POTENTIAL METABOLITES OF A NONCATALEPTIC NEUROLEPTICS: 2-CHLORO-8-HYDROXY-10-(4-METHYLPIPERAZINO)- AND -10-[4-(2-HYDROXYETHYL)PIPERAZINO]-10,11-DIHYDRODIBENZO-[*b,f*]THIEPIN*

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Starting from 5-chloro-2-(4-methoxyphenylthio)benzoic acid (*VIII*), five synthetic steps led to 2-chloro-8-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XIII*) which was converted *via* intermediates *XIV* and *XV* to 2-chloro-8-methoxy-10-(4-methylpiperazino)- and 10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*VI* and *VII*). Demethylation with the aid of boron tribromide led to the title compounds *IV* and *V* which are potential metabolites of noncataleptic neuroleptics doclothepin (*II*) and of VÚFB-10032 (*III*). The piperazine derivatives *IV*— *VII* are central depressants and, with the exception of *IV*, also cataleptics, the methoxy derivatives being more active than the hydroxy derivatives. Modified methods of preparation of 5-chloro-2-(phenylthio)benzoic acid (*XIX*) and of the corresponding alcohol *XX* are described. Attempts at preparing 7-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin were unsuccessful; demethylation of the corresponding 7-methoxy compound proceeds with elimination of methylpiperazine. The attempt at preparing 7-hydroxy derivatives of *II* and *III* was hence interrupted at the stage of 2-chloro-10-hydroxy-7-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXXIV*).

The discrepancy between the inactivity of clozapine (*I*), the prototype of noncataleptic neuroleptics[1], in basic tests on animals used for assessing neuroleptic activity (cataleptic, antiamphetamine and antiapomorphine activity), and its antipsychotic activity (with practical absence of extrapyramidal side effects) has not been satisfactorily resolved although several theories exist that operate with experimentaly established difference between the interactions of clozapine (*I*) and the classical neuroleptics with cerebral catecholamines, especially dopamine, in some parts of the brain, particularly in the striatum and in the limbic system[2-12]. In our work on the group of potential noncataleptic neuroleptics[13-15] we took up this discrepancy and formed a working hypothesis which considers the possibility of bioactivation of clozapine by metabolic reactions[16]. The hypothesis is based on data about the metabolism of chlorpromazine and on observations made in the series of 10-piperazinodibenzo[*b,f*]thiepin neuroleptics.

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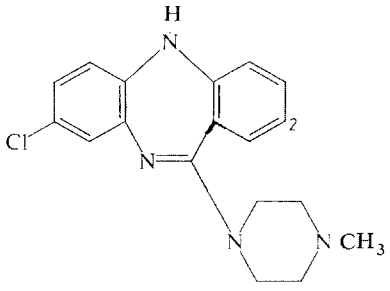
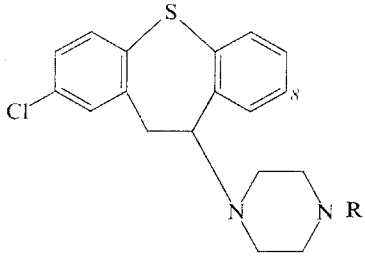
1. Some metabolic mechanisms may result in a partial or in a complete inactivation, others give rise to products of activity comparable with that of the starting compound or even higher (bioactivation). S-Oxidations and N-demethylations of chlorpromazine[17] as well as of octoclothepin[18,19] are basically inactivation mechanisms. On the other hand, the N-oxidation and particularly hydroxylation in some positions of aromatic rings may be in some cases bioactivating or at least activity-conserving processes (by activity we do not mean the central depressant activity but the neuroleptic activity proper). Thus, *e.g.*, octoclothepin N-oxide[19] at about half its toxicity displays about 50% cataleptic activity of octoclothepin. A similar relationship exists between noroxyclothepin and oxyclothepin[18] and their N-oxides[19,20]. Some of the N-oxides of this series are enormously cataleptically active[20]. Of the hydroxy derivatives of chlorpromazine, the most important metabolite appears to be 7-hydroxychlorpromazine which resembles chlorpromazine in its central depressant activity[21–23], in affecting conditioned reflexes of rats[24], in its effect on the accumulation of homovanillic acid in mouse brain[25,26], in its antiamphetamine activity[27,28] and cataleptic activity[29]. The 8-hydroxy derivative of perathiepin[30] (which has not been detected among perathiepin metabolites) is cataleptically more active than perathiepin. The 3-hydroxy derivative of octoclothepin (this was demonstrated as a metabolite) is less toxic and simultaneously more effective as a sedative and as a cataleptic than octoclothepin[31].

2. There exist considerable interspecies differences in the biotransformation of chlorpromazine[32–34], there being indications that in rodents the inactivating mechanisms predominate while in man the activity is preserved. There are differences in the metabolism of chlorpromazine between various patients; it is known[35] that those who mainly transform chlorpromazine to sulfoxide are resistant toward treatment with chlorpromazine. On the other hand, patients in whom 7-hydroxychlorpromazine is formed greatly as a metabolite, respond favourably to treatment with chlorpromazine.



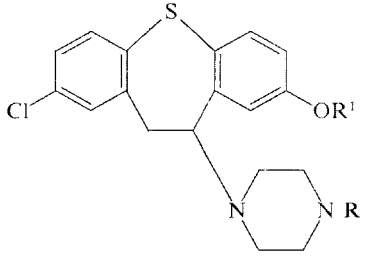
I



II, R = CH_3
III, R = CH_2CH_2OH

The possibility cannot be excluded that the neuroleptically inactive clozapine (*I*) is metabolized in rodents as well as in dogs to inactive metabolites. On the other hand, in humans a bioactivating mechanism generating the neuroleptically active substance may play an important role. This mechanism can be based on N-oxidation (the N-oxide of clozapine is reported to be the principal metabolite in man and dog[36,37]) or on hydroxylation (in man the formation of phenolic metabolites has been reported but none of them could be identified[36]). There are no reports on the pharmacology of the mentioned clozapine metabolites.

To contribute at least indirectly to the verification of this view, 8-hydroxy derivatives of two potential noncataleptic neuroleptics were synthesized, *viz.* doclothepin (*II*)[15,38] and VÚFB-10032 (*III*)[15,39–41]. In products *IV* and *V*, the hydroxyl group was placed in position 8 which is known to play a fundamental role for the localization of the neuroleptic substituent[38,42]. It was shown here[30] that the hydroxyl may function as a "neuroleptic substituent". Besides, position 8 in compounds *II* and *III* is the only free *para* position toward the sulfur atom, *i.e.* a position extraordinarily strongly activated; enzymic hydroxylation into this position is thus highly probable. Synthesis of *IV* and *V* is the main subject of the present communication.

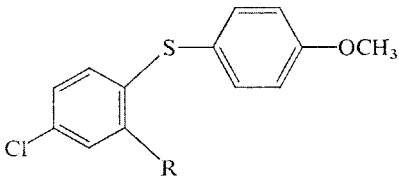


IV, R = CH_3, R^1 = H
V, R = CH_2CH_2OH, R^1 = H
VI, R = R^1 = CH_3
VII, R = CH_2CH_2OH, R^1 = CH_3

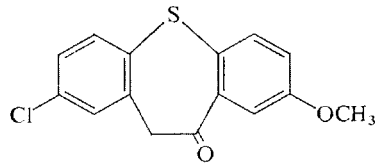
The usual procedure has been used for the synthesis[15,38] proceeding from 5-chloro-2-iodobenzoic acid[38] and 4-methoxythiophenol[43]. The starting compounds were condensed in the presence of potassium carbonate and copper in dimethylformamide at 150°C, with the formation of 5-chloro-2-(4-methoxyphenylthio)benzoic acid (*VIII*) which was reduced with lithium aluminium hydride in ether to the alcohol *IX*. Treatment with thionyl chloride in boiling benzene gave an almost theoretical yield of 5-chloro-2-(4-methoxyphenylthio)benzyl chloride (*X*), which, through treatment with sodium cyanide in dimethylformamide at 50°C yielded nitrile *XI*. Hydrolysis with aqueous-ethanolic potassium hydroxide yields acid *XII* which was cyclized with polyphosphoric acid in boiling toluene to 2-chloro-8-methoxydibenzo[*b*,*f*]-thiepin-10(11*H*)-one (*XIII*). Reduction with sodium borohydride in boiling ethanol resulted in alcohol *XIV* which was converted to chloride *XV* in a reaction with excess thionyl chloride in boiling benzene. Substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in boiling chloroform yielded 2-chloro-8-methoxy-10-(4-methylpiperazino)- and 10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VI*, *VII*) besides the usual elimination product, in this case a new 2-chloro-8-methoxydibenzo[*b*,*f*]thiepin (*XVI*). In both cases, the substitution predominated heavily over the elimination reaction.

Demethylation of *VI* and *VII* was done with boron tribromide in chloroform at room temperature (for method see[30,31,44,45]); decomposition of the primarily

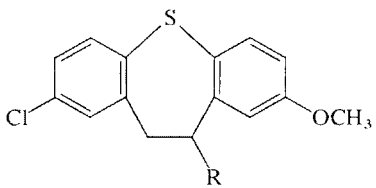
formed boric ester was done with ethanol. Dihydrobromides of phenolic bases *IV* and *V* crystallized and bases were liberated from them. Their high melting points suggest the character of internal salts; their identity was verified by spectra.



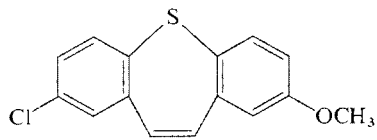
VIII, R = COOH
IX, R = CH_2OH
X, R = CH_2Cl
XI, R = CH_2CN
XII, R = CH_2COOH



XIII

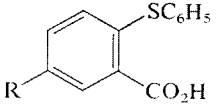


XIV, R = OH
XV, R = Cl

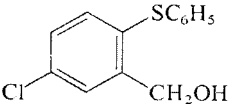


XVI

On this occasion we shall describe some contributions to the preparation of doclothepin (*II*) and of VÚFB-10032 (ref.[15,38–41]) (*III*). Firstly, attempts were made to modify the synthesis of 5-chloro-2-(phenylthio)benzoic acid (*XIX*), the preparation of which was described *e.g.* by reaction of 5-chloro-2-iodobenzoic acid with thiophenol[38]. This time, it was prepared by a sequence of steps proceeding from 2-iodo-5-nitrobenzoic acid[46] *via* intermediates *XVII* and *XVIII*. Reaction of 2-iodo-5-nitrobenzoic acid with thiophenol in boiling aqueous solution of potassium hydroxide in the presence of copper yielded 5-nitro-2-(phenylthio) benzoic acid (*XVII*), prepared here analogously before from 2-chloro-5-nitrobenzoic acid[14]. Subsequent reduction, carried out best with iron and acetic acid in aqueous dioxane, results in a high yield of 5-amino-2-(phenylthio)benzoic acid (*XVIII*) which was converted to acid *XIX* by Sandmeyer's reaction[38]. Reduction of this acid to 5-chloro-2-(phenylthio)benzyl alcohol[38] (*XX*) was done with diborane (for method see[13,14,47]). While reduction of acid *XIX* with lithium aluminium hydride[38] results in a crystalline and homogeneous product *XX*, application of sodium dihydridobis(2-methoxyethoxy)aluminate (*e.g.*[48] in the case of the position isomer) results here in a noncrystalline and nonhomogeneous product.

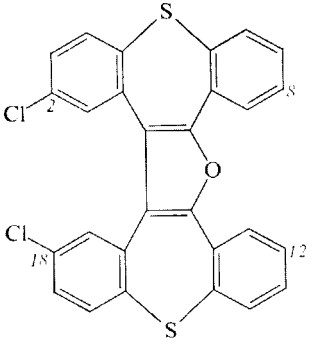


XVII, R = NO_2
XVIII, R = NH_2
XIX, R = Cl

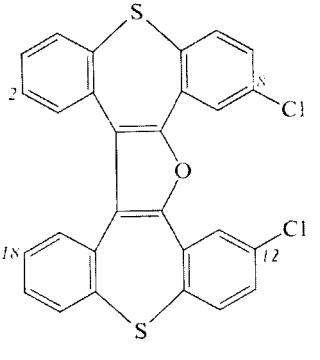


XX

When preparing larger batches of 2-chloro-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]-thiepin by reduction of 2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one with sodium borohydride[38] there was a small amount (some 0·5%) of a by-product which was poorly soluble, high-melting and which was present in the starting ketone (shown by TLC) and which, according to analysis, mass spectrum and from analogies[49-52], is 2,18-dichlorofuro[2,3-*m*; 4,5-*m'*]bis(dibenzo[*b*,*f*]thiepin) (*XXI*). Even if the structure of this type of compounds (see also[49-52]) cannot be considered as definitely established it is thought to be probable and it is assumed that compounds of this type are formed by dehydration of ketones of this series, giving rise to dienol ethers and by subsequent stabilization achieved through spontaneous dehydrogenation.



XXI



XXII

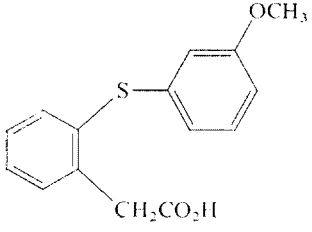
A certain analogy is found in the formation of 2,3,4,5-tetraphenylfuran in the reaction of benzoin with hydrochloric acid at 130°C where a primary disproportionation to benzil (which is discarded as a by-product) and deoxybenzoin[53] takes place, and further in the formation of diphenanthro[9,10-b; 9′,10′-*d*]furan by a thermic reaction from 10-acetoxy-9-phenanthrol[54] or by heating phenanthrene quinone with hydroiodic acid and phosphorus with the simultaneous rise of 9-phenanthrol and di(9-phenanthryl)ether[55]. As it was possible to envisage different mechanisms of formation of these compounds, such as that allowing the formation of an identical

product, namely the corresponding 2,12-dichloro derivative, from 2-chlorodibenzo-[*b*,*f*]thiepin-10(11*H*)-one[38] and from the isomeric 8-chlorodibenzo[*b*,*f*]thiepin--10(11*H*)-one[48,56], the above 8-chloroketone was subjected to treatment with polyphosphoric acid at 170°C. A high-melting product, clearly distinct from *XXI* was obtained in a 25% yield but it was isomeric with *XXI* according to analysis and mass spectrum. Hence it is ascribed the isomeric structure of 8,12-dichlorofuro[2,3-*m*;4,5-*m'*]bis(dibenzo[*b*,*f*]thiepin) (*XXII*). The result of this experiment is considered as evidence for the correctness of the above view on the mechanism of formation of heptacyclic furans of type *XXI* and *XXII* which may be a general phenomenon when treating ketones of the dibenzo[*b*,*f*]thiepin series with polyphosphoric acid under more stringent conditions (higher temperature, longer reaction period).

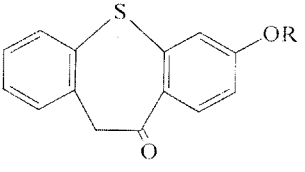
Like with the preparation of the 8-hydroxy derivatives of *II* and *III*, we attempted to prepare the analogous 7-hydroxy derivatives. The presence of methoxyl (and especially of hydroxyl) in the *para* position with respect to carbon $C_{(10)}$ is reflected in a marked labilization of the bond between $C_{(10)}$ and the heteroatom. This phenomenon had been encountered in the synthesis of 7-methoxy-10-(4-methylpiperazino)--10,11-dihydrodibenzo[*b*,*f*]thiepin[57] when it was not possible to prepare 10-chloro--7-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin in the pure state, due to its spotaneous elimination of hydrogen chloride with the appearance of 3-methoxydibenzo[*b*,*f*]-thiepin. Neither was it possible to carry out a substitution reaction of the crude chloride with 1-methylpiperazine since the elimination reaction took place quantitatively. As a model experiment we demethylated 7-methoxy-10-(4-methylpiperazino)-10,11--dihydrodibenzo[*b*,*f*]thiepin[57] with boron tribromide under similar conditions as used for the preparation of *IV* and *V*. On standing, hydrobromide of the base precipitated from the reaction mixture; it was identified as dihydrobromide of 1-methylpiperazine[58]. Because of the large amount of this product it was clear that the treatment with boron tribromide resulted practically solely in N-dealkylation, *i.e.* elimination.

We attempted to reach the desired phenolic amine by carrying out the demethylation at the stage of an intermediate. In this connection we developed a new procedure for preparing (2-iodophenyl)acetic acid[47,59] based on hydrolysis of oxindole[60] with barium hydroxide and diazotization of the formed (but not isolated) (2-aminophenyl)acetic acid and on the reaction of the diazonium salt with potassium iodide. A direct reaction of (2-iodophenyl)acetic acid with 3-methoxythiophenol[61] yielded 2-(3-methoxyphenylthio)phenylacetic acid (*XXIII*) which had been prepared by hydrolysis of the nitrile[57]. The 7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one[57] (*XXIV*), prepared before was demethylated by heating with pyridine hydrochloride to 200°C yielding 7-hydroxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXV*). Reaction of this phenol ketone with an equivalent of acetic anhydride and pyridine in acetone produced acetate *XXVI*. The ester was not found to be a suitable intermediate with a weakly protected phenolic group; during its reduction with sodium boro-

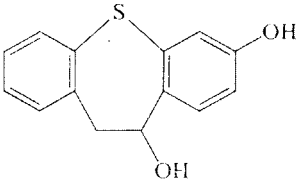
hydride in aqueous dioxane or lithium borohydride in a mixture of tetrahydrofuran and ether, the phenolic hydroxyl is always bared (either during the reaction or during treatment of the reaction mixture) so that there results 7,10-dihydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVII*). During the reaction of this compound with hydrogen chloride in benzene there arises an unusable mixture of substances (in analogy with the 10-chloro-8-hydroxy analogue[30]).



XXIII

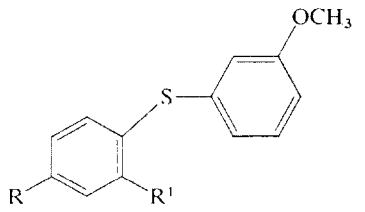


XXIV, R = CH_3
XXV, R = H
XXVI, R = $COCH_3$



XXVII

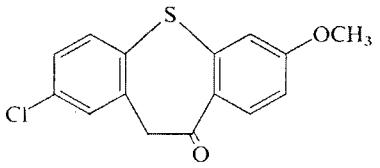
In parallel with this, the synthesis of 7-methoxy derivatives of *II* and *III* was developed which was interrupted at the stage of alcohol *XXXIV*. 2-Iodo-5-nitrobenzoic acid[46] was condensed with 3-methoxythiophenol[61] in boiling aqueous solution of potassium hydroxide in the presence of copper, giving rise to 2-(3-methoxyphenylthio)-5-nitrobenzoic acid (*XXVIIIa*) which was reduced with diborane to 2-(3-methoxyphenylthio)-5-nitrobenzyl alcohol (*XXIXa*). Acid *XXVIIIa* was also reduced with iron and with acetic acid in aqueous dioxane to 5-amino-2-(3-methoxyphenylthio)benzoic acid (*XXVIIIb*) which was converted to 5-chloro-2-(3-methoxyphenylthio)benzoic acid (*XXVIIIc*). Reduction of nitroalcohol *XXIXa* with stannous chloride yielded aminoalcohol *XXIXb* which was converted by Sandmeyer's reaction to 5-chloro-2-(3-methoxyphenylthio)benzyl alcohol (*XXIXc*). Subsequent reaction with thionyl chloride in benzene yielded chloride *XXXc* which reacted with potassium cyanide to nitrile *XXXIc*. Hydrolysis with aqueous–ethanolic KOH resulted in 5-chloro-2-(3-methoxyphenylthio)phenylacetic acid (*XXXIIc*) which was cyclized with polyphosphoric acid in boiling toluene to 2-chloro-7-methoxydibenzo[*b*,*f*]-thiepin-10(11*H*)-one (*XXXIII*). Reduction with sodium borohydride in aqueous dioxane yielded 2-chloro-10-hydroxy-7-methoxy-10,11-dihydrodibenzo[*b*,*f*]-thiepin (*XXXIV*).



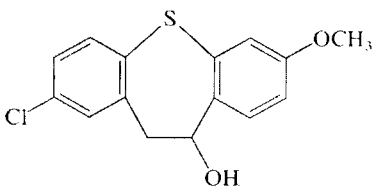
a, R = NO_2
b, R = NH_2
c, R = Cl

XXVIII, R^1 = COOH
XXIX, R^1 = CH_2OH
XXX, R^1 = CH_2Cl

XXXI, R^1 = CH_2CN
XXXII, R^1 = CH_2COOH



XXXIII



XXXIV

The 8-hydroxy and 8-methoxy derivatives of *II* and *III* (*IV*—*VII*) were evaluated pharmacologically after oral application for depressant and neuroleptic activity. The results are shown in Table I. The acute toxicity was determined in mice and is expressed in the form of mean lethal doses (LD_{50}). In the rotating-rod test in mice the mean effective doses at the time of maximum effect, bringing about ataxia were determined (ED_{50}). Catalepsy was determined in a test on rats and is expressed by the mean effective doses (ED_{50}). With two compounds (*VI* and *VII*) the depressant activity was checked by using the locomotor activity test in mice, the neuroleptic activity in the test of antiapomorphine effect in a test on rats, parameters of chewing and agitation being evaluated.

Values in Table I indicate that the new substances are about equally toxic as the prototypes from which they were derived (*II* and *III*). All four are clearly effective as central depressants, like *II* and *III*. They are about twice as active as octoclothepin and three times as effective as clozapine. With the exception of *IV* (which is somewhat unexpected) the new substances have cataleptic activity, the methoxy derivatives *VI* and *VII* being more active than the hydroxy derivative *V*. Methoxy derivatives *VI* and *VII* attain more than 50% of the cataleptic activity of octoclothepin; in the test of antiapomorphine activity in rats, their effect is little pronounced. The most important finding is the cataleptic activity of the 8-hydroxy derivative *V* of VÚFB-10032 which is about equally effective as chlorpromazine. This finding is in agreement with the view on bioactivation of the so-called noncataleptic neuroleptics in the human body (save for the fact that *V* has not been detected so far as a metabolite of VÚFB--10 032).

TABLE I

Pharmacological Properties of Prepared Compounds on Oral Administration (mg/kg)

Compound[a]	Code number	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
IV	VÚFB-10.682	c. 90	1·25	>50[b]
V	VÚFB-10·683	c. 80	1·0	18
VI	VÚFB-10.656	94	0·81[c]	6·4
VII	VÚFB-10.657	81	1·5[d]	7·0
Clozapine		210	3·8	>50[e]
Doclothepin (*II*)	VÚFB-10.030	70	1·2	>50[f]
III	VÚFB-10.032	84	0·8	>50[g]
Octoclothepin		78	2·2	4·3
Chlorpromazine		198	8·2	16·0

[a] The compounds were applied in the form of salts (see Experimental), the values in the table referring to the bases. [b] The dose shown brings about catalepsy with 10% animals. [c] The incoordinating and cataleptic activities were still apparent 24 h after administration with 40% animals; in the photo-cell method, the locomotor activity of mice was greatly inhibited, D_{50} 0·85 mg/kg (brings about a reduction of locomotor activity by 50% of the control); a dose of 10 mg/kg inhibits the apomorphine-induced chewing and agitation of rats to 85% of the control value. [d] The incoordinating and cataleptic activities could be demonstrated 24 h. after the administration with 40% animals; the inhibition of the locomotor activity of mice was shown in the photocell method, D_{50} 0·73 mg/kg; a dose of 10 mg/kg inhibits the apomorphine-induced chewing and agitation in rats to 98 and 94% of the control values (*i.e.* insignificantly). [e] The dose shown was completely inactive. [f] The dose shown active in 10% animals. [g] The dose shown active in 20% animals.

TABLE II

Antimicrobial Activity of the Prepared Compounds *in vitro* (mcg/ml)

Compound[a]	Microorganism[b]							
	1	2	3	4	5	6	7	8
IV	50	—	25	25	100	50	100	—
V	50	25	25	25	100	100	100	100
VI	50	25	25	<5	25	100	100	100
VII	—	50	50	<5	50	100	100	100

[a] The compounds were tested in the form of salts (Experimental part). [b] 1 *Streptococcus* β-*haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Mycobacterium tuberculosis* H37Rv, 5 *Saccharomyces pasterianus*, 6 *Trichophyton mentagrophytes*, 7 *Candida albicans*, 8 *Aspergillus niger*.

The compounds were tested at the bacteriological department of this institute (Drs J. Turinová and A. Čapek) for antimicrobial activity *in vitro* toward a standard set of microorganisms. The results are shown in Table II as the usual minimum inhibitory concentrations in μg/ml. All the four compounds were inactive against *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus vulgaris*. The marked antituberculosis activity of *VI* and *VII* should be noted.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in deuteriochloroform unless stated otherwise) in a Tesla BC 487 (80 MHz) spectrometer and mass spectra in a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

5-Chloro-2-(4-methoxyphenylthio)benzoic Acid (*VIII*)

Potassium carbonate (26·5 g) and 1·1 g copper (reduced from a solution of $CuSO_4$ and washed with dimethylformamide) were added to a solution of 50·0 g 5-chloro-2-iodobenzoic acid[38] and 30·4 g 4-methoxythiophenol[43] in 35 ml dimethylformamide and the mixture was heated to 110 to 115°C (a 125—130°C bath). The mixture was stirred at that temperature for 1 h and then on a 150°C bath for 2 h. After partial cooling, it was diluted with 250 ml hot water, after homogenization it was poured into 2 litres cold water, acidified with 115 ml hydrochloric acid and the product was extracted with 1·5 litre chloroform. The extract was dried with $CaCl_2$, filtered and evaporated. The residue was dissolved in 250 ml ethanol, the solution was filtered while hot with charcoal and the filtrate was combined with 200 ml hot water. On standing, 49·0 g (94%) product crystallized; m.p. 175—181°C. The analytical product melts at 182—183°C (aqueous ethanol). IR spectrum: 828, 903 (2 adjacent and solitary Ar—H), 923 (COOH), 1250 ($ArOCH_3$), 1499, 1552, 1577, 1593 (Ar), 1690 (ArCOOH), 2550, 2610, 2660, 2720 cm^{-1} (COOH). For $C_{14}H_{11}ClO_3S$ (294·7) calculated: 57·05% C, 3·76% H, 12·03% Cl, 10·88% S; found: 57·14% C, 3·80% H, 12·17% Cl, 10·80% S.

5-Nitro-2-(phenylthio)benzoic Acid (*XVII*)

Thiophenol (79·3 g) was dissolved under stirring in a solution of 85 g KOH in 1500 ml water. 2-Iodo-5-nitrobenzoic acid[46] (190 g, m.p. 197—199°C) and 2·0 g copper was then added and the mixture was refluxed for 3 h. It was filtered while hot with charcoal and the filtrate was cooled and acidified with hydrochloric acid. The product was filtered on the following day and recrystallized from ethanol; 143 g (78%), m.p. 228—232°C (ref.[14] reported a m.p. of 232—235°C).

2-(3-Methoxyphenylthio)-5-nitrobenzoic Acid (*XXVIIIa*)

Like in the preceding case, 100 g 2-iodo-5-nitrobenzoic acid[46], 120 g 3-methoxythiophenol[61] and 53 g KOH reacted in 1 litre water in the presence of 1·0 g Cu. A total of 86·5 g (83%) product was obtained; m.p. 190—199°C. This was recrystallized for analysis from methanol; m.p. 201 to 203°C. UV spectrum: λ_{max} 343 nm (log ε 4·17), infl. 260 nm (3·88). IR spectrum (KBr): 778, 808, 840, 870 (3 and 2 adjacent and solitary Ar—H), 912, 1233 (COOH), 1252 ($ArOCH_3$), 1345,

1520 (NO_2), 1577, 1594 (Ar), 1692 (ArCOOH), 2500, 2570 and 2640 cm^{-1} (COOH). For $C_{14}H_{11}NO_5S$ (305·3) calculated: 55·07% C, 3·63% H, 4·59% N, 10·50% S; found: 55·32% C, 3·80% H, 4·72% N, 10·74% S.

5-Amino-2-(phenylthio)benzoic Acid (*XVIII*)

A solution of 400 g *XVII* in 1 litre dioxane was added dropwise at 100°C to a stirred mixture of 2·2 litres dioxane, 500 ml water, 400 g powdery iron and 400 ml acetic acid. The mixture was refluxed under stirring for 4 h. After distillation of about 500 ml liquid a solution of 350 g NaOH in 500 ml water was added dropwise and distillation continued. A total of 3 litres solvent was removed by distillation. The residue was dissolved with 2 litres water, filtered and the filtrate was acidified with acetic acid. After 24 h of standing the precipitated product was filtered; 311g (87%), m.p. 225—229°C. The compound is poorly soluble in organic solvents and purification by crystallization is difficult. After recrystallization from dimethylformamide a product is obtained which melts lower than the crude substance. Therefore, a sample was neutralized with methanesulfonic acid in ethanol to prepare a solution of methanesulfonate which crystallized after an addition of ether; m.p. 232—234°C (ethanol–ether). For $C_{14}H_{15}NO_5S_2$ (341·4) calculated: 49·25% C, 4·43% H, 4·10% N, 18·78% S; found: 48·81% C, 4·55% H, 4·10% N, 18·54% S.

5-Amino-2-(3-methoxyphenylthio)benzoic Acid (*XXVIIIb*)

Like in the preceding case, 71·4 g acid *XXVIIIa* was reduced with 60 g Fe and 75 ml acetic acid in 650 ml dioxane and 100 ml water. A crude product (54·1 g, 84%) was precipitated from an aqueous solution of a sodium salt by acidification with acetic acid to pH 6·5; m.p. 219—222°C. UV spectrum: λ_{max} 263 nm (log ε 4·16), infl. 345 nm (3·44). IR spectrum: 785, 803, 855 (3 and 2 adjacent and solitary Ar—H), 1250 ($ArOCH_3$), 1481, 1539, 1573, 1591 (Ar), 1632 (COO^-), 2040, 2500 cm^{-1} (NH_3^+, COOH). For $C_{14}H_{13}NO_3S$ (275·3) calculated: 61·07% C, 4·76% H, 5·09% N, 11·65% S; found: 60·65% C, 4·83% H, 4·91% N, 11·43% S.

5-Chloro-2-(phenylthio)benzoic Acid (*XIX*)

A warm-prepared solution of 245 g *XVIII* in 500 ml concentrated hydrochloric acid was diluted with 300 ml water and the suspension formed was stirred at 0°C for 8 h, during which period a solution of 70 g $NaNO_2$ in 250 ml water was added dropwise. The suspension of the diazonium salt was stirred while it was introduced into a solution of 150 g CuCl in 500 ml hydrochloric acid which was overlayered with 1 litre toluene at 80°C. Then it was heated under stirring for 8·5 h to 100°C. After cooling, the toluene layer was separated, the acid product was extracted with excess 5% NaOH and the aqueous-ethanolic solution was acidified with hydrochloric acid. After 24 h of standing the precipitated product was filtered and recrystallized from aqueous ethanol: 194 g (74%), m.p. 162—164°C. Further recrystallization from aqueous ethanol yielded the analytical product; m.p. 166—167°C. The same product had been prepared before[38] using a different procedure.

5-Chloro-2-(3-methoxyphenylthio)benzoic Acid (*XXVIIIc*)

Like in the preceding case, 10·0 g *XXVIIIb* in 20 ml hydrochloric acid and 10 ml water was diazotized with 6·9 g $NaNO_2$ in 20 ml water and the suspension of the diazonium salt was decomposed by transferring it to a solution of 5·5 g CuCl in 25 ml hydrochloric acid. A total of 9·2 g (86%) crude product was obtained; this was crystallized from aqueous methanol; m.p. 159—161°C.

UV spectrum: λ_{max} 223 nm (log ε 4·39), 258 nm (4·05), infl. 280 nm (3·89), infl. 288 nm (3·83), 330 nm (3·63). IR spectrum: 780, 821, 858 (3 and 2 adjacent and solitary Ar—H), 920 (COOH), 1030 ($ArOCH_3$), 1250 and 1310 ($ArOCH_3$ and COOH), 1547, 1589 (Ar), 1682 cm^{-1} (ArCOOH). For $C_{14}H_{11}ClO_3S$ (294·8) calculated: 57·04% C, 3·76% H, 12·03% Cl, 10·88% S; found: 56·77% C, 3·75% H, 12·21% Cl, 10·98% S.

5-Chloro-2-(4-methoxyphenylthio)benzyl Alcohol (*IX*)

VIII (25·4 g) was added dropwise over a period of 15 min to a solution of 7·0 g $LiAlH_4$ in 250 ml ether and the mixture was refluxed for 7 h. After cooling, 7 ml 20% NaOH and 30 ml water were added dropwise. The mixture was combined with 7 g K_2CO_3 and, after 10 min of stirring, the solid fraction was filtered. Evaporation of the filtrate yielded the product; 22·8 g (94%), m.p. 65—67°C. An analytical sample melted at 66—68°C (benzene–cyclohexane). For $C_{14}H_{13}ClO_2S$ (280·8) calculated: 59·89% C, 4·67% H, 12·62% Cl, 11·42% S; found: 60·00% C, 4·69% H, 12·47% Cl, 11·36% S.

5-Chloro-2-(phenylthio)benzyl Alcohol (*XX*)

Sodium borohydride (61 g) was added to a solution of 320 g acid *XIX* in 700 ml tetrahydrofuran under stirring at 5—10°C over a period of 90 min and the mixture was stirred for 1 h. During 1 h a total of 160 ml boron trifluoride etherate (at below 25°C) was added and the mixture was stirred for 3·5 h. After standing overnight at room temperature, 200 ml 5% hydrochloric acid was added dropwise under stirring over a period of 4 h, the mixture was diluted with 500 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$, filtered with charcoal and evaporated. A total of 297 g (98%) residue melting at 52—56°C was obtained. This was used for further work. For a pure product, ref.[38] reported a m.p. of 57·5—58°C.

5-Amino-2-(3-methoxyphenylthio)benzyl Alcohol (*XXIXb*)

Like in the preceding case, nitro acid *XXVIIIa* (86 g) was reduced with 11·5 g $NaBH_4$ and 38 ml boron trifluoride etherate in 200 ml tetrahydrofuran. After standing overnight it was decomposed with 200 ml water and the product was isolated by extraction with dichloromethane. Processing of the extract yielded 83·9 g (theoretical amount) oily 2-(3-methoxyphenylthio)-5-nitrobenzyl alcohol (*XXIXa*). A solution of 80 g crude *XXIXa* in 1300 ml ether was combined with portions of 252 g $SnCl_2.2\,H_2O$ and the mixture was refluxed for 10 min during which period 250 ml hydrochloric acid was added. The mixture was stirred and refluxed for 4 h, cooled and neutralized by an addition of 20% NaOH (about 1 litre). After standing overnight the ether layer was separated, dried with MgSO4 and evaporated. The residue was recrystallized from benzene to 48·3 g (67%) amino alcohol *XXIXb*, melting at 68—70°C; analytical sample melted at 70—71°C (benzene). IR spectrum: 769, 845, 868, 890 (3 and 2 adjacent and solitary Ar—H), 1045, 1295 (CH_2OH), 1240 ($ArOCH_3$), 1472, 1576, 1596, 1610 (Ar), 3200 (OH), 3295, 3390 cm^{-1} (NH_2). For $C_{14}H_{15}NO_2S$ (261·3) calculated: 64·34% C, 5·78% H, 5·36% N, 12·27% S; found: 64·44% C, 5·76% H, 5·26% N, 11·93% S.

5-Chloro-2-(3-methoxyphenylthio)benzyl Alcohol (*XXIXc*)

Suspension of hydrochloride of aminoalcohol *XXIXb* which was prepared by dissolving 48 g *XXIXb* in 60 ml hot hydrochloric acid and subsequent dilution with 110 ml ice-cold water, was diazotized at 0°C with a solution of 13·5 g $NaNO_2$ in 70 ml water. The solution formed was

poured into a solution of 30 g CuCl in 125 ml hydrochloric acid at 10°C and heated for 1 h to 100°C. After cooling, the product was isolated by extraction with benzene. Processing of the extract yielded 46·2 g (80%) oil, a sample of which was redistilled for analysis; b.p. 173°C/1 Torr. For $C_{14}H_{13}ClO_2S$ (280·8) calculated: 12·63% Cl, 11·41% S; found: 12·34% Cl, 11·60% S.

5-Chloro-2-(4-methoxyphenylthio)benzyl Chloride (*X*)

A solution of 17·8 g $SOCl_2$ in 20 ml benzene was added dropwise to a solution of 22·8 g *IX* in 100 ml benzene, the mixture was heated to 50°C, stirred for 2 h at this temperature and refluxed for 2 h. After evaporation of the volatile fractions at reduced pressure the residue was dissolved in 100 ml benzene, the solution was filtered with charcoal and some $CaCl_2$ and the filtrate was evaporated. Yield 23·4 g (97%) residue, m.p. 66—70°C; the analytical sample melts at 71·5 to 72·5°C (cyclohexane–light petroleum). ^{1}H-NMR spectrum: δ 6·70—7·50 (m, 7 H, Ar—H), 4·68 (s, 2 H, $ArCH_2Cl$), 3·85 (s, 3 H, OCH_3). For $C_{14}H_{12}Cl_2OS$ (299·2) calculated: 56·19% C, 4·04% H, 23·70% Cl, 10·72% S; found: 56·32% C, 3·84% H, 23·57% Cl, 11·09% S.

5-Chloro-2-(3-methoxyphenylthio)benzyl Chloride (*XXXc*)

Like in the preceding case, 40·8 g *XXIXc* reacted with 19·1 g $SOCl_2$ in 250 ml boiling benzene. Yield 40·2 g (92%) oil, a sample of which was purified by distillation; b.p. 159°C/0·6 Torr. ^{1}H-NMR spectrum: δ 7·45 (bs, 1 H, 6-H in the benzyl chloride part), 6·60—7·30 (m, 6 H, remaining Ar—H), 4·65 (s, 2 H, $ArCH_2Cl$), 3·80 (s, 3 H, OCH_3). For $C_{14}H_{12}Cl_2OS$ (299·2) calculated: 56·19% C, 4·04% H, 23·70% Cl, 10·72% S; found: 56·59% C, 4·20% H, 23·34% Cl, 10·96% S.

5-Chloro-2-(4-methoxyphenylthio)phenylacetonitrile (*XI*)

A mixture of 18·5 g *X*, 5·5 g NaCN and 15 ml dimethylformamide was heated to 30°C, whereupon the mixture heated spontaneously to 50°C. After waning of the reaction, the mixture was stirred for 3·5 h at 30—35°C, diluted with 200 ml water and extracted with chloroform. The extract was washed with water, dried with K_2CO_3, filtered with charcoal and distilled; b.p. 152—154°C/0·2 Torr. The distillate was crystallized from 95% ethanol; 12·1 g (70%), m.p. 74—77°C. IR spectrum: 831, 867, 870 (2 adjacent and solitary Ar—H), 1034, 1248 ($ArOCH_3$), 1499, 1594 (Ar), 2255 cm^{-1} (CN). For $C_{15}H_{12}ClNOS$ (239·8) calculated: 62·17% C, 4·17% H, 4·83% N; found: 62·52% C, 4·23% H, 4·88% N.

5-Chloro-2-(3-methoxyphenylthio)phenylacetonitrile (*XXXIc*)

Like in the preceding case, 19·1 g *XXXc* reacted with 5·5 g NaCN in 45 ml dimethylformamide with the difference that after a spontaneous reaction the mixture was stirred for 4 h at 100°C. After evaporation of a part of dimethylformamide in vacuo the residue was diluted with water and the product was isolated by extraction with ether; 15·0 g (82%) oil, a sample of which was purified by distillation; b.p. 190°C/0·6 Torr. For $C_{15}H_{12}ClNOS$ (289·8) calculated: 62·17% C, 4·17% H, 12·24% Cl, 4·83% N, 11·07% S; found: 62·16% C, 4·37% H, 12·16% Cl, 4·28% N, 11·29% S.

5-Chloro-2-(4-methoxyphenylthio)phenylacetic Acid (*XII*)

A solution of 45 g KOH in 100 ml water was added to a mixture of 51·2 g *XI* and 170 ml ethanol and the mixture was stirred and refluxed for 3·5 h. Ethanol was then distilled away, the residue was diluted with 400 ml hot water, the cooled solution was washed with benzene and acidified

with 20% hydrochloric acid to pH 1. After standing overnight in a gerrefriator, the precipitated product was filtered, washed with water and dried; 51·1 g (94%), m.p. —120127°C. The analytical product melted at 127—128·5°C (aqueous ethanol). IR spectrum: 827, 876 (2 adjacent and solitary Ar—H), 915 (COOH), 1238 ($ArOCH_3$), 1253 ($ArOCH_3$ and COOH), 1499, 1592 (Ar), 1708, 2550, 2640, 2740 cm^{-1} (COOH). For $C_{15}H_{13}ClO_3S$ (308·8) calculated: 58·35% C, 4·24% H; found: 58·37% C, 4·23% H.

5-Chloro-2-(3-methoxyphenylthio)phenylacetic Acid (*XXXIIc*)

Like in the preceding case, 13·5 g crude *XXXIc* was hydrolyzed with 15 g KOH in a mixture of 50 ml ethanol and 30 ml water. After acidification of the aqueous solution of the potassium salt, oily acid *XXXIIc* separated and was extracted with a mixture of benzene and ether. A total of 12·6 g (88%) residue was obtained, a sample of which was recrystallized from a mixture of benzene and cyclohexane, m.p. 88—90°C. IR spectrum: 783, 830, 862 (3 and 2 adjacent and solitary Ar—H), 945 (COOH), 1037 ($ArOCH_3$), 1240 and 1253 ($ArOCH_3$ and COOH), 1483, 1560, 1578, 1592 (Ar), 1708 and 2645 cm^{-1} (COOH). For $C_{15}H_{13}ClO_3S$ (308·8) calculated: 58·34% C, 4·24% H, 11·48% Cl, 10·38% S; found: 58·52% C, 4·41% H, 11·41% Cl, 10·52% S.

(2-Iodophenyl)acetic Acid

A mixture of 12·0 g oxindole[60], 25 g $Ba(OH)_2.8\,H_2O$ and 100 ml water was refluxed under stirring for 24 h. After dilution with 50 ml water a drop of phenolphthalein solution was added and carbon dioxide introduced until decolorization. Then a 20% solution of Na_2CO_3 was added dropwise until a permanently red colour developed. The precipitated $BaCO_3$ was filtered and the filtrate evaporated *in vacuo*. The salt obtained was dissolved in 60 ml water, the solution was combined with 7·6 g $NaNO_2$ and the solution formed was added dropwise at 0°C to a stirred mixture of 35 ml hydrochloric acid and 30 g ice. The solution of the diazonium salt formed at 10°C was added dropwise at room temperature over a period of 30 min to a mixture of 25 g KI, 40 ml water and 6 ml H_2SO_4. The mixture was stirred for further 30 min at room temperature and then for 90 min at 100°C. Iodine was removed by steam distillation. The separating acid was extracted from the residue with chloroform, then shaken with excess 5% NaOH from which it was released by acidification with hydrochloric acid. After 1 h of standing and cooling, it was filtered, washed with water and dried in air; 18·0 g (69%), m.p. 113—116°C. By direct comparison it was found to be identical with the product prepared differently[47] (m.p. 114—116°C).

2-(3-Methoxyphenylthio)phenylacetic Acid (*XXIII*)

3-Methoxythiophenol[61] (30 g) was dissolved in a solution of 56 g KOH in 600 ml water; this was combined with 52·4 g (2-iodophenyl)acetic acid and 1·0 g Cu and the mixture was refluxed under stirring for 8 h. After filtration, the filtrate was acidified with hydrochloric acid and the oil was extracted with chloroform. Processing of the extract yielded a residue which was dissolved in warm benzene with some light petroleum; 36·4 g (67%), m.p. 60—62°C. The compound was found to be identical with the product (m.p. 65—66°C) prepared differently[57].

2-Chloro-8-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XIII*)

A mixture of 60 ml 86% H_3PO_4 and 90 g P_2O_5 was heated for 30 min under stirring at 130°C. Then it was combined with 24·8 g acid *XII* and stirred for 15 min at 115°C. This was followed by a slow addition of 90 ml toluene and the mixture was kept for 3·5 h at a temperature ensuring slow

refluxing of toluene. After the reaction was terminated, further 400 ml toluene was added and the mixture was poured into 600 g mixture of ice and water. The toluene layer was separated, washed with 10% NaOH and water, dried with K_2CO_3 and evaporated. Crystalline crude ketone *XIII* (23·2 g, theoretical amount) was crystallized for analysis from ethanol; m.p. 155—157°C. UV spectrum: λ_{max} 234 nm (log ε 4·48), infl. 256 nm (4·05), 348 nm (3·59). IR spectrum (KBr); 810, 820, 882, 893 (2 adjacent and solitary Ar—H), 1025, 1034, 1222, 1268 ($ArOCH_3$), 1555, 1572, 1592 (Ar), 1666 cm^{-1} (CO—Ar). ^{1}H-NMR spectrum: δ 7·72 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·55 (d, J = 8·5 Hz, 1 H, 4-H), 7·48 (d, J = 8·5 Hz, 1 H, 6-H), 7·42 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·15 (mcd, J = 8·5; 2·0 Hz, 1 H, 3-H), 6·97 (mcd, J = 8·5; 3·0 Hz, 1 H, 7-H), 4·30 (s, 2 H, $ArCH_2CO$), 3·75 (s, 3 H, OCH_3). For $C_{15}H_{11}ClO_2S$ (290·8) calculated: 61·96% C, 3·81% H; found: 61·45% C, 3·71% H.

2-Chloro-7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXXIII*)

Like in the previous case, 10·7 g acid *XXXIIc* was cyclized with 50 g polyphosphoric acid in 50 ml refluxing toluene (4 h). The yield was 9·3 g (92%) crude crystalline product which was crystallized from cyclohexane, m.p. 146—150°C. UV spectrum: λ_{max} 258 nm (log ε 4·36), 264 nm (4·36), infl. 312 nm (3·57). IR spectrum (KBr): 819, 835, 850, 874, 894 (2 adjacent and solitary Ar—H), 1036, 1236, 1256 ($ArOCH_3$), 1485, 1590 (Ar), 1658 cm^{-1} (CO—Ar). ^{1}H-NMR spectrum: δ 8·10 (d, J = 8·0 Hz, 1 H, 9-H), 7·48 (d, J = 8·0 Hz, 1 H, 4-H), 7·37 (mcs, J = 2·5 Hz, 1 H, 1-H), 7·08 (mcd, J = 8·0; 2·5 Hz, 1 H, 3-H), 6·98 (mcs, J = 3·0 Hz, 1 H, 6-H), 6·75 (mcd, J = 8·0; 3·0 Hz, 1 H, 8-H), 4·25 (s, 2 H, $ArCH_2CO$), 3·80 (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: 62·36% C, 3·85% H, 12·07% Cl, 11·34% S.

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

Sodium borohydride (16·0 g) was added to a mixture of 23·2 g ketone *XIII* and 400 ml ethanol and the mixture was refluxed for 4 h. After evaporation of ethanol it was diluted with 500 ml water and the product was extracted with benzene. Processing of the extract yielded a crystalline residue which was recrystallized from a mixture of cyclohexane and ethanol; 18·3 g (78%), m.p. 97—103°C. An analytical sample melts at 99—100°C (cyclohexane–ethanol). IR spectrum (KBr): 804, 812, 824, 885 (2 adjacent and solitary Ar—H), 1025, 1273, 1292 ($ArOCH_3$), 1092 (CHOH in the ring), 1556, 1576, 1597 (Ar), 3320 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 5 H, Ar—H except 7-H), 6·65 (mcd, J = 8·5; 2·0 Hz, 1 H, 7-H), 5·40 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·70 (s, 3 H, OCH_3), c. 3·45 (m, 2 H, $ArCH_2$), 2·46 (bs, disappears after D_2O, 1 H, OH). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H; found: 61·62% C, 4·48% H.

2-Chloro-10-hydroxy-7-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXXIV*)

A solution of 1·2 g $NaBH_4$ in 10 ml water with some NaOH was added dropwise over a period of 10 min under stirring at room temperature to a solution of 8·6 g ketone *XXXIII* in 180 ml dioxane. After further 10 min of stirring the mixture was left to stand for 3 days and then processed as in the preceding case. Yield 8·5 g (98%) crude product melting at 143—146°C. The analytical product melts at 144—146°C (benzene). IR spectrum: 820, 866 (2 adjacent and solitary Ar—H), 1041 (CHOH in the ring), 1236 ($ArOCH_3$), 1499, 1569, 1602 (Ar), 3310, 3337 cm^{-1} (OH). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·61% C, 4·45% H, 12·33% Cl, 10·91% S.

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

A solution of 50 ml $SOCl_2$ in 50 ml benzene was added dropwise to a suspension of 50·0 g alcohol *XIV* in 250 ml benzene, the mixture was slowly heated to boiling temperature and refluxed for 1 h. The volatile fractions were then evaporated *in vacuo*, the residue was dissolved in benzene, the solution was filtered with charcoal and some $CaCl_2$ and then evaporated. A total of 50·5 g (95%) residue melting at 101—104°C was obtained. In mixture with *XIV* it melts with a depression. An analytical sample was obtained by recrystallization from cyclohexane, m.p. 103—104·5°C. For $C_{15}H_{12}Cl_2OS$ (311·2) calculated: 57·88% C, 3·89% H, 22·79% Cl, 10·30% S; found: 57·92% C, 3·82% H, 22·71% Cl, 10·15% S.

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

A mixture of 9·3 g chloride *XV*, 30 g 1-methylpiperazine and 25 ml chloroform was refluxed under stirring for 6·5 h (a 100—110°C bath), diluted with 400 ml benzene and washed several times with water. The benzene solution was shaken with 100 ml 5M-HCl. The precipitated hydrochloride was filtered, washed with benzene and combined with the acid aqueous phase of the filtrate. Treatment with 20% NaOH released the base which was isolated by extraction with benzene; 8·5 g (76%). The base was recrystallized from a mixture of cyclohexane and light petroleum and melted at 94—96°C. ^{1}H-NMR spectrum: δ 7·43 (d, J = 8·0 Hz, 1 H, 4-H), 7·32 (d, J = 8·0 Hz, 1 H, 6-H), 7·25 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·22 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·03 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 6·63 (mcd, J = 8·0; 3·0 Hz, 1 H, 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (s, 3 H, OCH_3), 2·63 and 2·40 (2 def. t, 8 H, 4 CH_2 of piperazine), 2·22 (s, 3 H, NCH_3). For $C_{20}H_{23}ClN_2S$ (374·9) calculated: 64·07% C, 6·18% H, 9·46% Cl, 7·47% N; found: 64·01% C, 6·37% H, 9·59% Cl, 7·54% N.

Dihydrochloride which was prepared by neutralizing the base with an ether solution of hydrogen chloride in ethanol, crystallizes as monohydrate; m.p. 218—220°C under decomposition (95% ethanol–ether). For $C_{20}H_{27}Cl_3N_2O_2S$ (465·8) calculated: 51·56% C, 5·84% H, 6·01% N; found: 51·11% C, 5·53% H, 6·00% N.

Maleate was obtained by neutralization of the base with maleic acid in ethanol: m.p. 193—195°C (ethanol–ether). For $C_{24}H_{27}ClN_2O_5S$ (490·9) calculated: 58·71% C, 5·54% H, 7·21% Cl, 5·71 %N, 6·53% S; found: 58·77% C, 5·62% H, 7·31% Cl, 5·50% N, 6·72% S.

After filtration of hydrochloride of base *VI*, the benzene solution was washed with dilute hydrochloric acid and water, dried and evaporated to obtain 0·4 g neutral product which crystallized from a mixture of cyclohexane and ethanol to melt at 113°C. It is 2-chloro-8-methoxydibenzo-[*b,f*]thiepin (*XVI*). UV spectrum: λ_{max} 227 nm (log ε 4·58), 265 nm (4·43), 295 nm (3·78). ^{1}H-NMR spectrum: δ 6·60—7·50 (m, 8 H, 6 Ar—H and CH=CH), 3·70 (s, 3 H, OCH_3). For $C_{15}H_{11}ClOS$ (274·7) calculated: 65·57% C, 4·03% H, 12·91% Cl, 11·67% S; found: 65·02% C, 4·01% H, 13·09% Cl, 11·91% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-8-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*VII*)

Like in the preceding case, 9·33 g *XV* and 32·5 g 1-(2-hydroxyethyl)piperazine reacted in 35 ml boiling chloroform. A total of 10·2 g (84%) base was obtained. It was purified by crystallization from cyclohexane and it is a solvate with 1/3 molecule cyclohexane, m.p. 82—86°C. For $C_{23}H_{29}Cl.N_2O_2S$ (433·0) calculated: 63·79% C, 6·75% H, 8·20% Cl, 6·47% N, 7·41% S; found: 63·58% C, 6·74% H, 8·22% Cl, 6·33% N, 7·40% S.

Maleate, m.p. 171–172°C (ethanol–ether). IR spectrum: 842 872, 885 (2 adjacent and solitary Ar—H), 1500–1600 (a group of intense bands, Ar), 1617 (COO^-), 1704 (COOH), 3360 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·60–7·60 (m, 6 H, 6 Ar—H), 6·01 (s, 2 H, CH=CH of maleic acid), 3·00–4·00 (m, 5 H, $ArCH_2CHAr$ and CH_2O), 3·70 (s, 3 H, OCH_3), c. 3·20 and 2·80 (2m, 10 H, 5 NCH_2). For $C_{25}H_{29}ClN_2O_6S$ (521·0) calculated: 57·63% C, 5·61% H, 6·81% Cl, 5·38% N, 6·15% S; found: 58·15% C, 5·55% H, 7·16% Cl, 5·64% N, 6·38% S.

After filtering the hydrochloride of base *VII*, the benzene solution was processed to obtain 1·4 g *XVI*, m.p. 111–113°C, identical with *XVI*, isolated from the preceding experiment.

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

A solution of 8·0 g BBr_3 in 15 ml chloroform was added dropwise under stirring at 0°C to a solution of 3·9 g base *VI* in 25 ml chloroform. The mixture was stirred for 2·5 h at room temperature and, after standing overnight, it was decomposed by adding dropwise 30 ml ethanol (20–40°C). After 1 h of stirring the volatile fractions were evaporated *in vacuo*, the residue was dissolved in 35 ml ethanol and crystallization was induced by adding 35 ml ether. A total of 4·4 g (85%) dihydrobromide of base *IV* precipitated. It crystallizes from 90% ethanol (after adding ether) as dihydrate and melts at 209·5–210·5°C under decomposition. For $C_{19}H_{27}Br_2ClN_2O_3S$ (558·8) calculated: 40·84% C, 4·87% H, 6·34% Cl, 5·01% N; found: 40·66% C, 4·36% H, 6·00% Cl, 5·09% N.

Through the decomposition of dihydrobromide with aqueous NH_4OH and extraction with chloroform the base (*IV*) was isolated and recrystallized from ethanol to melt at 252–254°C under decomposition. IR spectrum: 800, 810, 820, 880, 894 (2 adjacent and solitary Ar—H), 1240 (Ar—OH), 1562, 1606 (Ar), 2580 cm^{-1} (NH^+ and OH). For $C_{19}H_{21}ClN_2OS$ (360·9) calculated: 63·23% C, 5·87% H, 9·82% Cl, 7·76% N, 8·89% S; found: 63·14% C, 5·82% H, 9·60% Cl, 7·41% N, 8·72% S.

Dihydrochloride was prepared from an ethanolic solution of the base by neutralization with an ether solution of hydrogen chloride; m.p. 212–214°C (95% ethanol). For $C_{19}H_{23}Cl_3N_2OS$ (433·8) calculated: 52·60% C, 5·34% H, 24·52% Cl, 6·46% N, 7·39% S; found: 52·60% C, 5·46% H, 24·31% Cl, 6·76% N, 7·59% S.

2-Chloro-8-hydroxy-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*V*)

Like in the preceding case, 4·05 g base *VII* was demethylated with 8·0 g BBr_3 in 45 ml chloroform. Analogous processing yielded 5·5 g crude dihydrobromide, m.p. 197–199°C. This was also converted to the base; 3·4 g (87%), m.p. 180–195°C. Pure base was obtained by crystallization from ethanol, m.p. 207–210°C. IR spectrum: 819, 869, 893 (2 adjacent and solitary Ar—H , 1089 (CH_2OH), 1285 (Ar—OH), 1562, 1600 (Ar), 3500 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3. .$SOCD_3$): δ 9·50 (bs, 1 H, Ar—OH), 7·00–7·50 (m, 4 H, 1,3,4,6-H_4), 6·99 (mcs, J = 2·5 Hz, 1 H, 9-H), 6·50 (mcd, J = 8·5; 2·5 Hz, 1 H, 7-H), 4·35 (bs, 1 H, aliphatic OH), 2·00–4·00 (m, 15 H, $ArCH_2CHAr$, CH_2O and 5 NCH_2). For $C_{20}H_{23}ClN_2O_2S$ (390·9) calculated: 61·44% C, 5·93% H, 9·07% Cl, 7·17% N, 8·20% S; found: 61·57% C, 5·93% H, 9·14% Cl, 6·76% N, 8·35% S.

The dihydrochloride crystallizes from a mixture of ethanol and ether as a solvate with one molecule of ethanol and one-half molecule of water, m.p. 166–168°C. For $C_{22}H_{32}Cl_3N_2O_{3.5}S$ (518·9) calculated: 50·92% C, 6·22% H, 20·50% Cl, 5·40% N, 6·18% S; found: 50·92% C, 6·23% H, 20·68% Cl, 5·43% N, 6·48% S.

Attempt at Demethylation of 7-Methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]-thiepin

A solution of 4·64 g BBr_3 in 10 ml chloroform was added dropwise over a period of 15 min to a solution of 2·1 g of the base[57] in 10 ml chloroform and the mixture was stirred for 4 h at room temperature. After standing overnight, the precipitated compound was filtered and recrystallized from ethanol; 0·80 g, m.p. 254—259°C. According to analysis it is dihydrobromide of 1-methylpiperazine. For $C_5H_{14}Br_2N_2$ (262·0) calculated: 22·91% C, 5·39% H, 10·70% N; found: 23·53% C, 5·40% H, 10·53% N. For comparison, 1-methylpiperazine dihydrobromide was prepared by neutralization of the base in ethanol with an ether solution of hydrogen bromide, m.p. 255—262°C (a crystal shape change at about 200°C which may indicate a crystal modification or loss of the solvating solvent). Our values do not agree with those in ref.[58] where a m.p. of 202—204°C is reported.

2,18-Dichlorofuro[2,3-*m*; 4,5-*m'*]bis(dibenzo[*b,f*]thiepin) (*XXI*)

During crystallization of 181 g 2-chloro-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin[38] from 400 ml ethanol, about 1 g substance remained undissolved. Filtration and crystallization from a mixture of 15 ml benzene and 20 ml light petroleum yielded a compound melting at 306—308°C which, according to the mass spectrum (*m/e* 500) has the composition $C_{28}H_{14}Cl_2OS_2$. Fragmentation is little pronounced and the compound is by analogy[49—55] ascribed the structure of *XXI*. For $C_{28}H_{14}Cl_2OS_2$ (501·4) calculated: 67·06% C, 2·81% H, 14·14% Cl, 12·79% S; found: 67·11% C, 3·01% H, 14·32% Cl, 12·95% S.

8,12-Dichlorofuro[2,3-*m*; 4,5-*m'*]bis(dibenzo[*b,f*]thiepin) (*XXII*)

Polyphosphoric acid prepared from 25 ml 85% H_3PO_4 and 50 g P_2O_5 was combined with 20 g 8-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one[56]. The mixture was stirred for 4 h on a 170°C bath, decomposed with ice and water, the aqueous liquid was separated by decanting from the insoluble fractions which were boiled with a mixture of ethanol and benzene. Filtration yielded 4·4 g substance, m.p. 381—385°C. On recrystallization from dimethylformamide or from xylene the melting point does not change. Analyses as well as IR spectrum indicate that the substance may contain a small amount of the starting ketone. The spectrum (*m/e* 499·9899) suggests it to have the formula $C_{28}H_{14}Cl_2OS_2$. Fragmentation is not pronounced. UV spectrum (C_2H_5OH): λ_{max} 316 nm, infl. 260 and 352 nm. IR spectrum (KBr): 750, 754, 817, 832, 886 (4 and 2 adjacent and solitary Ar—H), 1 037 (=C—O—C=), 1 107 (?), 1 494, 1 550, 1 611 (Ar), 1 683 cm^{-1} (a weak band corresponding to CO—Ar from a contamination). For $C_{28}H_{14}Cl_2OS_2$ (501·5) calculated: 67·07% C, 2·81% H, 14·14% Cl, 12·79% S; found: 66·42% C, 2·89% H, 13·76% Cl, 12·55% S.

7-Hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XXV*)

A solution of 130 ml pyridine in 150 ml ethanol was combined with 160 ml hydrochloric acid and the mixture was evaporated *in vacuo*. The residue was heated to 200°C and, over a period of 15 min, 22·5 g methoxyketone *XXIV*[57] was added under stirring. After partial cooling, it was diluted with 300 ml water and left to cool under stirring. The precipitated product (*XXV*) was filtered, washed with water and dried in air; 19·9 g (94 %), m.p. 215—223°C. A sample was recrystallized for analysis from acetone, m.p. 224—227°C. UV spectrum: λ_{max} 257 nm (log ε 4·36), 288 nm infl. (4·06), 315 nm (3·64). IR spectrum (KBr): 755, 775, 824, 860, 910 (4 and 2 adjacent and solitary Ar—H), 1 072 (C—O), 1 250, 1 272 (Ar—OH), 1 555, 1 565, 1 588 (Ar), 1 640 (CO—Ar), 2 690, 2 790 cm^{-1}

(Ar—OH···O=C—Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·60 (bs, 1 H, OH), 7·88 (d, J = = 8·0 Hz, 1 H, 9-H), 7·55 (mcd, J = 8·0 Hz, 1 H, 4-H), 7·00—7·40 (m, 3 H, 1,2,3-H_3), 6·90 (mcs, J = 2·5 Hz, 1 H, 6-H), 6·70 (mcd, J = 8·0; 2·5 Hz, 1 H, 8-H), 4·33 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}O_2S$ (242·3) calculated: 69·40% C, 4·16% H, 13·23% S; found: 69·28% C, 4·20% H, 12·99% S.

7-Acetoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XXVI*)

Pyridine (0·8 g) and 1·0 g acetic anhydride were added to a suspension of 2·4 g hydroxyketone *XXV* in 25 ml acetone and the mixture was refluxed for 4 h (the solution cleared shortly). After evaporation of acetone, the residue was divided between water and benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The crude product was obtained in a theoretical yield (2·8 g), m.p. 111—114°C. An analytical sample was obtained by crystallization from a mixture of benzene and light petroleum, m.p. 116—118°C. UV spectrum: λ_{max} 246·5 nm (log ε 4·34), 323 nm (3·57). IR spectrum: 742, 750, 825, 900 (4 and 2 adjacent and solitary Ar—H), 1190, 1230, 1285 (C—O), 1470, 1590 (Ar), 1668 (CO—Ar), 1753 cm^{-1} (COOAr). ^{1}H-NMR spectrum: δ 8·18 (d, J = 8·0 Hz, 1 H, 9-H), 6·90—7·70 (m, 6 H, remaining Ar—H), 4·30 (s, 2 H $ArCH_2CO$), 2·22 (s, 3 H, $COCH_3$). For $C_{16}H_{12}O_3S$ (284.3) calculated: 67·59% C, 4·25% H, 11·28% S; found: 67·79% C, 4·36% H, 11·04% S.

7,10-Dihydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVII*)

A) A solution of 1·6 g $NaBH_4$ in 15 ml water made alkaline with a drop of 20% NaOH was added dropwise under cooling with ice (at below 10°C) and under stirring to a solution of 7·6 g ketone *XXVI* in 80 ml dioxane. The mixture was stirred for 5 h and left to stand at room temperature overnight, dioxane was evaporated *in vacuo* and the residue was extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The yield was 5·4 g 83%) crude dihydroxy derivative *XXVII*, m.p. 133—139°C. Recrystallization from a mixture of acetone and benzene yielded an analytically pure product melting at 140—144°C. IR spectrum: 752, 830, 872, 900 (4 and 2 adjacent and solitary Ar—H), 1060 (CHOH in a ring), 1225, 1270 (Ar—OH), 1495, 1573, 1590, 1609 (Ar), 3320 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·48 (s, 1 H, Ar—OH), 6·90—7·50 (m, 5 H, 1,2,3,4,9-H_5), c. 6·70 (m, 2 H, 6,8—H_2), 5·40 (d, disappears after D_2O, 1 H, aliphatic OH), 5·00 (m, 1 H, Ar—CH—O), 3·30 (m, 2 H, $ArCH_2$). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·83% C, 4·95% H, 13·12% S; found: 68·96% C, 5·06% H, 12·87% S.

B) A solution of 0·1 g $LiBH_4$ in 10 ml tetrahydrofuran was added dropwise over a period of 1 h to a suspension of 3·0 g *XXVI* in 25 ml ether at below 3°C. The mixture was stirred for 30 min and then 5 ml 50% acetic acid was added dropwise. The organic layer was separated, washed with water, dried with $MgSO_4$ and evaporated. The residue (1·8 g, 70%) melts at 135—140°C and is identical with the product obtained under *A*.

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