because of its adhesiveness) but it was characterized by its spectra. UV spectrum: λ_{max} 227·5 nm (log ε 4·45), 256 nm (4·10), infl. 278·5 nm (3·87). IR spectrum: 838, 870 (2 adjacent and solitary Ar—H), 1250 (COOH), 1483, 1555, 1585 (Ar), 1700 (Ar—COOH), 2550, 2650, 3000 cm^{-1} (COOH). NMR spectrum (CD_3SOCD_3): δ 7·49 (d, J = 9·0 Hz, 1 H, 6-H), 7·55 (s, 4 H, aromatic protons of the chlorophenylthio group), 7·25 (bs, 1 H, COOH), 7·11 (q, J = 9·0; 2·0 Hz, 1 H, 5-H), 6·54 (d, J = 2·0 Hz, 1 H, 3-H).

4-Methoxy-2-(4-methylthiophenylthio)benzyl Alcohol (*VIIa*)

A. VIa (10·1 g) was slowly added under stirring to a mixture of 2·6 g $LiAlH_4$ in 250 ml ether and the mixture was refluxed for 5 h. After standing overnight, it was decomposed by adding dropwise under stirring and external cooling 4 ml water and 100 ml dilute (1 : 4) hydrochloric acid. After separation, the aqueous phase was extracted with 200 ml ether, the ether solutions were combined, washed with 20% K_2CO_3 and water and after drying ($MgSO_4$) it was evaporated: 7·1 g (74%) m.p. 48–54°C. Crystallization from a mixture of benzene and light petroleum yielded the pure product which melted at 53–54·5°C. IR spectrum: 813, 866 (2 adjacent and solitary Ar—H), 1045 (CH_2OH), 1055, 1226 ($ArOCH_3$), 1477, 1560, 1584, 1602 (Ar), 3360 cm^{-1} (OH). For $C_{15}H_{16}O_2S_2$ (292·4) calculated: 61·61% C, 5·52% H, 21·93% S; found: 61·61% C, 5·50% H, 21·69% S.

B. A suspension of 49·4 g *VIa* in 1000 ml benzene was treated dropwise at 45–55°C with 134 g 50% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate. The mixture was stirred for 4 h at room temperature, decomposed after standing overnight by a slow addition of 400 ml 2M-NaOH, the benzene layer was separated, washed with water, dried and evaporated at reduced pressure; 43·9 g (92%), m.p. 50–53·5°C.

4-Chloro-2-(4-fluorophenylthio)benzyl Alcohol (*VIIb*)

Sodium borohydride (8·95 g) was added under stirring in an atmosphere of nitrogen over a period of 10 min to a solution of 49 g *VIb* in 120 ml tetrahydrofuran. Boron trifluoride etherate (28·8 ml) was then added dropwise over a period of 20 min at 15—20°C. The mixture was stirred for 4 h, left to stand overnight and decomposed by adding dropwise 120 ml 5% hydrochloric acid; the precipitate was filtered, the filtrate combined with 120 ml benzene and separated after shaking. The organic phase was washed with 5% Na_2CO_3, dried with $MgSO_4$ and evaporated. A total of 45·8 g (theoretical amount) of crude product melting at 84—88°C was obtained which was recrystallized from a mixture of ether and light petroleum to melt at 86—88°C. IR spectrum: 817, 823, 831, 842, 863 (2 adjacent and solitary Ar—H), 1050 (CH_2OH), 1495, 1565, 1595 (Ar), 3220, 3315 cm^{-1} (OH). NMR spectrum: δ 6·80—7·50 (m, 7 H, aromatic protons), 4·67 (s, 2 H, $ArCH_2O$), 2·40 (s, 1 H, disappears after D_2O, OH). For $C_{13}H_{10}ClFOS$ (268·7) calculated: 58·10% C, 3·75% H, 13·20% Cl, 11·93% S; found: 58·27% C, 3·78% H, 13·21% Cl, 11·87% S.

4-Chloro-2-(4-chlorophenylthio)benzyl Alcohol (*VIIc*)

In analogy to the preceding case, reduction of 29·5 g *VIc* yielded 26·4 g (94%) crude crystalline product which was recrystallized for analysis from a mixture of ether and light petroleum: m.p. 72·5—73·5°C. For $C_{13}H_{10}Cl_2OS$ (285·2) calculated: 54·75% C, 3·64% H, 24·86% Cl, 11·24% S; found: 54·65% C, 3·54% H, 24·82% Cl, 11·19% S.

4-Methoxy-2-(4-methylthiophenylthio)benzyl Chloride (*VIIIa*)

A mixture of 5·7 g *VII*a, 2 ml pyridine and 10 ml benzene was homogenized by heating, then it was cooled to 10°C and, under stirring and external cooling, 2·9 g $SOCl_2$ was added dropwise at 10—17°C. The mixture was diluted with 20 ml benzene, stirred for 2 h at room temperature and for 1 h at 40°C. After standing overnight, it was decomposed under external cooling by adding dropwise 10 ml water and extracted with benzene. Processing of the extract yielded 5·5 g (91%) product (m.p. 59—68°C) which was recrystallized for analysis from a mixture of benzene and light petroleum: m.p. 63—71°C. For $C_{15}H_{15}ClOS_2$ (310·9) calculated: 57·95% C, 4·86% H, 11·41% Cl, 20·63% S; found: 58·32% C, 5·17% H, 11·45% Cl, 20·36% S.

4-Chloro-2-(4-fluorophenylthio)benzyl Chloride (*VIIIb*)

$SOCl_2$ (23·8 g) was added dropwise to a solution of 44·2 g *VIIb* in mixture with 65 ml chloroform and 16 ml pyridine at 15—20°C, the mixture was stirred for 5 h at room temperature and, after 48 h of standing, it was decomposed with water. The separated organic phase was washed with cold 5% NaOH and with water, dried with $CaCl_2$ and evaporated. A total of 47·2 g (theoretical amount) oil was obtained a sample of which was redistilled for analysis: b.p. 152—154°C/0·4 Torr. For $C_{13}H_9Cl_2FS$ (287·2) calculated: 54·37% C, 3·16% H, 11·16% S; found: 54·54% C, 3·22% H, 11·09% S.

4-Chloro-2-(4-chlorophenylthio)benzyl Chloride (*VIIIc*)

Like in the preceding case, 26·2 g *VIIc* yielded 31·2 g oil which crystallized from cyclohexane to yield 13·9 g (50%) crude crystalline product. A sample for analysis was redistilled (b.p. 190°C/1·2 Torr) and then recrystallized from cyclohexane, m.p. 64—69°C. For $C_{13}H_9Cl_3S$ (306·7) calculated: 10·56% S; found: 10·50% S.

4-Methoxy-2-(4-methylthiophenylthio)phenylacetonitrile (*IXa*)

A warm-prepared solution of 50·5 g *VIIIa* in 180 ml dimethylformamide was cooled and, at 22°C, 12·3 g NaCN was added under stirring. The mixture was stirred for 3 h at room temperature and 30 min at 40°C. After standing overnight, the solvent was evaporated *in vacuo*, the residue was diluted with water and the product was isolated by extraction with benzene; 45·0 g (92%) product, melting at 68—76°C. For analysis, it was recrystallized from cyclohexane, m.p. 75—77°C. For $C_{16}H_{15}NOS_2$ (301·4) calculated: 4·65% N, 21·28% S; found: 4·62% N, 20·95% S.

4-Chloro-2-(4-fluorophenylthio)phenylacetonitrile (*IXb*)

Sodium cyanide (12·5 g) was added under stirring over a period of 10 min at about 35 °C to a solution of 46·9 g *VIIIb* in 80 ml dimethyl sulfoxide. The mixture was stirred for 2·5 h at 35—40°C, diluted with 500 ml water and the product was isolated by extraction with ether. Distillation of the extract yielded 34·5 g (76%) product boiling at 172—174°C/0·8 Torr and melting at 60—67°C. For analysis it was recrystallized from ethanol, m.p. 68—69°C. For $C_{14}H_9ClFNS$ (277·8) calculated: 60·54%C, 3·27% H, 5·04% N, 11·54% S; found: 60·97% C, 3·29% H, 5·32% N, 11·50% S.

4-Chloro-2-(4-chlorophenylthio)phenylacetonitrile (*IXc*)

A mixture of 20·6 g *VIIIc*, 80 ml dimethylformamide and 5·0 g NaCN was heated under stirring for 5 h to 100°C. The solvent was evaporated *in vacuo* and the residue was diluted with water and extracted with benzene. Distillation of the extract yielded only 11·6 g (59%) product boiling at 180—210°C/0·8 Torr which was used for hydrolysis without further purification. After distillation of the product there remained a substantial residue.

4-Methoxy-2-(4-methylthiophenylthio)phenylacetic Acid (*Xa*)

A mixture of 45 g *IXa* in 200 ml ethanol and of a solution of 43 g KOH in 90 ml water was refluxed for 8 h. Ethanol was then evaporated at reduced pressure, the residue was diluted with 1 litre warm water, the solution was washed with benzene, cooled and acidified with hydrochloric acid. On the following day, the product was filtered, washed with water and dried; 41·4 g (86%), m.p. 128 to 133°C. Recrystallization from ethanol yielded a product melting at 129—132·5°C. IR spectrum (Nujol): 820, 870 (2 adjacent and solitary Ar—H), 960 (COOH), 1055, 1240 ($ArOCH_3$), 1490, 1600 (Ar), 1690, 1710 cm^{-1} (COOH). NMR spectrum: δ 10·04 (bs, 1 H, disappears after D_2O, COOH), 7·12 (s, 4 H, aromatic protons of 1,4-disubstituted benzene), 6·65—7·30 (m, 3 H, remaining aromatic protons), 3·71 (s, 2 H, $ArCH_2$), 3·65 (s, 3 H, OCH_3), 2·36 (s, 3 H, SCH_3). For $C_{16}H_{16}O_3S_2$ (320·4) calculated: 59·97 % C, 5·04% H, 20·01% S; found: 60·05% C, 5·21% H, 19·72% S.

4-Chloro-2-(4-fluorophenylthio)phenylacetic Acid (*Xb*)

Hydrolysis of 34 g *IXb* yielded analogously 30·8 g (85%) crude product which was recrystallized from cyclohexane to melt at 98—101°C. For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·66% C, 3·40% H, 10·81% S; found: 57·23% C, 3·65% H, 10·83% S.

4-Chloro-2-(4-chlorophenylthio)phenylacetic Acid (*Xc*)

Hydrolysis of 11·6 g crude *IXc* yielded analogously 12·8 g crude product which was recrystallized from a mixture of benzene and cyclohexane; 9·0 g (74%), m.p. 122—128°C; analytical sample,

m.p. 126–128°C (benzene–light petroleum). IR spectrum (Nujol): 812, 821, 829, 867, 890 (2 adjacent and solitary Ar—H), 930, 1240 (COOH), 1476, 1584 (Ar), 1700, 2630 cm^{-1} (COOH). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·69% C, 3·22% H, 10·24% S; found: 54·41% C, 3·66% H, 9·88% S.

3-Methoxy-8-(methylthio)dibenzo[*b,f*]thiepin-10(11*H*)-one (*XIa*)

Polyphosphoric acid was prepared by 4 h of stirring a mixture of 205 g phosphorus pentoxide and 140 ml 85% H_3PO_4 at 140°C. Toluene (330 ml) and 41·4 g *Xa* were added and the mixture was refluxed for 3 h under stirring. After cooling, it was poured into 1 kg of a mixture of ice and water and the product was extracted with benzene. The extract was washed with 5% NaOH and water, dried and evaporated. A total of 34·4 g (88%) ketone was obtained which melted at 118 to 128°C. The analytical product was obtained by crystallization from benzene, m.p. 128·5 to 131·5°C. For $C_{16}H_{14}O_2S_2$ (302·4) calculated: 63·54% C, 4·67% H; found: 63·56% C, 4·86% H.

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

Polyphosphoric acid prepared from 70 g P_2O_5 and 35 ml 85% H_3PO_4 was combined with 27·2 g *Xb* and the mixture was stirred for 3 h at 125–130°C. After cooling, it was decomposed with water, the solid product was filtered, extracted for 2 h with excess 10% NH_4OH, filtered, washed with water, dried and recrystallized from a mixture of ethanol and chloroform; 19·6 g (77%), m.p. 161–162°C. Analytical product, m.p. 162–163°C (ethanol–chloroform). UV spectrum: λ_{max} 231·5 nm (log ε 4·32), infl. 251 nm (4·01), 330 nm (3·57). IR spectrum: 829, 882, 900 (2 adjacent and solitary Ar—H), 1471, 1576, 1605 (Ar), 1695 cm^{-1} (Ar—CO). NMR spectrum: δ 7·81 (q, J = 9·0 (H—F); 3·0 Hz, 1 H, 9-H), 6·85–7·65 (m, 5 H, remaining aromatic protons), 4·26 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8ClFOS$ (278·7) calculated: 60·33% C, 2·89% H, 12·72% Cl, 6·82% F, 11·50% S; found: 60·30% C, 3·07% H, 12·26% Cl, 6·71% F, 11·16% S.

3,8-Dichlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XIc*)

Like in the preceding case, cyclization of 8·6 g *Xc* at 130–135°C yielded 7·1 g (88%) product, m.p. 166–166·5°C (chloroform–ethanol). UV spectrum: λ_{max} 233 nm (log ε 4·41), infl. 265 nm (4·01), 335 nm (3·59). IR spectrum (Nujol): 819, 879 (2 adjacent and solitary Ar—H), 1580 (Ar), 1681 cm^{-1} (Ar—CO). NMR spectrum: δ 8·16 (d, J = 2·5 Hz, 1 H, 9-H), 7·20–7·70 (m, 5 H, remaining aromatic protons), 4·30 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 56·91% C, 2·84% H, 23·90% Cl, 10·55% S.

10-Hydroxy-3-methoxy-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin(*XIIa*)

A solution of 6·8 g $NaBH_4$ in 70 ml water containing 3 drops of 5% NaOH was added dropwise under stirring to a refluxing solution of 33·4 g *XIa* in 1 litre ethanol. The mixture was refluxed under stirring for 3·5 h, the ethanol was evaporated, the residue was mixed with water and extracted with benzene. Processing of the extract yielded a crude product which was recrystallized from benzene; 26·2 g (78%), m.p. 128–130°C. Analytical product, m.p. 129–132°C (benzene). PMR spectrum (CD_3SOCD_3): δ 6·65–7·55 (m, 6 H, aromatic protons), 5·70 (d, J = 5·0 Hz, disappears after D_2O, 1 H, OH), 5·35 (m, 1 H, Ar—CH—O), 3·68 (s, 3 H, OCH_3), c. 3·20 (m, 2 H, $ArCH_2$), 2·44 (s, 3 H, SCH_3). For $C_{16}H_{16}O_2S_2$ (304·4) calculated: 63·12% C, 5·30% H, 21·07% S; found: 63·26% C, 5·44% H, 20·58% S.

3-Chloro-8-fluoro-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIb*)

A solution of 14·0 g *XIb* in a mixture of 100 ml dioxane and 100 ml ethanol was reduced like in the preceding case with 1·9 g $NaBH_4$ in 5 ml water. Crystallization of the crude product from a mixture of cyclohexane and light petroleum yielded 13·0 g (92%) compound melting at 114 to 116°C. Analytical sample, m.p. 115—116°C (cyclohexane). IR spectrum: 820, 860, 890 (2 adjacent and solitary Ar—H), 1025, 1075 (CHOH in a ring), 1475, 1590 (Ar), 3340 cm^{-1} (OH). For $C_{14}H_{10}ClFOS$ (280·8) calculated: 59·89% C, 3·59% H, 11·42% S; found: 59·82% C, 3·68% H, 11·22% S.

3,8-Dichloro-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIc*)

A solution of 6·35 g *XIc* in 100 ml dioxane was reduced similarly to the preceding cases with 0·82 g $NaBH_4$ in 3 ml water. After pouring of the reaction mixture into water, the precipitated product was filtered, dried and extracted with benzene. The undissolved substance (0·38 g) being more polar than the major reaction product was isolated, m.p. 234—236°C (ethanol–benzene). The compound was identified by spectra and analyses as *cis*-2,7-dichloro-10,11-dihydroxy-10,11--dihydrodibenzo[*b,f*]thiepin (*XIV*), the formation of which must be attributed to a contaminant in the starting ketone *XIc*. The mass spectrum with a molecular ion *m/e* 312 supports the composition $C_{14}H_{10}Cl_2O_2S$; the main fragments $C_{14}H_8Cl_2OS$ and $C_{13}H_7Cl_2S$ demonstrate the presence of a glycol grouping. UV spectrum: λ_{max} 231 nm (log ε 4·39), infl. 255 nm (3·85), 268·5 nm (4·05). IR spectrum (Nujol): 817, 878 (2 adjacent and solitary Ar—H), 1078, 1093, 1134 (CHOH in a ring), 1581 (Ar), 3220, 3390 cm^{-1} (OH). PMR spectrum (CD_3SOCD_3): δ 7·10—7·70 (m, 6 H, aromatic protons), 5·85 and 5·73 (2 d, disappears after D_2O, 2 H, 2 OH), 5·27 and 5·15 (2 d, after D_2O s, 2 H, *cis*-Ar—CH—CH—Ar). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·69% C, 3·22% H, 22·64% Cl, 10·24% S; found: 53·59% C, 3·19% H, 22·80% Cl, 10·23% S.

Evaporation of the benzene solution and recrystallization of the residue from ethanol yielded 5·73 g (90%) compound *XIIc*, m.p. 120—122°C. IR spectrum (Nujol): 818, 883 (2 adjacent and solitary Ar—H), 1050 (CHOH in a ring), 1581 (Ar), 3290, 3360 cm^{-1} (OH). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·58% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·04% C, 3·27% H, 23·79% Cl, 10·65% S.

10-Chloro-3-methoxy-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIa*)

Anhydrous $CaCl_2$ (10 g) was added to a solution of 26·2 g *XIIa* in 1700 ml benzene and the suspension was saturated for 4 h with anhydrous HCl. After standing overnight, it was filtered with charcoal and the filtrate was evaporated: 27·0 g (97%) compound melting at 117—121°C. Analytical sample, m.p. 121·5—123·5°C (cyclohexane). PMR spectrum: δ 7·40 and 7·10 (2 d, J = 2·5 Hz, 2 H, 4,9-H_2), 7·35 and 7·20 (2 d, J = 9·0 Hz, 2 H, 1,6-H_2), 7·00 and 6·76 (2 q, J = 9·0; 2·5 Hz, 2 H, 2,7-H_2), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH-Cl), 3·85 and 3·50 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·71 (s, 3 H, OCH_3), 2·40 (s, 3 H, SCH_3). For $C_{16}H_{15}ClOS_2$ (322·9) calculated: 59·52% C, 4·68% H, 10·98% Cl, 19·86% S; found: 59·83% C, 4·90% H, 10·76% Cl, 19·85% S.

3,10-Dichloro-8-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIb*)

A solution of 12·5 g *XIIb* in a mixture with 100 ml benzene and 20 ml chloroform with 4 g $CaCl_2$ was saturated for 2 h with hydrogen chloride and processed as in the preceding case. A total of 11·7 g (88%) product was obtained, m.p. 134—136°C (benzene–light petroleum). PMR spectrum:

δ 6·60—7·60 (m, 6 H, aromatic protons), 5·74 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·48 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_9Cl_2FS$ (299·2) calculated: 56·20% C, 3·03% H, 23·70% Cl, 10·72% S; found: 56·64% C, 3·14% H, 23·32% Cl, 10·52% S.

3,8,10-Trichloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIc*)

A solution of 5·60 g *XIIc* in 100 ml chloroform (3·0 g $CaCl_2$) was saturated for 4 h with hydrogen chloride and processed as in the preceding cases; 5·13 g (86%), m.p. 164—165°C (chloroform). For $C_{14}H_9Cl_3S$ (315·7) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·06% C, 3·03% H, 33·54% Cl, 10·06% S.

3-Chloro-8-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IIb*)

A mixture of 5·5 g *XIIIb*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 7 h. After cooling, it was diluted with water and the base was extracted with benzene. The extract was washed with water and shaken with 100 ml 5% hydrochloric acid. The precipitated hydrochloride was filtered, combined with the aqueous phase of the filtrate and treatment of the suspension with 20% NaOH released a base which was extracted with benzene; 3·7 g (55%), m.p. 92—94°C (ethanol). PMR spectrum: δ 6·50—7·60 (m, 6 H, aromatic protons), 2·90—4·00 (m, 3 H, $ArCH_2$ . . CHAr), 2·65 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{19}H_{20}ClFN_2S$ (362·9) calculated: 62·88% C, 5·56% H, 7·72% N; found: 63·25% C, 5·48% H, 7·55% N.

Sesquimethanesulfonate: Neutralization of the base with methanesulfonic acid gives rise to a salt containing 3 mol methanesulfonic acid per 2 mol base; m.p. 221—223°C (ethanol–ether). For $C_{20,5}H_{26}ClFN_2O_{4,5}S_{2,5}$ (507·1) calculated: 48·56% C, 5·17% H, 6·99% Cl, 3·75% F, 5·52% N, 15·81% S; found: 48·24% C, 5·18% H, 6·81% Cl, 4·17% F, 5·29% N, 15·70% S.

Evaporation of the benzene layer which was freed of basic components yielded 1·7 g 7-chloro--2-fluorodibenzo[*b,f*]thiepin (*XVb*); after recrystallization from ethanol, m.p. 111—113°C. UV spectrum: λ_{max} 263·5 nm (log ε 4·35), 291·5 nm (3·82). NMR spectrum: δ 6·75—7·50 (m, aromatic and olefinic protons). For $C_{14}H_8ClFS$ (262·7) calculated: 64·00% C, 3·07% H, 7·23% F, 12·20% S; found: 64·25% C, 3·20% H, 7·54% F, 11·71% S.

3,8-Dichloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IIc*)

Like in the preceding case, 5·0 g *XIIIc* yielded 4·25 g (71%) crude base which crystallizes from aqueous methanol and melts at 47—50°C. PMR spectrum: δ 7·66 (d, J = 2·5 Hz, 1 H, 9-H), 7·32 (d, J = 9·0 Hz, 1 H, 6-H), 7·02 (q, J = 9·0; 2·5 Hz, 1 H, 7-H), 7·15—7·50 (m, 3 H, remaining aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·56 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{19}H_{20}Cl_2N_2S$ (379·4) calculated: 60·16% C, 5·31% H, 18·69% Cl, 7·39% N, 8·45% S; found: 60·26% C, 5·58% H, 18·79% Cl, 7·46% N, 8·31% S.

Sesquimethanesulfonate, m.p. 238—239°C (aqueous ethanol–ether). For $C_{20,5}H_{26}Cl_2N_2O_{4,5}$ . . $S_{2,5}$ (523·5) calculated: 47·03% C, 4·99% H, 13·55% Cl 5·35% N, 15·32% S; found: 46·58% C, 5·07% H, 12·92% Cl, 4·98% N, 15·36% S.

As a neutral product we obtained 1·2 g 2,7-dichlorodibenzo[*b,f*]thiepin (*XVc*), m.p. 125—126°C (benzene–ethanol). UV spectrum: λ_{max} 218·5 nm (log ε 4·46), 226·5 nm (4·45), 265 nm (4·44), 298 nm (3·71), infl. 345 nm (3·01). IR spectrum (Nujol): 814, 827, 849, 886 (2 adjacent and solitary Ar—H), 1550, 1579 cm^{-1} (Ar). NMR spectrum: δ 7·40—7·60 (m, 6 H, aromatic protons),

7·00 (s, 2 H, CH=CH). For $C_{14}H_8Cl_2S$ (279·2) calculated: 60·23% C, 2·89% H, 25·40% Cl, 11·48% S; found: 60·06% C, 2·93% H, 25·69% Cl, 11·64% S.

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

Reaction of 5·5 g *XIIIb* with 15 ml 1-(2-hydroxyethyl)piperazine in 15 ml boiling chloroform yielded, like in the preceding cases, 4·97 g (69%) oily base which was neutralized with maleic acid in ethanol and, with an addition of ether, converted to di(hydrogen maleate) (7·3 g), m.p. 135–137°C (ethanol–ether). For $C_{28}H_{30}ClFN_2O_9S$ (625·1) calculated: 53·80% C, 4·84% H, 4·48% N, 5·13% S; found: 53·78% C, 4·70% H, 4·45% N, 5·01% S.

10-[4-(3-Hydroxypropyl)piperazino]-3-methoxy-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]-thiepin (*IVa*)

Like in the preceding cases, a reaction of 16·35 g *XIIIa* and 20·0 g 1-(3-hydroxypropyl)piperazine[13] in 75 ml chloroform yielded 15·0 g (69%) oily base which is not completely homogeneous and which was chromatographed on a column of 450 g alumina (activity II). Elution with benzene and with benzene plus 10% chloroform released the less polar fractions while application of benzene–chloroform (4 : 1) eluted 8·75 g homogeneous base, a part of which was converted to maleate, m.p. 136–138°C (ethanol–ether). IR spectrum: 870, 900 (2 adjacent and solitary Ar—H), 1360 (COOH), 1500 (COO^-), 1610 (Ar), 1630 (C=C), 1715 (C=C—COOH), 2510, 2630, 2650, 2750 (NH^+), 2845 (OCH_3), 3395 cm^{-1} (OH). For $C_{27}H_{34}N_2O_6S_2$ (546·7) calculated: 59·32% C, 6·27% H, 5·12% N, 11·73% S; found: 59·65% C, 6·48% H, 5·10% N, 11·54% S.

3-Chloro-8-fluoro-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*V*)

A solution of 2·0 g $TiCl_4$ in 20 ml benzene was added to a solution of 5·4 g *XIb* and 10 ml 1-methylpiperazine in 50 ml benzene and the mixture was refluxed under stirring for 24 h. After decomposition with water, the precipitate was filtered, the benzene layer of the filtrate was separated, washed with water, dried with K_2CO_3 and evaporated. Crystallization of the residue from ethanol yielded 4·40 g (68%) base which crystallized as a homogeneous product, melting at 155–157°C. UV spectrum: λ_{max} 214 nm (log ε 4·43), infl. 235 nm (4·18), 267·5 nm (4·01), 310 nm (3·95). IR spectrum (Nujol): 832, 837, 876, 897 (2 adjacent and solitary Ar—H), 1537, 1567, 1594, 1608 (Ar), 2800 cm^{-1} (N—CH_3). NMR spectrum: δ 6·80–7·70 (m, 6 H, aromatic protons), 6·28 (s, 1 H, Ar—CH=), 3·00 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·56 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·35 (s, 3 H, NCH_3). For $C_{19}H_{18}ClFN_2S$ (360·9) calculated: 63·23% C, 5·02% H, 7·76% N, 8·89% S; found: 63·30% C, 5·25% H, 7·67% N, 8·80% S.

Methanesulfonate (monohydrate), m.p. 278–280°C (95% ethanol–ether). For $C_{20}H_{24}Cl$ . . $FN_2O_4S_2$ (475·0) calculated: 50·57% C, 5·09% H, 7·46% Cl, 4·00% F, 5·90% N, 13·50% S; found: 51·08% C, 5·12% H, 7·17% Cl, 4·10% F, 5·96% N, 13·39% S.

3-Hydroxy-10-[4-(3-hydroxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]-thiepin (*I*)

A solution of 15·0 g BBr_3 in 15 ml chloroform was added dropwise over a period of 20 min at 20°C to a solution of 6·5 g base *IVa* in 25 ml chloroform. The mixture was stirred for 5 h at room temperature and left to stand overnight. Under external cooling, it was then combined with 30 ml ethanol and the mixture stirred for further 8 h. On the following day, 40 ml ether was added, the solid product was filtered, suspended in 100 ml dichloromethane and the suspension was

shaken with 100 ml 5% $NaHCO_3$. The dichloromethane layer was dried with $MgSO_4$ and evaporated. The residue crystallized after dissolving in benzene; 4·9 g (71%), m.p. 98–101°C. Further crystallization from a mixture of ethanol and benzene caused no change of melting point. According to analysis, it is a solvate of the base with one half benzene molecule. IR spectrum (Nujol): 810, 830, 862, 890 (2 adjacent and solitary Ar—H), 1059 (CH_2OH), 1142, 1229, 1350 (Ar—OH), 1498, 1578, 1600 (Ar), 2700, 3140 cm^{-1} (N···HO). NMR spectrum (CD_3SOCD_3): δ 7·46 (d, $J = 2.0$ Hz, 1 H, 9-H), 7·34 (d, $J = 8.0$ Hz, 1 H, 6-H), 7·17 (d, $J = 8.0$ Hz, 1 H, 1-H), 7·00 (q, $J = 8.0$; 2·0 Hz, 1 H, 7-H), 6·90 (d, $J = 2.5$ Hz, 1 H, 4-H), 6·68 (q, $J = 8.0$; 2·5 Hz, 1 H, 2-H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (t, $J =$ = 6·0 Hz, 2 H, CH_2O), c. 2·50 (m, 5 NCH_2), 2·40 (s, 3 H, SCH_3), 1·60 (m, 2 H, middle CH_2 of propyl). For $C_{25}H_{31}N_2O_2S_2$ (455·7) calculated: 65·89% C, 6·89% H, 6·15% N, 14·07% S; found: 65·49% C, 6·98% H, 6·09% N, 13·71% S. On using ethanol denatured with toluene, the base crystallized in the form of toluene solvates of varying composition, m.p. 122–125°C or 145 to 148°C. The higher-melting solvate contains according to analysis 1 molecule of toluene per 3 molecules of the base. The mass spectrum supports the presence of toluene and characterizes the base by the molecular ion *m/e* 416 which corresponds to $C_{22}H_{28}N_2O_2S_2$; fragmentation is in agreement with formula *I*. For $C_{22}H_{28}N_2O_2S_2 \cdot 1/3\ C_7H_8$ (447·3) calculated: 65·34% C, 6·91% H, 6·26% N, 14·34% S; found: 65·19% C, 6·93% H, 6·16% N, 14·37% S.

Hemioxalate is formed by neutralization of the base with oxalic acid in ethanol; m.p. 228 to 230°C under decomposition (aqueous ethanol). For $C_{23}H_{29}N_2O_4S_2$ (461·6) calculated: 59·84% C, 6·33% H, 6·07% N, 13·89% S; found: 59·83% C, 6·27% H, 5·86% N, 13·76% S.

Hemifumarate is formed similarly by neutralization of the base with fumaric acid; m.p. 241 to 243°C (aqueous ethanol). For $C_{24}H_{30}N_2O_4S_2$ (474·6) calculated: 60·73% C, 6·37% H, 5·90% N; found: 61·28% C, 6·48% H, 5·98% N.

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