POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENT OCTOCLOTHEPIN; SYNTHESIS OF 8-CHLORO-2,6-DIHYDROXY AND 8-CHLORO-3,6-DIHYDROXY DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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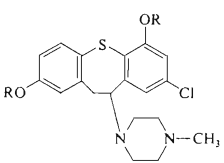
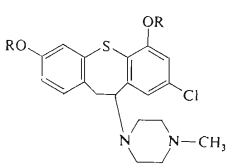
Received September 9th, 1980

[2-(4-Chloro-2-methoxyphenylthio)-5-methoxyphenyl]acetic acid (*V*) and [2-(4-chloro-2-methoxyphenylthio)-4-methoxyphenyl]acetic acid (*XVII*) were synthesized and cyclized to 8-chloro-2,6-dimethoxy (*VII*) and 8-chloro-3,6-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIII*). Two further steps afforded dichlorodimethoxy derivatives *XI* and *XXII* which reacted with 1-methylpiperazine and gave the 8-chloro-2,6-dimethoxy (*II*) and 8-chloro-3,6-dimethoxy derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IV*). Demethylations with boron tribromide resulted in the title compounds *I* and *III* being new potential metabolites of the neuroleptic agent octoclothepin.

With the help of synthetic hydroxylated potential metabolites[1-3] it was possible to prove the metabolic hydroxylation of the neuroleptic agent octoclothepin [clorothepin, 8-chloro derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]-thiepin] (refs[4,5]) in positions 2, 3 and 6 of the skeleton[6-8]. A simultaneous metabolic hydroxylation in two of the mentioned positions was also considered leading



I, R = H
II, R = CH_3

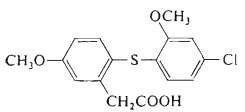


III, R = H
IV, R = CH_3

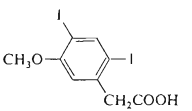
* Part CL in the series Neurotropic and Psychotropic Agents; Part CXLIX: This Journal *46*, 1188 (1981).

to the synthesis of the corresponding 2,3-dihydroxyderivative[9]. In the present communication we describe the preparation of the two remaining possible dihydroxy derivatives of octoclothepin (with hydroxyl groups in positions where the metabolic hydroxylation has already been established), *i.e.* the 2,6-dihydroxy derivative *I* and 3,6-dihydroxy derivative *III*.

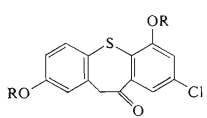
The synthetic methods used in this investigation were similar to those described in preceding papers of this series[1-3,9]. For synthesizing compound *I*, [2-(4-chloro--2-methoxyphenylthio)-5-methoxyphenyl]acetic acid (*V*) was the key intermediate; its easy preparation was enabled by the fact that (3-methoxyphenyl)acetic acid[10] can be iodinated with iodine chloride in acetic acid to (2-iodo-5-methoxyphenyl)-acetic acid[11]. This reaction proceeds satisfactorily (yield of about 80%) but the



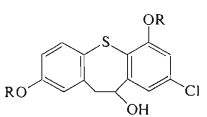
V



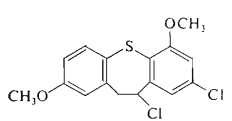
VI



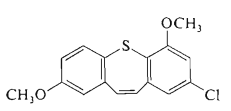
VII, R = CH_3
VIII, R = H



IX, R = CH_3
X, R = H



XI

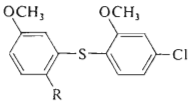


XII

use of an excess of iodine chloride leads to a mixture from which the new (2,4-diiodo-5-methoxyphenyl)acetic acid (*VI*) was isolated. A reaction of (2-iodo-5-methoxyphenyl)acetic acid with 4-chloro-2-methoxythiophenol[3] in a boiling aqueous solution of potassium hydroxide in the presence of copper resulted in the acid *V*.

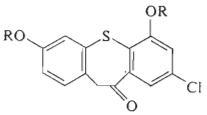
Its cyclization with polyphosphoric acid in boiling toluene afforded 8-chloro-2,6-dimethoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VII*) which was demethylated by heating with pyridine hydrochloride to 200°C to the dihydroxyketone *VIII*. Reduction of ketones *VII* and *VIII* with sodium borohydride in boiling aqueous ethanol gave alcohols *IX* and *X*. It was attempted to transform the compound *X* directly to compound *I* using the method described[12]. This method consists in a reaction of phenol-alcohols with methanesulfonyl chloride in triethylamine and in the treatment of the crude methanesulfonic esters with 1-methylpiperazine; the aliphatic methanesulfonyloxy group should undergo the substitution reaction and the aromatic methanesulfonyloxy group is supposed to undergo aminolysis with regeneration of the phenolic hydroxyl group. In our case this attempt resulted only in inhomogeneous amorphous products. For this reason, the dimethoxy alcohol *IX* was transformed by treatment with hydrogen chloride in benzene to the chloro derivative *XI* which was subjected to a substitution reaction with 1-methylpiperazine. The products were the dimethyl ether of the desired substance *II* on the one hand, and 2-chloro-4,8-dimethoxydibenzo[*b,f*]thiepin (*XII*) (product of elimination) on the other. Demethylation of compound *II* with boron tribromide in chlorobenzene afforded in a low yield the dihydroxy derivative *I* displaying properties corresponding to this type of substances, *i.e.* a high melting point of the base and bands of phenolic hydroxyl group in the IR spectrum.

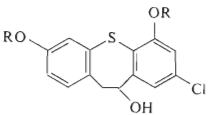
The synthesis of the isomer *III* was more tedious because for preparing [2-(4-chloro--2-methoxyphenylthio)-4-methoxyphenyl]acetic acid (*XVII*) it was necessary to use a sequence of five reactions. A reaction of 2-iodo-4-methoxybenzoic acid[1] with 4-chloro-2-methoxythiophenol[3] in a boiling aqueous solution of potassium hydroxide in the presence of copper gave 2-(4-chloro-2-methoxyphenylthio)-4-methoxybenzoic acid (*XIII*). Its transformation to the homologous acid *XVII* used the conventional procedures leading *via* the alcohol *XIV*, chloride *XV* and nitrile *XVI* which were not isolated. The alkaline hydrolysis of the crude nitrile *XVI* gave the acid *XVII*. The cyclization to the ketone *XVIII*, its demethylation to the dihydroxy ketone *XIX* as well as the reduction to the dimethoxy alcohol *XX* were carried out similarly like in the preceding series. Reduction of the dihydroxy ketone *XIX* gave the triol *XXI* which also was subjected to treatment with methanesulfonyl chloride and to the following reaction with 1-methylpiperazine[12]. The attempt to prepare the compound *III* directly was again unsuccessful. For this reason it was necessary to transform the dimethoxy alcohol *XXI* to the chloro compound *XXII* and carry out the substitution reaction with 1-methylpiperazine. In addition to the base *IV*, the product of elimination was isolated again: 2-chloro-4,7-dimethoxydibenzo[*b,f*]thiepin (*XXIII*). The demethylation of compound *IV* was carried out by treatment with boron tribromide in chlorobenzene. After separation of the mixture formed, the phenolic base *III* was obtained in a low yield; its identity was confirmed by analysis and by the mass and IR spectra.



XIII, R = COOH
XIV, R = CH_2OH

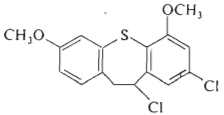
XV, R = CH_2Cl
XVI, R = CH_2CN
XVII, R = CH_2COOH

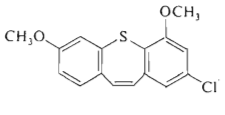




XVIII, R = CH_3
XIX, R = H

XX, R = CH_3
XXI, R = H





XXII

XXIII

The dimethoxy derivatives of octoclothepin *II* and *IV* were pharmacologically tested in the form of dimethanesulfonates for the incoordination effect in the rotarod test in mice and for the cataleptic activity in rats; the doses given were calculated for the bases (Dr J. Metyšová, pharmacological department of this institute). Compound *II* brings about ataxia in mice only in relatively high doses; ED_{50} = 32·8 mg/kg orally. It has practically no cataleptic effect; an oral dose of 50 mg/kg was cataleptic for 10% animals. Compound *IV* is a little more active in the rotarod test: ED_{50} = 7·2 mg/kg orally. In the test of catalepsy it equals the preceding substance: an oral dose of 50 mg/kg brings about catalepsy in 10% animals only. Compound *II* in concentrations of 50—100 μg/ml inhibits *in vitro* the growth of some microorganisms: *Streptococcus* β-*haemolyticus*, *Streptococcus faecalis*, *Staphylococcus pyogenes aureus*, *Escherichia coli*, *Mycobacterium tuberculosis* H37Rv (Dr J. Turinová, bacteriological department of this institute).

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer and the

mass spectrum was recorded on the Varian MAT 44S and MCH-1320 spectrometers. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

(2,4-Diiodo-5-methoxyphenyl)acetic Acid (*VI*)

A solution of 26·7 g (3-methoxyphenyl)acetic acid[10] in 325 ml acetic acid was stirred and treated with 71·5 g iodine chloride; the temperature rose spontaneously to 45—50°C. The mixture was allowed to stand for 7 days at room temperature, poured into 3 l cold water and stirred for 1 h. The precipitated mixture of acids was filtered, washed with water, suspended in 100 ml water and iodine was removed by steam distillation. After cooling the product was filtered again and recrystallized from 100 ml 50% aqueous ethanol. There were obtained 45 g mixture of acids melting at 113—118°C. The mixture was dissolved in 130 ml boiling benzene, the solution was cooled quickly and the precipitated acid *VI* was filtered and dried; 15·2 g (23%), m.p. 172—175°C. Analytical sample, m.p. 174—177°C (benzene–light petroleum). IR spectrum: 871 (solitary Ar—H), 927, 1 700, 1 721, 2 520, 2 600, 2 700, infl. 3 100 (COOH), 1 248, 1 362, (ArOR, COOH), 1 543, 1 570 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·09 (s, 1 H, 3-H), 7·08 (s, 1 H, 6-H), 3·80 (s, 3 H, OCH_3), 3·69 (s, 2 H, $ArCH_2CO$). For $C_9H_8I_2O_3$ (418·0) calculated: 25·86% C, 1·93% H, 60·73% I; found: 26·33% C, 1·85% H, 60·50% I.

2-(4-Chloro-2-methoxyphenylthio)-4-methoxybenzoic Acid (*XIII*)

4-Chloro-2-methoxythiophenol[3] (122 g) was added to a solution of 146 g KOH in 1·5 l water, the mixture was stirred for 30 min at 55—60°C, treated with 187 g 2-iodo-4-methoxybenzoic acid[1] and 3 g Cu and the mixture was stirred and refluxed for 16 h. After cooling it was diluted with 500 ml water, filtered with charcoal and the filtrate acidified with 1 : 1 dilute hydrochloric acid. After standing overnight the precipitated product was filtered, washed with water, dried *in vacuo* and crystallized from a mixture of 800 ml benzene and 350 ml light petroleum; 145 g (70%), m.p. 175—178°C. Analytical sample, m.p. 183—185°C (aqueous ethanol). UV spectrum: λ_{max} 237·5 nm (log ε 4·52), infl. 263 nm (4·12), infl. 291·5 nm (3·96), infl. 305 nm (3·89). IR spectrum: 830, 862, 880 (2 adjacent and solitary Ar—H), 913, 1 673, infl. 3 100 (ArCOOH), 1 032 (ArOR), 1 231, 1 258, 1 272 (COOH and ArOR), 1 550, 1 563, 1 575, 1 580, 1 600, 3 000, 3 040, 3 060 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·95 (d, J = 8·0 Hz, 1 H, 6-H), 7·52 (d, J = 8·0 Hz, 1 H, 6′-H), 7·28 (mcs, J = 2·0 Hz, 1 H, 3′-H), 7·12 (mcd, J = 8·0; 2·0 Hz, 1 H, 5′-H), 6·78 (mcd, J = 8·0; 2·5 Hz, 1 H, 5-H), 6·00 (mcs, J = 2·5 Hz, 1 H, 3-H), 3·80 and 3·61 (2 s, 6 H, 2 OCH_3). For $C_{15}H_{13}ClO_4S$ (324·8) calculated: 55·47% C, 4·03% H, 10·92% Cl, 9·87% S; found: 55·72% C, 4·26% H, 10·86% Cl, 10·00% S.

[2-(4-Chloro-2-methoxyphenylthio)-5-methoxyphenyl]acetic Acid (*V*)

A solution of 109 g 85% KOH and 86 g 4-chloro-2-methoxythiophenol[3] in 1 l water was treated at 55°C with 129 g (2-iodo-5-methoxyphenyl)acetic acid[11] and 2 g Cu and the mixture was stirred and refluxed for 24 h. After cooling it was filtered with charcoal and the filtrate was acidified with dilute hydrochloric acid. The separated oily product was extracted with benzene, the extract was dried and evaporated. The residue crystallized from a mixture of benzene and light petroleum; 99 g (67%), m.p. 118—121°C. Analytical sample, m.p. 122—125°C. IR spectrum (KBr): 799, 880 (2 adjacent and solitary Ar—H), 640, 1 243, 1 704, 2 525, 2 605, 2 710 (COOH), 1 028, 1 063 (ArOR), 1 478, 1 577, 1 598 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 10·35 (bS, 1 H, COOH), 6·30—7·50 (m, 6 H, Ar—H), 3·80 and 3·75 (2 s, 6 H, 2 OCH_3), 3·75 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{15}ClO_4S$ (338·8) calculated: 56·72% C, 4·46% H, 10·47% Cl, 9·46% S; found: 57·07% C, 4·56% H, 10·54% Cl, 9·57% S.

[2-(4-Chloro-2-methoxyphenylthio)-4-methoxyphenyl]acetic Acid (*XVII*)

A stirred suspension of 145 g *XIII* in 800 ml benzene was treated at 35—40°C over 45 min with 360 ml 50% solution of sodium dihydridobis(2-methoxyethoxy)aluminate in benzene. The solution formed was stirred for 5 h at room temperature and allowed to stand overnight. Then it was decomposed under stirring and external cooling with 1·7 l 10% NaOH. The mixture was stirred for 1 h, the benzene layer was separated, washed with water, dried with $MgSO_4$ and evaporated; 113 g crude *XIV*.

The product of the preceding reaction was shaken for 20 min with 113 ml hydrochloric acid at 20°C. The crude *XV* was extracted with benzene, the extract dried with $MgSO_4$ and evaporated. The oily residue (115 g) was dissolved in 230 ml acetone and the solution treated with 21 g 95% NaCN and 3·0 g NaI. The mixture was stirred and refluxed for 20 h. After cooling the precipitated solid was filtered off, the filtrate was evaporated, the residue dissolved in benzene, the solution washed with water, dried and evaporated; 116 g crude oily *XVI*.

A solution of the crude *XVI* in 600 ml ethanol was treated with a solution of 104 g KOH in 500 ml water and the mixture was refluxed for 18 h. Ethanol was evaporated under reduced pressure, the residue diluted with 1·5 l water and washed with benzene. The aqueous layer was filtered with charcoal and the filtrate acidified with 1 : 1 dilute hydrochloric acid. The oily product crystallized on standing overnight; 113 g (75% calculated on the starting *XIII*), m.p. 119—122°C. Analytical sample, m.p. 135—137°C (aqueous ethanol). IR spectrum: 791, 830, 878 (2 adjacent and solitary Ar—H), 927, 1254, 1710, infl. 3100 (COOH), 1031, 1056, 1254 (ArOR), 1481, 1495, 1582, 1607, 3000, 3048 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 9·18 (bs, 1 H, COOH), 6·70—7·30 (m, 6 H, Ar—H), 3·80 and 3·70 (2 s, 6 H, 2 OCH_3), 3·78 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{15}ClO_4S$ (338·8) calculated: 56·72% C, 4·46% H, 10·46% Cl, 9·46% S; found: 56·83% C, 4·30% H, 10·23% Cl, 9·16% S.

8-Chloro-2,6-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VII*)

A mixture of 750 g polyphosphoric acid, 75 g *V* and 400 ml toluene was stirred and refluxed for 3 h (bath temperature 130°C). After partial cooling it was poured into 5 l ice-cold water and extracted with benzene. The extract was washed with water and 5% NaOH, dried with $MgSO_4$ and evaporated; 47 g (66%) crude product, m.p. 190—200°C. Analytical product, m.p. 201—202°C (benzene). UV spectrum: λ_{max} 240 nm (log ε 3·94), 258 nm (4·01), 360 nm (3·80). IR spectrum (KBr): 800, 848, 876, 892 (2 adjacent and solitary Ar—H), 1249, 1260, 1269, 1320 (ArOR), 1480, 1559, 1572, 1580, 1599, 3030, 3053 (Ar), 1676 cm^{-1} (ArCO). For $C_{16}H_{13}ClO_3S$ (320·8) calculated: 59·90% C, 4·09% H, 11·05% Cl, 10·00% S; found: 59·64% C, 4·04% H, 11·06% Cl, 9·91% S.

8-Chloro-3,6-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIII*)

XVII (80 g) was similarly cyclized with 800 g polyphosphoric acid in 330 ml refluxing toluene; 64·5 g (85%), m.p. 157—165°C. Analytical sample, m.p. 181—183°C (benzene–light petroleum). UV spectrum: λ_{max} 238 nm (log ε 4·36), infl. 260 nm (4·20), 348 nm (3·79). IR spectrum (KBr): 793, 817, 840, 844, 881, 894 (2 adjacent and solitary Ar—H), 1241, 1258, 1288, 1321 (ArOR), 1488, 1530, 1552, 1600, 3030, 3047 (Ar), 1676 cm^{-1} (ArCO). For $C_{16}H_{13}ClO_3S$ (320·8) calculated: 59·90% C, 4·09% H, 11·05% Cl, 10·00% S; found: 60·52% C, 4·03% H, 10·61% Cl, 9·68% S.

8-Chloro-2,6-dihydroxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VIII*)

A mixture of 60·5 g pyridine, 62 ml ethanol and 81 ml hydrochloric acid was evaporated under reduced pressure to dryness giving pyridine hydrochloride. *VII* (11·6 g) was added and the mixture was heated under stirring for 75 min to 200°C (bath temperature). After cooling to 80°C the mixture was diluted with 250 ml water and the product was filtered after standing overnight. It was washed with water and dried *in vacuo*; 9·0 g (85%), m.p. 219—223°C. Analytical sample, m.p. 223—225°C (aqueous ethanol). UV spectrum: λ_{max} 229 nm (infl.) (log ε 4·30), 241 nm (4·19), 258 nm (4·26), 362 nm (3·72). IR spectrum (KBr): 820, 830, 870 (2 adjacent and solitary Ar—H), 1170, 1225, 1245, 1270, 1315 (ArOH), 1475, 1580 (Ar), 1653 (H-bonded ArCO), 3200 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 11·10 and 10·00 (2 bs, 2 H, 2 OH), 7·48 (d, J = 8·0 Hz, 4-H), 7·40 (mcs, 1 H, 9-H), 7·05 (mcs, 1 H, 7-H), 6·88 (mcs. J = 2·5 Hz, 1 H, 1-H), 6·65 (mcd, J = 8·0; 2·5 Hz, 1 H, 3-H), 4·10 (s, 2 H, $ArCH_2CO$). For $C_{14}H_9ClO_3S$ (292·7) calculated: 57·44% C, 3·10% H, 12·11% Cl, 10·95% S; found: 57·11% C, 3·05% H, 12·04% Cl, 10·98% S.

8-Chloro-3,6-dihydroxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XIX*)

XVIII (25 g) was similarly demethylated with pyridine hydrochloride prepared from 130 g pyridine; 20·3 g (89%), m.p. 215—218°C. Analytical sample, m.p. 226—229°C (aqueous ethanol). IR spectrum (KBr): 820, 833, 850, 859, 880 (2 adjacent and solitary Ar—H), 1230, 1252, 1325 (ArOH), 1496, 1565, 1580, 1603 (Ar), 1650 (H-bonded ArCO), 3230 cm^{-1} (OH). For $C_{14}H_9$. $.ClO_3S$ (292·7) calculated: 57·44% C, 3·10% H, 12·11% Cl, 10·95% S; found: 57·27% C, 3·24% H, 12·05% Cl, 11·05% S.

8-Chloro-2,6-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IX*)

A suspension of 41 g *VII* in 600 ml ethanol was stirred and treated at 70°C with a solution of 19 g $NaBH_4$ in 190 ml water containing 3 ml 20% NaOH. The mixture was refluxed for 5 h, ethanol was evaporated *in vacuo*, the residue diluted with water and extracted with warm benzene. The extract was washed with 2% NaOH and water, dried ($MgSO_4$), filtered with charcoal and evaporated under reduced pressure. The oily residue crystallized over 5 days standing; 40·2 g (97%), m.p. 102—104°C. Analytical sample, m.p. 104—105°C (benzene–light petroleum). IR spectrum: 820, 837, 852, 881, 890 (2 adjacent and solitary Ar—H), 1038 (CHOH), 1223, 1279 (ArOR), 1481, 1566, 1590, 3045 (Ar), 3455 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·39 (d, J = 9·0 Hz, 1 H, 4-H), 7·10 (mcs, J = 2·0 Hz, 1 H, 9-H), *c.* 6·60 (m, 3 H, remaining Ar—H), 5·35 (m, 1 H, Ar—CH—O), 3·80 and 3·68 (2 s, 6 H, 2 OCH_3), 3·58 and 3·11 (2 dd, 2 H, $ArCH_2$), 2·35 (bd, 1 H, OH). For $C_{16}H_{15}ClO_3S$ (322·8) calculated: 59·53% C, 4·68% H, 10·98% Cl, 9·93% S; found: 59·65% C, 4·58% H, 11·25% Cl, 9·72% S.

8-Chloro-3,6-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XX*)

XVIII (48·5 g) was similarly reduced with 21·6 g $NaBH_4$ and gave 47 g (95%) crude *XX*, m.p. 142—143°C. Analytical sample, m.p. 146—147°C (benzene). IR spectrum: 839, 892 (2 adjacent and solitary Ar—H), 1021, 1043 (CHOH), 1279 (ArOR), 1500, 1568, 1607, 3050 (Ar), 3385, 3480 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·60—7·40 (m, 5 H, Ar—H), 5·80 (bs, 1 H, OH), 5·49 (dd, 1 H, Ar—CH—O), 3·85 and 3·70 (2 s, 6 H, 2 OCH_3), *c.* 3·20 (m, 2 H, $ArCH_2$). For $C_{16}H_{15}ClO_3S$ (322·8) calculated: 59·53% C, 4·68% H, 10·98% Cl, 9·93% S; found: 59·56% C, 4·79% H, 10·94% Cl, 9·90% S.

8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-2,6,10-triol (*X*)

A solution of 8·5 g *VIII* in 130 ml ethanol was reduced with a solution of 3·8 g $NaBH_4$ in 38 ml water containing 1 ml 20% NaOH similarly like in the preceding cases; 7·1 g (83%), m.p. 182 to 187°C. Analytical sample, m.p. 215—217°C (aqueous ethanol). IR spectrum: 806, 870 (2 adjacent and solitary Ar—H), 1 045, 1 240, 1 250, 1 260 (CHOH and ArOH), 1 485, 1 576, 1 594, 1 611, 3 053 (Ar), 3 338, 3 493 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·20 and 9·52 (2 s, 2 H, 2 ArOH), 7·20 (d, J = 8·0 Hz, 1 H, 4-H), 7·02 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·78 (mcs, J = 2·0 Hz, 1 H, 7-H), *c.* 6·50 (m, 2 H, 1,3-H_2), 5·68 (d, J = 5·0 Hz, 1 H, 10-OH), 5·45 (m, 1 H, Ar—CH—O), *c.* 3·20 (m, 2 H, $ArCH_2$). For $C_{14}H_{11}ClO_3S$ (294·7) calculated: 57·04% C, 3·76% H, 10·88% S; found: 57·61% C, 3·94% H, 10·94% S.

8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-3,6,10-triol (*XXI*)

XIX (20 g) was similarly reduced with 8·9 g $NaBH_4$ and gave 14·0 g (70%) crude *XXI*, m.p. 217—222°C. Analytical sample, m.p. 246—248°C (aqueous ethanol). IR spectrum: 800, 851, 860 (2 adjacent and solitary Ar—H), 1 230, 1 274 (ArOH), 1 500, 1 574, 1 594, 1 619 (Ar), 3 165, 3 320, 3 360 cm^{-1}(OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·30 and 9·45 (2 bs, 2 H, 2 ArOH), 7·05 (mcs, J = 2·5 Hz, 1 H, 9-H), 6·98 (d, J = 8·5 Hz, 1 H, 1-H), *c* 6·82 (m, 2 H, 4,7-H_2), 6·60 (mcd, J = 8·5; 2·5 Hz, 1 H, 2-H), 5·72 (d, J = 5·0 Hz, 1 H, 10-OH), 5·55 (m, 1 H, Ar—CH—O), *c.* 3·15 (m, 2 H, $ArCH_2$). For $C_{14}H_{11}ClO_3S$ (294·4) calculated: 57·04% C, 3·76% H, 12·03% Cl, 10·88% S; found: 57·01% C, 3·96% H, 11·81% Cl, 11·01% S.

2,11-Dichloro-4,8-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XI*)

A solution of 35·7 g *IX* in 600 ml benzene was stirred and saturated for 3·5 h with anhydrous hydrogen chloride in the presence of 50 g $CaCl_2$ powder. The mixture was filtered and the filtrate evaporated under reduced pressure; 36·3 g (93%) crude *XI*, m.p. 143—146°C. Analytical sample, m.p. 145—148°C (benzene). IR spectrum: 800, 838, 879 (2 adjacent and solitary Ar—H), 1 275 (ArOR), 1 570, 1 602 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·40 (d, J = 8·0 Hz, 1 H, 6-H), 7·10 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·50—6·80 (m, 3 H, remaining Ar—H), 5·78 (dd, 1 H, Ar—CH—Cl), *c.* 3·70 (m, 2 H, $ArCH_2$), 3·81 and 3·71 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{14}Cl_2O_2S$ (341·3) calculated: 56·31% C, 4·13% H, 20·78% Cl, 9·40% S; found: 56·52% C, 4·07% H, 20·79% Cl, 9·29% S.

2,11-Dichloro-4,7-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXII*)

A solution of 46 g *XX* in 800 ml benzene was treated with HCl in the presence of 50 g $CaCl_2$ similarly like in the preceding case and gave 47 g (96%) crude product melting at 90—110°C. Analytical sample, m.p. 135—137°C (benzene). ^{1}H-NMR spectrum: δ 6·70—7·40 (m, 5 H, Ar—H), 5·85 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·75 (2 s, 6 H, 2 OCH_3), *c.* 3·70 (m, 2 H, $ArCH_2$). For $C_{16}H_{14}Cl_2O_2S$ (341·3) calculated: 56·31% C, 4·13% H, 20·78% Cl, 9·40% S; found: 56·64% C, 4·05% H, 20·66% Cl, 9·78% S.

2-Chloro-4,8-dimethoxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*II*)

A mixture of 3·7 g *XI*, 3·2 g 1-methylpiperazine and 10 ml chloroform was refluxed for 7 h. Chloroform was evaporated, the residue was diluted with benzene, the solution was washed with 3% NaOH and the base was extracted into 1·25M-H_2SO_4. The aqueous layer was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with $MgSO_4$,

filtered with charcoal and evaporated under reduced pressure. The oily residue crystallized from light petroleum; 3·4 g (77%), m.p. 116—118°C. Analytical sample, m.p. 135—137°C (methanol). ^{1}H-NMR spectrum: δ 7·41 (d, J = 9·0 Hz, 1 H, 6-H), 7·21 (mcs, J = 2·0 Hz, 1 H, 1-H), 6·75 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·60 (mcs, J = 2·0 Hz, 1 H, 3-H), 6·58 (mcd, J = 9·0; 2·0 Hz, 1 H, 7-H), 3·00—4·00 (m, 3 H, ArCH_2CHAr), 3·81 and 3·70 (2 s, 6 H, 2 OCH_3), 2·55 (m, 4 H, CH_2N^{1}CH_2 of piperazine), 2·40 (m, 4 H, CH_2N^{4}CH_2 of piperazine), 2·20 (s, 3 H, NCH_3). 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: 62·52% C, 6·09% H, 8·97% Cl, 6·82% N, 8·01% S.

Di(methanesulfonate), m.p. 205—206°C (ethanol). 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: 46·08% C, 5·44% H, 6·19% Cl, 4·66% N, 15·88% S.

The benzene layer, from which the base was removed by extraction with dilute H_2SO_4, was washed with 3% NaOH and water, dried, and evaporated giving 0·8 g 2-chloro-4,8-dimethoxydibenzo[*b,f*]thiepin (*XII*), m.p. 112—114°C (ethanol). UV spectrum: λ_{max} 226 nm (log ε 4·37), infl. 241 nm (4·45), 263 nm (4·32), 308 nm (3·89). IR spectrum: 772, 777 (olefinic CH=CH), 811, 821, 840, 860, 903 (2 adjacent and solitary Ar—H), 1270, 1280 (ArOR), 1560, 1578, 1592, 3020, 3080 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·42 (d, J = 8·0 Hz, 1 H, 6-H), 6·60—7·00 (m, 6 H, remaining Ar—H and olefinic CH=CH), 3·82 and 3·70 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05% C, 4·30% H, 11·63% Cl, 10·52% S; found: 63·31% C, 4·27% H, 11·72% Cl, 10·71% S.

2-Chloro-4,7-dimethoxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*)

A mixture of 3·4 g *XXII*, 3·0 g 1-methylpiperazine and 8 ml chloroform was refluxed for 8 h and processed similarly like in the preceding case; 2·3 g (57%) base *IV*, m.p. 110—114°C (light petroleum). Analytical sample, m.p. 118—120°C (ethanol). IR spectrum: 808, 825, 856, 886, 900 (2 adjacent and solitary Ar—H), 1010, 1045, 1240, 1280 (ArOR), 1487, 1560, 1570, 1598, 3020, 3040 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·28 (mcs, J = 3·0 Hz, 1 H, 1-H), 7·18 (d, J = = 8·0 Hz, 1 H, 9-H), 7·10 (mcs, J = 3·0 Hz, 1 H, 6-H), 6·78 (mcd, J = 8·0; 3·0 Hz, 1 H, 8-H), 6·70 (mcs, J = 3·0 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, ArCH_2CHAr), 3·89 and 3·75 (2 s, 2 OCH_3). 2·60 (m, 4 H, CH_2N^{1}CH_2 of piperazine), 2·50 (m, 4 H, CH_2N^{4}CH_2 of piperazine), 2·30 (s, 3 H, NCH_3). 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: 62·33% C, 6·41% H, 9·10% Cl, 7·09% N, 8·17% S.

Di(methanesulfonate), m.p. 194—197°C (ethanol). 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: 46·69% C, 5·60% H, 6·30% Cl, 4·64% N, 15·92% S.

The neutral product was purified by chromatography on a column of 50 g neutral Al_2O_3 (activity II) and eluted with a mixture of light petroleum with 20% benzene; 1·2 g 2-chloro-4,7-dimethoxydibenzo[*b,f*]thiepin (*XXIII*), m.p. 138—140°C (ethanol). UV spectrum: λ_{max} 228 nm (log ε 4·38), infl. 255 nm (4·25), infl. 290 nm (3·95), infl. 325 nm (3·55), 402 nm (3·55). IR spectrum (KBr): 835, 870 (2 adjacent and solitary Ar—H), 1058, 1240 (ArOR), 1487, 1560, 1600 (Ar), 1623 cm^{-1} (Ar—C=C—Ar). For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05% C, 4·30% H, 11·63% Cl, 10·52% S; found: 62·82% C, 4·60% H, 10·91% Cl, 10·00% S.

2-Chloro-4,8-dihydroxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

A solution of 6·6 g *II* in 100 ml chlorobenzene was stirred and treated dropwise at 15—20°C over 10 min with a solution of 25 g BBr_3 in 40 ml chlorobenzene. The mixture was stirred for 8 h at room temperature, allowed to stand overnight and treated with a solution of 3·3 g methane-

sulfonic acid in 60 ml water. The mixture was stirred for 15 min, the solid was filtered off and combined with the aqueous layer. The suspension was made alkaline with 33 ml 25% NaOH to pH 8·0. Ethanol (150 ml) was added and the solution was refluxed for 4 h; for maintaining the pH of 7·5—8·0 there were gradually added 8 ml 20% NaOH. Ethanol was evaporated, the residue diluted with 100 ml water, the solid was filtered, washed with water and dried *in vacuo*; 3·4 g mixture of two components. It was chromatographed on a column of 105 g silica gel 60 (Merck). Elution with chloroform containing 5 and then 8% ethanol gave 2·1 g of the less polar component. Elution with ethanol gave 0·75 g (12%) desired *I*, m.p. 263—264°C (ethanol–benzene). UV spectrum: λ_{max} 225 nm (infl.) (log ε 4·38), infl. 255 nm (3·96), infl. 270 nm (3·83), 303 nm (3·85). IR spectrum (KBr): 822, 844, 864 (2 adjacent and solitary Ar—H), 1126, 1158, 1242, 1283 (ArOH), 1470, 1562, 1580 (Ar), 3390 cm^{-1} (OH). For $C_{19}H_{21}ClN_2O_2S$ (376·9) calculated: 60·55% C, 5·62% H, 9·41% Cl, 7·43% N, 8·50% S; found: 60·02% C, 6·08% H, 9·54% Cl, 7·16% N, 8·41% S.

2-Chloro-4,7-dihydroxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*III*)

IV (2·3 g) was demethylated with 8·65 g BBr_3 in 65 ml chlorobenzene and the mixture processed like in the preceding case. Chromatography of the crude product on silica gel gave 0·33 g (15%) *III*, m.p. 156—158°C (aqueous ethanol). Mass spectrum, *m/e* (%): 376 (M^+, corresponds to $C_{19}H_{21}ClN_2O_2S$, 1·3%), 291 (6·7), 276 (10·8), 113 (8·0), 112 (10·8), 101 (22·8), 99 (48·4), 97(25·6), 86 (23·2), 85 (28·8), 72 (62), 70 (100), 58 (41), 56 (44). UV spectrum: λ_{max} 230 nm (infl.) (log ε 4·39), 260 nm (3·89), 300 nm (3·92). IR spectrum: 842, 857 (2 adjacent and solitary Ar—H), 1240, 1255, 1276 (ArOH), 1460, 1495, 1542 (Ar), 3365 cm^{-1} (OH). For $C_{19}H_{21}ClN_2O_2S$ (376·9) calculated: 60·54% C, 5·62% H, 9·41% Cl, 7·43% N, 8·51% S; found: 60·15% C, 5·25% H, 9·62% Cl, 7·23%N, 8·59% S.

Dr K. Šindelář of this laboratory carried out the experiments aiming at the direct conversion of compounds X *and* XXI *to the title compounds* I *and* III. *The authors are indebted to Dr J. Jilek of this laboratory for a stimulating discussion on the demethylation procedures, to Drs M. Ryska and J. Schlanger for recording and interpretation of the mass spectrum, to Mrs A. Hrádková for recording the* UV *and* IR *spectra (department of physical chemistry of this institute) and finally to Mrs J. Komancová, Mrs V. Šmidová, Mr M. Čech and Mrs J. Kropáčová (analytical department of this institute) for carrying out the analyses.*

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Translated by the author (M. P.).