POTENTIAL NONCATALEPTIC NEUROLEPTIC AGENTS: 2,4-DICHLORO- AND 2,4,8-TRICHLORO-10-PIPERAZINO--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS*

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3,5-Dichloro-2-iodobenzoic acid (*IV*), prepared from 3,5-dichloroanthranilic acid (*III*), was transformed in 5 steps into the diphenyl sulfide-2-acetic acids *IXab*. Cyclization resulted in ketones *XVab* which were processed in further 3 steps into the title compounds *Iab* and *IIa*. These products are mild tranquilizers devoid of cataleptic and antiapomorphine activity.

The original synthesis of the noncataleptic neuroleptic agents doclothepin [2-chloro--10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin, ref.[1]] and docloxythepin (2-chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin, ref.[2]) started from the chlorination of anthranilic acid with sulfuryl chloride in ether[3]. This reaction results in a mixture of the desired 5-chloroanthranilic acid with a relatively great amount of 3,5-dichloroanthranilic acid (*III*), which is separated by fractional crystallization. While 5-chloroanthranilic acid was the starting product of the synthesis of the two mentioned compounds, the acid *III* has now been used as the basis for synthesizing the title compounds *Iab* and *IIa*. Compound *Ia* is a further dichloro derivative of perathiepin [10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin]; the following derivatives of perathiepin have been described by our group heterofore: 2,8-dichloro[1], 3,8-dichloro[4], 6,8-dichloro[5], 6,9-dichloro[5] and 7,8-dichloro[6]. Compound *Ia* is simultaneously a 4-chloro derivative of doclothepin, as well as compound *IIa* is a 4-chloro derivative of docloxythepin. For both it was possible to expect the properties of the noncataleptic neuroleptic agents[7]. Compound *Ib*, containing the "neuroleptic substituent" (the atom of chlorine in position 8), represents the first known dichloro derivative of the neuroleptic agent octoclothepin (8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin, ref.[8-10]); for this product it was not possible to exclude beforehand an indication of the cataleptogenic character or at least an increased central depressant activity.

The syntheses of compounds *Iab* and *IIa* used in the individual stages mostly the methods described in the preceding communications[1,2,4-9]. 3,5-Dichloroanthra-

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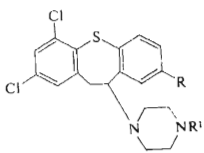
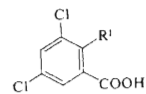


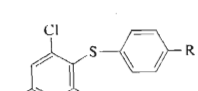
a, R = H
b, R = Cl



I, $R^1 = CH_3$
II, $R^1 = CH_2CH_2OH$

III, $R^1 = NH_2$
IV, $R^1 = I$

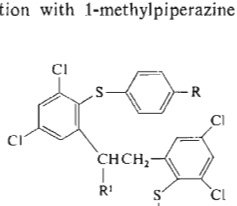
nilic acid (*III*) (ref.[3]) was transformed by diazotization and the following reaction with potassium iodide to 3,5-dichloro-2-iodobenzoic acid (*IV*) which was mentioned in the literature[11,12] (the synthetic procedure was not described). This acid was further condensed with thiophenol and 4-chlorothiophenol giving the acids *Va* and *Vb*. Since the usual procedure for carrying out these reactions[9], *i.e.* in a boiling aqueous solution of potassium hydroxide in the presence of copper as a catalyst, gave only low yields of the desired products, a modified procedure was used consisting in reacting the components in dimethylformamide at 130–140°C in the presence of potassium carbonate and cuprous chloride. The reduction of acids *Vab* was carried out with lithium aluminium hydride in ether and alcohols *VIab* were obtained. Their transformation to the chloro derivatives *VIIab* proceeded by treatment with thionyl chloride in boiling benzene.



V, $R^1 = COOH$
VI, $R^1 = CH_2OH$
VII, $R^1 = CH_2Cl$
VIII, $R^1 = CH_2CN$
IX, $R^1 = CH_2COOH$

For converting the chlorides *VIIab* to nitriles *VIIIab*, reactions with sodium cyanide in dimethylformamide at 35–60°C were used. The nitriles resulted in yields of about 50% and in both cases important amounts of by-products with higher melting points and higher molecular weight were separated. They were identified by the IR and ^{1}H-NMR spectra as the nitriles *Xab*. This formulation assumes that the desired reaction is accompanied partly by alkylation of the formed nitriles *VIIIab* with the starting chlorides *VIIab*; the basicity of sodium cyanide was evidently sufficient for the formation of the needed carbonium anion. In the case of *Xb*, the identity was confirmed by the mass spectrum. We met with products of this type heretofore[7,13,14] and a similar product was obtained in a reaction of benzyl chloride with sodium

cyanide in dimethyl sulfoxide or dimethylformamide[15]. An attempt to suppress the formation of *Xa* by carrying out the reaction of compound *VIIa* with sodium cyanide in boiling acetone in the presence of potassium iodide had the opposite result: *Xa* resulted in a high yield as the only product to be isolated. With regard to the fact that nitriles *Xab* were obtained in larger quantities, they have been used to the synthesis of several further compounds. Their reduction with lithium aluminium hydride in ether gave the primary amines *XIab*; the identity of *XIa* was confirmed by the mass spectrum. This compound afforded by methylation with formaldehyde and formic acid the dimethylamino compound *XIIa*. *XIb* was processed by treatment with chloroacetyl chloride in benzene in the presence of anhydrous sodium carbonate and the intermediate *XIIIb* was subjected without characterization to a substitution reaction with 1-methylpiperazine and gave the piperazine derivative *XIVb*.



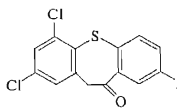
X, $R^1 = CN$ *XII*, $R^1 = CH_2N(CH_3)_2$

XI, $R^1 = CH_2NH_2$ *XIII*, $R^1 = CH_2NHCOCH_2Cl$

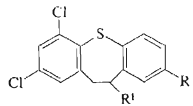
XIV, $R^1 = CH_2NHCOCH_2N\langle\rangle NCH_3$

Hydrolysis of the nitriles *VIIIab* with ethanolic potassium hydroxide gave the acids *IXab* which were cyclized with polyphosphoric acid at 130°C to give the ketones *XVab*. Reduction with sodium borohydride in boiling ethanol resulted in the alcohols *XVIab*; the former (*XVIa*) was transformed to the chloro compound *XVIIa* by treatment with hydrogen chloride in benzene. In the case of the analogous compound *XVIb*, a similar reaction proceeded incompletely and it was necessary to use thionyl chloride to obtain the chloro compound *XVIIb*. Compound *XVIIa* was subjected to substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine and compound *XVIIb* was reacted with 1-methylpiperazine. The reactions were carried out in small amounts of boiling chloroform and the bases *Iab* and *IIa* were obtained as the main products; 2,4-dichlorodibenzo[*b*,*f*]thiepin (*XVIIIa*) (ref.[5])

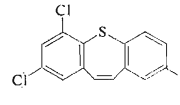
and 2,4,8-trichlorodibenzo[*b,f*]thiepin (*XVIIIb*) resulted as by-products of the simultaneous elimination reactions. Compound *XVIIIb* was prepared for comparison also by dehydrochlorination of *XVIIb* by treatment with boiling 2,4,6-collidine.



XV



XVI, R^1 = OH
XVII, R^1 = Cl



XVIII

Compounds *Iab* and *IIa* were evaluated pharmacologically in the form of salts as potential noncataleptic neuroleptic agents; oral administration was used and the doses given were calculated for the bases. Compound *Ia* is very little toxic; a dose of 600 mg/kg has not lethal effect in mice. Its incoordinating activity in the rotarod test in mice is weak; ED_{50} = 70 mg/kg. In a dose of 100 mg/kg it has not cataleptic action in rats and a dose of 50 mg/kg has not the antiapomorphine effect in rats (influences neither the apomorphine-induced chewing, nor the agitation). Compound *Ib*: LD_{50} > 500 mg/kg; rotarod, ED_{50} = 31·9 mg/kg; no cataleptic effect at a dose of 100 mg/kg. Compound *IIa*: LD_{50} > 600 mg/kg; rotarod, ED_{50} = 158 mg/kg; no cataleptic effect at a dose of 100 mg/kg; no antiapomorphine effect at a dose of 50 mg/kg. These results indicated a very low psychotropic activity of the products and did not warrant any more detailed investigation.

Compounds *XIa*, *XIIa* and *XIVb* were subjected to a general pharmacological screening in the affiliated unit of this institute at Rosice n/L (Dr M. Bartošová). They proved a very low toxicity (LD_{50} > 2500 mg/kg orally in mice) and inactivity in doses of 300 mg/kg orally in the tests directed to neurotropic and cardiovascular activities.

The products obtained were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus faecalis*. *XIVb* 100; *Staphylococcus pyogenes aureus*, *XIVb* 100; *Mycobacterium tuberculosis* H37Rv, *Ia* 12·5, *IIa* 12.5, *XIa* 25, *XIVb* 6·25; *Saccharomyces pasterianus*, *Ia* 12·5, *IIa* 6·2, *XIa* 100, *XIIa* 100, *XIVb* 100; *Trichophyton mentagrophytes*, *Ia* 12·5, *IIa* 6·2, *XIa* 100, *XIIa* 100, *XIVb* 100; *Candida albicans*, *Ia* 100, *IIa* 100, *XIa* 100, *XIIa* 100, *XIV*b 100; *Aspergillus niger*, *Ia* 50, *IIa* 100, *XIVb* 100. The relatively high activity of the piperazine derivatives *Ia* and *IIa* towards *Mycobacterium tuberculosis*, *S. pasterianus* and *T. mentagrophytes* is considered to be worth mentioning.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487 C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds and composition of the reaction mixtures was checked by chromatography on thin layers of silica gel (Silufol).

3,5-Dichloro-2-iodobenzoic Acid (*IV*)

A solution of 103 g 3,5-dichloroanthranilic acid[3], 35 g $NaNO_2$ and 100 ml 5M-NaOH in 800 ml water was slowly added to a stirred and cooled solution of 165 ml hydrochloric acid in 650 ml water (0—5°C). The formed solution of the diazonium salt was stirred for 30 min with cooling and then added over 30 min to a stirred solution of 125 g KI and 37·5 ml H_2SO_4 in 200 ml water. The mixture was slowly heated to 50°C, stirred for 30 min at this temperature which was then raised to 100°C and iodine was removed by steam distillation. After 2 h the mixture was cooled, treated with 7·0 g $Na_2S_2O_5$ and allowed to stand overnight. The precipitated product was filtered, washed with water and dried *in vacuo*; 148 g (94%), m.p. 175—180°C. Analytical sample, m.p. 183·5—185°C (aqueous ethanol). ^{1}H-NMR spectrum (CD_3OD): δ 7·74 (mcs, J = 3·0 Hz, 1 H, 6-H), 7·55 (mcs, J = 3·0 Hz, 1 H, 4-H). For $C_7H_3Cl_2IO_2$ (316·9) calculated: 26·53% C, 0·95% H, 22·37% Cl, 40·05% I; found: 26·96% C, 1·04% H, 22·58% Cl, 39·60% I.

3,5-Dichloro-2-(phenylthio)benzoic Acid (*Va*)

A stirred solution of 63·4 g *IV* and 26·6 g thiophenol in 40 ml dimethylformamide was slowly treated with 31·5 g K_2CO_3, then with 5·0 g CuCl. The mixture was heated to 130—140°C and kept for 4 h at this temperature. After cooling to 80°C the mixture was diluted with 500 ml water and acidified with 50 ml 5M-HCl. After cooling and standing overnight the product was filtered and recrystallized from aqueous ethanol; 46·4 g (78%), m.p. 135—138°C. Analytical sample, m.p. 141—143°C (benzene). IR spectrum (KBr): 708, 750, 892 (5 adjacent and solitary Ar—H), 925, 1277, 1685, 1705 (ArCOOH), 1484, 1540, 1570, 1583 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 11·26 (s, disappears after ^2H_2O, 1 H, COOH), 7·72 (m, 2 H, 4,6-H_2), 7·25 (s, 5 H, C_6H_5). For $C_{13}H_8Cl_2O_2S$ (299·2) calculated: 52·19% C, 2·70% H, 23·70% Cl, 10·72% S; found: 52·42% C, 2·82% H, 23·55% Cl, 10·80% S.

3,5-Dichloro-2-(4-chlorophenylthio)benzoic Acid (*Vb*)

A mixture of 94·8 g *IV*, 52·5 g 4-chlorothiophenol, 70 ml dimethylformamide, 52 g K_2CO_3 and 8·25 g CuCl was processed similarly like in the preceding case and gave 83·2 g (83%) product melting at 157—161°C. Analytical sample, m.p. 158—161°C (aqueous ethanol). UV spectrum: λ_{max} 251 nm (log ε 4·16), infl. 285 nm (3·76). IR spectrum: 822, 880 (2 adjacent and solitary Ar—H), 900, 1241, 1272, 1693, 2630 (ArCOOH), 1479, 1548, 1563 cm^{-1} (Ar). For $C_{13}H_7Cl_3O_2S$ (333·6) calculated: 46·80% C, 2·12% H, 31·88% Cl, 9·61% S; found: 46·96% C, 2·11% H, 31·69% Cl, 9·97% S.

3,5-Dichloro-2-(phenylthio)benzyl Alcohol (*VIa*)

A solution of 61·5 g *Va* in 400 ml ether was slowly added to a stirred suspension of 16 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 2·5 h. After cooling it was decomposed with 16 ml 20% NaOH and 50 ml water added dropwise, 16 g K_2CO_3 were added and the mixture was filtered after 1 h standing. The solid was washed with ether and the filtrate was evaporated. The residue crystallized by standing; 49·6 g (87%), m.p. 53—57°C. Analytical sample, m.p. 58—60°C (cyclohexane–light petroleum). IR spectrum: 683, 730, 865 (5 adjacent and solitary Ar—H), 1056 (CH_2OH), 1478, 1547, 1570 (Ar), 3320 cm^{-1} (OH). For $C_{13}H_{10}Cl_2OS$ (285·2) calculated: 54·75% C, 3·54% H, 24·86% Cl, 11·24% S; found: 55·10% C, 3·56% H, 24·68% Cl, 11·32% S.

3,5-Dichloro-2-(4-chlorophenylthio)benzyl Alcohol (*VIb*)

Vb (33·3 g) was reduced with 7·6 g $LiAlH_4$ in 270 ml ether similarly like in the preceding case; 29·5 g (92%), m.p. 98—105°C. Analytical sample, m.p. 110—112°C (cyclohexane). IR spectrum: 813, 860 (2 adjacent and solitary Ar—H), 1009 (CH_2OH), 1544, 1569 (Ar), 3250 cm^{-1} (OH). For $C_{13}H_9Cl_3OS$ (319·6) calculated: 48·85% C, 2·84% H, 33·28% Cl, 10·03% S; found: 48·86% C, 2·84% H, 33·09% Cl, 10·03% S.

3,5-Dichloro-2-(phenylthio)benzyl Chloride (*VIIa*)

A solution of 44·4 g *VIa* in 80 ml benzene was stirred and treated over 20 min with a solution of 37 g $SOCl_2$ in 25 ml benzene at 25—30°C. The mixture was stirred for 1 h at 50—60°C and refluxed for 1·5 h. The solvent and the excess of $SOCl_2$ were distilled off and the residue crystallized on standing; 45·1 g (96%), m.p. 66—70°C. Analytical sample, m.p. 66—68°C (cyclohexane–light petroleum). For $C_{13}H_9Cl_3S$ (303·6) calculated: 51·42% C, 2·99% H, 10·56% S; found: 51·78% C, 3·22% H, 11·09% S.

3,5-Dichloro-2-(4-chlorophenylthio)benzyl Chloride (*VIIb*)

A reaction of 28·7 g *VIb* and 25 g $SOCl_2$ in 65 ml benzene, carried out similarly like in the preceding case, gave 24·0 g (80%) product, m.p. 50—55°C. Analytical sample, m.p. 57—60°C (light petroleum). ^{1}H-NMR spectrum: δ 7·48 (s, 2 H, 4,6-H_2), 7·18 (d, J = 8·0 Hz, 2 H, 3,5-H_2 in chlorophenyl), 6·90 (d, J = 8·0 Hz, 2 H, 2,6-H_2 in chlorophenyl), 4·74 (s, 2 H, $ArCH_2Cl$). For $C_{13}H_8Cl_4S$ (338·1) calculated: 46·18% C, 2·38% H, 41·95% Cl, 9·48% S; found: 46·43% C, 2·34% H, 41·74% Cl, 9·70% S.

[3,5-Dichloro-2-(phenylthio)phenyl]acetonitrile (*VIIIa*)

A solution of 73·1 g *VIIa* in 105 ml dimethylformamide was treated with 13·8 g NaCN and the mixture was stirred for 2 h at 35°C. It was then diluted with 1000 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue was extracted with 400 ml ethanol at 60—70°C. The undissolved component was filtered off; 18·5 g (29%) *Xa*, m.p. 151—154°C (for further characterization, *cf.* the following paragraph.) The ethanolic extract was evaporated under reduced pressure and *VIIIa* crystallized; 34·1 g (50%), m.p. 106—111°C. Analytical sample, m.p. 111—114°C (cyclohexane). IR spectrum (KBr): 689, 741, 860 (5 adjacent and solitary Ar—H), 1480, 1549, 1574 (Ar), 2245 cm^{-1} (R—CN). ^{1}H-NMR spectrum: δ 7·12 (s, 2 H, 4,6-H_2), 7·15 and 6·98 (2 m, 5 H, C_6H_5), 3·90 (s, 2 H, $ArCH_2CN$). For $C_{14}H_9Cl_2NS$ (294·3) calculated: 57·14% C, 3·08% H, 24·10% Cl, 4·77% N, 10·89% S; found: 57·45% C, 3·19% H, 24·09% Cl, 4·56% N, 11·00% S.

2,3-Bis[3,5-dichloro-2-(phenylthio)phenyl]propionitrile (*Xa*)

A mixture of 10·0 g *VIIa*, 16 ml acetone, 2·5 g NaCN and 0·5 g KI was stirred and refluxed for 5 h. The solid was filtered off, washed with acetone and benzene and the combined filtrates were evaporated under reduced pressure giving a solid residue; 7·8 g (85%) crude *Xa*, m.p. 142 to 151°C. Analytical sample, m.p. 152—154°C (ethanol–cyclohexane). The compound is identical with the by-product of the preceding experiment. ^{1}H-NMR spectrum: δ 6·60—7·80 (m, 14 H, Ar—H), 5·08 (t, J = 4·0 Hz, 1 H, ArCHCN), 3·36 (d, J = 4·0 Hz, 2 H, $ArCH_2$). For $C_{27}H_{17}Cl_4NS_2$ (561·4) calculated: 57·76% C, 3·05% H, 25·26% Cl, 2·49% N, 11·43% S; found: 58·06% C, 3·04% H, 25·47% Cl, 2·45% N, 11·27% S.

[3,5-Dichloro-2-(4-chlorophenylthio)phenyl]acetonitrile (*VIIIb*)

A mixture of 20·4 g *VIIb*, 6·0 NaCN, 40 ml dimethylformamide and 16 ml water was stirred for 1 h at 60°C and for 4 h at 35—40°C and then diluted with 100 ml water, the solid was filtered off and extracted with 500 ml boiling ethanol. After cooling to 30°C, the separated solid was filtered; 7·3 g (39%) 2,3-bis[3,5-dichloro-2-(4-chlorophenylthio)phenyl]propionitrile (*Xb*), m.p. 152—153°C. Analytical sample, m.p. 152—153°C (cyclohexane–ethanol). Mass spectrum, *m/e*: 626·8776 (M^+ corresponding to $C_{27}H_{15}Cl_6NS_2$), 484. UV spectrum: λ_{max} 248 nm (log ε 4·53), infl. 288 nm (3·88). IR spectrum: 812, 833, 865 (2 adjacent and solitary Ar—H), 1 550, 1 572 (Ar), 2 230 cm^{-1} (CN). ^{1}H-NMR spectrum: δ 6·60—7·60 (m, 12 H, Ar—H), 5·00 (*t*, 1 H, ArCHCN), 3·30 (d, 2 H, $ArCH_2$). For $C_{27}H_{15}Cl_6NS_2$ (630·3) calculated: 51·45% C, 2·40% H, 33·75% Cl, 2·22% N, 10·17% S; found: 51·51% C, 2·42% H, 33·62% Cl, 1·94% N, 10·02% S.

The ethanolic mother liquor was evaporated under reduced pressure nad the residue crystallized; 10·2 g (52%) of *VIIIb*, m.p. 108—114°C. Analytical sample, m.p. 118—120°C (cyclohexane–light petroleum). IR spectrum: 820, 850, 870, 890 (2 adjacent and solitary Ar—H), 1 479, 1 548, 1 571, 3 070 (Ar), 2 245, 2 265 cm^{-1} (CN). ^{1}H-NMR spectrum: δ 7·52 (s, 2 H, 4,6-H_2), 7·18 (d, J = 8·0 Hz, 2 H, 3,5-H_2 in chlorophenyl), 6·90 (d, J = 8·0 Hz, 2 H, 2,6-H_2 in chlorophenyl), 3·90 (s, 2 H, $ArCH_2$). For $C_{14}H_8Cl_3NS$ (328·6) calculated: 51·16% C, 2·45% H, 32·37% Cl, 4·26% N, 9·76% S; found: 50·97% C, 2·41% H, 32·17% Cl, 4·15% N, 9·90% S.

2,3-Bis[3,5-dichloro-2-(phenylthio)phenyl]propylamine (*XIa*)

A mixture of 2·0 g $LiAlH_4$, 125 ml ether and 11·2 g *Xa* was refluxed for 2·5 h. Under cooling it was decomposed by a slow addition of 20 ml 20% NaOH and 6 ml water, 50 ml ether and 3 g K_2CO_3 were added and the mixture stirred for 30 min. The solid was filtered off, washed with ether and the filtrate was evaporated. The oily base was dissolved in 25 ml ethanol and the solution neutralized with a solution of HCl in ether. Addition of 50 ml ether precipitated the hydrochloride; 10·6 g (88%), m.p. 225—229°C (ethanol–ether). Mass spectrum, *m/e*: 565 (M^+ corresponding to $C_{27}H_{21}Cl_4NS_2$), 535, 456, 38, 36. For $C_{27}H_{22}Cl_5NS_2$ (601·9) calculated: 53·88% C, 3·68% H, 29·45% Cl, 2·33% N, 10·66% S; found: 54·27% C, 3·82% H, 29·22% Cl, 2·31% N, 10·66% S.

2,3-Bis[3,5-dichloro-2-(4-chlorophenylthio)phenyl]propylamine (*XIb*)

Xb (30·8 g) was reduced with 5·0 g $LiAlH_4$ in 375 ml ether similarly like in the preceding case and gave 29·0 g (94%) of a base, m.p. 45—52°C. Analytical sample, m.p. 94—97°C (cyclohexane–light petroleum). UV spectrum: λ_{max} 250·5 nm (log ε 4·50), infl. 285 nm (3·95). For $C_{27}H_{19}Cl_6NS_2$ (634·3) calculated: 2·21% N, 10·11% S; found: 1·92% N, 10·21% S.

Hydrochloride, m.p. 252—253° (ethanol–ether). For $C_{27}H_{20}Cl_7NS_2$ (670·8) calculated: 48·34% C, 3·00% H, 2·09% N, 9·56% S; found: 47·87% C, 2·94% H, 2·11% N, 9·40% S.

N,N-Dimethyl-2,3-bis[3,5-dichloro-2-(phenylthio)phenyl]propylamine (*XIIa*)

A mixture of 11·2 g *XIa*, 12·5 g 36% formaldehyde, 10·2 g 100% formic acid and 12·5 ml water was stirred for 12·5 h at 100°C. After cooling it was treated with 45 ml 20% NaOH and extracted with chloroform. Processing of the extract gave 11·7 g crude base *XIIa* which was converted to the hydrochloride (treatment with HCl in ethanol–ether); 9·5 g (75%), m.p. 214—218°C. Analytical sample, m.p. 228—230°C (acetone–ethanol–ether). For $C_{29}H_{26}Cl_5NS_2$ (629·9) calculated: 55·29% C, 4·16% H, 28·14% Cl, 2·22% N, 10·18% S; found: 55·18% C, 4·25% H, 28·01% Cl, 2·40% N, 10·55% S.

N-[2,3-Bis(3,5-dichloro-2-[4-chlorophenylthio]phenyl)propyl]-4-methylpiperazinoacetamide (*XIVb*)

A stirred mixture of 25·3 g *XIb*, 90 ml benzene and 3·0 g Na_2CO_3 was treated over 45 min with a solution of 6·0 g chloroacetyl chloride in 25 ml benzene. The mixture was stirred for 1 h at room temperature and for 30 min at 45°C. It was then stirred with 100 ml water and extracted with benzene. The extract was filtered, dried (Na_2SO_4) and evaporated; 18·6 g (66%) crude *XIIIb* which was used without further purification and characterization.

A mixture of 16·8 g crude *XIIIb*, 7·5 g 1-methylpiperazine and 35 ml toluene was refluxed for 3 h and evaporated. The residue was dissolved in 100 ml chloroform, the solution was washed with water and the base was extracted into 1M-H_2SO_4 (4 times 100 ml). The aqueous solution of the sulfate was made alkaline with 20% NaOH and the base extracted with chloroform. Processing of the extract gave 17·6 g (98%) oily base *XIVb* which was converted to bis(hydrogen maleate) (neutralization with maleic acid in ethanol and treatment with ether); 15·9 g, m.p. 124—127°C (ethanol). For $C_{42}H_{39}Cl_6N_3O_9S_2$ (1006·6) calculated: 50·11% C, 3·90% H, 4·17% N; found: 50·02% C, 3·88% H, 4·20% N.

[3,5-Dichloro-2-(phenylthio)phenyl]acetic Acid (*IXa*)

A solution of 34·1 g *VIIIa* in 135 ml ethanol was treated with a solution of 38·2 g KOH in 40 ml water and the mixture was refluxed for 3 h. Ethanol was evaporated and the residue cooled to —3°C which led to crystallization of the potassium salt of *IXa*. After 30 min the salt was filtered, dissolved in water and the solution was acidified with 55 ml 2·5M-HCl. The product was filtered after cooling and standing overnight; 35·4 g (98%), m.p. 178—190°C. Analytical sample, m.p. 197—198°C (aqueous ethanol). IR spectrum: 685, 749, 862 (5 adjacent and solitary Ar—H), 952, 1269, 1699, 2530, 2640, 2666, 2750 (COOH), 1479, 1544, 1572 cm^{-1} (Ar). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·68% C, 3·22% H, 22·64% Cl, 10·24% S; found: 53·73% C, 3·42% H, 22·82% Cl, 9·80% S.

[3,5-Dichloro-2-(4-chlorophenylthio)phenyl]acetic Acid (*IXb*)

VIIIb (44 g) was hydrolyzed with 40 g KOH in 130 ml ethanol and 40 ml water similarly like in the preceding case and gave 44·5 g (95%) crude *IXb*, m.p. 130—152°C. Analytical sample, m.p. 165—168°C (benzene–light petroleum). IR spectrum: 820, 864 (2 adjacent and solitary Ar—H), 920, 1260, 1700, 2650 (COOH), 1478, 1550, 1578, 1600 cm^{-1} (Ar). For $C_{14}H_9Cl_3O_2S$ (347·6) calculated: 48·37% C, 2·61% H, 30·60% Cl, 9·22% S; found: 49·00% C, 2·78% H, 30·00% Cl, 9·11% S.

2,4-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVa*)

IXa (47·6 g) was stirred with polyphosphoric acid (prepared from 110 ml 85% H_3PO_4 and 185 g P_2O_5) for 7·5 h and heated to 130°C. After cooling to 60°C the mixture was decomposed with 500 ml water and extracted with benzene. The extract was washed with 5M-NaOH and water, dried with K_2CO_3 and evaporated; 43·9 g (97%), m.p. 154—165°C. Analytical sample, m.p. 164—166°C (cyclohexane–ethanol). UV spectrum: λ_{max} 235 nm (log ε 4·41), infl. 275 nm (3·85), 327 nm (3·58). IR spectrum: 750, 860 (4 adjacent and solitary Ar—H), 1246 (CO), 1553, 1572, 1590 (Ar), 1682 (ArCO), 3080 cm^{-1} (Ar). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 57·33% C, 2·77% H, 23·95% Cl, 11·07% S.

2,4,8-Trichlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XVb*)

IXb (44·0 g) was cyclized with polyphosphoric acid (from 100 ml 88% H_3PO_4 and 170 g P_2O_5) by heating to 130°C for 10·5 h. The mixture was processed similarly like in the preceding case and gave 40·9 g (97%) crude *XVb*, m.p. 188—198°C. Analytical sample, m.p. 201·5—202·5°C (toluene–ethanol). UV spectrum: λ_{max} 233 nm (log ε 4·46), infl. 267·5 nm (3·95), infl. 292 nm (3·60), 337 nm (3·60). IR spectrum: 820, 868, 905 (2 adjacent and solitary Ar—H), 1 550, 1 568, 1 577 (Ar), 1 672 cm^{-1} (ArCO). For $C_{14}H_7Cl_3OS$ (329·6) calculated: 51·01% C, 2·14% H, 32·27% Cl, 9·72% S; found: 51·27% C, 2·10% H, 32·60% Cl, 9·80% S.

2,4-Dichloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XVIa*)

A mixture of 43·9 g *XVa*, 550 ml ethanol and 20 g $NaBH_4$ was stirred and refluxed for 3·5 h. Ethanol was evaporated, the residue diluted with 300 ml water and extracted with benzene. Processing of the extract gave 40·1 g (91%) crude *XVIa*, m.p. 146—149°C. Analytical sample, m.p. 147—150°C (cyclohexane–light petroleum). ^{1}H-NMR spectrum (hexadeuterodimethyl sulfoxide): δ 7·00—7·50 (m, 6 H, Ar—H), 5·02 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·30 (m, 3 H, $ArCH_2$ and OH). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·58% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·63% C, 3·27% H, 23·94% Cl, 11·10% S.

2,4,8-Trichloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XVIb*)

XVb (28 g) was reduced with 15 g $NaBH_4$ in 400 ml boiling ethanol similarly like in the preceding case; 27·2 g (97%) crude *XVIb*, m.p. 150—156°C. Analytical sample, m.p. 158—160°C (cyclohexane–ethanol). IR spectrum: 825, 868, 894 (2 adjacent and solitary Ar—H), 1110 (CHOH), 1520, 1552, 1570 (Ar), 3275 cm^{-1} (OH). ^{1}H-NMR spectrum (hexadeuterodimethyl sulfoxide): δ 7·00—7·50 (m, 5 H, Ar—H), 5·85 (d, disappears after ^2H_2O, 1 H, OH), 5·08 (m, 1 H, Ar—CH—O), 3·30 (m, 2 H, $ArCH_2$). For $C_{14}H_9Cl_3OS$ (331·6) calculated: 50·70% C, 2·74% H, 32·07% Cl, 9·67% S; found: 50·66% C, 2·71% H, 31·80% Cl, 9·80% S.

2,4,10-Trichloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIIa*)

A solution of 40·1 g *XVIa* in 2000 ml benzene was treated with 40 g $CaCl_2$ (powder) and saturated for 6 h with anhydrous HCl at 20°C. After standing for 12 h the mixture was filtered and the filtrate evaporated. The residue was induced to crystallize by a mixture of cyclohexane and light petroleum; 30·2 g (71%), m.p. 118—124°C. Analytical sample, m.p. 122—124°C (cyclohexane–light petroleum). For $C_{14}H_9Cl_3S$ (315·6) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·58% C, 2·80% H, 33·60% Cl, 10·46% S.

2,4,8,10-Tetrachloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIIb*)

A solution of 8·7 g *XVIb* in 35 ml benzene was stirred and treated dropwise over 45 min with a solution of 5·5 ml $SOCl_2$ in 5 ml benzene at 50—60°C. The mixture was refluxed for 1 h, filtered with charcoal and the filtrate evaporated under reduced pressure. The residue was crystallized from 20 ml benzene; 4·7 g (52%) pure *XVIIb*, m.p. 148—150°C. Analytical sample, m.p. 148·5 to 150·5°C (benzene). For $C_{14}H_8Cl_4S$ (350·1) calculated: 48·03% C, 2·30% H, 40·51% Cl, 9·15% S; found: 47·92% C, 2·24% H, 40·03% Cl, 9·00% S.

2,4-Dichloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

A mixture of 9·5 g *XVIIa*, 30 g 1-methylpiperazine and 25 ml chloroform was refluxed for 8 h.

The mixture was diluted with 200 ml benzene, washed with water and the base was extracted with 5M-HCl. The separated suspension of the hydrochloride in the aqueous layer was made alkaline with 20% NaOH and the base was extracted with benzene. Processing of the extract gave 7·1 g (63%) oily base *Ia* which crystallized after treatment with a drop of cyclohexane, m.p. 124—125°C (cyclohexane–light petroleum). ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). For $C_{19}H_{20}Cl_2N_2S$ (379·4) calculated: 60·15% C, 5·32% H, 18·70% Cl, 7·38% N, 8·45% S; found: 59·94% C, 5·33% H, 18·80% Cl, 7·44% N, 8·59% S.

Maleate, m.p. 97—101°C (acetone–ether). For $C_{23}H_{24}Cl_2N_2O_4S$ (495·4) calculated: 55·76% C, 4·88% H, 14·31% Cl, 5·65% N, 6·47% S; found: 55·77% C, 4·93% H, 13·94% Cl, 5·31% N, 6·34% S.

2,4-Dichloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIa*)

A mixture of 9·5 g *XVIIa*, 40 g 1-(2-hydroxyethyl)piperazine and 25 ml chloroform was processed similarly like in the preceding case and gave 8·7g (71%) oily base which crystallized from cyclohexane, m.p. 105—107°C. ^{1}H-NMR spectrum: δ 7·00—7·60 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·52 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00 (bs, 1 H, OH), *c.* 2·50 (m, 10 H, 5 NCH_2). For $C_{20}H_{22}Cl_2N_2OS$ (409·4) calculated: 58·68% C, 5·42% H, 17·32% Cl, 6·84% N, 7·83% S; found: 58·62% C, 5·49% H, 17·33% Cl, 6·78% N, 7·86% S.

Maleate, m.p. 152—153°C (ethanol–ether). For $C_{24}H_{26}Cl_2N_2O_5S$ (525·4) calculated: 54·86% C, 4·99% H, 13·50% Cl, 5·33% N, 6·10% S; found: 54·88% C, 5·12% H, 13·62% Cl, 5·50% N, 6·30% S.

The organic layer, from which the base was extracted with dilute hydrochloric acid, was evaporated and the residue gave by crystallization from cyclohexane 0·9 g 2,4-dichlorodibenzo-[*b,f*]thiepin (*XVIIa*), m.p. 126—127°C. IR spectrum: 740, 784, 834, 860, 880 (Ar—H and CH=CH), 1 542, 1 569 cm^{-1} (Ar). The compound was prepared in this laboratory[5] by a different way and the melting point of 125—127°C was reported.

2,4,8-Trichloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

A mixture of 3·5 g *XVIIb*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 11 h and the mixture processed similarly like in the preceding cases. There were obtained only 1·5 g (36%) oily base which was neutralized with maleic acid in ethanol. Treatment with ether gave the crystalline bis(hydrogen maleate), m.p. 150·5—152·5°C (2-propanol). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 7·00—7·60 (m, 5 H, Ar—H), 2·80—4·10 (m, 11 H, $ArCH_2$. CHAr and 4 NCH_2, of piperazine), 2·70 (s, 3 H, NCH_3). For $C_{27}H_{27}Cl_3N_2O_8S$ (645·9) calculated: 50·20% C, 4·21% H, 16·47% Cl, 4·34% N, 4·96% S; found: 50·44% C, 4·15% H, 16·27% Cl, 4·44% N, 5·17% S.

The organic layer, from which the base was extracted with dilute hydrochloric acid, was evaporated and the residue crystallized from a mixtue of cyclohexane and benzene; 2·2 g (35%) 2,4,8-trichlorodibenzo[*b,f*]thiepin (*XVIIIb*), m.p. 186—189°C. UV spectrum: λ_{max} 226·5 nm (log ε 4·56), 268 nm (4·36), 302 nm (3·67). For $C_{14}H_7Cl_3S$ (313·6) calculated: 53·61% C, 2·25% H, 33·92% Cl, 10·22% S; found: 53·33% C, 2·32% H, 33·57% Cl, 9·94% S. The same compound was obtained by refluxing 0·55 g *XVIIb* with 10 ml 2,4,6-collidine for 5 h; 0·40 g (85%) *XVIIIb*, m.p. 186·5 to 188·5°C (cyclohexane).

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