POTENTIAL METABOLITES OF NEUROLEPTICS OF THE 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN SERIES: 2,3-DIHYDROXY DERIVATIVES OF PERATHIEPIN AND OCTOCLOTHEPIN AND SOME RELATED COMPOUNDS*

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Received July 29th, 1975

Reactions of 2-iodo-4,5-dimethoxyphenylacetic acid with thiophenol and 4-chlorothiophenol yielded acids *VIIa* and *VIIb* which were cyclized with the aid of polyphosphoric acid or of the polyphosphoric ester to ketone *Xa* and *Xb*. Reduction led to alcohols *XIIIab* which were converted to chlorides *XIVab* at 0°C. Similarly, but at room temperature, alcohol *XIIIa* formed a mixture from which the rearrangement product *XX* was isolated. Its reaction with 1-methylpiperazine yielded a dimer, probably of dispirocyclobutane structure *XXII*. Substitution reactions of chlorides *XIVab* with 1-methylpiperazine resulted in amines *VIab* (besides elimination products *XXIab*) which were demethylated with boron tribromide to the potential metabolites of perathiepin (*Va*) and octoclothepin (*Vb*). Formamide *XVIa* was prepared from ketone *Xa*; the formamide was further converted to amines *XVIIa*—*XIXa* and these were demethylated to cyclic analogues of dopamine *XXVI*—*XXVIII*. The 2,3-dimethoxy derivative of octoclothepin (*VIb*) was converted by selective oxidation reactions to the sulfoxide *XXIV* and to the N-oxide *XXV*. The piperazine derivatives *Vab* and *VIab* are very little toxic, possess a weak central depressant activity and are practically ineffective as cataleptics.

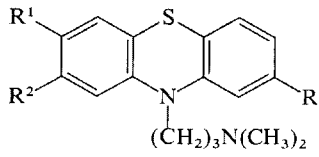
In a previous communication of this series[1] we described the synthesis and pharmacological properties of the 2-hydroxy derivative (*B*, R = Cl, R^1 = H, R^2 = OH) and of the 3-hydroxy derivative (*B*, R = Cl, R^1 = OH, R^2 = H) of the neuroleptic octoclothepin (*B*, R = Cl, R^1 = R^2 = H) (ref.[2]). Both compounds were identified as metabolites of octoclothepin and the 3-hydroxy derivative was found to be less toxic and neuroleptically more active than octoclothepin[1]. When formulating the structure of the two hydroxy derivatives as potential metabolites of octoclothepin we proceeded from the data on the biotransformation of the prototype of the whole group of neuroleptics, *i.e.* chlorpromazine (*A*, R = Cl, R^1 = R^2 = H) which are rather extensive[3,4]. Using the analogy with the chlorpromazine series, we proceeded

* Part C in the series Neurotropic and Psychotropic Agents; Part XCIX: This Journal *41*, 1035 (1976).

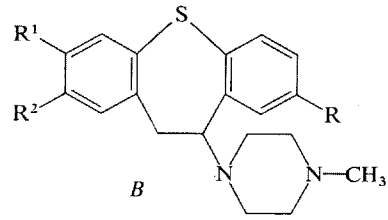
now to synthesize the 2,3-dihydroxy derivatives (*Va*, *Vb*) of perathiepin (*B*, R = R^1 = = R^2 = H) (ref.[5]) and octoclothepin as potential catechol metabolites of these neuroleptic agents.

Axelrod and coworkers[6] described the transformation of pharmacodynamically active phenolic amines *in vitro* to the corresponding O-methylated dihydroxy derivatives with the aid of liver enzyme preparations (catechol-O-methyltransferase) in the presence of [$^{14}CH_3$]-S-adenosyl-methionine. Daly and Manian[7,8] used the method to study 7-hydroxychloropromazine (*A*, R = = Cl, R^1 = OH, R^2 = H) and 8-hydroxychlorpromazine (*A*, R = Cl, R^1 = H, R^2 = OH) and found both of them to be transformed *via* the labile 7,8-dihydroxy derivative *Ib* to a mixture of predominantly 7-hydroxy-8-methoxy derivative *IIb* and some 8-hydroxy-7-methoxy derivative *IIIb* (for syntheses see[9,10]). 2,3-Dimethoxypromazine[11] (*IVa*) and 2,3-dihydroxypromazine[10] (*Ia*) were also obtained synthetically. A method of identification of catechol *Ib* was developed, based on a combination of gas chromatography and mass spectrometry[12] and the compound was identified as a metabolite in the urine of chronic schizophrenics on a prolonged chlorpromazine therapy[13]. The highly reactive catechol *Ib* was studied from the point of view of biochemical interactions and as a potential source of some side effects of chlorpromazine[14–24]. In its reaction with oxygen and with oxygen radicals the products obtained were hydrogen peroxide, a peroxide radical and a hydroxyl radical[25,26]. Compound *Ib* was identified as a product of hydroxylation of 7-hydroxychlorpromazine by mushroom tyrosinase which further catalyzes its transformation to another unstable and highly reactive compound, 7,8-dioxochlorpromazine (*o*-quinone)[27] which was also prepared synthetically[28]. In a series of papers[29–33] the basic pharmacology of *Ib*—*IVb* was described.

The synthesis of *Va* and *Vb* was done by using analogous methods as in some of our earlier studies[1,2,34,35]. The starting compound was the known 2-iodo-4,5--dimethoxyphenylacetic acid[36] obtained by iodination of homoveratric acid with iodine chloride in a mixture of acetic and hydrochloric acids. The acid was condensed with thiophenol and with 4-chlorothiophenol in boiling aqueous solution of potassium hydroxide in the presence of copper, which resulted in acids *VIIa* and *VIIb*. The first of these was cyclized by polyphosphoric acid and by polyphosphoric ester in boiling benzene, the second only by the polyphosphoric ester. This resulted in a non-homogeneous neutral mixture from which ketones *Xa* and *Xb* were isolated by chromatography on alumina or on silica gel. In both cases only a single somewhat more polar crystalline by-product was isolated. In series *a* it is a high-melting substance, according to analysis and mass spectrum with a formula of $C_{32}H_{24}O_5S_2$. ^{1}H-NMR spectrum shows signals only in the region of aromatic protons and further two singlets of methyls of the four methoxy groups. According to analogy with previous cases[37–39] the product has the structure of heptacyclic furan *XI*. Likewise, in series *b* the molecule is doubled but, in contrast with the first case, it contains one more oxygen atom and is richer in hydrogen atoms. According to mass spectrum and analysis it has the formula $C_{32}H_{26}Cl_2O_6S_2$. The IR spectrum contains a band at 1754 cm^{-1} which is apparently due to the enol-ester grouping —COO—C=C—; the ^{1}H-NMR spectrum was not sufficiently informative. Final evidence was provided by alkaline hydrolysis of the product which resulted in the starting acid *VIIb* and in ketone *Xb*; the product is thus an ester of acid *VIIb* with the enolic form of ketone *Xb*, *i.e. XII*.



A

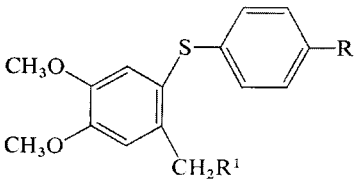


B

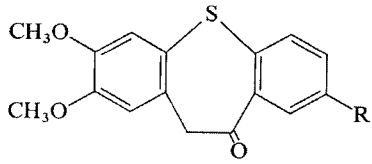
I, $R^1 = R^2 = OH$
II, $R^1 = OH$, $R^2 = OCH_3$
III, $R^1 = OCH_3$, $R^2 = OH$
IV, $R^1 = R^2 = OCH_3$

V, $R^1 = R^2 = OH$
VI, $R^1 = R^2 = OCH_3$

In all formulae: *a*, R = H
b, R = Cl



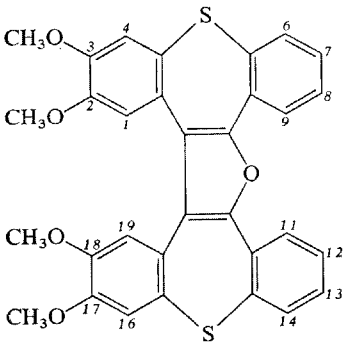
VII, $R^1 = COOH$
VIII, $R^1 = COOC_2H_5$
IX, $R^1 = CH_2OH$



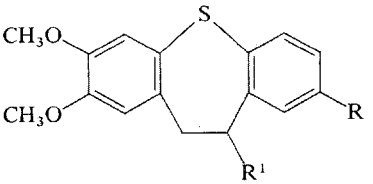
X

Pure ketones *Xa* and *Xb* were readily reduced with sodium borohydride in aqueous dioxane to alcohols *XIIIa* and *XIIIb*. On using crude ketone *Xb* a nonhomogeneous product was obtained which could be separated by chromatography on alumina. Besides product *XIIIb*, two crystalline compounds were isolated, the less polar of which was identified as ethyl ester *VIIIb*, the more polar one as alcohol *IXb*.The ethyl ester *VIIIb* is apparently contained in the starting compound and was formed by esterification of acid *VIIb* by treatment with the polyphosphoric ester. As to alcohol *IXb* one cannot decide whether it was formed merely by reduction of enol-ester *XII* (also present in the starting compound) or also of ester *VIIIb*. When treating alcohol *XIIIa* in chloroform with hydrogen chloride at room temperature (an analogy of a commonly used procedure[1,2,34,35]) a nonhomogeneous product was obtained which was separated by crystallization into approximately equal amounts of two isomeric chlorides. The higher-melting product was identified as the expected chloride *XIVa*. On the other hand, the lower-melting isomer was shown by its ^{1}H-NMR spectrum to have the structure of the thioxanthene derivative *XX* which was formed apparently by a Wagner–Meerwein rearrangement[40] when the primarily formed

secondary carbonium cation was rearranged under migration of the aryl to the primary carbonium cation which was stabilized by combination with the chloride anion. When carrying out the reaction of alcohol *XIIIa* with hydrogen chloride in dichloromethane at 0°C no rearrangement takes place and a high yield of chloride *XIVa* is obtained. Chloride *XIVb* was obtained analogously. During crystallization of this compound from ethanol, a solvolytic transformation to the ethoxy derivative *XVb* takes place.

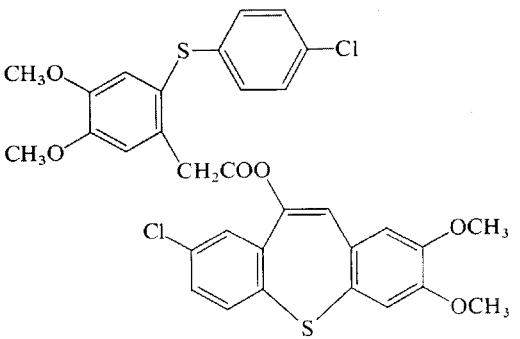


XI



XIII, R^1 = OH
XIV, R^1 = Cl
XV, R^1 = OC_2H_5

XVI, R^1 = NHCHO
XVII, R^1 = NH_2
XVIII, R^1 = $NHCH_3$
XIX, R^1 = $N(CH_3)_2$



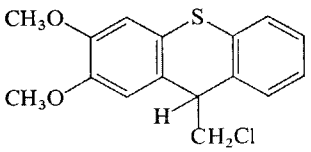
XII

Substitution reactions of chlorides *XIVa* and *XIVb* with 1-methylpiperazine in chloroform (in the first case by prolonged standing of the mixture at room temperature, in the second case by boiling the mixture) proceeded normally. The main products were amines *VIa* and *VIb*; elimination occurred to a lesser degree, its products being identified as 2,3-dimethoxydibenzo[*b*,*f*]thiepin (*XXIa*) and 8-chloro-2,3-dimethoxydibenzo[*b*,*f*]thiepin (*XXIb*). Likewise, chloride *XX* was subjected to the

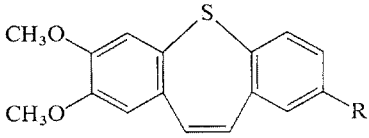
action of excess 1-methylpiperazine in boiling chloroform. The only characterized product was a crystalline neutral substance, the mass spectrum of which indicated an empirical formula $C_{32}H_{28}O_4S_2$. Hence probably the olefin, formed primarily from chloride *XX* by dehydrohalogenation, was dimerized. On the basis of the absence of signals of benzyl hydrogens in the ^{1}H-NMR spectrum and of a broad singlet at 1·61 p.p.m., which corresponds to two isolated methylene groups in the cyclobutane ring, the product is formulated as 2,3,2″,3″-tetramethoxydispiro(thioxanthene-9,1′-cyclobutane-3′,9″-thioxanthene) (*XXII*). The *trans* configuration indicated in formula *XXII* is based on its steric preference over the corresponding *cis*-configuration. The formation of the cyclobutane derivative *XXII* is somewhat surprising since the formation of cyclobutanes by cyclodimerization of olefins was noted only under the conditions of the photochemical reaction, catalysis by some metal compounds and on the assumption of cationic radicals as intermediates[41,42]. Nevertheless, similar dispirocyclobutane structures were recently ascribed[43] to products resulting from the action of phenylmagnesium bromide on 9-fluorenylidenemalononitrile and 9-xanthenylidenemalononitrile.

Demethylation of the dimethoxy derivatives *VIa* and *VIb* was done by treatment with boron tribromide in chloroform at room temperature, subsequent decomposition with ethanol and crystallization from aqueous ethanol, yielding relatively stable dihydrobromides of catecholamines *Va* and *Vb*. During liberation of these bases decomposition occurs, resulting in an intense red colour (probably due to formation of *o*-quinone and its further decomposition). During the reaction of ketone *Xa* with 1-methylpiperazine and titanium tetrachloride in benzene, enamine *XXIII* was formed. An attempt at its reduction to *VIa* with diborane generated in a reaction of sodium borohydride with acetic acid[44] was unsuccessful. The crystalline product obtained contains boron and probably has the structure of the corresponding amine–borane (R_3N^+—BH_3^-). Enamine *XXIII* is regenerated from it by alkaline hydrolysis. Oxidation of an aqueous solution of dimethanesulfonate of base *VIb* with excess hydrogen peroxide at room temperature[45] yields the sulfoxide *XXIV*. In an attempt at demethylation of the compound with boron tribromide like in previous cases, the sulfoxide is simultaneously reduced to sulfide and catecholamine *Vb* is formed. The literature does not appear to contain any data on the reduction of sulfoxide with boron tribromide but there exist reductions of sulfoxides with phosphorus trichloride[46,47], phosphorus oxychloride[48], dichloroborane[49] ($BHCl_2$) and hexachlorodisilane[50] (Si_2Cl_6), some of which are not pronounced reducing agents which lends plausibility to the present case. Oxidation of base *VIb* with hydrogen peroxide in a mixture of ethanol with dioxane[45] yielded the N-oxide *XXV*.

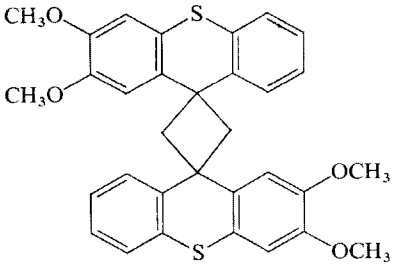
Compounds *Va* and *Vb* are complex cyclic analogues of dopamine [2-(3,4-dihydroxyphenyl)ethylamine]; in view of the importance ascribed now to the effect of neuroleptics on dopamine turnover in some brain areas during the process of antipsychotic action[51,52] and in view of the role of dopamine and dopaminergic compounds in



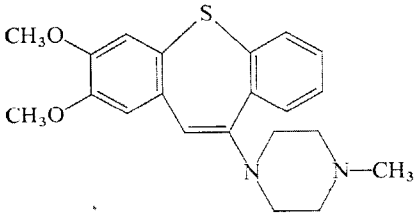
XX



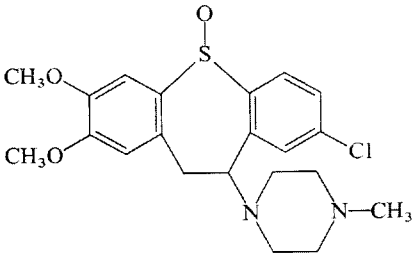
XXI



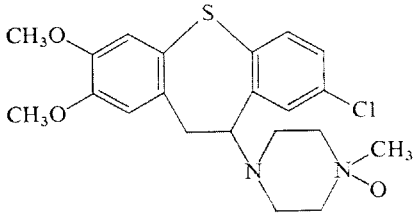
XXII



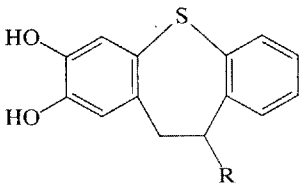
XXIII



XXIV



XXV



XXVI, R = NH_2
XXVII, R = $NHCH_3$
XXVIII, R = $N(CH_3)_2$

the therapy of Parkinson's disease[53-57] we considered it useful to prepare some other derivatives resembling dopamine structurally. Reaction of ketone *Xa* with formamide and formic acid yielded the formamide derivative *XVIa*, the alkaline hydrolysis of which resulted in the primary amine *XVIIa*. Reduction of formamide *XVIa* with diborane or with sodium dihydridobis(2-methoxyethoxy)aluminate produced the methylamino derivative *XVIIIa*. Finally, methylation of the primary amine *XVIIa* with formaldehyde and formic acid yielded the dimethylamino derivative *XIXa*. Amine *XVIIa* was demethylated either with boiling hydrobromic acid or with boron tribromide in chloroform and subsequent decomposition with ethanol; in both cases

TABLE I

Pharmacological Properties of Some New Dibenzo[*b*,*f*]thiepin Derivatives (mg/kg)

Compound[a]	Method of application[b]	Acute toxicity[c] LD_{50}	Incoordinating effect[d] ED_{50}	Cataleptic effect[e] ED_{50}
Va-2 HBr[f]	*p.o.*	> 500[g]	52	> 50[h]
Vb-2 HBr[f]	*p.o.*	> 500[i]	34	> 50[j]
VIa-2 M[k]	*p.o.*	>1 000[i]	>100[m]	> 50[n]
VIb-2 MS	*p.o.*	640	80	> 50[o]
XVIIIa-HCl	*i.v.*[q]	50	10[p]	> 10[j]
XXVI-HBr	*p.o.*[s]	> 500[i]	>300[r]	>100[j]
XXVII-HBr	*p.o.*[s]	> 500[i]	>300[r]	>100[j]
XXVIII-HBr[k]	*p.o.*[t]	—	130	—
Per[u]	*p.o.*	63	2·4	45
Oct[v]	*p.o.*	78	2·2	4·3

[a] M Maleate, MS methanesulfonate; the compounds were administered in the form of the salt shown but the doses refer to the base. [b] *p.o.*, *per os*; *i.v.*, intravenously. [c] Mean lethal doses for white mice. [d] Mean effective doses bringing about ataxia in mice in the rotating-rod test at the time of maximum effect. [e] Mean effective doses bringing about catalepsy in rats. [f] Dihydrate. [g] The dose shown is lethal for 10% animals. [h] The dose shown brings about catalepsy in 20% animals. [i] The dose shown is not lethal. [j] The dose shown is cataleptically ineffective.. [k] Hemihydrate. [m] The dose shown brings about ataxia in 10% animals. [o] The dose shown is cataleptic for 40% animals. [p] The dose shown has no incoordinating effect. [q] At doses greater than 10 mg/kg *i.v.* there are signs of central depression in mice; at a concentration of 25–50 μg/ml it depresses heart inotropy and frequency by about 25% in isolated rabbit atrium. [r] Discoordinating effect in less than 50% animals. [s] At a dose of 100 mg/kg *p.o.* there was no effect on oxotremorin tremors in mice; after *i.p.* administration of the compound at doses of 50 and 100 mg/kg in the test of interaction with oxotremorin the mice died. [t] After *i.p.* administration to mice in doses of 50 to 200 mg/kg in the oxotremorin test the compound brings about tremor and convulsions and potentiates the effect of tremorin; on the other hand, it has a slight anticonvulsant effect in mice toward pentetrazol. [u] Perathiepin (maleate). [v] Octoclothepin (maleate).

the hydrobromide of catecholamine *XXVI* resulted directly. The N-methylated amino-ethers *XVIIIa* and *XIXa* were demethylated with boron tribromide, giving rise to the hydrobromides of catecholamines *XXVII* and *XXVIII*. These compounds also are relatively stable in the form of salts but after treatment with alkali they are rapidly decomposed under formation of intense colour.

The piperazine derivatives *Vab* and *VIab* and further catecholamines *XXVI* to *XXVIII* underwent orientation pharmacological tests for expected central neurotropic activity. The compounds were applied *p.o.* in the form of salts and their acute toxicity for mice, their incoordinating effect in the rotating-rod test in mice and their cataleptic activity in rats was examined. The results are summarized in Table I which includes perathiepin[5] and octoclothepin[2] as standards. The new substances are at least an order of magnitude less toxic than the standards. In the rotating-rod test the mean effective dose could be determined only for four of the compounds. The relatively highest activity in this test which indicates central depressant action, was found with the 2,3-dihydroxy derivative of octoclothepin (*Vb*) but it is still 15 times less effective than octoclothepin itself. In the catalepsy test the mean effective dose could not be determined for any of the new compounds; the clearest sign of effect was found with the 2,3-dimethoxy derivative of octoclothepin (*VIb*) which, at the high dose of 50 mg/kg *p.o.*, brings about catalepsy in 40% rats. Most of the new compounds

TABLE II

Antimicrobial Activity of Dibenzo[*b*,*f*]thiepin Derivatives *in vitro* (minimum inhibitory concentrations in μg/ml are shown)

Compound[a]	Microorganisms[b]									
	1	2	3	4	5	6	7	8	9	10
Va-2 HBr[c]	—	—	—	—	—	100	—	50	—	100
Vb-2 HBr[c]	100	100	50	100	100	50	100	25	100	100
VIa-2 M[d]	—	—	—	—	—	—	100	100	100	100
VIb-2 MS	100	—	100	—	—	25	100	50	100	100
XVIIIa-HCl	—	—	—	—	—	100	100	50	100	100
XXVI-HBr	50	50	50	—	—	—	100	50	100	100
XXVII-HBr	50	50	50	—	—	—	100	50	100	100
XXVIII-HBr[d]	—	—	—	—	—	100	100	50	—	100

[a] M maleate, MS methanesulfonate. [b] 1 *Streptococcus β-haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Pseudomonas aeruginosa*, 5 *Proteus vulgaris*, 6 *Mycobacterium tuberculosis* H37Rv, 7 *Saccharomyces pasterianus*, 8 *Trichophyton mentagrophytes*, 9 *Candida albicans*, 10 *Aspergillus niger*. [c] Dihydrate. [d] Hemihydrate.

showed no cataleptic effect even at the high doses used. Somewhat surprising is especially the inactivity of the 2,3-dihydroxy derivative of octoclothepin (*Vb*) which contrasts sharply with the high activity of the 3-hydroxy derivative of octoclothepin[1]. For comparison let us mention that ref.[29,31,33] report the 7,8-dihydroxy derivative of chlorpromazine (*Ib*) to be about five times more toxic than chlorpromazine on intraperitoneal application and, in a number of tests, find it less effective as central depressant than chlorpromazine (about 10 times in the rotating-rod test). The 2,3-dimethoxy derivative of chlorpromazine (*IVb*) is about 50 times less effective in the rotating-rod test than chlorpromazine[29]. There are no reports in the literature on the neuroleptic activity of these compounds, such as expressed by cataleptic action.

The hydrochloride of amine *XVIIIa* was subjected to systematic pharmacological screening after parenteral application in the affiliated unit of this institute at Rosice n/L, under the direction of Dr J. Němec. It is also included in Table I and does not exhibit any interesting properties. Catecholamines *XXVI—XXVIII* were tested at the pharmacological department of this institute by Dr A. Dlabač in tests of interaction with oxotremorin in mice, from the point of view of possible antiparkinsonian effects but none of them showed the desired activity. Many of the new compounds were further tested by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) for antimicrobial activity *in vitro* toward a standard set of microorganisms. Table II shows the minimum inhibitory concentrations as long as the compounds were active. Inhibitory effects are observed always only at rather high concentrations.

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. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer and the mass spectra in a MS 902 (AEI) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on alumina or silica gel. Likewise, preparative chromatography was done on Al_2O_3 (activity II) or on SiO_2.

2-(Phenylthio)-4,5-dimethoxyphenylacetic Acid (*VIIa*)

A mixture of 85 g 2-iodo-4,5-dimethoxyphenylacetic acid[36] (m.p. 164—166°C), 32 g thiophenol, solution of 52 g KOH in 520 ml water and 4·0 g Cu (paste) was refluxed for 7 h under stirring. It was filtered while hot and the cooled filtrate was acidified with hydrochloric acid. The precipitated acid was filtered on the following day, washed with water and dried. Crystallization from benzene and processing of the mother liquor yielded 68 g (85%) product melting at 144—146°C. On crystallization from aqueous ethanol a product is obtained which melts at 132—133°C, crystallizes again (a change of modification) and melts at 145—146°C. IR spectrum: 691, 740, 867 (5 adjacent and solitary. Ar—H), 949, 1332, 1702, 2550, 2635 (COOH), 1026, 1051, 1267 ($ArOCH_3$), 1516, 1576, 1601 cm^{-1} (Ar). For $C_{16}H_{16}O_4S$ (304·4) calculated: 63·14% C, 5·30% H, 10·54% S; found: 63·44% C, 5·38% H, 10·57% S.

2-(4-Chlorophenylthio)-4,5-dimethoxyphenylacetic Acid (*VIIb*)

Like in the preceding case, reaction of 50 g 2-iodo-4,5-dimethoxyphenylacetic acid[36] with 25 g 4-chlorothiophenol in a solution of 30 g KOH in 300 ml water in the presence of 3·0 g Cu gave rise to 47 g (87%) product melting at 129—131·5°C (benzene). An analytical sample was obtained by further crystallization from aqueous ethanol; m.p. 131—133°C. The substance is a hemihydrate. IR spectrum: 825, 875 (2 adjacent and solitary Ar—H), 905, 1700, 2640 (COOH), 1230, 1270 ($ArOCH_3$), 1485, 1520, 1605 (Ar), 2855 (OCH_3), 3460 and 3600 cm^{-1} (OH and H_2O). ^{1}H-NMR spectrum: δ 7·60 (bs, disappears after D_2O, 1 H, COOH), 7·12 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of chlorophenyl), 7·00 (s, 1 H, 6-H of phenylacetic acid), 6·89 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of chlorophenyl), 6·82 (s, 1 H, 3-H of phenylacetic acid), 3·86 and 3·79 (2 s, 8 H, 2 OCH_3 and $ArCH_2CO$). For $C_{16}H_{16}ClO_{4,5}S$ (347·8) calculated: 55·25% C, 4·64% H, 10·19% Cl, 9·22% S; found: 55·42% C, 4·56% H, 9·90% Cl, 8·51% S.

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

A solution of 28·6 g *VIIa* in 300 ml benzene was added at 80°C to polyphosphoric acid prepared from 75 ml 85% H_3PO_4 and 150 g P_2O_5 and the mixture was refluxed under vigorous stirring for 7 h at 110°C. After cooling, the benzene layer was decanted, the residue washed with benzene, the benzene solutions were pooled, washed with 5% NaOH, dried with $MgSO_4$ and evaporated. The residue crystallized from cyclohexane to 5·67 g product. Another fraction was obtained by chromatography of mother liquors on a column of 300 g alumina, eluting with benzene. The first to be eluted was 0·28 g unidentified less polar substance melting at 104—105·5°C (light petroleum) and then 2·93 g ketone *Xa*; the total yield was 8·60 g (32%), m.p. 116—118°C (cyclohexane). UV spectrum: λ_{max} 233 nm (log ε 4·40), 251 nm (4·20), infl. 290 nm (3·49), 336 nm (3·52). IR spectrum: 761, 887 (4 adjacent and solitary. Ar—H), 1055, 1222 ($ArOCH_3$), 1510, 1598 (Ar), 1679 (ArCOR), 2845 cm^{-1} (OCH_3). ^{1}H-NMR spectrum: δ 8·12 (m, 1 H, 9-H), 7·10—7·60 (m, 3 H, 6,7,8-H_3), 6·85 and 7·03 (2 s, 2 H, 1,4-H_2), 4·20 (s, 2 H, $ArCH_2CO$), 3·79 and 3·84 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{14}O_3S$ (286·4) calculated: 67·11% C, 4·93% H, 11·20% S; found: 67·13% C, 4·83% H, 11·02% S.

On continuing the chromatography, benzene eluted 0·55 g more polar compound which was crystallized twice from a mixture of benzene and cyclohexane to melt at 316—318°C. The analyses shown below and analogies with ref.[37—39] suggest it to be 2,3,17,18-tetramethoxyfuro-[2,3 m; 4,5-m']bis(dibenzo[*b*,*f*]thiepin) (*XI*). Mass spectrum exhibits a molecular ion at *m/e* 552·1086, corresponding to empirical formula $C_{32}H_{24}O_5S_2$. Fragmentation is not pronounced. ^{1}H-NMR spectrum: δ 7·15—7·90 (m, 8 H, aromatic protons in positions 6,7,8,9,11,12,13,14), 7·11 and 6·55 (2 s, 4 H, aromatic protons in positions 1,4,16,19), 3·81 and 3·35 (2 s, 12 H, 4 OCH_3). For $C_{32}H_{24}O_5S_2$ (552·5) calculated: 69·56% C, 4·38% H, 11·60% S; found: 69·60% C, 4·41% H, 11·68% S.

A somewhat higher yield of ketone *Xa* was obtained on cyclization of acid *VIIa* (40·0 g) with the aid of polyphosphoric ester (prepared by adding dropwise 44 ml ethanol to a stirred suspension of 88 g P_2O_5 in 660 ml benzene; the mixture was refluxed for 7 h). Processing yielded 22·3 g (59%) higher-melting modification (m.p. 127—129°C) which crystallizes from a mixture of benzene and light petroleum to the compound melting at 116—118°C as shown above.

8-Chloro-2,3-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xb*)

Ethanol (50 ml) was added dropwise under stirring to a mixture of 800 ml benzene and 100 g P_2O_5 and, after 1 h of refluxing, 45 g acid *VIIb* was added. The mixture was refluxed under stirring for 16 h. The benzene layer was then separated by decanting, the residue was dissolved

in a small amount of warm water and the solution was extracted with benzene. The pooled benzene solutions were washed with 5% NaOH and with water and dried and evaporated. As the crystallization of the residue (37·3 g) from a mixture of benzene and light petroleum did not result in a homogeneous compound, the whole quantity was chromatographed on a column of 400 g silica gel. The first to be washed out was 11·42 g (28%) ketone *Xb* which is pure after crystallization from a mixture of ethanol and benzene and melts at 179—180°C. UV spectrum: λ_{max} 233 nm (log ε 4·46), infl. 265 nm (4·09), 342 nm (3·65). IR spectrum: 825, 880 (2 adjacent and solitary Ar—H), 1225, 1270 ($ArOCH_3$), 1510, 1585, 1600 (Ar), 1680 (CO—Ar), 2840 cm^{-1} (OCH_3). ^{1}H-NMR spectrum: δ 8·08 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·43 (d, J = 9·0 Hz, 1 H, 6-H), 7·25 (mcd, J = 9·0; 2·0 Hz, 1 H, 7-H), 7·02 (s, 1 H, 4-H), 6·85 (s, 1 H, 1-H), 4·16 (s, 2 H, $ArCH_2COO$), 3·82 and 3·77 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{13}ClO_3S$ (320·8) calculated: 59·90% C, 4·09% H, 11·05% Cl, 10·00% S; found: 59·99% C, 4·07% H, 11·20% Cl, 9·51% S.

(8-Chloro-2,3-dimethoxydibenzo[*b*,*f*]thiepin-10-yl) 2-(4-Chlorophenylthio)-4,5-dimethoxyphenylacetate (*XII*)

On continuing the chromatography from the preparation of *Xb*, elution with chloroform yielded 15·87 g (38%) enol ester *XII*; m.p. 195·5—196°C (benzene). The mass spectrum exhibits a molecular ion at *m/e* 640 corresponding to an empirical formula $C_{32}H_{26}Cl_2O_6S_2$; typical fragments are at *m/e* 321 and 320, 305, 293 ($C_{15}H_{14}ClO_2S$) and 258 (293 minus Cl). IR spectrum (Nujol): 819, 883 (2 adjacent and solitary Ar—H), 1050, 1212, 1253 ($ArOCH_3$), 1502, 1592 (Ar), 1754 cm^{-1} (C=C—OCO). ^{1}H-NMR spectrum contains a multiplet in the region of aromatic protons and a multiplet at 3·70—4·00 (4 OCH_3 and CH_2). For $C_{32}H_{26}Cl_2O_6S_2$ (641·6) calculated: 59·90% C, 4·09% H, 11·05% Cl, 10·00% S; found: 60·32% C, 4·13% H, 10·86% Cl, 9·80% S.

A hot solution of 3·60 g *XII* in 100 ml dioxane was combined with 10 ml 20% NaOH, after 5 min it was diluted with 80 ml water and after 2 h of standing the precipitated crystals were filtered; 0·93 g ketone *Xb*, m.p. 178—179°C. Dilution of the mother liquor with water and extraction with benzene yielded further 0·82 g ketone *Xb*. Acidification of the aqueous layer with hydrochloric acid and recrystallization of the crude product from benzene yielded 1·63 g acid *VIIb* melting at 132—133°C.

10-Hydroxy-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIIIa*)

A solution of 2·27 g $NaBH_4$ in 5 ml water containing 1 drop of 20% NaOH was added dropwise under stirring to a solution of 11·4 g *Xa* in 150 ml dioxane (25°C). The mixture was stirred for 4 h at room temperature, after 12 h of standing it was diluted with water, acidified with 7 ml hydrochloric acid and, after 2 h of standing, the product was filtered; 10·7 g (93%), m.p. 160 to 161·5°C. Analytical product melts at 161·5—162°C (chloroform–benzene). IR spectrum: 774, 868 (4 adjacent and solitary Ar—H), 1040 (CHOH in a ring), 1052, 1165, 1201, 1219, 1236, 1264 ($ArOCH_3$), 1511, 1600 (Ar), 2845 (OCH_3), 3510 cm^{-1} (OH). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 67·06% C, 5·96% H, 11·25% S.

8-Chloro-10-hydroxy-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIIIb*)

A solution of 4·0 g $NaBH_4$ in 10 ml water (5 drops 20% NaOH) was added dropwise to a solution of 15·0 g crude ketone *Xb* (nonchromatographed product) in 150 ml dioxane. The mixture was stirred for 6 h at room temperature and then heated for 4 h to 80°C. After standing overnight, the dioxane was evaporated, the residue was decomposed with acidified water and extracted

with chloroform. Chloroform was evaporated and the product obtained (13·9 g) was chromatographed on a colum of 500 g Al_2O_3. Elution with a mixture of toluene and chloroform washed out 0·58 g substance which crystallizes from a mixture of cyclohexane and light petroleum and melts at 85°C. According to analysis and spectra it is ethyl 2-(4-chlorophenylthio)-4,5-dimethoxyphenylacetate (*VIIIb*). UV spectrum: λ_{max} 253·5 nm (log ε 4·33), 280 nm (4·01). IR spectrum: 825, 845, 875 (2 adjacent and solitary Ar—H), 1060, 1225, 1270 ($ArOCH_3$), 1160, 1270, 1325 (ester C—O—C), 1485, 1520, 1580, 1605 (Ar), 1740 cm^{-1} (RCOOR). NMR spectrum: δ 7·14 and 6·92 (ABq, J = 9·0 Hz, 4 H, 2,3,5,6-H_4 of chlorophenyl), 7·00 (s, 1 H, 6-H of phenylacetate), 6·86 (s, 1 H, 3-H of phenylacetate), 4·00 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·88 and 3·78 (2 s, 6 H, 2 OCH_3), 3·72 (s, 2 H, $ArCH_2CO$), 1·15 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{18}H_{19}ClO_4S$ (366·9) calculated: 58·93% C, 5·22% H, 9·67% Cl, 8·74% S; found: 59·10% C, 5·24% H, 10·06% Cl, 8·63% S.

Elution with chloroform produced 7·81 g (52%) alcohol *XIIIb*, m.p. 125—127°C (benzene–light petroleum). IR spectrum: 815, 870, 896 (2 adjacent and solitary Ar—H), 1065 (CHOH in a ring and $ArOCH_3$), 1218, 1250, 1270 ($ArOCH_3$), 1520, 1575, 1590, 1606 (Ar), 3335 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·50 (mcs, J = 2·5 Hz, 1 H, 9-H), 7·33 (d, J = 9·0 Hz, 1 H, 6-H), 7·06 (mcd, J = 9·0; 2·5 Hz, 1 H, 7-H), 6·94 and 6·69 (2 s, 1,4-H_2), 5·22 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·79 (s, 6 H, 2 OCH_3), 3·57 and 3·11 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·25 (s, disappears after D_2O, 1 H, OH). For $C_{16}H_{15}ClO_3S$ (322·8) calculated: 59·53% C, 4·68% H, 10·98% Cl, 9·94% S; found: 59·35% C, 4·63% H, 11·19% Cl, 9·75% S.

Further elution with chloroform yielded 2·6 g nonhomogeneous fractions which crystallized from a mixture of benzene and light petroleum to 0·37 g 2-[2-(4-chlorophenylthio)-4,5-dimethoxyphenyl]ethanol (*IXb*), m.p. 131—132°C. UV spectrum: λ_{max} 253·5 nm (log ε 4·31), 280 nm (4·00). IR spectrum: 825, 880 (2 adjacent and solitary Ar—H), 1060 (CH_2OH and $ArOCH_3$), 1225, 1260 ($ArOCH_3$), 1480, 1510, 1575, 1605 (Ar), 3330 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·14 and 6·90 (ABq, J = 9·0 Hz, 4 H, 2,3,5,6-H_4 of chlorophenyl), 6·95 (s, 1 H, 6-H of phenylethanol), 6·84 (s, 1 H, 3-H of phenylethanol), 3·85 and 3·75 (2 s, 6 H, 2 OCH_3), 3·70 (t, J = 6·5 Hz, 2 H, CH_2O), 2·90 (t, J = 6·5 Hz, 2 H, $ArCH_2$), 1·75 (s, disappears after D_2O, 1 H, OH). For $C_{16}H_{17}ClO_3S$ (324·8) calculated: 59·16% C, 5·28% H, 10·91% Cl, 9·87% S; found: 59·52% C, 5·28% H, 10·66% Cl, 9·75% S.

From a reduction of pure ketone *Xb* (20·7 g), like by preparation of *XIIIa*, the product was 19·0 g (91%) almost pure alcohol *XIIIb*, m.p. 122—124°C. When heated above this temperature the substance forms another crystal modification and melts again at 141—142°C.

10-Chloro-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVa*)

A solution of 9·0 g *XIIIa* in 100 ml dichloromethane, to which 6·0 g powdery $CaCl_2$ was added, was saturated for 2·5 h with gaseous hydrogen chloride at 0°C. The mixture was stirred for 3 h at 0°C, filtered and the filtrate was evaporated at reduced pressure. The residue crystallized from benzene to 8·45 g (88%) product, m.p. 152—159°C. The analytical product melts at 155 to 157·5°C (benzene). The mass spectrum exhibits a molecular ion $C_{16}H_{15}ClO_2S$. UV spectrum: λ_{max} 259 nm (log ε 3·91), 270 nm (3·90), infl. 282·5 nm (3·79). IR spectrum: 770, 850, 885 (4 adjacent and solitary Ar—H), 1064, 1215, 1270 ($ArOCH_3$), 1520, 1605 (Ar), 2845 cm^{-1} (OCH_3). ^{1}H-NMR spectrum: δ 7·15—7·65 (m, 4 H, 6,7,8,9-H_4), 7·05 and 6·82 (2 s, 2 H, 1,4-H_2), 5·76 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·84 and 3·81 (2 s, 6 H, 2 OCH_3), 3·92 and 3·55 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{16}H_{15}ClO_2S$ (306·8) calculated: 62·64% C, 4·93% H, 11·55% Cl, 10·45% S; found: 61·81% C, 4·90% H, 11·93% Cl, 10·32% S.

9-Chloromethyl-2,3-dimethoxythioxanthene (*XX*)

$CaCl_2$ (4·0 g) was added to a solution of 6·2 g *XIIIa* in 100 ml chloroform and the suspension was saturated under stirring for 2 h with hydrogen chloride at room temperature. After standing overnight it was filtered and evaporated. The residue crystallized from a mixture of benzene and light petroleum to 2·98 g contaminated *XIVa*, melting at 138–142°C which attained the quality of the crude product from the preceding experiment only after three crystallizations from benzene (1·34 g, m.p. 151–155°C). The mother liquor after the first crystallization was combined with light petroleum to precipitate 2·82 g (43%) of a nearly homogeneous compounds melting at 125 to 128°C; the analytical product melted at 127–128·5°C (benzene–light petroleum). The compound is isomeric with *XIVa* but is clearly different from it. ^{1}H-NMR spectrum: δ 7·10–7·50 (m, 4 H, 5,6,7,8-H_4), 6·90 (s, 2 H, 1,4-H_2), 4·20 (t, J = 7·0 Hz, 1 H, Ar_2CH), 3·86 and 3·84 (2 s, 6 H, 2 OCH_3), 3·65 (d, J = 7·0 Hz, 2 H, CH_2Cl). For $C_{16}H_{15}ClO_2S$ (306·8) calculated: 62·64% C, 4·93% H, 11·55% Cl, 10·45% S; found: 62·63% C, 5·01% H, 11·62% Cl, 10·23% S.

8,10-Dichloro-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVb*)

A solution of 7·62 g *XIIIb* in 100 ml dichloromethane with 4 g $CaCl_2$ was processed like in the preparation of chloride *XIVa*. A total of 7·95 g (99%) crude product melting at 131–141°C was obtained; analytical product, m.p. 139–141°C (benzene–light petroleum). In another experiment, crystallization from a mixture of benzene and light petroleum yielded a modification melting at 113–117°C, solidifying again at higher temperature and melting then at 151–152°C. ^{1}H-NMR spectrum: δ 7·47 (mcs, J = 2·5 Hz, 1 H, 9-H), 7·30 (d, J = 9·0 Hz, 1 H, 6-H), 7·17 (mcd, J = 9·0; 2·5 Hz, 1 H, 7-H), 6·96 and 5·79 (2 s, 2 H, 1,4-H_2), 5·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·82 and 3·80 (2 s, 6 H, 2 OCH_3), 3·85 and 3·47 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{16}H_{14}Cl_2O_2S$ (341·3) calculated: 56·32% C, 4·13% H, 20·78% Cl, 9·40% S; found: 56·86% C, 4·22% H, 21·10% Cl, 9·14% S.

8-Chloro-10-ethoxy-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVb*)

Crystallization of chloride *XIVb* from ethanol gives rise to a substance which melts in the crude state at 92–98°C, after recrystallization from a mixture of benzene and light petroleum then at 107–108°C. IR spectrum (Nujol): 801, 821, 852, 890 (2 adjacent and solitary Ar—H), 1 049, 1 216 ($ArOCH_3$), 1 100 (R—O—R'), 1 513, 1 602 cm^{-1} (Ar). For $C_{18}H_{19}ClO_3S$ (350·9) calculated: 61·60% C, 5·46% H, 10·11% Cl, 9·14% S; found: 60·99% C, 5·44% H, 10·53% Cl, 8·62% S.

2,3-Dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIa*)

A mixture of 8·4 g *XIVa*, 30 ml 1-methylpiperazine and 30 ml chloroform was heated to dissolve the solid and left for 30 days at room temperature. After dilution with water it was extracted with benzene, the extract was washed with water and shaken with 5% hydrochloric acid. Evaporation of the benzene solution yielded 1·2 g neutral oil which crystallizes from ethanol: 0·35 g, m.p. 104–106°C. It is 2,3-dimethoxydibenzo[*b*,*f*]thiepin (*XXIa*), an analytical sample of which melts at 123–124°C (benzene–light petroleum followed by ethanol). UV spectrum: λ_{max} 248 nm (log ε 4·37), 264·5 nm (4·41), infl. 300 nm (3·67), infl. 340 nm (3·37). ^{1}H-NMR spectrum: δ 7·15 to 7·65 (m, 4 H, 6,7,8,9-H_4), 6·99 (s, 1 H, 4 H), 6·95 (s, 2 H, olefinic 10,11-H_2), 6·70 (s, 1 H, 1-H), 3·82 and 3·78 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{14}O_2S$ (270·4) calculated: 71·08% C, 5·22% H, 11·86% S; found: 70·95% C, 5·37% H, 11·56% S.

The acid aqueous phase containing the hydrochloride of product *VIa* was made alkaline with NH_4OH and the base was isolated by extraction with benzene; 9·5 g (84%) solvate with one-half benzene molecule; m.p. 64—69°C (benzene). IR spectrum: 755, 875 (4 adjacent and solitary Ar—H), 1020, 1070, 1230, 1270 ($ArOCH_3$), 1510, 1605 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 4 H, 6,7,8,9-H_4), 7·05 and 6·80 (2 s, 2 H, 1,4-H_2), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 3·84 and 3·79 (2 s, 6 H, 2 OCH_3), 2·64 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·42 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{24}H_{29}N_2O_2S$ (409·6) calculated: 70·38% C, 7·14% H, 6·84% N, 7·83% S; found: 70·14% C, 7·39% H, 6·76% N, 7·88% S. Neutralization of the base with maleic acid in ethanol and crystallization from ethanol yielded a dimaleate hemihydrate, m.p. 121—122°C. For $C_{29}H_{35}N_2O_{10,5}S$ (611·7) calculated: 56·95% C, 5·77% H, 4·58% N, 5·24% S; found: 56·84% C, 6·16% H, 4·42% N, 5·17% S.

8-Chloro-2,3-dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*VIb*)

A mixture of 16·5 g *XIVb*, 30 ml 1-methylpiperazine and 30 ml chloroform was heated until the solid dissolved, left for 48 h at room temperature and refluxed for 8 h. After diluting with benzene it was washed with water and shaken with excess 5% hydrochloric acid. The hydrochloride precipitated as a solid, was filtered and decomposed with NH_4OH to release the base which was extracted with benzene; 15·0 g (77%), m.p. 169—172°C (benzene–light petroleum). NMR spectrum: δ 7·69 (mcs, J = 2·5 Hz, 1 H 9-H) 7·35 (d, J = 9·0 Hz, 1 H, 6-H), 7·02 (mcd, J = 9·0; 2·5 Hz, 1 H, 7-H), 7·02 and 6·79 (2 s, 2 H, 1,4-H_2), 3·85 and 3·80 (2 s, 6 H, 2 OCH_3), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·46 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·27 (s, 3 H, NCH_3). For $C_{21}H_{25}ClN_2O_2S$ (405·0) calculated: 8·76% Cl, 6·92% N; found: 8·61% Cl, 6·78% N.

Dimethanesulfonate, m.p. 188·5—189·5°C (ethanol–ether). For $C_{23}H_{33}ClN_2O_8S_3$ (597·2) calculated: 46·26% C, 5·57% H, 5·94% Cl, 4·69% N, 16·11% S; found: 46·43% C, 5·51% H, 6·19% Cl, 4·58% N, 16·02% S.

Evaporation of the benzene layer of the filtrate after filtration of the hydrochloride and crystallization of the residue from ethanol yielded 0·60 g 8-chloro-2,3-dimethoxydibenzo[*b,f*]thiepin (*XXIb*), m.p. 124—125°C. UV spectrum: λ_{max} 226 nm (log ε 4·57), infl. 245 nm (4·41), 266 nm (4·39), infl. 305 nm (3·67), infl. 340 nm (3·35). IR spectrum (Nujol): 803, 820, 871 (2 adjacent and solitary Ar—H), 1053, 1253 ($ArOCH_3$), 1503, 1562, 1592 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·90—7·80 (m, 5 H, 6,7,9,10,11-H_5), 6·97 and 6·71 (2 s, 2 H, 1,4-H_2), 3·85 and 3·81 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05%, C, 4·30% H, 11·63% Cl, 10·52% S; found: 62·72% C, 4·50% H, 11·42% Cl, 10·44% S.

2,3,2″,3″-Tetramethoxydispiro(thioxanthene-9,1′-cyclobutane-3′,9″-thioxanthene) (*XXII*)

A mixture of 2·41 g *XX*, 10 ml 1-methylpiperazine and 10 ml chloroform was left to stand for 48 h and then refluxed for 6 h, washed with water and 5% hydrochloric acid (a small amount of a tar-like substance separated at this stage), the benzene solution was dried with $MgSO_4$ and evaporated. A total of 2·13 g neutral oil was obtained which crystallized from ethanol to 0·4 g compound; m.p. 194—196°C. The mass spectrum with a molecular ion at m/e 540 suggests the formula $C_{32}H_{28}O_4S_2$. UV spectrum: λ_{max} 277·5 nm (log ε 4·29), 335 nm (3·69). IR spectrum: 765, 875 (4 adjacent and solitary Ar—H), 1050, 1225, 1270 ($ArOCH_3$), 1515, 1610 (Ar) 2850 cm^{-1} (OCH_3). ^{1}H-NMR spectrum: δ 6·20—8·00 (m, 12 H, aromatic protons), 3·74, 3·69, 3·66 and 2·96 (4 s, 12 H, 4 OCH_3), 1·61 (bs, 4 H, 2 CH_2 of cyclobutane). For $C_{32}H_{28}O_4S_2$ (540·8) calculated: 71·08% C, 5·22% H, 11·86% S; found: 70·84% C, 5·26% H, 11·58% S.

2,3-Dihydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Va*)

Boron tribromide (19·6 g) in 15 ml chloroform was added dropwise over a period of 15 min in the atmosphere of nitrogen at 20°C to a solution of 10·5 g *VIa* (benzene solvate) in 40 ml chloroform. The mixture was stirred for 5 h, left to stand for 12 h, and 50 ml ethanol was added to it under cooling. The mixture was stirred for 8 h, left to stand overnight and diluted with 90 ml ether. The precipitated substance was filtered and recrystallized from a mixture of 95% ethanol and ether; 6·30 g (46%) dihydrate of dihydrobromide *Va*, m.p. 160—161°C under decomposition. IR spectrum: 760, 885, 910 (4 adjacent and solitary Ar—H), 1170, 1300 (Ar—OH), 1510, 1600 (Ar), 2445, 2485, 2575, 2610, 2670 (NH^+), 3345 cm^{-1} (H_2O). For $C_{19}H_{28}Br_2N_2.O_4S$ (540·3) calculated: 42·23% C, 5·22% H, 29·58% Br, 5·19% N, 5·93% S; found: 41·75% C, 5·16% H, 29·34% Br, 5·14% N, 5·87% S.

Standing of 0·50 g of the preceding salt in 100 ml water for 4 days at room temperature yielded 0·40 g solid which was filtered and identified as monohydrobromide *Va*, m.p. 228—230°C under decomposition. For $C_{19}H_{23}BrN_2O_2S$ (423·9) calculated: 53·90% C, 5·48% H, 18·87% Br, 6·62% N, 7·57% S; found: 53·67% C, 5·75% H, 18·62% Br, 6·57% N, 7·76% S.

2,3-Dimethoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*XXIII*)

Titanium tetrachloride (1·5 g) in 10 ml benzene was added dropwise over a period of 10 min under stirring to a solution of 2·85 g *Xa* in 20 ml benzene containing 7·5 g 1-methylpiperazine. The mixture was stirred for a week at room temperature, decomposed with water, the solid was filtered and the benzene layer separated from the filtrate. The crude residue obtained by its processing was recrystallized first from ethanol and then from a mixture of benzene and light petroleum; 1·28 g (35%) base, m.p. 211—211·5°C. UV spectrum: λ_{max} 237 nm (log ε 4·41), 273·5 nm (4·17), infl. 333 nm (3·84). IR spectrum (Nujol): 762, 863 (4 adjacent and solitary Ar—H), 1064, 1222, 1260 ($ArOCH_3$), 1505, 1610 cm^{-1} (Ar). NMR spectrum: δ 7·10—7·80 (m, 4 H, 6,7,8,9-H_4), 6·95 and 6·71 (2 s, 2 H, 1,4-H_2), 625 (s, 1 H, ArCH=C), 3·77 and 3·75 (2 s, 6 H, 2 OCH_3), 2·96 and 2·41 (2 t, 8 H, 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{21}H_{24}N_2.O_2S$ (368·5) calculated: 68·45% C, 6·57% H, 7·60% N, 8·70% S; found: 68·63% C, 6·86% H, 7·20% N, 8·55% S.

8-Chloro-2,3-dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin 5-Oxide (*XXIV*)

30% H_2O_2 (16 ml) was added to a solution of 8·5 g dimethanesulfonate of *VIb* in 50 ml water and the mixture was left to stand for 20 h at room temperature; it was then made alkaline with NH_4OH and the base was isolated by extraction with benzene; the crude product crystallized from a mixture of benzene and light petroleum to yield 3·70 g (62%) substance melting at 178 to 179°C. IR spectrum: 818, 850, 870, 874 (2 adjacent and solitary Ar—H), 1054, 1060, 1075 and 1094 (Ar—SO and $ArOCH_3$), 1220, 1266 ($ArOCH_3$), 1574, 1603 cm^{-1} (Ar). The presence of the sulfoxide group was demonstrated by a positive polarographic reduction wave in 0·5M-HCl. For $C_{21}H_{25}ClN_2O_3S$ (421·0) calculated: 59·91% C, 5·99% H, 8·42% Cl, 6·66% N, 7·62% S; found: 60·16% C, 5·99% H, 8·21% Cl, 6·48% N, 7·38% S. Evaporation of the mother liquor recovered 1·33 g base *VIb* (m.p. 160—163°C).

8-Chloro-2,3-dihydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Vb*)

A. Like in the preparation of *Va*, 4·26 g *VIb* was treated with 7·9 g BBr_3 in 20 ml chloroform. Crystallization of the crude product from a mixture of 95% ethanol and ether yielded 2·63 g

(44%) dihydrate of dihydrobromide *Vb*, m.p. 173–175°C, under decomposition. IR spectrum (Nujol): 813, 880 (2 adjacent and solitary Ar—H), 1159, 1291 (ArOH), 1502, 1589 (Ar), 1629, 3380 (H_2O), 2660 cm^{-1} (NH^+). For $C_{19}H_{27}Br_2ClN_2O_4S$ (574·8) calculated: 39·70% C, 4·74% H, 27·81% Br, 6·17% Cl, 4·87% N, 5·58% S; found: 39·94% C, 4·62% H, 27·28% Br, 6·84% Cl, 4·98% N, 5·64% S.

B. Like in the preceding case, 3·34 g *XXIV* reacted with 6·0 g BBr_3 in 17 ml chloroform. Crystallization of the crude salt from a mixture of 95% ethanol and ether yielded 3·68 g (81%) dihydrate of dihydrobromide *Vb*, m.p. 176–178°C. The IR spectrum is identical with the spectrum of the product according to *A*. The compound does not behave like a sulfoxide and shows no reduction wave of S—O on polarography in 0·5M-HCl. For $C_{19}H_{27}Br_2ClN_2O_4S$ (574·8) calculated: 39·70% C, 4·74% H, 6·17% Cl, 4·87% N, 5·58% S; found: 40·56% C, 4·58% H, 6·39% Cl, 4·93% N, 5·72% S.

8-Chloro-2,3-dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin N-Oxide (*XXV*)

30% H_2O_2 (2·5 ml) was added to a solution of 5·0 g base *VIb* in 25 ml ethanol and 10 ml dioxane, the mixture was left to stand for 12 h at room temperature, refluxed for 3 h, slightly acidified with hydrochloric acid, evaporated *in vacuo* and the residue was crystallized from a mixture of ethanol and ether to yield 3·3 g (50%) dihydrate of dihydrochloride *XXV*, m.p. 177–179°C (ethanol). IR spectrum: 828, 898 (2 adjacent and solitary Ar—H), 1080, 1282 ($ArOCH_3$), 1506, 1585, 1600 (Ar), 1630, 3440 (H_2O), 2480, 2580, 2650, 2700 cm^{-1} (NH^+). For $C_{21}H_{31}Cl_3N_2.O_5S$ (529·9) calculated: 47·60% C, 5·90% H, 20·07% Cl, 5·29% N; found: 47·51% C, 5·58% H, 19·65% Cl, 5·52% N.

N-(2,3-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-formamide (*XVIa*)

A mixture of 5·0 g *Xa*, 25 ml formamide and 5 ml 98% formic acid was heated for 1 h to 120°C and for 8 h in a bath at 190–200°C. After cooling, it was diluted with water, the precipitated product was filtered and, after drying, it was recrystallized from trichloroethylene; 4·5 g (82%), m.p. 225–226°C (chloroform–ethanol). IR spectrum (Nujol): 768, 843, 864 (4 adjacent and solitary Ar—H), 1052, 1216 ($ArOCH_3$), 1509 and 1645 (HCONH), 1595 (Ar), 3305 cm^{-1} (NH). For $C_{17}H_{17}NO_3S$ (315·4) calculated: 64·74% C, 5·43% H, 4·44% N, 10·17% S; found: 64·53% C, 5·55% H, 4·45% N, 10·33% S.

10-Amino-2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIIa*)

A mixture of 8·0 g *XVIa*, 8·0 g KOH and 10·5 ml ethanol was refluxed for 4·5 h in a 120–130°C bath. After cooling, it was diluted with water, the precipitated solid base was filtered and dried and finally recrystallized from benzene; 6·4 g (88%), m.p. 136·5–138·5°C (benzene–light petroleum). IR spectrum (Nujol): 765, 860 (4 adjacent and solitary Ar—H), 1049, 1258 ($ArOCH_3$), 1502, 1570, 1592 (Ar), 3400, 3500 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·00–7·55 (m, 4 H, 6,7,8,9-H_4). 7·00 (s, 1 H, 4-H), 6·70 (s, 1 H, 1-H), 4·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—N), 3·80 (s, 6 H, 2 OCH_3), 3·61 and 3·05 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 1·52 (bs, disappears after D_2O, 2 H, NH_2). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·87% C, 5·96% H, 4·87% N, 11·16% S; found: 67·09% C, 5·95% H, 5·21% N, 11·25% S.

Hydrochloride, m.p. 268–271°C under decomposition (95% ethanol–ether). For $C_{16}H_{18}Cl.NO_2S$ (323·9) calculated: 59·34% C, 5·60% H, 10·95% Cl, 4·33% N, 9·90% S; found: 59·24% C, 5·82% H, 10·88% Cl, 4·33% N, 9·77% S.

2,3-Dimethoxy-10-methylamino-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIIIa*)

A. Sodium borohydride (3·8 g) was added at 10°C to a solution of 8·5 g *XVIa* in 100 ml tetrahydrofuran and this was followed over a period of 2 h by a dropwise addition in a nitrogen atmosphere of 5·4 g acetic acid in 20 ml tetrahydrofuran. The mixture was stirred for 1 h at room temperature, refluxed for 3 h, left to stand for 2 days, decomposed by adding 100 ml 20% hydrochloric acid and the volatile fractions were evaporated. The residue was made alkaline with 20% NH_4OH and the product was isolated by extraction with benzene. Crystallization of the crude base from a mixture of benzene and light petroleum yielded 6·9 g (85%) compound melting at 83—89°C; the analytical product melted at 90—91°C (cyclohexane). ^{1}H-NMR spectrum: δ 7·00—7·53 (m, 4 H, 6,7,8,9-H_4), 6·90 and 6·62 (2 s, 2 H, 1,4-H_2), 4·45 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—N), 3·80 (s, 6 H, 2 OCH_3), 3·43 and 3·05 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·44 (s, 3 H, NCH_3), 1·40 (s, disappears after D_2O, 1 H, NH). For $C_{17}H_{19}NO_2S$ (301·4) calculated: 67·74% C, 6·35% H, 4·76% N, 10·64% S; found: 67·63% C, 6·45% H, 4·69% N, 10·50% S.

Hydrochloride, m.p. 268—270°C under decomposition (aqueous ethanol). For $C_{17}H_{20}ClNO_2S$ (338·0) calculated: 60·42% C, 5·97% H, 10·49% Cl, 4·15% N, 9·49% S; found: 59·89% C, 6·08% H, 10·60% Cl, 4·13% N, 9·36% S.

B. 6·0 ml 50% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate was added to a solution of 1·58 g *XVIa* in 5 ml benzene, the mixture was heated to boiling, then stirred for 1·5 h without heating, left to stand overnight, decomposed with 20% NaOH, the solid was filtered, the benzene layer of the filtrate was separated and the aqueous layer was extracted with benzene. The combined benzene solutions were dried and evaporated and the residue was treated with an ether solution of HCl to convert it to the hydrochloride; 1·3 g (86%), m.p. 260—267°C. The product thus obtained is less pure than that obtained under *A*.

2,3-Dimethoxy-10-dimethylamino-10,11-dihydrodibenzo[*b,f*]thiepin (*XIXa*)

A mixture of 4·79 g *XVIIa*, 12 ml 36% solution of formaldehyde and 8 ml 98% formic acid was heated for 9 h in a boiling water bath. After cooling, it was acidified with 5 ml hydrochloric acid, the solution was washed with ether, made alkaline with NH_4OH and the base was isolated by extraction with benzene; 4·2 g (80%), m.p. 61—64°C (light petroleum). IR spectrum: 760, 860 (4 adjacent and solitary Ar—H), 1230, 1265 ($ArOCH_3$), 1510, 1605 (Ar), 2830 cm^{-1} (OCH_3 and NCH_3). NMR spectrum: δ 7·00—7·60 (m, 4 H, 6,7,8,9-H_4), 7·00 (s, 1 H, 4-H), 6·75 (s, 1 H, 1-H), 2·80—4·00 (m, 3 H, $ArCH_2CHAr$), 3·88 and 3·79 (2 s, 6 H, 2 OCH_3), 2·34 (s, 6 H, CH_3NCH_3). For $C_{18}H_{21}NO_2S$ (315·4) calculated: 68·54% C, 6·71% H, 4·44% N, 10·17% S; found: 68·34% C, 6·81% H, 4·60% N, 9·99% S.

Hydrochloride, m.p. 240—245°C under decomposition (95% ethanol–ether). For $C_{18}H_{22}$·.$ClNO_2S$ (351·9) calculated: 61·44% C, 6·30% H, 10·08% Cl, 3·98% N, 9·11% S; found: 61·22% C, 6·48% H, 10·13% Cl, 3·87% N, 9·00% S.

10-Amino-2,3-dihydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVI*)

A. A solution of 5·57 g BBr_3 in 10 ml chloroform was added dropwise over a period of 10 min at 10—20°C to a solution of 3·19 g *XVIIa* in 20 ml chloroform, the mixture was stirred for 6 h at room temperature, left to stand overnight and then 25 ml ethanol was added dropwise under cooling. The mixture was then stirred for 8 h at room temperature. After standing overnight, 3·09 g (82%) hydrobromide was filtered. It was crystallized from a mixture of ethanol and ether,

m.p. 221–222°C, under decomposition. IR spectrum (Nujol): 756, 888 (4 adjacent and solitary Ar—H), 1140, 1278 (Ar—OH), 1490, 1510, 1588 (Ar), 2580, 2630 (NH_3^+), 3420 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·26 (bs, disappears after D_2O, 2 H, 2 OH), 8·56 (bs disappears after D_2O, 3 H, NH_3^+), 7·20–7·80 (m, 4 H, 6,7,8,9-H_4), 6·98 and 6·89 (2 s, 2 H, 1,4-H_2), 5·06 (m, 1 H, Ar—CH—N), c. 3·50 (m, 2 H, $ArCH_2$). For $C_{14}H_{14}BrNO_2S$ (340·3) calculated: 49·42% C, 4·15% H, 23·49% Br, 4·12% N, 9·42% S; found: 49·12% C, 4·11% H, 23·39% Br, 4·39% N, 9·23% S.

B. A solution of 0·28 g *XVIIa* in 2 ml 48% hydrobromic acid was refluxed for 2 h. After standing overnight it was evaporated at reduced pressure and the residue was crystallized from a mixture of ethanol and ether; 0·27 g (81%) hydrobromide, m.p. 221–223°C, identical with the product obtained under *A*.

2,3-Dihydroxy-10-methylamino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVII*)

Like with the preparation of *XXVI* under (*A*), 4·2 g *XVIIIa* reacted with 7·0 g BBr_3 in 30 ml chloroform and the primary product was decomposed with ethanol; 3·35 g (67%) crude hydrobromide, which was recrystallized from a mixture of ethanol and ether and then melted at 226 to 227°C under decomposition. IR spectrum: 770, 880, 895 (4 adjacent and solitary Ar—H), 1280 (Ar—OH), 1525, 1600 (Ar), 2695 (NH_2^+), 3290 and 3330 cm^{-1} (OH and NH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·26 (bs, 2 H, 2 OH), 9·12 (bs, 2 H, NH_2^+), 7·10–7·80 (m, 4 H, 6,7,8,9-H_4), 6·90 (s, 1 H, 4-H), 6·82 (s, 1 H, 1-H), 5·05 (t, J = 6·0 Hz, 1 H, Ar—CH—N), 3·45 (d, 2 H, $ArCH_2$), 2·52 (s, 3 H, N—CH_3). For $C_{15}H_{16}BrNO_2S$ (356·3) calculated: 50·56% C, 5·09% H, 22·43% Br, 3·93% N, 9·00% S; found: 50·70% C, 4·65% H, 22·52% Br, 3·78% N, 9·07% S.

2,3-Dihydroxy-10-dimethylamino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVIII*)

Like in the preceding cases, 3·76 g *XIXa* reacted with 6·0 g BBr_3 in 22 ml chloroform, followed by decomposition with ethanol. Analogous procedure then led to 3·13 g (70%) crude hydrobromide hemihydrate which was obtained in the pure state after dissolving in water, filtration of the solution, evaporation and crystallization of the residue from a mixture of ethanol and ether, m.p. 216–218°C under decomposition. IR spectrum: 755, 873 (4 adjacent and solitary Ar—H), 1295 (Ar—OH), 1510, 1605 (Ar), 2720 (NH^+), 3140, 3380 and 3472 cm^{-1} (OH and H_2O). For $C_{16}H_{19}BrNO_{2,5}S$ (377·3) calculated: 50·93% C, 5·08% H, 21·18% Br, 3·71% N, 8·50% S; found: 50·85% C, 5·08% H, 21·60% Br, 3·86% N, 8·33% S.

The authors are indebted to Mrs E. Princová for technical assistance with the synthesis of compounds and to Mrs. J. Komancová, Mrs A. Slavíková, Mrs Z. Volková, Mr M. Čech, Miss J. Hrdá, Mrs V. Šmidová and Mr J. Komínek of the analytical department of this Institute for carrying out the analyses.

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Translated by A. Kotyk.