POTENTIAL METABOLITES OF PERATHIEPIN: 6-HYDROXY-10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]-THIEPIN AND ITS DERIVATIVES*

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Acid *VI* obtained in a reaction of *o*-iodophenylacetic acid with 2-methoxythiophenol was cyclized to 6-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIb*) which was further converted either to enamine *IV* or to its dihydro derivative *Ib*. Demethylation of *Ib* with boron tribromide yielded the title compound (*Ia*). Specific oxidation procedures led to the sulfoxides *IIa* and *IIb* and to the N-oxide *III*. Of the compounds prepared (potential metabolites of perathiepin) phenol *Ia* resembles perathiepin most closely in its pharmacological properties.

On the basis of analogy with what is known about the biotransformation of chlorpromazine[1-4] and some related phenothiazine derivatives with the piperazine fragment in the side chain[5,6], one can predict the following biotransformations of perathiepin, *i.e.* 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[7-9]: S-oxidation, N-oxidation, N-demethylation and subsequent N-oxidation to the hydroxylamine derivative, hydroxylation of the aromatic rings (single and multiple), subsequent O-methylation and formation of glucuronides or O-sulfates, a partial or complete degradation of the piperazine ring and finally the formation of nitrogen free cleavage products. The individual metabolic mechanisms may function isolated or in combination. Starting from the derived potential metabolites the following compounds were synthesized for comparative purposes and for pharmacological studies: perathiepin S-oxide[8,10-13] (demonstrated as a metabolite in humans and in rats[14,15]), perathiepin S,S-dioxide[12,16,17], perathiepin N-oxide[10], perathiepin S,N-dioxide[10], desmethylperathiepin[8,18] (demonstrated as a metabolite in humans and in rats[14,15]), 2-methoxyperathiepin[19], 8-hydroxyperathiepin[20], 8-methoxyperathiepin[21] and 10-amino-10,11-dihydrodibenzo[*b*,*f*]thiepin[7]. From the point of view of pharmacological activity, the 8-methoxy[21] and the 8-hydroxy derivative[20] are most interesting both surpassing perathiepin in the catalepsy test and the first also with regard to central depressant activity. The presence of at least two phenolic metabolites of perathiepin was demonstrated qualitatively in human and rat urine[14,15]; they have not been identified so far. The 8-hydroxy derivative[20] can be considered as one of the probable potential phenolic metabolites; its biochemical formation would represent an interesting bioactivation process (see also[22]). The hypothesis on the bioactivation of some tricyclic neuroleptics by metabolic hydroxylation in aromatic rings is investigated systematically and the attempts at its verification constitute a part of our experimental work.

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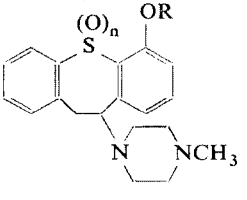
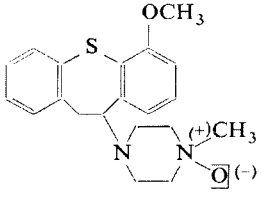
In the present study, we have taken up a group of less probable potential metabolites of perathiepin, containing a hydroxyl or a methoxyl group in position 6 of the skeleton, *i.e.* 6-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]-thiepin (*Ia*), its methyl ether *Ib*, sulfoxides derived from the two compounds (*IIa*, *IIb*) and the N-oxide *III*. In connection with this, the enamine *IV* was also prepared. These compounds are considered as less probable potential metabolites since, with chloropromazine, no metabolic hydroxylation into the corresponding positions 4 or 6 has been found. On the other hand, the 4-hydroxy derivative of promazine (*V*) directly corresponding to the present compound *Ia* was considered as a potential metabolite of promazine and its pharmacology was studied[23,24].

When synthesizing compounds *I*–*IV*, a modification of the basic synthetic pattern was used[7,21], the starting compound being *o*-iodophenylacetic acid[25]. Its reaction with 2-methoxythiophenol[26,27] in a boiling aqueous solution of potassium hydroxide in the presence of copper yielded the *o*-(2-methoxyphenylthio)phenylacetic acid (*VI*). Its cyclization with polyphosphoric acid in the presence of boiling toluene (for analogy see *e.g.*[21]) yielded 6-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIb*) which was demethylated by fusion with pyridine hydrochloride to 6-hydroxy ketone *VIIa*. Reduction of methoxy ketone *VIIb* with sodium borohydride in aqueous ethanol led to the alcohol *VIIIb* which by treatment with hydrogen chloride in benzene gave chloride *IXb*. Its reaction with potassium hydroxide in boiling ethanol did not lead to the expected dehydrochlorination; a high yield of the ethoxy derivative *Xb* was obtained as a product of the substitution reaction. In agreement with this, during the reaction of chloride *IXb* with 1-methylpiperazine in boiling chloroform, the elimination reaction is markedly suppressed and a practically 90% yield of the

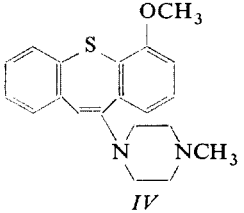


I, $n = 0$
II, $n = 1$

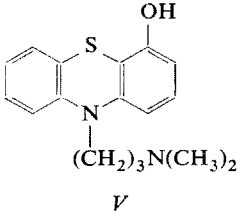
In formulae:
a, R = H
b, R = CH_3



III

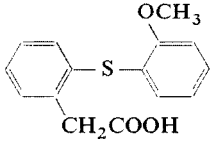


IV

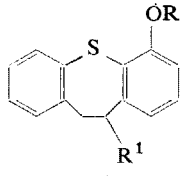


V

substitution product is obtained, *viz.* the piperazine derivative *Ib*. Oxidation of its methanesulfonate in an aqueous solution with excess hydrogen peroxide at room temperature (for analogy see[10]) resulted in sulfoxide *IIb*; the presence of the S—O group is indicated by the IR spectrum ($\nu_{(S-O)}$ 1034 cm^{-1}) and supported by the polarographic method[15]. For the oxidation of *Ib* to N-oxide *III*, oxidation of the base with a theoretical amount of hydrogen peroxide in ethanol was used; the identity of the compound can be taken as proven even if the spectral evidence is not unequivocal. However, the compound clearly differs from sulfoxide *IIb*, the base crystallizes as dihydrate and is water-soluble which is typical for the N-oxides of this series[10]. Compound *Ib* was further demethylated by treatment with boron tribromide in chloroform (for analogy see[22]): the primary product was hydrolyzed with dilute ethanolic sodium hydroxide and a phenolic base *Ia* was obtained which was identified analytically and spectrally and characterized by crystalline salts. Oxidation by the mentioned method converted also this compound to the corresponding sulfoxide, *i.e. IIa*. Reaction of ketone *VIIb* with 1-methylpiperazine and titanium tetrachloride in boiling benzene (see ref.[28]) led to enamine *IV*.



VI



VII, $R^1 = =O$
VIII, $R^1 = OH$
IX, $R^1 = Cl$
X, $R^1 = OC_2H_5$

The prepared compounds *Ia*, *Ib*, *IIb*, and *IV* in the form of salts and compound *III* as base dihydrate were subjected to an orientative pharmacological testing for potential neuroleptics. The results are summarized in Table I, as mean lethal doses LD_{50} (acute toxicity estimated in mice) and mean effective doses ED_{50} (the mean effective doses bringing about ataxia in mice in the rotating-rod test and the mean effective doses bringing about catalepsy in rats are shown). The compounds were administered *per os* and all the doses shown refer to the base. For comparison, the table includes perathiepin[9], its 2-methoxy derivative[19] and its 8-methoxy derivative[21].

Table I indicates that the new compounds are relatively little toxic; the most toxic compound is the sulfoxide *IIb* which is equally toxic as perathiepin. The low toxicity of enamine *IV* is surprising. As sedatives, all the new compounds are less effective than perathiepin and its 8-methoxy derivative. The most active was aminophenol *Ia* which possesses about 50% of the activity of perathiepin. In the catalepsy test, some indication of an effect is displayed only by enamine *IV*. With the other new compounds, the mean effective dose in the catalepsy test is always higher than 50 mg/kg, *i.e.* it lies at least partly in the subtoxic range. In this respect, the new

compounds resemble the 2-methoxy derivative of perathiepin[19]. Let us note that for the 4-hydroxy derivative of promazine (*V*), ref.[23] indicates that in the tests for central depressant activity it equals promazine while in the test of inhibition of conditioned reactions it is much weaker than promazine.

Compounds *I*—*IV* were also tested for antimicrobial activity toward a standard set of microorganisms *in vitro* (Dr J. Turinová, Dr A. Čapek). A certain activity was found only with *III* and *IV*, specifically against yeasts and lower fungi. The minimum inhibitory concentrations in μg/ml are shown: *Saccharomyces pasterianus*, *III*, 100; *Trichophyton mentagrophytes*, *III*, 50; *IV*, 125; *Candida albicans*, *III*, 100; *Aspergillus niger*, *III*, 100.

TABLE I

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

Compound	Toxicity LD_{50}	Ataxia ED_{50}	Catalepsy ED_{50}
Ia	175	5·1	$>50^a$
Ib	105	15·0	$>50^b$
IIb	62	7·8	$>50^c$
III	220	15·0	$>50^a$
IV	360	6·0	—[d]
Perathiepin[9]	63	2·4	45
2-Methoxyperathiepin[19]	93	14·0	$>50^c$
8-Methoxyperathiepin[21]	36	1·5	4·0

[a] The dose shown brings about catalepsy in 3 rats out of 10. [b] In 4 rats out of 10. [c] In 2 rats out of 10. [d] Doses of 2·5—25 mg/kg bring about catalepsy in 4—6 rats out of 10; no dependence of effect on dose could be demonstrated.

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) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G or an Infrascan (Hilger and Watts) spectrophotometer. The NMR spectra were recorded in $CDCl_3$ (unless stated otherwise), using a ZKR 60 (Zeiss Jena) spectrometer.

o-(2-Methoxyphenylthio)phenylacetic Acid (*VI*)

2-Methoxythiophenol[26] (39 g) was added to a solution of 63 g 85% KOH in 560 ml water and, after 15 min of stirring, this was followed by 73 g *o*-iodophenylacetic acid[25] and 2 g copper paste. The mixture was refluxed for 7 h, partly cooled and the solution was filtered with charcoal.

The filtrate was acidified with hydrochloric acid and the precipitated product crystallized upon standing overnight; 45 g (59%), m.p. 93–95°C. For analysis the sample was recrystallized from aqueous ethanol, m.p. 99–101°C. For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·67% C, 5·14% H, 11·69% S; found: 65·90% C, 5·34% H, 11·44% S.

6-Methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIb*)

Toluene (50 ml) and 10·0 g acid *VI* was added to 40 g polyphosphoric acid and the mixture was refluxed under stirring for 4 h. After cooling, it was decomposed with 100 ml water, the organic layer was diluted with toluene and washed with 5% solution of NaOH and water, dried with K_2CO_3 and evaporated; 8·5 g (91%) product melting at 93–95°C. Sample for analysis melted at 100–102°C (benzene–light petroleum). UV spectrum: λ_{max} 237 nm (log ε 4·27), infl. 244 nm (4·24), infl. 261 nm (3·96), infl. 275 nm (3·81), infl. 283 nm (3·71), 345 nm (3·73). IR spectrum: 757, 770, 790 (4 and 3 adjacent Ar—H), 1260 ($ArOCH_3$), 1560, 1585 (Ar), 1675 cm^{-1} (ArCO). NMR spectrum: 6·80–7·80 (m, 7 H, aromatic protons), 4·17 (s, 2 H, $ArCH_2CO$), 3·85 (s, 3 H, OCH_3). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·28% C, 4·72% H, 12·51% S; found: 70·27% C, 4·86% H, 12·37% S.

6-Hydroxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIa*)

Hydrochloric acid (95 ml) was slowly added to a solution of 80 ml pyridine in 80 ml ethanol. The ethanol was evaporated from the solution of pyridine hydrochloride and its remainder removed by heating to 200°C. At this temperature, 14 g ketone *VIIb* were added and the mixture was heated for 1 h to 200°C. After partial cooling, 180 ml water was added and the mixture was stirred to complete cooling. The crude product was filtered and recrystallized from ethanol; 10·8 g (84%), m.p. 174–176°C. UV spectrum: λ_{max} 237 nm (log ε 4·22), infl. 262 nm (3·92), infl. 276 nm (3·79), infl. 284 nm (3·74), 348 nm (3·67). IR spectrum: 755, 795 (4 and 3 adjacent Ar—H), 1285 (Ar—OH), 1565 (Ar), 1645 (ArCO...HOAr), 2500 cm^{-1} (Ar—OH...O=C). NMR spectrum (CD_3SOCD_3): δ 10·60 (bs, disappears after D_2O, 1 H, OH), 7·00–7·75 (m, 7 H, aromatic protons), 4·09 (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: 69·57% C, 4·27% H, 12·94% S.

10-Hydroxy-6-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIIb*)

A solution of 0·7 g $NaBH_4$ in 6 ml water with 0·1 ml 20% NaOH was added dropwise under stirring to a solution of 12·8 g ketone *VIIb* in 230 ml ethanol at 70°C. The mixture was refluxed under stirring for 3 h, ethanol was evaporated at reduced pressure, the residue was mixed with 100 ml water and extracted with benzene. The extract was washed with 3% NaOH and water, dried with $MgSO_4$, filtered and evaporated; 13·0 g (theoretical yield) product which crystallizes from a mixture of benzene and light petroleum; m.p. 127–129°C. IR spectrum: 750, 765, 795 (4 and 3 adjacent Ar—H), 1042 (CHOH in the ring), 1253 ($ArOCH_3$), 1565 (Ar), 3190 cm^{-1} (OH). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 70·22% C, 5·67% H, 12·30% S.

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

11·0 g *VIIIb* was dissolved in 100 ml warm benzene, the solution was cooled to 20°C, 10 g $CaCl_2$ (powder) was added and the suspension was saturated for 4 h under stirring with gaseous anhydrous hydrogen chloride. It was left to stand overnight at room temperature, filtered with

charcoal and the filtrate was evaporated: 11·0 g (94%) crude product, m.p. 114—118°C. A sample was recrystallized for analysis from a mixture of benzene and light petroleum, m.p. 116—118°C. NMR spectrum: δ 7·54 (m, 1 H, 4-H), 6·60—7·40 (m, 6 H, remaining aromatic protons), 5·86 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·91 and 3·59 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 3·82 (s, 3 H, OCH_3). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·09% C, 4·73% H, 12·81% Cl, 11·59% S; found: 65·33% C, 4·81% H, 12·79% Cl, 11·40% S.

10-Ethoxy-6-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*Xb*)

A solution of 3·5 g KOH in 30 ml ethanol was added to a warm solution of 4·3 g *IXb* in 20 ml ethanol and the mixture was refluxed for 3 h. After evaporation of ethanol, the remainder was mixed with 60 ml water and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated. The residue (4·0 g) was recrystallized from a mixture of benzen and light petroleum: 3·2 g, m.p. 91—93°C (ethanol): UV spectrum: λ_{max} 253 nm (log ε 3·75), 269 nm (3·75), 282 nm (3·80). IR spectrum: 740, 760, 797 (4 and 3 adjacent Ar—H), 1081, 1280 (Ar—O—R), 1476, 1580 cm^{-1} (Ar). NMR spectrum: δ 7·50 (m, 1 H, 4-H), 6·90—7·35 (m, 5 H, 1,2,3,8,9-H_5), 6·75 (q, J = 8·0; 2·5 Hz, 1 H, 7-H), 5·55 (dd, J = 12·0; 5·0 Hz, 1 H, Ar—CH—O), 3·81 (s, 3 H, OCH_3), 3·56 (q, J = 7·0 Hz, 2 H, CH_2 of ethyl), 3·58 and 3·15 (2 dd, J = 16·0; 5·0 and 16·0; 12·0 Hz, 2 H, $ArCH_2$), 1·25 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{17}H_{18}O_2S$ (286·3) calculated: 71·31% C, 6·34% H, 11·19% S; found: 70·90% C, 6·20% H, 11·10% S.

6-Methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

1-Methylpiperazine (6·5 g) was added to a solution of 6·0 g *IXb* in 10 ml chloroform and the mixture was refluxed for 6 h. After evaporation of the chloroform the residue was decomposed with 50 ml 10% NaOH and extracted with benzene. The extract was washed with water and shaken with excess 1·25M-H_2SO_4. The separated aqueous solution of sulfate was made alkaline with NH_4OH and the product was isolated by extraction with benzene; 6·4 g (87%) oily base. After dissolving in 15 ml ethanol it was neutralized while hot with 1·8 g methanesulfonic acid. On adding ether and after standing overnight in a refrigerator, methanesulfonate was obtained, m.p. 192 to 195°C (ethanol–ether) which is soluble in water. IR spectrum: 750, 762, 772, 787 (4 and 3 adjacent Ar—H), 1040, 1155 (SO_3H), 1238 ($ArOCH_3$), 1575 (Ar), 2500 cm^{-1} (NH^+). NMR spectrum: δ 7·60 (m, 1 H, 4-H), 6·60—7·40 (m, 6 H, remaining aromatic protons), 3·85 (s, 3 H, OCH_3), 2·75 and 2·72 (2 s, 6 H, NCH_3 and CH_3SO_3), 2·70—4·20 (m, 11 H, 4 CH_2 of piperazine and $ArCH_2CHAr$). For $C_{21}H_{28}N_2O_4S_2$ (436·6) calculated: 57·77% C, 6·46% H, 6·42% N, 14·69% S; found: 57·76% C, 6·54% H, 6·08% N, 14·62% S.

6-Methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin 5-Oxide (*IIb*)

Crude base *Ib* was dissolved in a solution of 3·4 g 90% methanesulfonic acid in 120 ml water, 75 ml 30% H_2O_2 was added and the mixture was left to stand overnight at room temperature. Then it was filtered with charcoal, the filtrate made alkaline with NH_4OH and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The oily residue crystallized after mixing with 30 ml acetone; 5·0 g (48%), m.p. 164—166°C (acetone). IR spectrum: 750, 770 (4 and 3 adjacent Ar—H), 1034 (S—O), 1270 ($ArOCH_3$), 1474, 1577 cm^{-1} (Ar). For $C_{20}H_{24}N_2O_2S$ (356·5) calculated: 67·38% C, 6·79% H, 7·86% N, 8·99% S; found: 67·10% C, 7·14% H, 7·97% N, 9·05% S.

Methanesulfonate, m.p. 195—196°C (ethanol–ether). For $C_{21}H_{28}N_2O_5S_2$ (452·6) calculated: 55·73% C, 6·23% H, 6·19% N, 14·17% S; found: 55·40% C, 6·48% H, 6·16% N, 14·22% S.

6-Methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin N-Oxide (*III*)

25% hydrogen peroxide (3·5 ml) was added dropwise to a solution of 8·5 g crude base *Ib* in 40 ml ethanol. The mixture was left to stand overnight at room temperature, refluxed for 3 h, a platinum foil was added and refluxing continued for another hour. After cooling, 50 ml water was added and the solution was evaporated at reduced pressure. The oily residue was combined with 50 ml acetone which led to the precipitation of 5·7 g (64%) crude product, m.p. 155–159°C which was recrystallized from acetone and then melted constantly at 203–206°C. It is the dihydrate of base *III*, slightly soluble in water (to a 2% solution). IR spectrum: 765, 790 (4 and 3 adjacent Ar—H), 1 270 ($ArOCH_3$), 1 575 (Ar), 1 700 and 3 450 cm^{-1} (H_2O). NMR spectrum: δ 6·70–7·70 (m, 7 H, aromatic protons), 3·90 (s, 3 H, OCH_3), 3·12 (s, 3 H, NCH_3), 2·50–4·50 (m, remaining CH_2 and CH groups). For $C_{20}H_{28}N_2O_4S$ (392·4) calculated: 61·21% C, 7·19% H, 7·14% N, 8·16% S; found: 61·77% C, 6·78% H, 7·03% N, 8·42% S.

6-Hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

A solution of 44 g BBr_3 in 120 ml chloroform was added dropwise under stirring to a solution of 20·0 g crude base *Ib* in 120 ml chloroform. The thickened mixture was left to stand overnight at room temperature. The chloroform was evaporated and the residue was combined with 600 ml ethanol and 460 ml 3% NaOH and the mixture was refluxed under stirring for 6 h. After evaporation of ethanol at reduced pressure, the residue was combined with 250 ml water, the solution formed was filtered with charcoal and the filtrate (pH 12) was neutralized with 10% acetic acid to pH 8. The precipitated product was filtered on the following day; 9·5 g (48%), m.p. 79–84°C. After recrystallization from light petroleum, the product melts at 148–151°C. IR spectrum (Nujol): 760, 790 (4 and 3 adjacent Ar—H), 1 131, 1 151, 1 169, 1 286 (Ar—OH), 1 576 cm^{-1} (Ar). NMR spectrum: δ 6·60–7·60 (m, 7 H, aromatic protons), 6·56 (bs, disappears after D_2O, 1 H, OH), 3·00–4·20 (m, 3 H, $ArCH_2CHAr$), 2·30–2·80 (m, 8 H, 4 CH_2 of piperazine), 2·28 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2OS$ (326·4) calculated: 69·90% C, 6·79% H, 8·58% N, 9·82% S; found: 69·99% C, 7·09% H, 8·41% N, 9·93% S.

Maleate, m.p. 179–181°C (ethanol). For $C_{23}H_{26}N_2O_5S$ (442·5) calculated: 62·42% C, 5·92% H, 6·33% N, 7·25% S; found: 62·23% C, 6·24% H, 6·00% N, 7·32% S.

Methanesulfonate (hemihydrate), m.p. 186–187°C (ethanol–ether). For $C_{20}H_{27}N_2O_{4.5}S_2$ (431·6) calculated: 55·66% C, 6·30% H, 6·49% N; found: 55·56% C, 6·29% H, 6·26% N.

6-Hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo [*b,f*]thiepin 5-Oxide (*IIa*)

Base *Ia* (3·3 g) was dissolved in a solution of 1·1 g 90% methanesulfonic acid in 40 ml water; 25 ml 30% H_2O_2 was then added and the mixture was left to stand overnight, filtered with charcoal, the filtrate was made alkaline with NH_4OH and the base was isolated by extraction with benzene; 1·1 g (32%), m.p. 174–176°C (acetone). IR spectrum: 725, 775 (4 and 3 adjacent Ar—H), 1 005 (S—O), 1 115, 1 175, 1 265, 1 310 (ArOH), 1 462, 1 596 (Ar), 3 100 cm^{-1} (O—H...N). NMR spectrum: δ *c.* 10·60 (bs, 1 H, OH), 8·00 (m, 1 H, 4-H), 7·00–7·60 (m, 5 H, 1,2,3,7,8-H_5), 6·65 (m, 1 H, 7-H), 3·00–4·30 (m, 3 H, $ArCH_2CHAr$), 2·30–2·80 (m, 8 H, 4 CH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For. $C_{19}H_{22}N_2O_2S$ (342.4) calculated: 66·64% C, 6·48% H, 8·18% N, 9·36% S; found: 66·90% C, 6·63% H, 8·04% N, 9·49% S.

6-Methoxy-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IV*)

1-Methylpiperazine (15 g) was added to a solution of 7·7 g ketone *VIIb* in 65 ml benzene and then a solution of 3·0 g $TiCl_4$ in 20 ml benzene was added dropwise. The mixture was refluxed under stirring for 24 h. After cooling, it was decomposed with 100 ml water, stirred for 10 min, the precipitate was filtered and washed with benzene. The organic layer was separated from the filtrate, washed with water, dried with Na_2SO_4 and evaporated. The residue was crystallized from ethanol to yield 5·9 g (58%) pure product, m.p. 156—159°C (ethanol or cyclohexane). UV spectrum: λ_{max} 230 nm (log ε 4·36), 265 nm (4·01), 310 nm (4·00). IR spectrum: 755, 768, 803 (4 and 3 adjacent Ar—H), 1267 ($ArOCH_3$), 1565, 1615 (Ar), 2720 cm^{-1} ($N—CH_2$). NMR spectrum: δ 7·50 (m, 1 H, 4-H), 6·70—7·30 (m, 6 H, remaining aromatic protons), 6·36 (s, 1 H, Ar—CH=), 3·80 (s, 3 H, OCH_3), 2·92 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, 4 H, CH_2. .N^4CH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{20}H_{22}N_2OS$(338·5) calculated: 70·97% C, 6·55% H, 8·28% N, 9·47% S; found: 70·79% C, 6·60% H, 8·27% N, 9·53% S.

Maleate, m.p. 184—186°C (ethanol–ether). For $C_{24}H_{26}N_2O_5S$ (454·5) calculated: 63·41% C, 5·77% H, 6·16% N, 7·05% S; found: 62·94% C, 6·06% H, 6·26% N, 7·43% S.

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