POTENTIAL NONCATALEPTIC NEUROLEPTIC AGENTS: 2,3-DICHLORO-10-[4-(2-HYDROXYETHYL)PIPERAZINO]-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN

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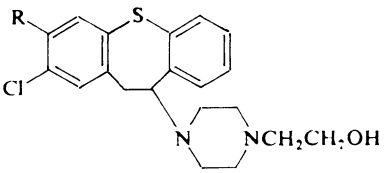
The 6-nitro derivative *V*, obtained by nitration of 3,4-dichlorobrombenzene, was transformed *via* the amine *VI* and nitrile *VII* to 2-bromo-4,5-dichlorobenzoic acid (*IX*). Its reaction with thiophenol in 3-methyl-1-butanol in the presence of potassium carbonate and catalytic amounts of copper and cuprous iodide afforded 4,5-dichloro-2-(2-phenylthio)benzoic acid (*Xa*) which was reduced to the alcohol *XIa*. The transformation to the homologous acid *XIVa* proceeded *via* noncharacterized intermediates *XIIa* and *XIIIa*. The cyclization with polyphosphoric acid at 150°C resulted in 2,3-dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XV*) which was reduced to the alcohol *XVI*. Treatment with hydrogen chloride gave the unstable chloro derivative *XVII* whose substitution reaction with 1-(2-hydroxyethyl)piperazine led to the title compound *II*. Its dimethanesulfonate showed properties of a little toxic and noncataleptic tranquillizer. Because it does not influence the dopamine metabolism in rat brain in a rather high dose, it cannot be considered a neuroleptic.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*, *f*]thiepin (*I*, docloxythepin) in the form of succinate[1,2] displayed properties of a noncataleptic neuroleptic agent[3-9] with a somewhat similar pharmacological profile like the well-known agent clozapine[10]. Modifications of its structure may be considered an approach to further potential noncataleptic neuroleptics. One of these modifications is the introduction of a further chlorine atom in the tricyclic skeleton. Out of the monochloro derivatives of docloxythepin, only the 4-chloro derivative[11] is known so far which, indeed, is noncataleptic and little toxic but at the same time it does not show any indication of activity typical for neuroleptics or tranquillizers. The 8-chloro derivative of the closely related N-methyl analogue[12] was further prepared but its profile is distorted by the fact that the second chlorine atom is located just in position 8 and has thus the function of a "neuroleptic substituent" (it is known that substitution in position 8 in the 10-piperazino-10,11-dihydrodibenzo[*b*, *f*]thiepin derivatives exerts a cataleptic effect enhancing influence[13-15]). In the present communication, the synthesis of the new 3-chloro derivative of docloxythepin *II* is described and a short report on its pharmacology is presented. The location of the second chlorine atom in position 3 has its good reason in the fact that this atom blocks the possiblity

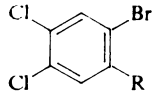
of metabolic hydroxylation proceeding in this series extensively just into this position[16].



I, R = H
II, R = Cl

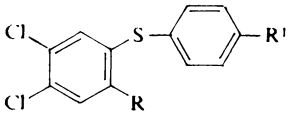
In the synthesis of *II* an analogy of the procedure has been used which has repeatedly been described for the preparation of compounds of this series (*e.g.*[2,11,12]). Attempts to use (4,5-dichloro-2-nitrophenyl)acetic acid[17] or 2-amino-4,5-dichloroacetophenone[18] as intermediates were discontinued due to experimental difficulties. Finally, a multi-step synthesis was chosen starting from the bromination of 1,2-dichlorobenzene to 3,4-dichlorobromobenzene (*III*). The preparation of compound *III* was described by diazotization and Sandmeyer reaction from 4-bromo-2-chloroaniline[19] on the one hand, and from 3,4-dichloroaniline[20] on the other. The bromination of 1,2-dichlorobenzene has been carried out without solvent at 110°C in the presence or iron as a catalyst (method[21,22]). The wanted product was obtained in a yield of about 80% and from the distillation residue 1,2-dibromo-4,5-dichlorobenzene (*IV*) was isolated. 3,4-Dichlorobromobenzene (*III*) was nitrated with 99% nitric acid on the one hand, and by the mixed acid on the other, at a maximum temperature of 50°C, and both methods gave in a satisfactory yield the desired 2-bromo-4,5-dichloronitrobenzene (*V*). This compound was reduced to 2-bromo-4,5-dichloroaniline (*VI*) (its preparation was described by bromination of 3,4-dichloroacetanilide and by the following hydrolysis[23]); the reduction has been carried out (yields of 60 to 70%) by the Bechamp method, *i.e.*with iron in boiling ethanol in the presence of a small amount of hydrochloric acid (method[24,25]), with iron in boiling aqueous ethanol in the presence of ammonium chloride (method[26,27]) and finally with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and charcoal (method[28,29]). The obtained aniline derivative *VI* was further converted by the Sandmeyer method to 2-bromo-4,5-dichlorobenzonitrile (*VII*) (method[30-32]). We did not succeed in preparing the nitrile *VII* in a pure state (neither by sublimation, nor by crystallization). The identity of the impurity was solved only in the next stage which was the hydrolysis of the crude nitrile with a boiling mixture of acetic acid and diluted sulfuric acid. 2,4,5-Trichlorobromobenzene (*VIII*) was isolated in a small amount as the neutral by-product of this reaction (was prepared formerly[33,34] by different procedures) and its identity was corroborated by analysis and spectra. It is evidently

formed in the Sandmeyer reaction due to the presence of chloride ions in the reaction mixture (the solution of cuprous cyanide was obtained by a reaction of cuprous chloride with aqueous solutions of alkali cyanides). The main product of the hydrolysis of the crude nitrile *VII* is the desired 2-bromo-4,5-dichlorobenzoic acid (*IX*).



III, R = H
IV, R = Br
V, R = NO_2
VI, R = NH_2
VII, R = CN
VIII, R = Cl
IX, R = COOH

The acid *IX* was subjected to a reaction with thiophenol in boiling 3-methyl-1-butanol in the presence if potassium carbonate and small amounts if copper and cuprous iodide; 4,5-dichloro-2-(phenylthio)benzoic acid (*Xa*) was obtained in a high yield. The use of 4-chlorothiophenol led to the analogous dichloro acid *Xb*. Both acids were reduced with lithium aluminium hydride in ether, the acid *Xa* was also reduced with sodium dihydridobis(2-methoxyethoxy)aluminate; the alcohols *XIa* and *XIb* were obtained. The alcohol *XIa* was then processed by a reaction wtih thionyl chloride in chloroform in the presence of pyridine at room temperature, the crude chloride *XIIa* was refluxed with sodium cyanide in ethanol and the crude nitrile *XIIIa* was subjected to alkaline hydrolysis to 4,5-dichloro-2-(phenylthio)phenyl acetic acid (*XIVa*); the overall yield (calculated from the alcohol *XIa*) was about 30%.

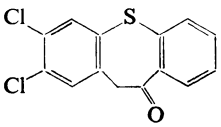


X, R = COOH
XI, R = CH_2OH
XII, R = CH_2Cl
XIII, R = CH_2CN
XIV, R = CH_2COOH

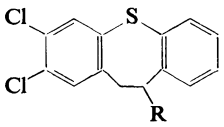
In formulae: *X*–*XIV*: *a*, R^1 = H, *b*, R^1 = Cl

The acid *XIVa* was cyclized in a yield of 80% by heating with polyphosphoric acid to 150°C to 2,3-dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XV*) whose identity was confirmed by spectra. The following reduction with sodium borohydride in ethanol resulted in the alcohol *XVI* which was transformed by treatment with hydrogen chloride in benzene at room temperature to the chloro derivative *XVII*. This compound eliminates during crystallization partly hydrogen chloride and was, therefore,

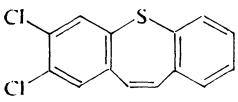
used in the crude state in the final substitution reaction with 1-(2-hydroxyethyl)-piperazine in boiling chloroform. The title compound *II* was obtained in a yield of 62% as a crystalline base and its identity was corroborated by spectra. 2,3-Dichlorodibenzo[*b*,*f*]thiepin (*XVIII*) was obtained as a by-product in a considerable amount and was found identical with the compound obtained previously by our group[35]. The base *II* was transformed to the dimethanesulfonate for pharmacological testing.



XV



XVI, R = OH
XVII, R = Cl



XVIII

The dimethanesulfonate of compound *II* was pharmacologically tested as a potential noncataleptic neuroleptic agent; in all tests the substance was administered orally. The doses given were calculated for the base. The compound is little toxic in mice; a dose of 500 mg/kg is lethal only for 30% of animals (LD_{50} > 500 mg/kg). In the rotarod test the compound displaas a rather high discoordinating activity in mice; ED_{50} = 6·5 mg/kg. In the photo-cell method of Dews a dose of 10 mg/kg inhibits the locomotor activity of mice in the interval of 1 h after the administration to 59·4% of the control value; after 3 h the inhibition of activity was no more significant. The compound may be characterized as noncataleptic because a dose of 50 mg/kg does not produce catalepsy in rats. In the same dose it does not influence catalepsy in rats elicited by perphenazine (*i.e.* compound *II* is not procataleptogenic). Neither has it an antiapomorphine effect: a dose of 50 mg/kg does not influence the apomorphine stereotypies in rats. In a relatively high dose of 80 mg/kg it does not enhance the concentration of dopamine metabolites (homovanillic and 3,4-dihydroxyphenylacetic acid) in rat brain and thus does not influence the dopamine turnover; it cannot, therefore, be considered a neuroleptic agent. It may be characterized only as a noncataleptic tranquillizer.

Compound *II* has a rather high antimicrobial effects in the tests *in vitro* (Dr V. Holá, bacteriological department of this institute): in a concentration of 25 μg/ml it inhibits the growth of *Aspergillus niger*, in concentrations of 12·5 μg/ml the growth of *Saccharomyces pasterianus* and

Trichophyton mentagrophytes and towards some further microorganisms it displays an inhibitory action in concentrations even lower than 12·5 μg/ml: *Streptococcus β-haemolyticus, Streptococcus faecalis, Staphylococcus pyogenes aureus, Proteus vulgaris.*

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 over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Perkin Elmer 298 spectrophotometer and the ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and the composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

3,4-Dichlorobromobenzene (*III*)

A stirred mixture of 650 g 1,2-dichlorobenzene and 45 g Fe was heated to 110°C and treated dropwise at this temperature with 785 g Br_2 over 2·5 h. The mixture was stirred for 2 h at the same temperature, cooled and the solid was filtered off and washed with tetrachloromethane. The filtrate was distilled *in vacuo*; 804 g (80%) *III*, b.p. 80°C/0·5 kPa or 92°C/0·87 kPa. Lit.[19], b.p. 124°C/4·4 kPa. Distillation of the residue gave a small quantity of another homogeneous product, b.p. 120°C/0·72 kPa, m.p. 150–150·5°C (chloroform–ethanol), identified as 1,2-dibromo-4,5-dichlorobenzene (*IV*). ^1H NMR spectrum: δ 7·68 (s, 2 ArH in symmetrically 2,3,5,6-tetrasubstituted benzene). For $C_6H_2Br_2Cl_2$ (304·9) calculated: 23·64% C, 0·66% H, 52·43% Br, 23·16% Cl; found: 23·72% C, 0·65% H, 51·84% Br, 23·10% Cl.

2-Bromo-4,5-dichloronitrobenzene (*V*)

A) *III* (43 g) was slowly added at room temperature to 143 ml stirred 99% HNO_3. The temperature of the mixture rose spontaneously to 50°C; it was maintained by cooling for 10 minat this temperature and then decomposed by pouring into 250 ml water. After cooling the separated product was filtered, washed with water and crystallized from a mixture of chloform and ethanol; 34·1 g (66%), m.p. 58–62°C. Analytical sample, m.p. 62–65°C (chloroform–ethanol). IRspectrum: 900 (solitary Ar—H), 1 330, 1 352, 1 362, 1 530, 1 550 ($ArNO_2$), 1 575, 3 080 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·00 (s, 1 H, 6-H), 7·85 (s, 1 H, 3-H). For $C_6H_2BrCl_2NO_2$ (270·9) calculated: 26·60% C, 0·75% H, 29·50% Br, 26·17% Cl, 5·17% N; found: 26·35% C, 0·70% H, 29·02% Br, 25·96% Cl, 5·32% N.

B) *III* (22·6 g) was slowly added to a stirred mixture of 66 ml 68% HNO_3 and 93 ml 96% H_2SO_4 at room temperature. The mixture was stirred for 3 h at 40–45°C (external cooling until the cessation of the exothermic reaction), cooled and decomposed by pouring into a mixture of ice and water. Processing like under A gave 18·9 g (70%) *V*, m.p. 58–62°C. Nitration of *III* (39·8 g) with a mixture of 50 ml 99% HNO_3 and 70 ml H_2SO_4 under similar conditions gave 59·2 g (almost theoretical yield) of the same product.

2-Bromo-4,5-dichloroaniline (*VI*)

A) A mixture of 15 g *V*, 100 ml ethanol, 15 g Fe and 3 ml hydrochloric acid was stirred and refluxed for 3 h. It was filtered while hot, the filtrate was evaporated *in vacuo*, the residue was decomposed with a solution of Na_2CO_3 and extracted with ether. The extract was dried with

Na_2SO_4, evaporated and the residue was crystallized from a mixture of acetone and aqueous ethanol; 8·2 g (62%), m.p. 80–84°C. Recrystallization gave a product melting at 90–93°C. Lit.[23], m.p. 91–93°C.

B) A mixture of 479 g *V*, 2·6 l ethanol, 50 g NH_4Cl in 900 ml water and 470 g Fe was stirred and refluxed for 20 h. After filtration the solution was evaporated *in vacuo*, the residue was diluted with water and the product was isolated by extraction with ether. Processing of the extract and crystallization of the crude product from a mixture of actone and 60% ethanol gave 286 g (67%) product of the same quality like under *A*.

C) A solution of 15 g *V* in 100 ml ethanol was treated with 2 g charcoal, 7·5 ml 100% $N_2H_4 . H_2O$ and a solution of 0·5 g $FeCl_3$ in 10 ml ethanol, the mixture was stirred and refluxed for 5 h. After cooling the mixture was filtered, the filtrate evaporated *in vacuo*, the residue decomposed with a solution of Na_2CO_3 and extracted with ether. Similar processing of the extract gave 8·8 g (66%) crude *VI*, m.p. 80–85°C, after recrystallization 90–93°C (acetone–aqueous ethanol).

2-Bromo-4,5-dichlorobenzoic Acid (*IX*)

A solution of 120 g *VI* in 800 ml acetic acid was added dropwise into a stirred solution of 51 g $NaNO_2$ in a mixture of 320 ml H_2SO_4 and 350 ml acetic acid at 10°C over 30 min (external cooling). The mixture was then stirred for 2 h at 20°C and added dropwise over 1 h into a stirred mixture, obtained by dissolving 101 g CuCl in a solution of 184 g KCN in 700 ml water and addition of a suspension of 1·76 kg Na_2CO_3 in 2·4 l water, which was heated to 60–70°C. The mixture was stirred for 3 h at 80–85°C, allowed to stand overnight at room temperature, the solid was filtered, extracted with benzene, the extract was washed with water, dilute NaOH and water, dried and evaporated. The residue (104 g) is crude nitrile *VII*. It was dissolved in 450 ml acetic acid, the solution was treated with a solution of 450 ml H_2SO_4 in 450 ml water and the mixture was stirred and refluxed for 16 h. After cooling it was diluted with 1·5 l water and extracted with ether. From this extract the product was transferred by shaking into an excess of 10% aqueous NH_3, the aqueous layer was separated, heated for a short time to 100°C, cooled, acidified with hydrochloric acid and allowed to crystallize; 81·6 g (61%), m.p. 165–166 °C. Analytical sample, m.p. 167–168°C (chloroform–ethanol). UV spectrum: λ_{max} 291·5 nm (log ε 2·95), inflexes at 237 nm (3·97), 284 nm (2·86) and 299 nm (2·89). IR spectrum: 870 (solitary Ar-H), 905, 1 258, 1 300, 1 670, 2 538, 2 590, 2 655, 3 150 (ArCOOH), 1 530, 1 575, 3 080 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·03 (s, 1 H, 6-H), 7·98 (s, 1 H, 3-H). For $C_7H_3BrCl_2O_2$ (269·9) calculated: 31·15% C, 1·12% H, 29·60% Br, 26·27% Cl; found: 31·22% C, 1·11% H, 29·31% Br, 26·00% Cl.

The organic layer after the extraction of *IX* with aqueous NH_3 was washed with dilute hydrochloric acid and water, and processed by distillation. A homogeneous fraction was obtained, boiling at 71°C/13 Pa, and crystallizing from a mixture of chloroform and ethanol, m.p. 141·5 to 142·5°C. It was identified as 2,4,5-trichlorobromobenzene (*VIII*). IR spectrum: 880 (solitary Ar-H), 3 080 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·69 (s, 1 H, 6-H), 7·52 (s, 1 H, 3-H). For $C_6H_2BrCl_3$ (260·3) calculated: 27·68% C, 0·78% H, 30·69% Br, 40·85% Cl; found: 27·37% C, 0·84% H, 30·70% Br, 41·17% Cl. Lit.[33,34], m.p. 138°C, and 139°C, respectively.

4,5-Dichloro-2-(phenylthio)benzoic Acid (*Xa*)

A mixture of 99 g *IX*, 520 ml 3-methyl-1-butanol, 71 g thiophenol, 73 g K_2CO_3, 3·1 g Cu and 3·1 g CuI was stirred and refluxed for 7 h. After cooling it was poured into excessive dilute H_2SO_4 and extracted with ether. From the extract the acid was transferred into the aqueous layer by shaking with excessive 10% aqueous ammonia, the separated aqueous layer was heated for a short

time to 100°C, cooled, acidified with hydrochloric acid and allowed to crystallize in a refrigerator; 104 g (94%) crude *Xa*, m.p. 215–220°C. Analytical sample, m.p. 223°C (acetone–ethanol). UV spectrum: λ_{max} 234·5 nm (log ε 4·37), 264 nm (3·91), 270 nm (3·91), 329 nm (3·51). IR spectrum: 899 (solitary Ar—H), 933, 1 250, 1 310, 1 678, 2 528, 2 595, 3 060 (ArCOOH), 1 520, 1 570, 3 070, 3 090 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·05 (s, 1 H, 6-H), 7·50 (s, 5 H, C_6H_5), 6·68 (s, 1 H, 3-H). For $C_{13}H_8Cl_2O_2S$ (299·2) calculated: 52·19% C, 2·70% H, 23·70% Cl, 10·72% S; found: 52·04% C, 2·71% H, 23·52% Cl, 10·67% S.

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

A mixture of 95 g *IX*, 80g 4-chlorothiophenol, 500 ml 3-methyl-1-butanol, 75 g K_2CO_3, 3·1 g Cu and 3·1 g CuI was processed similarly like in the preceding case; 90·8 g (85%) crude *Xb* which was crystallized from a mixture of acetone and ethanol, m.p. 245°C. UV spectrum: λ_{max} 229 nm (log ε 4·50), 262·5 nm (4·13), 327 nm (3·61), infl. 281 nm (3·92). IR spectrum: 819, 831, 895 (2 adjacent and solitary Ar—H), 895, 1 250, 1 688, 2 520, infl. 3 140 (ArCOOH), 1 520, 1 570 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·03 (s, 1 H, 6-H), 7·60 (s, 4 H, ArH of 4-chlorophe-, nylthio), 6·72 (s, 1 H, 3-H). For $C_{13}H_7Cl_3O_2S$ (333·6) calculated: 46·80% C, 2·12% H, 31·88% Cl 9·61% S; found: 47·07% C, 2·10% H, 31·46% Cl, 9·82% S.

4,5-Dichloro-2-(phenylthio)benzyl Alcohol (*XIa*)

A) *Xa* (71·7 g) was slowly added to a stirred suspension of 24·7 g $LiAlH_4$ in 900 ml ether, the mixture was stirred for 3 h and allowed to stand overnight. It was then slowly treated with 50 ml ethanol under stirring, water was added and the mixture was acidified with hydrochloric acid. The organic layer was washed with a solution of $NaHCO_3$, dried and evaporated; 63·3 g (93%) homogeneous product. Crystallization from a mixture of chloroform and heptane gave the analytical sample, m.p. 103–105°C. IR spectrum: 690, 750, 879 (5 adjacent and solitary Ar—H), 1 045 (CH_2OH), 1 571, 3 065, 3 080 (Ar), 3 205, 3 288 cm^{-1} (OH). ^1H NMR spectrum: δ 7·59 (s, 1 H, 6-H), 7·25 (s, 6 H, remaining ArH), 4·70 (s, 2 H, $ArCH_2O$), 2·18 (bs, 1 H, OH). For $C_{13}H_{10}Cl_2OS$ (285·2) calculated: 54·75% C, 3·54% H, 24·86% Cl, 11·24% S; found: 55·35% C, 3·59% H, 24·46% Cl, 11·56% S.

B) A suspension of 103·6 g *Xa* in 1·2 l benzene was stirred and treated at 15°C with 270 ml 59% sodium dihydridobis(2-methoxyethoxy)aluminate in benzene, the mixture was stirred for 3 h at room temperature and allowed to stand overnight. It was decomposed by a slow addition of 50 ml ethanol (with stirring) and then with a slight excess of 10% NaOH. The organic layer was washed with dilute hydrochloric acid and water, dried and evaporated; 68·2 (69%) crude *XIa* which crystallized from a mixture of chloroform and heptane, m.p. 103–105·5°C.

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

Xb (90·8 g) was reduced similarly with 31·2 g $LiAlH_4$ in 1 150 ml ether; 71·5 g (82%) crude product. A sample was purified by chromatography on Al_2O_3 and the less polar impurity was removed by elution with a 1 : 1 mixture of benzene and light petroleum. The pure *XIb* was eluted with benzene and a mixture of benzene and ether, m.p. 128·5–129°C (acetone–heptane). IR spectrum: 821, 880 (2 adjacent and solitary Ar—H), 1 050 (CH_2OH), 1 492, 1 570, 3 085 (Ar), 3 200, 3 280 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·72 (s, 1 H, 6-H), 7·40 and 7·20 (ABq, J = 8·5 Hz, 2 + 2 H, ArH of 4-chlorophenylthio), 7·30 (s, 1 H, 3-H), 5·48 (t, J = 5·0 Hz, 1 H, OH), 4·53 (d, J = 5·0 Hz, 2 H, $ArCH_2$). For $C_{13}H_9Cl_3OS$ (319·6) calculated: 48·85% C, 2·84% H, 33·27% Cl, 10·03% S; found: 49·04% C, 2·80% H, 33·02% Cl, 9·96% S.

[4,5-Dichloro-2-(phenylthio)phenyl]acetic Acid (*XIVa*)

A stirred solution of 68·2 g *XIa* in 200 ml chloroform and 30 ml pyridine was slowly treated at 15–20°C with 62 g thienyl chloride. The mixture was stirred for 3 h at room temperature and allowed to stand for 48 h. Chloroform was evaporated *in vacuo*, the residue was dissolved in ether, the solution was washed with diluted hydrochloric acid and $NaHCO_3$ solution, dried and evaporated *in vacuo*. The residue (61·9 g, crude *XIIa*) was dissolved in 1·1 l ethanol, the solution was treated with 80 g NaCN and the mixture was stirred and refluxed for 16 h. After cooling the solid was filtered off and the filtrate was evaporated *in vacuo*. The residue (42 g, crude *XIIIa*) was dissolved in 950 ml ethanol, a solution of 170 g KOH in 850 ml water was added and the mixture was stirred and refluxed for 8 h. It was diluted with water, heated with charcoal, filtered and the filtrate was partly evaporated *in vacuo* in order to remove ethanol. The aqueous solution was acidified with hydrochloric acid and allowed to crystallize in a refrigerator. The product was filtered, washed with water and dried *in vacuo*; 20·2 g (27% calculated for *XIa*), m.p. 119–122°C (chloroform–aqueous ethanol). For $C_{14}H_{10}Cl_2O_2S$ (312·2) calculated: 53·68% C, 3·22% H; found: 54·23% C, 3·36% H.

2,3-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XV*)

A mixture of 19·7 g *XIVa* and 200 g polyphosphoric acid was stirred and heated for 4·5 h to 140–150°C. It was then poured into ice and water and the product was extracted with ether. The extract was washed with a solution of NaOH, dried and evaporated *in vacuo*. The residue was crystallized from a mixture of chloroform and ethanol; 16·3 g (88%), m.p. 150–155°C. Analytical sample, m.p. 152–158°C. UV spectrum: λ_{max} 234 nm (log ε 4·33), 328 nm (3·55), infl. 265 nm (3·96). IR spectrum: 765, 875 (4 adjacent and solitary Ar—H), 1 585, 3 050, 3 070 (Ar), 1 667 cm^{-1} (ArCO). ^1H NMR spectrum: δ 8·15 (m, 1 H, 9-H), 7·69 (s, 1 H, 1-H), 7·48 (s, 1 H, 4-H), 7·10 to 7·60 (m, 3 H, 6,7,8-H_3), 4·30 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·74% H, 24·02% Cl, 10·86% S; found: 57·03% C, 2·72% H, 23·80% Cl, 10·96% S.

2,3-Dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XVI*)

A stirred solution of 15·1 g *XV* in 350 ml ethanol was slowly treated with 10·5 g $NaBH_4$ and the mixture was refluxed for 5 h. Ethanol was evaporated, the residue was dissolved in ether, the solution was washed with water, dried and evaporated; 13·4 g (88%), m.p. 124°C (chloroform–ethanol). IR spectrum (KBr): 755, 766, 886 (4 adjacent and solitary Ar—H), 1 080 (CHOH in the ring). 1 455, 1 470, 1 588, 3 060 (Ar), 3 370 cm^{-1} (OH). ^1H NMR spectrum: 7·53 (s, 1 H, 4-H), 7·28 (s, 1 H, 1-H), 7·00–7·50 (m, 4 H, 6,7,8,9-H_4), 5·25 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·22 (2 dd, J = 15·0; 4·0 and 15·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·10 (s, 1 H, OH). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·57% C, 3·40% H, 23·86% Cl, 10·79% S; found: 56·57% C, 3·47% H, 23·61% Cl, 10·93% S.

2,3-Dichloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*)

A solution of 9·0 g *XVI* in 260 ml benzene was treated with 14 g powdered $CaCl_2$ and saturated for 24 h with HCl under stirring at room temperature. After filtration benzene was evaporated and the residue (9·4 g, crude *XVII* which eliminated HCl in an attempt at crystallization of a sample from a mixture of benzene and heptane) was dissolved in 35 ml chloroform, 12·0 g 1-(2-hydroxy, ethyl)piperazine were added and the mixture was refluxed for 8·5 h. The solvent was evaporated-the residue was dissolved in benzene, the solution was washed with water and dilute NaOH and the base was transferred into the aqueous layer by shaking with an excess of 10% H_2SO_4. The

benzene layer was washed with a solution of Na_2CO_3, dried and evaporated; 1·9 g (22%) 2,3-dichlorodibenzo[*b*,*f*]thiepin (*XVIII*), m.p. 113–116°C (chloroform–ethanol). Lit.[35], m.p. 114 to 115°C.

The aqueous acid layer was made alkaline with aqueous NH_3 and the base was extracted with ether. Processing of the extract gave 7·5 g (61%) crude base which was crystallized from a mixture of chloroform and heptane, m.p. 146–148°C. IR spectrum: 750, 757, 890 (4 adjacent and solitary Ar—H), 1 041 (CH_2OH), 1 540, 1 560, 1 585, 3 045, 3 073 (Ar), 3 170 cm^{-1} (OH). ^1H NMR spectrum: δ 7·60 (s, 1 H, 4-H), 7·32 (s, 1 H, 1-H), 7·00–7·40 (m, 4 H, 6,7,8,9-H_4). 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 6·5 Hz, 2 H, CH_2O), 2·98 (bs, 1 H, OH), 2·55 (bm, 10 H, 5 CH_2N). For $C_{20}H_{22}Cl_2N_2OS$ (409·4) calculated: 58·67% C, 5·43% H, 17·32% Cl, 6·84% N, 7·83% S; found: 59·24% C, 5·38% H, 17·12% Cl, 6·48% N, 8·00% S.

Dimethanesulfonate monohydrate, m.p. 169–171°C (96% ethanol–ether). For $C_{22}H_{30}Cl_2.N_2O_7S_3 + H_2O$ (619·6) calculated: 42·64% C, 5·22% H, 11·44% Cl, 4·52% N, 15·52% S; found: 42·60% C, 4·96% H, 11·60% Cl, 4·51% N, 15·67% S.

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