POTENTIAL METABOLITES OF CLOROTEPIN: 2- AND 3-HYDROXY DERIVATIVES OF 8-CHLORO-10-(4-METHYLPIPERAZINO)--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN AND THEIR METHYL ETHERS*

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Received February 25th, 1974

8-Chloro-2-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIIIa*) and its 3-methoxy isomer *XVIIIb* were synthesized from 2-bromo-5-methoxybenzoic acid and from 2-iodo-4-methoxybenzoic acid in six steps. In three further steps, the products were converted to the 2-methoxy and 3-methoxy (*IV* and *V*) derivatives of clorotepin (*I*). Demethylation with boron tribromide and subsequent hydrolysis led to the phenolic bases *II* and *III*. While the 2-substitution derivatives *II* and *IV* show no central neurotropic activity, the 3-substituted derivatives *III* and *V* are highly active and the hydroxy derivative *III* is in two principal tests more effective than clorotepin (*I*).

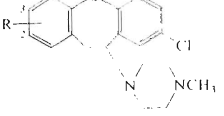
In the present study we describe the synthesis and some properties of potential metabolites of the neuroleptic clorotepin[1], *i.e.* 8-chloro-10-(4-methylpiperazino)--10,11-dihydrodibenzo[*b*, *f*] thiepin (*I*, octoclothepin, Clotepin^R)[2-4], in particular of the phenolic bases *II* and *III* (the existing information on the metabolism of clorotepin is to be found in refs[5-8]). In view of the analogy of the neuroleptics of the dibenzo[*b*, *f*]thiepin series with some other tricyclic neuroleptics (phenothiazines, thioxanthenes, dibenzo[*b*,*f*]-1,4-thiazepins, dibenz[*b*, *f*]-1,4-oxazepins) which is displayed in the structure, pharmacodynamic properties, antipsychotic activity and apparently also in metabolic transformation[9], it might be useful to summarize briefly what is known about the compounds of these series, which are analogous to substances *II* and *III* of this paper.

Of the series of neuroleptics derived from phenothiazine most information on the biotransformations is available for chlorpromazine (*VI*), *i.e.* 2-chloro-10-(3-dimethylaminopropyl)phenothiazine. The monohydroxylated (phenolic) metabolites of chlorpromazine present in human urine[10] are excreted either as such or conjugated, mostly as glucuronides, to a lesser extent as O-sulfates[11]. The predominant phenolic metabolite was identified[12-14] as the 7-hydroxy derivative *VII* and synthesized[15]. Significant species differences were observed in the role of 7-hydroxylation in the total biotransformation of chlorpromazine: in a rat liver preparation in an *in vitro* experiment it amounts to 2% (ref.[16]), in the dog to about 20% (ref.[17]) but in man it amounts

* Part LXXVII in the series Neurotropic and Psychotropic Agents; Part LXXVI: This Journal *39*, 3338 (1974).

to 80% of the metabolite total[18]. Significant differences in the metabolism of chloropromazine exist even among individual patients; in some the 7-hydroxylation, in others the S-oxidation is predominant[19]. 8-Hydroxylation of chlorpromazine plays apparently a rather minor role; for this reason the detection of *VIII* in the urine is less convincing[20] even if the authentic substance *VIII* is available[21,22]. However, the compound is considered to be a metabolite[23]. According to more recent work[24,25], compounds *VII* and *VIII* are further metabolized to the unstable 7,8-dihydroxy derivative of *VI* which is O-methylated mostly to the 7-hydroxy-8-methoxy derivative and, to a lesser extent to the 7-methoxy-8-hydroxy derivative of *VI*. In the thioxanthene series of neuroleptics the principal compound is chlorprothixene, *i.e. cis*-2-chloro-9-(3-dimethylaminopropylidene)thioxanthene; its metabolism has been studied relatively little[26]. While no phenolic metabolites have been detected in rat urine, dog urine was found to contain two such substances but their structure remains unknown. A similar situation exists with respect to clothiapine, 2-chloro-11-(4-methylpiperazino)dibenzo[*b,f*]-1,4-thiazepin[27]. In dog urine[27] three such compounds were detected, in human urine[28] actually four phenolic metabolites, the structure of which is not known. With loxapine, *i.e.* 2-chloro-11-(4-methylpiperazino)dibenz[*b,f*]-1,4-oxazepin (*X*) the 7-hydroxy derivative *XI* was predicted to occur[29] and its synthesis was described[30,31]. Judging mainly from the metabolic hydroxylation of chlorpromazine, the view appears tenable that phenols *II* and *III* might represent metabolites of clorotepin (*I*). It is likely, at the same time, that the corresponding positions 2 and 3 of dibenzo[*b,f*]thiepin and 8 and 7 of phenothiazine are not equally active with respect to enzymic hydroxylation.

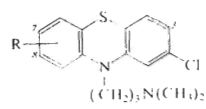
In the synthesis of phenols *II* and *III*, the first task was to prepare the corresponding methyl ethers *IV* and *V* which was carried out using the procedures commonly employed here[2,32–34]. The synthesis of *IV* proceeded from the known 2-bromo-5-methoxybenzoic acid[35] and continued *via* the intermediates *XIIa*–*XIVa*. In the reaction of chloride *XIVa* with sodium cyanide in boiling acetone in the presence of sodium iodide, both the liquid nitrile *XVa* and a considerable amount of *XVII* were obtained, substance *XVII* being the product of alkylation of nitrile *XVa* by chloride *XIVa*. An analogous type of product was observed in the reaction of benzyl chloride with sodium cyanide in dimethyl sulfoxide or dimethylformamide[36]. Hydrolysis of nitrile *XVa* produced the acid *XVIa* which was cyclized by polyphosphoric acid in boiling toluene. Ketone *XVIIIa* obtained in a fine yield was converted to chloride *XXa via* the alcohol *XIXa*. Its substitution reaction with 1-methylpiperazine in boiling chloroform yielded the desired amine *IV* together with a substantial amount of 2-chloro-8-methoxydibenzo[*b, f*]thiepin (*XXI*) formed by elimination.



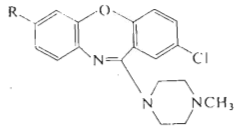
I, R = H
II, R = 2-OH

III, R = 3-OH
IV, R = 2-OCH_3

V, R = 3-OCH_3

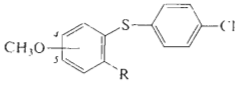


VI, R = H
VII, R = 7-OH
VIII, R = 8-OH
IX, R = 7-OCH_3

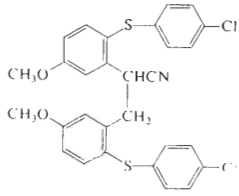


X, R = H
XI, R = OH

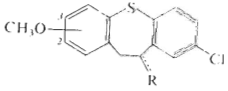
Preparation of ether *V* started from 4-methoxyanthranilic acid[37] which was converted to 2-iodo-4-methoxybenzoic acid. The synthesis proceeded *via* the intermediates *XIIb*–*XVIb* and *XVIIIb*–*XXb*. In the products of the reaction of chloride *XXb* with 1-methylpiperazine, the base *V* was accompanied by the elimination product, 2-chloro-7-methoxydibenzo[*b*, *f*]thiepin (*XXII*). During the demethylation of ethers *IV* and *V* to phenols *II* and *III* we proceeded from previous experience with the preparation of 8-hydroxy-10-(4-methylpiperazino)-10,11-di-



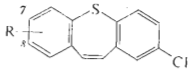
[Position of CH_3O: *a*, 5; *b*, 4]
XII, R = COOH
XIII, R = CH_2OH
XIV, R = CH_2Cl
XV, R = CH_2CN
XVI, R = CH_2COOH



XVII



[Position of CH_3O: *a*, 2; *b*, 3]
XVIII, R = =O
XIX, R = OH
XX, R = Cl



XXI, R = 8-OCH_3
XXII, R = 7-OCH_3

hydrodibenzo[*b*, *f*]thiepin[38] and it was accomplished with the aid of boron tribromide[39]. While in the first case the hydrolysis of the primarily formed boric ester was achieved merely by heating with aqueous ethanol, in the second case (preparation of *III*) it was necessary to hydrolyze the product with boiling dilute solution of sodium hydroxide. The phenolic bases obtained were characterized by their spectra. Bases *II* – *V* were converted for this purpose and for pharmacological tests to appropriate salts (methanesulfonates, maleates).

Compounds *II* (base), *III* (methanesulfonate), *IV* bis(methanesulfonate)) and *V* bis(hydrogen maleate)) were tested pharmacologically after oral administration. The acute toxicity for mice was determined only with compounds *III*–*V*. Table I summarizes the mean lethal doses LD_{50}. The incoordinating effect of the products was tested by the rotating-rod test with mice the mean effective doses ED_{50} being shown. Finally, the cataleptic effect was estimated in a test on rats and is expressed by the mean effective doses ED_{50}. All the numerical values of Table I (in mg/kg) refer to the bases. For the sake of comparison, the table includes clorotepin[2–4] (*I*). It may be seen that while the 2-substitution derivatives *II* and *IV* show an about 10 times lower activity than clorotepin (*I*) and cataleptically are practically ineffective, both 3-substitution derivatives are highly active. The methyl ether *V* has the same depressant effect as clorotepin and is only slightly weaker in the catalepsy test. The high activity of phenol *III* in both tests is rather surprising; it is about three times more potent as a depressant and about twice more potent as a cataleptic than clorotepin. If the hypothesis should prove right that the 3-hydroxy derivative of clorotepin (*III*) is a metabolite of clorotepin (*I*) it would indicate that one of the metabolic pathways of this neuroleptic agent has the character of bio-activation.*

For the sake of comparison, the data on pharmacodynamic activity of analogous derivatives of chlorpromazine (*VI*) are included. The 7-hydroxy derivative of chlorpromazine (*VII*) shows a high degree of central depressant activity[41,42] in tests based on an effect on the spontaneous locomotor activity in mice, in the rotating-rod test, in the test of potentiation of hexobarbital narcosis in mice and in the test of influencing conditioned reflexes. In most of the tests it is 2–4 times weaker than chlorpromazine but in the series of chlorpromazine metabolites it represents one of the most potent compounds. It antagonizes amphetamine-caused stereotype movements of rats[43] and the reserpine hypothermia with mice[42]. It increases the level of homovanillic acid in the brain to about the same degree as chloropromazine[44]. The view has been advanced that it might represent a toxic metabolite of chlorpromazine responsible for some of its side effects[45]. The literature does not appear to contain data on the cataleptic or antiapomorphine effects although these very data might provide an explanation for the finding that patients with a predominance of 7-hydroxychlorpromazine (*VII*) in their metabolite spectrum respond more readily to

* The urine of rats given clorotepin (*I*) was shown by chromatography to contain two phenolic metabolites with R_F values corresponding to those of phenols *II* and *III*. Schizophrenic patients (Research Institute of Psychiatry, Prague - Bohnice) treated with clorotepin contained in their urine only the 2-hydroxy derivative *II* which was shown to be identical with the present substance by UV, IR and mass spectra[40].

TABLE I

Pharmacological Properties of Phenols and Ethers *II*—*V* (mg/kg, oral administration)

Compound	Toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
I[2-4]	78	2·2	4·3
II	—	37·5	> 50[a]
III	350	0·84	2·4
IV	320	20	>100[b]
V	185	2·1	7·2

[a] A dose of 50 mg/kg brings about catalepsy in one rat out of ten. [b] A dose of 100mg/kg brings about catalepsy in 4 rats out of ten.

chlorpromazine treatment than those with a predominance of chlorpromazine S-oxide[19]. The 8-hydroxy derivative of chlorpromazine (*VIII*) display only light sings of central depressant activity[41] and it is fully inactive in the test of antagonizing amphetamine stereotypies[43]. The 7-methoxy derivative of chlorpromazine[15] (*IX*) shows no central depressant activity[41] and does not potentiate hexobarbital narcosis[41,46]. The 8-methoxy derivative of chlorpromazine has not yet been described.

The ethers *IV* and *V* were tested for their antimicrobial effect using *in vitro* tests, the antibacterial potency being rather high. In the following the tested organisms and the minimum inhibitory concentrations in μg/ml are shown: *Streptococcus* β-*haemolyticus*, IV, 25; V, 50; *Staphylococcus pyogenes aureus*, IV, 25; V, 50; *Mycobacterium tuberculosis* H37Rv, IV, 6·25; V, 12·5; *Sacharomyces pasterianus*, V, 125; *Trichophyton mentagrophytes*, IV, 62·5; V, 125.

EXPERIMENTAL

The melting points of the analytical preparations have been determined in Kofler's block and are not corrected; the samples were dried at about 0·5 Torr over P_2O_5 at room temperature or at a suitably raised temperature (100°C at most). The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200 G spectrophotometer or in a Hilger and Watts Infrascan, and the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of compounds was tested by chromatography on a thin layer of silica gel or alumina.

2-Iodo-4-methoxybenzoic Acid

A solution of 16·7 g 4-methoxyanthranilic acid[37,47] (m.p. 178—180°C) was prepared in a 75°C mixture of 150 ml water and 20 ml concentrated hydrochloric acid, the solution was cooled to 0°C and the suspension formed was diazotized by adding dropwise a solution of 7·25 g $NaNO_2$ in 15 ml water, under stirring. The mixture was stirred for 30 min at 0°C and then a solution of 25 g KI in 40 ml water and 5·5 ml H_2SO_4 was added dropwise under stirring. The temperature of the solution was 20°C. The mixture was heated for 2 h in a boiling water bath and the released iodine was steam-distilled. Cooling to 10—15°C and standing overnight precipitated a product;

21·9 g (79%), m.p. 188°C (benzene). NMR spectrum (CD_3SOCD_3): δ 7·94 (d, J = 9·0 Hz, 1 H, aromatic proton in the vicinity of carboxyl), 7·65 (d, J = 3·0 Hz, 1 H, aromatic proton, between the methoxyl and the iodine atom), 7·13 (q, J = 9·0; 3·0 Hz, 1 H, remaining aromatic proton), 3·80 (s, 3 H, OCH_3). For $C_8H_7IO_3$ (278·1) calculated: 34·56% C, 2·54% H, 45·65% I; found: 34·80% C, 2·61% H, 45·61% I.

2-(4-Chlorophenylthio)-5-methoxybenzoic Acid (*XIIa*)

A solution of 1·84 g Na in 50 ml methanol was added to a solution of 8·3 g 2-bromo-5-methoxybenzoic acid[35] (m.p. 159–161°C) and 5·8 g 4-chlorothiophenol in 100 ml methanol, the solvent was evaporated at reduced pressure, the residue was combined with 80 ml dimethylformamide and 1 g copper paste (freed of water by washing with dimethylformamide) and the mixture was refluxed for 10 h. After evaporation of the solvent *in vacuo*, the residue was diluted with 200 ml water, filtered and the filtrate acidified with concentrated hydrochloric acid; 7·8 g (74%), m.p. 161·5 to 163°C (aqueous ethanol). IR spectrum (Nujol): 814, 836, 870 (2 adjacent and solitary Ar—H), 925 (COOH), 1018, 1032, 1230, 1265, 1270, 1332 ($ArOCH_3$, COOH), 1562, 1602 (Ar), 1690 (ArCOOH), 3020 and 3060 cm^{-1} (Ar—H). For $C_{14}H_{11}ClO_3S$ (294·8) calculated: 57·05% C, 3·76% H, 12·03% Cl, 10·88% S; found: 57·48% C, 3·75% H, 11·83% Cl, 11.01% S.

2-(4-Chlorophenylthio)-4-methoxybenzoic Acid (*XIIb*)

4-Chlorothiophenol (10·35 g), 1 g Cu paste and, after brief mixing, 20·0 g 5-iodo-4-methoxybenzoic acid was added to a solution of 14 g KOH in 150 ml water at 50°C. The mixture was refluxed under stirring for 7h, filtered while hot and the filtrate was acidified with concentrated hydrochloric acid; 20·7 g, m.p. 215–216°C (ethanol). NMR spectrum (CD_3SOCD_3): δ 8·10 (d, J = 9·0 Hz, 1 H, aromatic proton in the vicinity of carboxyl), 7·66 (s, 4 H, aromatic protons of 4-chlorophenyl sulfide), 6·86 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 5-H in the residue of benzoic acid), 6·18 (d, J = 3·0 Hz, 1 H, remaining aromatic proton), 3·62 (s, 3 H, OCH_3). For $C_{14}H_{11}ClO_3S$ (294·8) calculated: 57·05% C, 3·76% H, 12·03% Cl, 10·88% S; found, 57·23% C, 3·80% H, 12·03% Cl, 10·98% S.

2-(4-Chlorophenylthio)-5-methoxybenzyl Alcohol (*XIIIa*)

30 g of a 55% solution of sodium bis(2-methoxyethoxy)dihydridoaluminate[48] was added dropwise at room temperature under stirring, over a period of 15 min, to a suspension of 11·5 g *XIIa* in 50 ml benzene. It was stirred for 2 h, left to stand overnight, decomposed with excess dilute solution of NaOH, the benzene layer was washed with water, dried with $MgSO_4$ and evaporated: 9·07 g (83%), b.p. 173°C/0·2 Torr, m.p. 61–63°C (benzene–light petroleum). IR spectrum (Nujol): 805, 818, 878 (2 adjacent and solitary Ar—H), 1052 (CH_2OH), 1230, 1274, 1468 ($ArOCH_3$), 1568, 1600 (Ar), 3250 cm^{-1} (OH). For $C_{14}H_{13}ClO_2S$ (280·8) calculated: 59·89% C, 4·67% H, 12·63% Cl, 11·42% S; found: 60·17% C, 4·75% H, 12·31% Cl, 11·70% S.

2-(4-Chlorophenylthio)-4-methoxybenzyl Alcohol (*XIIIb*)

Reduction of 19·0 g *XIIb* yielded analogously 16·0 g (89%) crude product which was recrystallized from aqueous ethanol; m.p. 73–74°C. IR spectrum ($CHCl_3$): 820, 885 (2 adjacent and solitary Ar—H), 1052 (CH_2OH), 1235, 1280, 1475 ($ArOCH_3$), 1572, 1597 (Ar), 3590 cm^{-1} (OH). NMR spectrum: δ 7·45 (d, J = 9·0 Hz, 1 H, aromatic proton in the vicinity of CH_2OH), 7·25 (s, 4 H, aromatic protons of 4-chlorophenyl sulfide), 6·89 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 5-H),

6·88 (d, $J = 3·0$ Hz, 1 H, remaining aromatic proton), 4·68 (s, 2 H, $ArCH_2O$), 3·70 (s, 3 H, OCH_3), 2·20 (bs, disappears after deuterization, 1 H, OH). For $C_{14}H_{13}ClO_2S$ (280·8) calculated: 59·89% C, 4·67% H, 12·63% Cl, 11·42% S; found: 59·59% C, 4·68% H, 12·82% Cl, 11·55% S.

2-(4-Chlorophenylthio)-5-methoxyphenylacetonitrile (*XVa*)

$SOCl_2$ (12·5 g) was added dropwise under stirring at 10—20°C over a period of 30 min to a mixture of 25·7 g *XIIIa*, 30 ml chloroform and 9·0 ml pyridine. The mixture was stirred for 4 h at room temperature, left to stand for 48 h, decomposed with water, the chloroform layer was washed with 5% hydrochloric acid, 5% NaOH and water, dried with $MgSO_4$ and evaporated. A total of 27·4 g (the theoretical yield) of an oily chloride was obtained (*XIVa*) which was not characterized further. It was dissolved in 100 ml acetone, combined with 7·0 g NaCN and 1·0 g NaI and the mixture was refluxed for 20 h. After filtration, the filtrate was evaporated at reduced pressure, the residue was divided between benzene and water, the benzene solution was dried and evaporated. Dissolution of the residue in a small volume of ethanol and standing led to crystallization of 8·3 g compound melting at 149—151°C which was identified as 1,2-bis[2-(4-chlorophenylthio)--5-methoxyphenyl]propionitrile (*XVII*). IR spectrum ($CHCl_3$): 818, 855 (2 adjacent and solitary Ar—H), 1010, 1238, 1472 ($ArOCH_3$), 1565, 1593 (Ar), 2244 (R—CN), 2835 cm^{-1} ($ArOCH_3$). NMR spectrum: δ 6·75—7·70 (m, 14 H, aromatic protons), 4·84 (t, $J = 7·5$ Hz, 1 H, ArCHCN), 3·82 and 3·77 (2 s, 6 H, 2 OCH_3), 3·24 (d, $J = 7·5$ Hz, 2 H, $ArCH_2$). For $C_{29}H_{23}Cl_2NO_2S_2$ (552·6) calculated: 63·04% C, 4·20% H, 12·83% Cl, 2·54% N, 11·61% S; found: 63·23% C, 4·29% H, 12·50% Cl, 2·58% N, 11·54% S.

Evaporation of the mother liquor yielded 17·1 g (65%) crude nitrile *XVa*, a sample of which was redistilled; b.p. 180°C/0·5 Torr. For $C_{15}H_{12}$ ClNOS (289·8) calculated: 4·84% N; found: 4·61% N.

2-(4-Chlorophenylthio)-4-methoxybenzyl Chloride (*XIVb*)

Reaction of 9·0 g *XIIIb*, 3·1 ml pyridine and 4·5 g $SOCl_2$ at a temperature below 20°C and processing as in the preceding case yielded 8·6 g (90%) product, m.p. 69°C (light petroleum). NMR spectrum: δ 7·44 (d, $J = 9·0$ Hz, 1 H, aromat. 6-H of benzyl chloride), 7·25 (s, 4 H, aromatic protons of 4-chlorophenyl sulfide), 6·86 (q, $J = 9·0$; 3·0 Hz, 1 H, aromatic 5-H of benzyl chloride), 6·85 (d, $J = 3·0$ Hz, 1 H, aromatic 3-H of benzyl chloride), 4·70 (s, 2 H, $ArCH_2Cl$), 3·65 (s, 3 H, OCH_3). For $C_{14}H_{12}Cl_2OS$ (299·2) calculated: 56·20% C, 4·04% H, 23·70% Cl, 10·71% S; found: 56·13% C, 4·07% H, 23·50% Cl, 10·49% S.

2-(4-Chlorophenylthio)-5-methoxyphenylacetic Acid (*XVIa*)

A mixture of solutions of 17·1 g crude *XVa* in 70 ml ethanol and of 15 g KOH in 40 ml water was refluxed for 4 h. The ethanol was evaporated, the residue was diluted with water and, after washing with benzene, the aqueous liquid was acidified with hydrochloric acid. The precipitated product was filtered; 10·5 g (56%), m.p. 133—135°C (aqueous ethanol). IR spectrum: 815, 853, 865 (2 adjacent and solitary Ar—H), 930, 1305, 1325, 1702 (COOH), 1240 ($ArOCH_3$), 1575, 1597 cm^{-1} (Ar). For $C_{15}H_{13}ClO_3S$ (308·8) calculated: 58·34% C, 4·25% H, 11·49% Cl, 10·38% S; found: 58·47% C, 4·26% H, 11·43% Cl, 10·44% S.

2-(4-Chlorophenylthio)-4-methoxyphenylacetic Acid (*XVIb*)

NaCN (26 g) was added to a solution of 52·6 g crude *XIVb* in 130 ml dimethylformamide, the mixture was stirred for 15 min without heating and for 8 h at 100—105°C. After evaporation

of the solvent, the residue was divided between water and benzene and processing of the benzene layer yielded 49 g crude nitrile *XVb* which was not characterized further. It was hydrolyzed as in the preparation of *XVIa*, a total of 45·2 g (87%) acid *XVIb* being obtained; it crystallizes from benzene as a solvate with 1/2 molecule of benzene, m.p. 128—130°C. NMR spectrum: δ 10·55 (bs, 1 H, COOH), 6·80—7·60 (aromatic protons), 3·82 (s, 2 H, $ArCH_2COO$), 3·76 (s, 3 H, OCH_3). For $C_{18}H_{16}ClO_3S$ (347·9) calculated: 62·15% C, 4·64% H, 10·20% Cl, 9·21% S; found: 62·14% C, 4·75% H, 10·50% Cl, 9·23% S.

2-Methoxy-8-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XVIIIa*)

A mixture of 9·3 g *XVIa*, polyphosphoric acid (prepared from 25 g P_2O_5 and 15 ml 85% H_3PO_4) and 200 ml toluene was refluxed under stirring for 20 h. The toluene layer was then separated, the polyphosphoric acid was washed with toluene and the toluene layers were combined, washed with dilute NaOH, dried with $MgSO_4$ and evaporated. A total of 6·7 g (77%) product was obtained; m.p. 157—159°C (ethanol–benzene). UV spectrum (ethanol): λ_{max} 229 nm (log ε 4·40), 249 nm (4·22), 348 nm (3·57). IR spectrum (Nujol): 823 and 860 (2 adjacent and solitary Ar—H), 1025, 1106, 1163, 1245, 1270 ($ArOCH_3$), 1573 (Ar), 1593 (Ar), 1677 cm^{-1} (Ar-CO). NMR spectrum: δ 8·21 (d, J = 3·0 Hz, 1 H, aromatic 9 H), 7·60 (d, J = 9·0 Hz, 2 H, aromatic 4,6-H_2), 7·38 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 7-H), 7·01 (d, J = 3·0 Hz, 1 H, aromatic 1-H), 6·75 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 3-H), 4·30 (s, 2 H, $ArCH_2CO$), 3·76 (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: 62·12% C, 3·99% H, 12·22% Cl, 10·88% S.

3-Methoxy-8-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XVIIIb*)

Cyclization of 45·2 g acid *XVIb*, carried out as in the preceding case, yielded 37·0 g (87%) product, m.p. 138—139°C (ethanol). UV spectrum (ethanol): λ_{max} 237 nm (log ε 4·43), 264 nm (4·04), 293 nm (3·25), 341 nm (3·37). IR spectrum ($CHCl_3$): 825 and 875 (2 adjacent and solitary Ar-H), 1035, 1257, 1285 ($ArOCH_3$), 1490, 1577, 1597 (Ar), 1675 cm^{-1} (Ar—CO). NMR spectrum: δ 8·23 (d, J = 3·0 Hz, 1 H, aromatic 9 H), 7·56 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·39 (d, J = 9·0 Hz, 1 H, aromatic 1-H), 7·36 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 7-H), 7·20 (d, J = 3·0 Hz, 1 H, aromatic 4-H), 6·90 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 2-H), 4·22 (s, 2 H, $ArCH_2CO$), 3·74 (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: 62·24% C, 4·01% H, 12·21% Cl, 11·06% S.

8-Chloro-10-hydroxy-2-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIXa*)

A solution of 0·90 g $NaBH_4$ in 1 ml water with 1 drop 20% NaOH was added dropwise to a solution of 6·5 g ketone *XVIIIa* in a mixture of 80 ml ethanol and 80 ml dioxane. The mixture was refluxed for 3 h, evaporated and the residue was divided between water and chloroform. Processing of the chloroform layer yielded 6·05 g (93%) product, m.p. 105—106°C (benzene–light petroleum). IR spectrum: 1060, 3420 (OH), 1250 ($ArOCH_3$), 1490 and 1595 cm^{-1} (Ar). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·59% C, 4·68% H, 11·94% Cl, 11·24% S.

3-Methoxy-8-chloro-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIXb*)

A solution of 3·0 g ketone *XVIIIb* in 60 ml ethanol was reduced with a solution of 1·0 g $NaBH_4$ in 10 ml water and, after 3·5 h of refluxing, it was processed similarly to the preceding case. A total of 2·9 g (96%) product was obtained; m.p. 107—108°C (cyclohexane). IR spectrum: 820,

870, 896 (2 adjacent and solitary Ar—H), 1056 (CHOH), 1240 ($ArOCH_3$), 1494, 1570, 1602 (Ar), 3340 cm^{-1} (OH). NMR spectrum: δ 7·60 (d, J = 2·5 Hz, 1 H, aromatic 9-H), 7·45 (d, J = 9·0 Hz, 1 H, aromat. 6-H), 7·20 (d, J = 9·0 Hz, 1 H, aromat. 1-H), 7·13 (q, J = 9·0; 2·5 Hz, 1 H, aromat. 7-H), 7·09 (d, J = 2·5 Hz, 1 H, aromatic 4-H), 6·80 (q, J = 9·0; 2·5 Hz, 1 H, aromatic 2-H), 5·30 (m, after deuterization dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·70 (s, 3·H, OCH_3), 3·62 and 3·25 (2q, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·30 (bs, disappears after deuterization, 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: 61·42% C, 4·28% H, 12·18% Cl, 11·21% S.

8,10-Dichloro-2-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXa*)

Powdered $CaCl_2$ (2 g) was added to a solution of 6·3 g *XIXa* in 80 ml chloroform and the suspension was saturated for 1 h with anhydrous hydrogen chloride. After standing overnight it was filtered, the filtrate was evaporated and the residue recrystallized from cyclohexane; 5·0 g (75%), m.p. 92—93°C. NMR spectrum: δ 7·55 (d, J = 3·0 Hz, 1 H, aromatic 9-H), 7·50 (d, J = 9·0 Hz, 1 H, aromatic 4-H), 7·43 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·07 (q, J = 9·0; 3·0 Hz, 1 H, aromatic 7-H), 6·90 (d, J = 3·0 Hz, 1 H, aromatic 1-H), 6·73 (d, J = 9·0 Hz, 1 H, aromatic 3-H), 5·70 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·75 (s, 3 H, OCH_3), 3·92 and 3·60 (2q, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{15}H_{12}Cl_2OS$ (311·2) calculated: 57·88% C, 3·89% H, 22·78% Cl, 10·30% S; found: 58·19% C, 4·10% H, 22·86% Cl, 10·32% S.

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

A solution of 2·0 g *XIXb* in 50 ml benzene was processed as in the preceding case and a total of 2·08 g (97%) product was obtained; this was recrystallized from light petroleum; m.p. 105°C. NMR spectrum: δ 7·62 (d, J = 2·5 Hz, 1 H, aromatic 9-H), 7·50 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·32 (d, J = 9·0 Hz, 1 H, aromatic 1-H), 7·18 (q, J = 9·0; 2·5 Hz, 1 H, aromat. 7-H), 7·18 (d, J = 2·5 Hz, 1 H, aromat. 4-H), 6·88 (q, J = 9·0; 2·5 Hz, 1 H, aromat. 2-H), 5·75 (dd, J = 9·0; 5·0 Hz, 1 H, Ar—CH—Cl), 3·75 (s, 3 H, OCH_3), 3·90 and 3·55 (2dd, J = 16·0; 5·0 and 16·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{15}H_{12}Cl_2OS$ (311·2) calculated: 57·88% C, 3·89% H, 22·78% Cl, 10·30% S; found: 58·00% C, 4·12% H, 22·99% Cl, 10·45% S.

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

A mixture of 2·25 g crude *XXa*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 6h, divided between benzene and water, the benzene layer was washed with water and shaken with excess dilute HCl. The precipitated hydrochloride was filtered, combined with the aqueous layer of the filtrate and the suspension was made alkaline with NH_4OH. The liberated base was isolated by extraction with benzene; 1·65 g (61%). Neutralization with maleic acid in ethanol and an addition of ether produced a bis(hydrogenmaleate) crystallizing as hemihydrate, m.p. 98 to 100°C (ethanol–ether). For $C_{28}H_{32}ClN_2O_{9\cdot5}S$ (616·1) calculated: 54·58% C, 5·24% H, 5·75% Cl, 4·55% N, 5·21% S; found: 54·76% C, 5·50% H, 5·92% Cl, 4·66% N, 5·56% S.

In another batch, 4·0 g pure *XXa* yielded similarly 3·85 g (80%) oily base, which was converted in the usual way to bis(methanesulfonate) crystallizing as monohydrate; m.p. 125—130°C and again 197·5—199°C (ethanol–ether). For $C_{22}H_{33}ClN_2O_8S_3$ (585·2) calculated: 45·16% C, 5·68% H, 6·06% Cl, 4·79% N, 16·44% S; found: 45·48% C, 5·75% H, 6·10% Cl, 4·71% N, 16·53% S.

Treatment of the benzene solution after removing the basic fraction by shaking with hydrochloric acid yielded 0·86 g 2-chloro-8-methoxydibenzo[*b,f*]thiepin (*XXI*); m.p. 112—114°C (ethanol). UV spectrum: λ_{max} 228 nm (log ε 4·18), 267 nm (4·04), 291 nm (3·77). NMR spectrum: δ 6·75

to 7·70 (m, 8 H, aromatic and olefinic protons), 3·77 (s, 3 H, OCH_3). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·57% C, 4·04% H, 12·90% Cl, 11·67% S; found: 65·40% C, 4·09% H, 13·17% Cl, 11·80% S.

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

Like in the preceding case, a reaction of 19·0 g *XXb* with 20 g 1-methylpiperazine in 25 ml boiling chloroform yielded 14·0 g (61%) base which crystallized from ethanol and light petroleum; m.p. 130–131°C. IR spectrum: 838 and 896 (2 adjacent and solitary Ar—H), 1030, 1150, 1250 ($ArOCH_3$), 1495, 1551, 1600 (Ar), 2799 and 2839 cm^{-1} (N—CH_3). NMR spectrum: δ 7·80 (d, J = 2·5 Hz, 1 H, aromatic 9-H), 7·45 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·22 (d, J = 9·0 Hz, 1 H, aromatic 1-H), 7·10 (d, J = 2·5 Hz, 1 H, aromatic 4-H), 7·08 (q, J = 9·5; 2·5 Hz, 1 H, aromatic 7-H), 6·80 (d, J = 9·0 Hz, 1 H, aromatic 2-H), 3·00–4·00 (m, 3 H, Ar—CH_2CH—Ar), 3·72 (s, 3 H, OCH_3), 2·60 (m, 4 H, $CH_2N^1CH_2$), 2·48 (m, 4 H, $CH_2N^4CH_2$), 2·27 (s, 3 H, NCH_3). For $C_{20}H_{23}ClN_2OS$ (374·9) calculated: 64·07% C, 6·18% H, 9·46% Cl, 7·47% N, 8·55% S; found: 64·10% C, 6·49% H, 9·71% Cl, 7·60% N, 8·51% S.

Bis(hydrogen maleate), m.p. 165–166°C (acetone). For $C_{28}H_{31}ClN_2O_9S$ (607·0) calculated: 55·40% C, 5·15% H, 5·84% Cl, 4·61% N, 5·28% S; found: 55·41% C, 5·21% H, 6·13% Cl, 4·55% N, 5·57% S.

Processing of the benzene solution freed from bases yielded 5·06 g crude neutral fraction which was chromatographed on a column of 130 g alumina (activity II). Elution with benzene produced 4·01 g compound obtained in the crystalline form from a mixture of light petroleum and ether; m.p. 108–109°C (ethanol). It is 2-chloro-7-methoxydibenzo[*b,f*]thiepin (*XXII*). UV spectrum: λ_{max} 230 nm (log ε 4·44), 270 nm (4·39), 303 nm (3·74), 340 nm (3·43). IR spectrum: 782 (*cis*-CH=CH), 823, 838, 867, 887 (2 adjacent and solitary Ar—H), 1040, 1235 ($ArOCH_3$), 1490, 1550 and 1595 cm^{-1} (Ar). NMR spectrum: δ 6·50–7·50 (m, 8 H, aromatic and olefinic protons), 3·73 (s, 3 H, OCH_3). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·57% C, 4·04% H, 12·90% Cl, 11·67% S; found: 65·70% C, 4·05% H, 12·64% Cl, 11·66% S.

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

A solution of 1·55 g BBr_3 in 10 ml chloroform was added dropwise to a solution of 0·77 g base *IV* in 10 ml chloroform, the mixture was stirred for 6 h at room temperature, left to stand overnight, the chloroform was removed by distillation, the residue was refluxed for 4 h with a mixture of 50 ml ethanol and 10 ml water, the ethanol was evaporated and the residue divided between benzene and a solution of sodium carbonate. Processing of the benzene layer yielded 0·82 g solvate of a base melting first at 113–118°C, then again at 198–205°C. Recrystallization from benzene yielded 0·55 g (75%) substance which after 8 h of drying at 150°C *in vacuo* melts at 211–213°C. UV spectrum: λ_{max} 269 nm (log ε 4·03). IR spectrum: 820, 832, 862 (2 adjacent and solitary Ar—H) 1275 (Ar—OH), 1591 (Ar), 2690 cm^{-1} (NH^+), 2750 and 2820 cm^{-1} (N—CH_3, N—CH_2). For $C_{19}H_{21}ClN_2OS$ (360·9) calculated: 63·23% C, 5·87% H, 9·82% Cl, 7·76% N, 8·88% S; found: 63·26% C, 5·94% H, 9·93% Cl, 7·36% N, 9·16% S.

Bis(methanesulfonate) (monohydrate), m.p. 152–155°C (ethanol–ether). For $C_{21}H_{31}ClN_2O_8S_3$ (571·2) calculated: 44·16% C, 5·47% H, 6·21% Cl, 4·91% N; found: 43·97% C, 5·45% H, 6·16% Cl, 4·90% N.

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

Like in the preceding case, 3·75 g base *V* reacted with 7·5 g BBr_3 in 65 ml chloroform and the primary product was hydrolyzed with aqueous ethanol. After extraction with chloroform and a solu-

tion of Na_2CO_3, the chloroform solution was processed to obtain 2·1 g compound melting at 205 to 210°C which, however, still contains boron. Therefore, 1·35 g of the substance was dissolved in 40 ml ethanol and, after adding 30 ml 3% NaOH, it was refluxed for 6 h. After evaporation of ethanol, the residue was diluted with water. The precipitated compound (1·13 g) melted at 222 to 223°C (aqueous ethanol). IR spectrum: 800, 827, 857 (2 adjacent and solitary Ar—H), 1258 (Ar—OH), 1578, 1600 (Ar), 2580 and 2660 (NH^+), 2750 (N—CH_3), 3·440 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 7·62 (d, $J = 3·0$ Hz, 1 H, aromatic 9-H), 7·38 (d, $J = 9·0$ Hz, 1 H, aromatic 6-H), 7·15 (q, $J = 9·0$; 3·0 Hz, 1 H, aromatic 7-H), 7·15 (d, $J = 9·0$ Hz, 1 H, aromatic 1-H), 6·90 (d, $J = 3·0$ Hz, 1 H aromatic 4-H), 6·67 (q, $J = 9·0$; 3·0 Hz, 1 H, aromatic 2-H), 3·00—4·50 (m, 4 H, Ar—CH_2CH—Ar and OH), 2·50 (m, 4 H, $CH_2N^1CH_2$), 2·32 (m, 4 H, $CH_2N^4CH_2$), 2·12 (s, 3 H, NCH_3). For $C_{19}H_{21}ClN_2OS$ (360·9) calculated: 63·23% C, 5·78% H, 9·82% Cl, 7·76% N, 8·88% S; found: 63·21% C, 6·17% H, 9·79% Cl, 7·89% N, 9·05% S.

Methanesulfonate (*monohydrate*), m.p. 142—145°C (ethanol–acetone–ether). The substance is hygroscopic. For $C_{20}H_{27}ClN_2O_5S_2$ (475·0) calculated: 50·57% C, 5·73% H, 7·46% Cl, 5·90% N, 13·50% S; found: 51·33% C, 5·80% H, 6·96% Cl, 5·57% N, 12·99% S.

The spectra were recorded and interpreted by Drs B. Kakáč, E. Svátek and J. Holubek at the physico-chemical department, the analyses were done at the analytical department by Mr M. Čech, Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mrs A. Slavíková and Mrs J. Hrdá. Antimicrobial activity was estimated by Dr J. Turinová at the bacteriological department, all of this institute. The cooperation of Mrs H. Nováková and Mrs E. Princová with the preparative part of the work is acknowledged. Mrs M. Jandová assisted with the pharmacological evaluation.

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Translated by A. Kotyk.