POTENTIAL METABOLITES OF THE NONCATALEPTIC NEUROLEPTICS: SYNTHESIS OF 2-CHLORO-6-HYDROXY(AND METHOXY)-10-[4-(2-HYDROXYETHYL)PIPERAZINO]-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN*

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[5-Chloro-2-(2-methoxyphenylthio)phenyl]acetic acid (*VI*), obtained *via* the acetophenone derivative *IV*, was cyclized to 2-chloro-6-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VIIIa*). 2,10-Dichloro-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*Xa*) was prepared *via* the alcohol *IXa* and its substitution reaction with 1-(2-hydroxyethyl)piperazine gave the compound *III*. Demethylation with boron tribromide in chlorobenzene resulted in the title compound *II* which is a potential metabolite of the noncataleptic neuroleptic agent docloxythepin.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]-thiepin (docloxythepin, *I*) (ref.[1]) is the most interesting noncataleptic neuroleptic agent in the series of 10-piperazinodibenzo[*b,f*]thiepin derivatives; its properties were confirmed by pharmacological and biochemical investigations[2-5] (for preceding references *cf.*[6]). The metabolic studies in rats, carried out heretofore[7,8], are to be considered preliminary. As potential metabolites, all compounds related to substance *I* have to be considered, which can be derived by reactions and mechanisms known as being at disposal to the animal and human organism (oxidation, reduction, acetylation, methylation *etc.*). In our studies we limited ourselves until now to the synthesis of basic potential metabolites with molecules containing at least one nitrogen atom preserved. We have described the synthesis of 16 compounds considered as potential metabolites of docloxythepin (*I*): S-oxide[6], N^4-oxide[6], S,N^4-dioxide[6], O-acetyl derivative[9], 10(11)-dehydro analogue[9], 8-hydroxy and 8-methoxy derivative[10], *cis*- and *trans*-11-hydroxy derivative[9], N^4-desalkyl analogue ("nor"-*I*) (ref.[6]), "nor"-*I* S-oxide[6], 10(11)-dehydro-"nor"-*I* (ref.[9]), 10-(2-aminoethylamino) analogue[6] and its S-oxide[6], 10-amino analogue[6] and its S-oxide[6]). With regard to the fact that in the isomeric 8-chloro series a metabolic hydroxylation to position 6 has been proven[11,12], we considered also in the case of docloxythepin useful to prepare its

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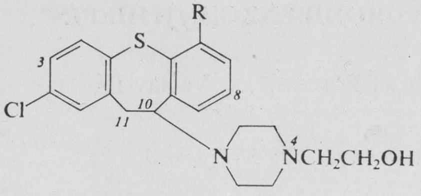
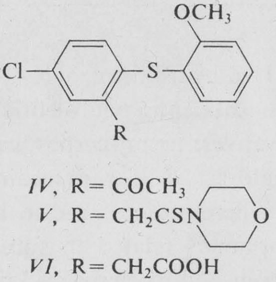
6-hydroxy derivative *II*, as well as the corresponding methyl ether *III*, the description of which forms the object of the present communication.

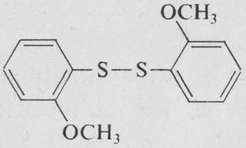


I, R = H
II, R = OH
III, R = OCH_3

Similar methods as in our preceding studies[12-15] were used in the synthesis of compounds *II* and *III*. Heating of 2,5-dichloroacetophenone[13] with 2-methoxythiophenol[16], potassium carbonate and copper to 140°C gave in a moderate yield 5-chloro-2-(2-methoxyphenylthio)acetophenone (*IV*). On the basis of lower solubility, a small amount of bis(2-methoxyphenyl) disulfide (*VII*) (ref.[17]) was isolated. The following Willgerodt reaction of the ketone *IV* with sulfur and morpholine afforded in a yield of 60% the thiomorpholide *V* whose alkaline hydrolysis resulted in [5-chloro-2-(2-methoxyphenylthio)phenyl]acetic acid (*VI*).

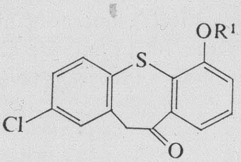


IV, R = $COCH_3$
V, R = CH_2CSN O
VI, R = CH_2COOH



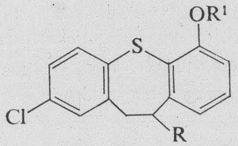
VII

Cyclization of the acid *VI* with polyphosphoric acid in boiling toluene gave in a satisfactory yield 2-chloro-6-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VIIIa*) which was demethylated by heating with pyridine hydrochloride to 200°C. The resulting hydroxy ketone *VIIIb* was reduced with sodium borohydride in aqueous ethanol to the diol *IXb*. An attempt at a direct transformation of this substance to the title compound *II* by treatment with methanesulfonyl chloride in triethylamine and by the following reaction of the crude product with 1-(2-hydroxyethyl)piperazine (for the method, *cf.*[15]) led only to a product of polymeric character which could not be characterized. For this reason, a conventional route was used. The methoxy ketone *VIIIa* was reduced with sodium borohydride to the methoxy alcohol *IXa* which was transformed by treatment with hydrogen chloride in benzene to the dichloro derivative *Xa*. A substitution reaction with 1-(2-hydroxyethyl)piperazine in boiling chloroform afforded the base *III* as the main product; a neutral substance was isolated as a by-product and identified by analyses and spectra as the ethoxy derivative *XIa*. We are thus not dealing here with the usual product of elimination but with a product of ethanolysis of the chloro derivative *Xa*. The only source of ethanol was chloroform which was stabilized by a small addition of this alcohol. Demethylation of the methyl ether *III* was carried out with boron tribromide in chlorobenzene at room temperature; the primary product was subjected to hydrolysis with a boiling dilute ethanolic sodium hydroxide solution and the phenolic base *II* was isolated on the basis of its amphoteric character. The identity of the product was corroborated by the infrared spectrum.



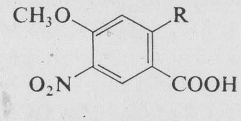
VIIIa, b

$R^1 = CH_3$
$R^1 = H$

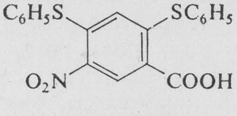


IX, R = OH
X, R = Cl
XI, R = OC_2H_5

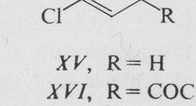
Two synthetic experiments were carried out, directed to the 3-hydroxy derivative of docloxythepin; both were discontinued in the intermediate stage. 2-Chloro-4-methoxy-5-nitrobenzoic acid (*XII*) (ref.[18]), obtained by methanolysis of 2-chloro-4,5-dinitrobenzoic acid, afforded by reaction with thiophenol in a boiling aqueous solution of potassium hydroxide in the presence of copper the acid *XIII*. When the crude acid *XII* was used, which was evidently contaminated with the starting dinitro acid, the reaction with thiophenol in dimethylformamide in the presence of potassium carbonate and copper at 140°C resulted in a double substitution and 2,4-bis(phenylthio)-5-nitrobenzoic acid (*XIV*) was obtained. 2,5-Dichloroanisole (*XV*), prepared in two steps from 2,5-dichloroaniline[19,20], gave by Friedel–Crafts reaction with acetyl chloride and aluminium chloride at 110°C in a moderate yield 2,5-dichloro-4-hydroxy-



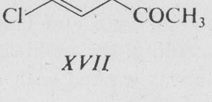
XII, R = Cl
XIII, R = SC_6H_5



XIV



XV, R = H
XVI, R = $COCH_3$



XVII

acetophenone (*XVII*); simultaneously with the Friedel–Crafts reaction demethylation by the action of the excessive aluminium chloride took place. Methylation of the product with dimethyl sulfate in an alkaline solution resulted in 2,5-dichloro-4-methoxyacetophenone (*XVI*), another potential intermediate.

Compound *III* was pharmacologically tested in the form of bis(methanesulfonate) (Dr A. Dlabač, pharmacological department of this institute); it was administered orally and the doses given were calculated for the base. Acute toxicity in mice, $LD_{50} = 440$ mg/kg. Rotarod test in mice, $ED_{50} = 3{\cdot}1$ mg/kg. A dose of 100 mg/kg has not cataleptic effect in rats and does not inhibit the oral stereotypies in rats elicited with apomorphine; there is only some inhibition of the apomorphine-induced agitation. The compound was also tested for its antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, 100; *Staphylococcus pyogenes aureus*, 100; *Escherichia coli*, 50; *Trichophyton mentagrophytes*, 50.

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. The UV spectra (methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^1H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum with the MCH-1320 spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

5-Chloro-2-(2-methoxyphenylthio)acetophenone (*IV*)

A mixture of 44 g 2,5-dichloroacetophenone[13], 34 g 2-methoxythiophenol[16], 38 g K_2CO_3 and 1 g Cu was stirred and heated for 1 h to 140°C. After cooling to 80°C, the mixture was diluted with 10 ml ethanol and refluxed for 3 h. After standing overnight it was diluted with 200 ml water and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated. Crystallization of the residue from methanol gave 4·7 g of bis(2-methoxyphenyl) disulfide (*VII*), m.p. 120–122°C (ethanol); lit.[17], m.p. 119–120°C. Processing of the mother liquor gave 19·3 g (28%) *IV*, m.p. 81–82°C (methanol). UV spectrum: λ_{max} 230 nm (log ε 4·49), 274 nm (3·98), 346 nm (3·59). IR spectrum (KBr): 753, 802, 824, 836, 841, 870, 878 (4 and 2 adjacent and solitary Ar—H), 1 030, 1 043, 1 052, 1 232, 1 277, 1 300 ($ArOCH_3$); 1 480, 1 587, 3 035, 3 055, 3 070 (Ar), 1 678 cm^{-1} (ArCO). ^1H-NMR spectrum: δ 7·75 (mcs, $J = 2{\cdot}0$ Hz, 1 H, 6-H), 6·60–7·60 (m, 6 H, remaining Ar—H), 3·72 (s, 3 H, OCH_3), 2·61 (s, 3 H, $COCH_3$). For $C_{15}H_{13}.ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·58% C, 4·48% H, 12·15% Cl, 10·84% S.

[5-Chloro-2-(2-methoxyphenylthio)phenyl]acetic Acid Thiomorpholide (*V*)

A mixture of 28·5 g *IV*, 4·7 g S and 17 g morpholine was stirred and heated at 145°C for 4·5 h under reflux. After cooling, the mixture was diluted with 150 ml chloroform and filtered with harcoal. The filtrate was washed with water and dilute hydrochloric acid, dried with $MgSO_4$

and evaporated. The residue was crystallized from a mixture of benzene and light petroleum; 23 g (60%), m.p. 153—156°C. Analytical sample, m.p. 162—163°C (benzene). IR spectrum: 759, 820, 843, 880, 887 (4 and 2 adjacent and solitary Ar—H), 1 116, 1 255, 1 281 ($ArOCH_3$), 1 467, 1 484 (CSN and Ar), 1 589, 3 023, 3 050 cm^{-1} (Ar). ^1H-NMR spectrum: δ 7·50 (mcs, 1 H, 6-H), 6·70—7·40 (m, 6 H, remaining Ar-H), 4·35 (s, 2 H, $ArCH_2$), 3·45—4·30 (m, 8 H, 4 CH_2 of morpholine), 3·81 (s, 3 H, OCH_3). For $C_{19}H_{20}ClNO_2S_2$ (393·9) calculated: 57·92% C, 5·12% H, 9·00% Cl, 3·56% N, 16·28% S; found: 58·44% C, 4·91% H, 8·92% Cl, 3·43% N, 15·98% S.

[5-Chloro-2-(2-methoxyphenylthio)phenyl]acetic Acid (*VI*)

V (25·5 g) was added to a solution of 18 g KOH in 45 ml ethanol and the mixture was stirred and refluxed for 2 h (bath of 120°C). After cooling, the mixture was diluted with 250 ml water, the solution filtered and the filtrate acidified with dilute hydrochloric acid. The precipitated product was filtered, washed with water and crystallized from aqueous ethanol; 18·0 g (91%), m.p. 127—132°C. Analytical sample, m.p. 137—138°C (70% ethanol). IR spectrum: 749, 821, 876 (4 and 2 adjacent and solitary Ar—H), 920, 1 698, 2 530, 2 630, 2 705, infl. 3 150 (COOH), 1 027, 1 030, 1 068, 1 238, 1 250, 1 273 ($ArOCH_3$), 1 480, 1 560, 1 580 cm^{-1} (Ar). ^1H-NMR spectrum: δ 11·28 (bs, 1 H, COOH), 6·60—7·40 (m, 7 H, Ar—H), 3·81 (s, 2 H, $ArCH_2CO$), 3·76 (s, 3 H, OCH_3). For $C_{15}H_{13}ClO_3S$ (308·8) calculated: 58·34% C, 4·24% H, 1·48% Cl, 10·39% S; found: 58·84% C, 4·30% H, 1·70% Cl, 9·98% S.

2-Chloro-6-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIIa*)

A mixture of 15·8 g *VI*, 80 ml toluene and 100 g polyphosphoric acid was stirred and refluxed for 11 h. After cooling the mixture was poured into 250 ml ice-cold water and the product extracted with benzene. The extract was washed with water and 3% NaOH, dried with $MgSO_4$ and evaporated; 12·9 g (87%) of *VIIIa*, m.p. 134—137°C. Analytical sample, m.p. 137—139°C (benzene). UV spectrum: λ_{max} 237·5 nm (log ε 4·33), 249 nm (4·13), 267·5 nm (3·93), infl. 281 nm (3·80), infl. 290 nm (3·67), 345 nm (3·71). IR spectrum: 718, 773, 805, 816, 869, 890 (3 and 2 adjacent and solitary Ar—H), 1 258, 1 317 ($ArOCH_3$), 1 562, 1 588 (Ar), 1 667 cm^{-1} (ArCO). ^1H-NMR spectrum: δ 7·75 (mcd, $J = 8·0$; 1·7 Hz, 1 H, 9-H), 7·56 (d, $J = 8·0$ Hz, 1 H, 4-H), 7·40 (mcs, $J = 2·0$ Hz, 1 H, 1-H), 7·21 (t, $J = 8·0$ Hz, 1 H, 8-H), 7·05 (mcd, $J = 8·0$; 2·0 Hz, 1 H, 3-H), 6·99 (mcd, $J = 8·0$; 1·7 Hz, 1 H, 7-H), 4·22 (s, 2 H, $ArCH_2CO$), 3·95 (s, 3 H, OCH_3). For $C_{15}H_{11}ClO_2S$ (290·8) calculated: 61·96% C, 3·81% H, 12·19% Cl, 11·03% S; found: 62·05% C, 4·01 % H, 12·00% Cl, 10·93% S.

2-Chloro-6-hydroxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIIb*)

Pyridine (63 g) was dropped under cooling and stirring into 80 ml hydrochloric acid and the solution evaporated under reduced pressure. *VIIIa* (11·5 g) was added and the mixture was stirred and heated for 1 h to 200°C. After partial cooling the mixture was poured into 800 ml water, the precipitated product was filtered, washed with water, suspended in 250 ml ethanol, the mixture heated for 1 min to boil, cooled and filtered; 8·7 g (80%), m.p. 237—242°C. Analytical sample, m.p. 247—249°C (ethanol). UV spectrum: λ_{max} 237 nm (log ε 4·42), 269 nm (4·06), infl. 282 nm (3·94), infl. 290 nm (3·85), 348 nm (3·78). IR spectrum: 699, 710, 779, 809 (Ar—H), 1 244, 1 288, 1 310 (ArOH), 1 569, 1 590 (Ar), 1 642 (ArCO), 3 150 cm^{-1} (OH). ^1H-NMR, spectrum (CD_3SOCD_3): δ 10·70 (bs, 1 H, OH), 7·70 (d, $J = 8·5$ Hz, 1 H, 4-H), 7·00—7·60 (m, 5 H, remaining Ar—H), 4·21 (s, 2 H, $ArCH_2CO$). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·28% H, 12·81% Cl, 11·58% S; found: 60·93% C, 3·28% H, 12·57% Cl, 11·55% S.

2-Chloro-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IXa*)

A suspension of 11·0 g *VIIIa* in 160 ml ethanol was stirred and treated at 75°C over 15 min with a solution of 7·2 g $NaBH_4$ in 70 ml water containing 1 ml 20% NaOH. The mixture was refluxed for 6 h and a solution was formed. Ethanol was evaporated under reduced pressure, the residue was diluted with 150 ml water and the product was extracted with warm benzene. The extract was washed with 2% NaOH and water, dried ($MgSO_4$) and evaporated; 11·0 g (100%), m.p. 133—135°C. Analytical sample, m.p. 137—138°C (benzene–light petroleum). IR spectrum: 800, 882, 900 (Ar-H), 1 073 (CHOH in the cycle), 1 257 ($ArOCH_3$), 1 570 (Ar), 3 360, 3 390 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·41 (d, $J =$ 8·5 Hz, 1 H, 4-H), 6·90—7·30 (m, 4 H, 1,3,8,9-H_4), 6·71 (m, 1 H, 7-H), 5·45 (bm, 1 H, Ar—CH—O), 3·84 (s, 3 H, OCH_3), 3·55 and 3·20 (2 dd, $J =$ 15·0; 4·00 and 15·0; 8·0 Hz, 2 H, $ArCH_2$), 2·38 (bd, disappears after D_2O, 1 H, OH). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·34% C, 4·48% H, 12·26% Cl, 11·02% S.

2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-6,10-diol (*IXb*)

A suspension of 8·0 g *VIIIb* in 120 ml ethanol was treated with stirring at 70°C with a solution of 3·3 g $NaBH_4$ in 30 ml water containing 0·5 ml 20% NaOH over 15 min. The mixture was refluxed for 5 h, evaporated under reduced pressure, the residue was dissolved in 600 ml water, and the solution acidified with dilute hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 6·8 g (85%), m.p. 143—145°C. Analytical sample, m.p. 145 to 147°C (70% ethanol). IR spectrum: 702, 709, 762, 800, 827, 877 (3 and 2 adjacent and solitary Ar—H), 1 030, 1 169, 1 200 (ArOH), 1 110 (CHOH in the cycle), 1 552, 1 574 (Ar), 3 388, 3 515 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·80 (s, 1 H, ArOH), 7·40 (d, $J =$ 8·5 Hz, 1 H, 4-H), 7·18 (m, 2 H, 1,3-H_2), 7·10 (m, 2 H, 8,9-H_2), 6·75 (mcd, 1 H, 7-H), 5·60 (bs, 1 H, R—OH), 6·50 (m, 1 H, Ar—CH—O), 3·40 and 3·10 (2 dd, 2 H, $ArCH_2$). For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·98% H, 12·72% Cl, 11·50% S; found: 59·87% C, 4·08% H, 12·98% Cl, 11·77% S.

2,10-Dichloro-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*Xa*)

A solution of 14·7 g *IXa* in 250 ml benzene containing 20 g $CaCl_2$ powder was saturated at 20°C with hydrogen chloride for 4 h. $CaCl_2$ was filtered off, washed with benzene and the filtrate evaporated under reduced pressure. The residue crystallized after the addition of hexane; 13·9 g (88%), m.p. 83—85°C. Analytical sample, m.p. 85—87°C (benzene–light petroleum). IR spectrum: 723, 797, 817, 867 (3 and 2 adjacent and solitary Ar—H), 1 257 ($ArOCH_3$), 1 572 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·46 (d, $J =$ 8·0 Hz, 1 H, 4-H), 6·90—7·30 (m, 4 H, 1,3,8,9-H_4), 6·70 (m, 1 H, 7-H), 5·85 (dd, $J =$ 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·85 and 3·52 (2 dd, $J =$ 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·83 (s, 3 H, OCH_3). For $C_{15}H_{12}Cl_2OS$ (311·2) calculated: 57·88% C, 3·89% H, 22·79% Cl, 10·30% S; found: 57·60% C, 3·75% H, 22·59% Cl, 10·18% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A solution of 11·4 g *Xa* and 9·5 g 1-(2-hydroxyethyl)piperazine in 35 ml chloroform was refluxed for 6 h. Chloroform was evaporated under reduced pressure, the residue was diluted with water and extracted with benzene. The extract was washed with water and the base was transferred into the aqueous layer by shaking with 1·25M-H_2SO_4. The separated benzene solution, containing neutral by-products was evaporated and the residue gave by crystallization from cyclohexane a small amount of 2-chloro-10-ethoxy-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIa*), m.p. 105—107°C. Mass spectrum, *m/z* (%): 320 (M^+ corresponding to $C_{17}H_{17}ClO_2S$, 100), 287 (14), 274 (45), 259 (86), 243 (96), 231 (33), 228 (28), 227 (28), 224 (40), 208 (50), 165 (24), 63 (26), 45 (29). IR spectrum: 700, 789, 827, 860, 867 (3 and 2 adjacent and solitary Ar—H), 1 050, 1 078, 1 112, 1 230 ($ArOCH_3$, ROR′), 1 470, 1 580, 3 010, 3 055, 3 070 cm^{-1} (Ar). ^1H-NMR spectrum: δ 6·60—7·50 (m, 6 H, Ar—H), 5·50 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·81 (s, 3 H, OCH_3), 3·58 (q, J = 7·0 Hz, 2 H, OCH_2), 3·50 and 3·12 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 1·27 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{17}H_{17}ClO_2S$ (320·8) calculated: 63·64% C, 5·34% H, 11·05% Cl, 9·99% S; found: 63·80% C, 5·33% H, 11·25% Cl, 9·94% S.

The aqueous solution of the sulfate was made alkaline with NH_4OH and the base extracted with benzene. The extract was washed with water, dried ($MgSO_4$), and evaporated. The oily base *III*, 11·0 g (74%), crystallized from a mixture of benzene and light petroleum, m.p. 136 to 138°C. IR spectrum: 724, 777, 830, 870 (3 and 2 adjacent and solitary Ar—H), 1 048, 1 057 (CH_2OH), 1 151, 1 250, 2 815 ($ArOCH_3$), 1 567, 1 580, 3 050 (Ar), 3 150 cm^{-1} (OH). ^1H-NMR spectrum: δ 7·50 (d, J = 8·5 Hz, 1 H, 4-H), 7·00—7·40 (m, 3 H, 1,3,8,9-H_4), 6·75 (m, 1 H, 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·90 (s, 3 H, OCH_3), 3·60 (t, J = 5·0 Hz, 2 H, CH_2O), 2·98 (bs, 1 H, OH), *c.* 2·50 (bm, 10 H, 5 NCH_2). For $C_{21}H_{25}ClN_2O_2S$ (404·9) calculated: 62·28% C, 6·22% H, 8·76% Cl, 6·92% N, 7·92% S; found: 62·55% C, 6·21% H, 8·95% Cl, 6·78% N, 7·75% S.

Bis(methanesulfonate), m.p. 192—194°C (ethanol–ether). For $C_{23}H_{33}ClN_2O_8S_3$ (597·2) calculated: 46·26% C, 5·57% H, 5·94% Cl, 4·69% N, 16·11% S; found: 46·52% C, 5·62% H, 6·22% Cl, 4·53% N, 15·79% S.

2-Chloro-6-hydroxy-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*II*)

A solution of 3·1 g *III* in 50 ml chlorobenzene was stirred and treated at 15°C over 15 min with a solution of 5·76 g BBr_3 in 30 ml chlorobenzene. The mixture was stirred for 7 h at room temperature, allowed to stand overnight and decomposed by addition of a solution of 1·5 g methanesulfonic acid in 30 ml water, the mixture was stirred and cooled for 5 min and the precipitated solid was filtered with suction. The solid was combined with the aqueous layer of the filtrate, the suspension was made alkaline with 10% NaOH (to pH of 8·0), 80 ml ethanol were added and the mixture was refluxed for 5·5 h. Ethanol was then distilled off, the residue diluted with 60 ml water and the mixture neutralized with 2·0 ml acetic acid. There were obtained 0·45 g (15%) crude base *II*, m.p. 165—168°C. The crude product was extracted with a boiling mixture of 15 ml ethanol and 2 ml water and the undissolved fraction repeatedly crystallized from a mixture of ethanol and benzene, m.p. 197·5—200°C. IR spectrum: 692, 788, 819, 875 (3 and 2 adjacent and solitary Ar—H), 1 093 (CH_2OH), 1 151, 1 248 (ArOH), 1 464, 1 570, 3 010 (Ar), 2 720, 2 780 (NCH_2), 3 350 cm^{-1} (OH). For $C_{20}H_{23}ClN_2O_2S$ (390·9) calculated: 61·45% C, 5·93% H, 9·07% Cl, 7·16% N, 8·20% S; found: 61·02% C, 5·74% H, 9·08% Cl, 6·92% N, 8·58% S.

4-Methoxy-5-nitro-2-(phenylthio)benzoic Acid (*XIII*)

A solution of 2·5 g thiophenol and 5·0 g KOH in 30 ml water was treated with 5·0 g *XII* (ref.[18]) and 0·5 g Cu and the mixture was refluxed for 6 h. The hot mixture was filtered and the filtrate acidified with hydrochloric acid. After standing overnight the product was filtered, washed with water and dried *in vacuo*; 5·1 g (78%), m.p. 234—244°C. Analytical sample, m.p. 248—250°C (ethanol). UV spectrum: λ_{max} 243 nm (infl.) (log ε 4·20), 323 nm (4·02), infl. 340 nm (3·99). IR spectrum: 709, 756, 845, 880 (5 adjacent and solitary Ar-H), 880, 1 319, 1 341, 1 549 ($ArNO_2$), 1 250, 1 341 ($ArOCH_3$), 1 279, 1 679, 2 500—2 600, infl. 3 140 (ArCOOH), 1 506, 1 600), 3 020, 3 040, 3 080 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·44 (s, 1 H, 6-H), 7·55 (s, 5 H, C_6H_5), 6·25 (s, 1 H, 3-H), 3·45 (s, 3 H, OCH_3). For $C_{14}H_{11}NO_5S$ (305·3) calculated: 55·08% C, 3·63% H, 4·56% N, 10·50% S; found: 55·52% C, 3·55% H, 4·79% N, 10·78% S.

5-Nitro-2,4-bis(phenylthio)benzoic Acid (*XIV*)

A mixture of 2·0 g *XII* (contaminated with the starting 2-chloro-4,5-dinitrobenzoic acid) (ref.^{18}), 1·5 g thiophenol, 3·1 g K_2CO_3, 10 ml dimethylformamide and 0·5 g Cu was stirred and heated for 5 h to 140°C. After partial cooling, the mixture was diluted with water, filtered and the filtrate was acidified with hydrochloric acid. After standing overnight the precipitated solid was filtered and crystallized from acetone; 1·2 g, m.p. 309—311°C. UV spectrum: λ_{max} 265 nm (infl.) (log ε 4·08), 288 nm (4·23), 344 nm (4·15). IR spectrum: 706, 744, 870 (5 adjacent and solitary Ar—H), 925, 1 256, 1 678, 2 480, 2 535, 2 568, 2 615, 2 720, 2 775, 3 160 (ArCOOH), 1 334, 1 534 ($ArNO_2$) 1 587, 3 020, 3 070 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·80 (s, 1 H, 6-H), *c.* 7·30 (m, 10 H, 2 C_6H_5), 6·31 (s, 1 H, 3-H). For $C_{19}H_{13}NO_4S_2$ (383·3) calculated: 59·53% C, 3·42% H, 3·66% N, 16·70% S; found: 59·66% C, 3·33% H, 3·65% N, 16·69% S.

2,5-Dichloro-6-hydroxyacetophenone (*XVII*)

A stirred mixture of 16·5 g *XV* (ref.^{19,20}) and 37 g $AlCl_3$ was treated at room temperature over 20 min with 13·0 g acetyl chloride. The mixture was slowly heated to 110°C and maintained at this temperature for 1·5 h. After partial cooling the mixture was poured into 160 g ice and 100 ml hydrochloric acid. The product was extracted with chloroform, the extract dried and evaporated. The residue was dissolved in 50 ml benzene, the solution filtered with charcoal and evaporated. The residue crystallized on standing; 6·8 g (36%), m.p. 144—150°C. Analytical sample, m.p. 151—152°C (benzene). UV spectrum: λ_{max} 220 nm (log ε 4·33), 265 nm (3·99). IR spectrum: 887 (Ar—H), 1 250, 1 298 (ArOH), 1 490, 1 549, 1 590 (Ar), 1 667 (ArCO), 3 090 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 11·40 (bs, 1 H, OH), 7·81 (s, 1 H, 6-H), 7·07 (s, 1 H, 3-H), 2·58 (s, 3 H, $COCH_3$). For $C_8H_6Cl_2O_2$ (205·0) calculated: 46·86% C, 2·95% H, 34·58% Cl; found: 46·97% C, 2·99% H, 34·31% Cl.

2,5-Dichloro-4-methoxyacetophenone (*XVI*)

A solution of 18·7 g *XVII* and 4·5 g KOH in 150 ml water was stirred and treated dropwise at 35—40°C with 11·5 g dimethyl sulfate. The mixture was heated for 2 h to 100°C, treated with 5 ml 20% NaOH for decomposing the excess of dimethyl sulfate, cooled and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated; 12·0 g (60%), m.p. 90·5—91·5°C (methanol). For $C_9H_8Cl_2O_2$ (219·1) calculated: 49·35% C, 3·68% H, 32·37% Cl; found: 50·03% C, 3·76% H, 32·10% Cl.

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