POTENTIAL METABOLITES OF TRICYCLIC NEUROLEPTICS: 3,7-DIMETHOXY AND 7,8-DIMETHOXY DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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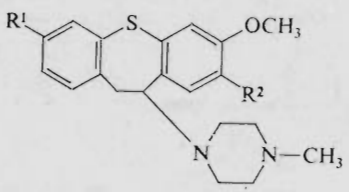
Reaction of 2-iodo-4-methoxybenzoic acid with 3-methoxythiophenol resulted in the acid *II* which was transformed *via* the alcohol *III* and the nitrile *IV* to [4-methoxy-2-(3-methoxyphenylthio)phenyl]acetic acid (*V*). Reaction of (2-iodophenyl)acetic acid with 3,4-dimethoxythiophenol gave the isomeric [2-(3,4-dimethoxyphenylthio)phenyl]acetic acid (*XI*). Acids *V* and *XI* afforded by cyclization the ketones *VIa* and *VIb* which were converted by reactions with 1-methylpiperazine and titanium tetrachloride to the enamines *IXa* and *IXb*. Reduction of these enamines with diborane led to the title compounds. Attempts to reduce the enamines with zinc in acetic acid resulted in hydrogenolysis, the main products being 2,3-dimethoxy- and 3,7-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Xab*).

The present communication represents continuation of our efforts to make available most of the possible hydroxylated potential metabolites of the tranquillizer and neuroleptic agent perathiepin, *i.e.* 10-(4-methylpiperazino)-10,11-dihydrodibenzo-[*b*,*f*]thiepin[1,2]. The last paper of this type described the synthesis of 2,8-dihydroxy and 3,8-dihydroxy derivatives of this psychotropic agent[3]. The goal of the present investigation was the synthesis of 3,7-dihydroxy and 7,8-dihydroxy derivatives of perathiepin. Since in the meantime all our attempts at preparing 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepins with a free hydroxyl group in position 7 failed (elimination of methylpiperazine takes place, ref.[4-7]), our present work



a, $R^1 = OCH_3$ $R^2 = H$
b, $R^1 = H$, $R^2 = OCH_3$

I

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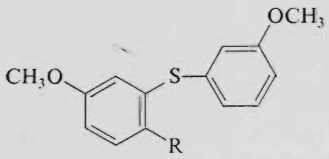
was discontinued in the stage of the methyl ethers, *i.e.* the title compounds *Ia* and *Ib*

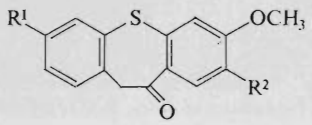
In the first part of the syntheses of compounds *Ia* and *Ib*, similar methods were used like in the syntheses of the 2,8-dimethoxy and 3,8-dimethoxy derivatives of perathiepin[3]. Starting compounds in the synthesis of the 3,7-dimethoxy derivative *Ia* were 2-iodo-4-methoxybenzoic acid[8] and 3-methoxythiophenol[9]. Their reaction in a boiling aqueous solution of potassium hydroxide in the presence of copper gave 4-methoxy-2-(3-methoxyphenylthio)benzoic acid (*II*) which was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene to the alcohol *III*. This alcohol, which is a derivative of 4-methoxybenzyl alcohol, is very easily converted to the corresponding benzyl chloride by treatment with hydrochloric acid at room temperature[10]. The crude chloride obtained was transformed by treatment with sodium cyanide in acetone in the presence of sodium iodide to the nitrile *IV* (for the method[10]), which was hydrolyzed with potassium hydroxide to [4-methoxy-2-(3-methoxyphenylthio)phenyl]acetic acid (*V*). Cyclization of this acid was carried out with polyphosphoric acid in the presence of boiling toluene and resulted in 3,7-dimethoxydibenzo-[*b*,*f*]thiepin-10(11*H*)-one (*VIa*), obtained in an almost theoretical yield. Its reduction with sodium borohydride in boiling aqueous ethanol afforded the alcohol *VIIa*. An attempt at its transformation to the corresponding 10-chloro derivative by treatment with hydrogen chloride in benzene was unsuccessful; an inhomogeneous chlorine-free product was obtained consisting apparently mainly of the elimination product *VIIIa*. For this reason, an alternative method was used, similarly like in the synthesis of the 7-methoxy derivative of perathiepin[11]: a reaction of the ketone *VIa* with 1-methylpiperazine and titanium tetrachloride in boiling benzene gave the enamine *IXa* which was reduced with diborane, generated by decomposition of sodium borohydride with acetic acid in tetrahydrofuran. In a moderate yield there was obtained the 10,11-dihydro base *Ia* which gave a crystalline maleate. In an attempt to reduce the enamine *IXa* with zinc in acetic acid (for method[12]), the desired product was not obtained at all; hydrogenolysis takes place resulting in 3,7--dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Xa*) as the main product and in 3,7--dimethoxydibenzo[*b*,*f*]thiepin (*VIIIa*) as an important by-product. Both compounds were identified in the mixture obtained by means of the mass spectrum and the ^{1}H-NMR spectrum. Complete separation could not be achieved by repeated chromatography and crystallization; a product, corresponding by its analysis to the dihydro compound *Xa*, still contains some 15% of the unsaturated analogue *VIIIa* (*cf.* ^{1}H-NMR spectrum).

In the isomeric series we started from a reaction of (2-iodophenyl)acetic acid[13] with 3,4-dimethoxythiophenol[14] (it has been prepared by reduction of 3,4-dimethoxybenzenesulfonyl chloride[15,16] using the Wagner's method[17]); the reaction was carried out again in a boiling aqueous potassium hydroxide solution in the presence of copper. The resulting [2-(3,4-dimethoxyphenylthio)phenyl]acetic acid (*XI*) did not crystallize and was cyclized without characterization similarly like in the preceding

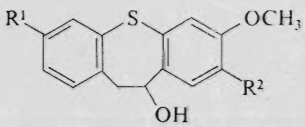
case to 7,8-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIb*). The course of the following reactions was analogous like in the preceding case. Reduction of the ketone *VIb* with sodium borohydride gave the alcohol *VIIb* which was treated with hydrogen chloride in chloroform in order to obtain the corresponding 10-chloro derivative. The attempt was again unsuccessful: the only substance obtained was the elimination product *VIIIb*, identical with the compound prepared previously by our group[18].



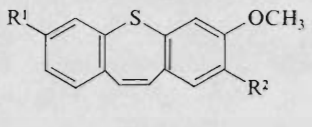
II, R = COOH *IV*, R = CH_2CN
III, R = CH_2OH *V*, R = CH_2COOH



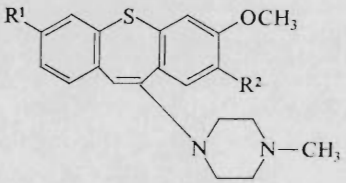
VI



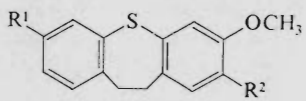
VII



VIII

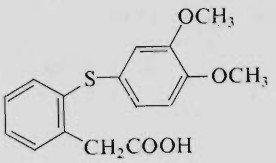


IX



X

It was necessary again to transform the ketone *VIb* first to the enamine *IXb* which was reduced with diborane and gave the dihydro base *Ib* in a satisfactory yield. This is evidently unstable in contact with strong acids; and attempt at preparing its dimethanesulfonate resulted in a cleavage leading to 1-methylpiperazine dimethanesulfonate. On the other hand, the neutralization with maleic acid proceeds without difficulties and affords the desired maleate. An attempt to reduce the enamine *IXb* with zinc in acetic acid resulted even in this case in hydrogenolysis to 2,3-dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Xb*) and 2,3-dimethoxydibenzo[*b*,*f*]thiepin (*VIIIb*) (ref.[18]); the mass spectrum and the ^{1}H-NMR spectrum were again used for the characterization of the mixture obtained



XI

Compounds *Iab* and the enamines *IXab* were tested in the form of maleates by methods of the general pharmacological screening.

Compound *Ia*: Acute toxicity in mice, LD_{50} = 40 mg/kg *i.v.*; the dose D., used in the screening, was 8 mg/kg *i.v.* The compound showed central depressant effects in mice in doses higher than D; there were no typical central effects after the dose D. At concentrations of 0·5–1·0% the compound had local anaesthetic effect in the test of infiltration anaesthesia (complete anaesthesia in 50% guinea-pigs in the experiment) and in the test of corneal anaesthesia (complete anaesthesia of the eye cornea in 50% rabbits). It exhibited spasmolytic effects in concentrations of 0·1–1·0 μg/ml towards the barium chloride contractions of the isolated rat duodenum (reduction by 50%) and in concentrations of 1–10 μg/ml towards the acetylcholine contractions (reduction by 50%). Intravenous doses of 0·5–1·0 mg/kg brought about drops of the blood pressure of normotensive rats by 20% for at least 10 min. The compound has thus a very high papaverine-like spasmolytic effect *in vitro* (for papaverine the active concentration is 5 μg/ml) and a significant hypotensive effect. Compound *Ib*: LD_{50} = = 31·2 mg/kg *i.v.*, D = 6 mg/kg *i.v.* Incoordinating activity in the rotarod test in mice, ED = 6 mg/kg *i.v.* In doses higher than D significant central depression in mice. Antihistamine activity: a dose of 2·5 mg/kg *s.c.* protects 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly (5% activity of mebrophenhydramine). Corneal anaesthesia at concentrations of 0·5–1·0%. Spasmolytic effect *in vitro* at concentrations of 1–10 μg/ml (towards acetylcholine as well as barium chloride). Compound *IXa*: LD_{50} = 2 000 mg/kg *p.o.*, D = 300 mg/kg orally. Rotarod in mice: ataxia at 10 mg/kg *p.o.* Inhibits the locomotor activity of mice to 50% in a dose of 10 mg/kg orally. Cataleptic activity in rats, ED = 150 mg/kg orally. Compound *IXb*: LD_{50} = 750 mg/kg orally, D = 150 mg/kg orally. Rotarod in mice: ataxia at 50 mg/kg orally. Inhibits the locomotor activity of mice to 50% in oral doses of 150 mg/kg (known surroundings) and 25–50 mg/kg (unknown surroundings). The dose D brings about catalepsy in 30% rats.

In conclusion, the dihydro compounds are inactive as neuroleptics and reveal some structurally less specific neurotropic and cardiovascular effects; the enamines, on the other hand, have the character of neuroleptic agents.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). Microorganisms, numbers of compounds and the minimum inhibitory concentrations (in μg/ml) unless they exceed 100 μg/ml are given: *Strepto-*

coccus β-haemolyticus, *IXa* 50; *Streptococcus faecalis Ia* 100, *IXa* 100; *Staphylococcus pyogenes aureus*, *Ia* 50, *IXa* 50; *Escherichia coli*, *Ia* 50, *Ib* 100, *IXa* 50; *Mycobacterium tuberculosis* H37Rv, *Ia* 12·5, *Ib* 12·5, *IXa* 25, *IXb* 25; *Trichophyton mentagrophytes*, *Ia* 50, *Ib* 50, *IXa* 50, *IXb* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registed with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200 G spectrophotometer, ^{1}H-NMR spectra ($CDCl_3$) were produced with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra were recorded on a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

3,4-Dimethoxythiophenol

A solution of 210 g 3,4-dimethoxybenzenesulfonyl chloride[15,16] (m.p. 67—69°C) in 270 ml acetic acid was added dropwise over 1 h to a stirred refluxing mixture of 430 ml acetic acid, 87 g red phosphorus and 13·7 g iodine. The mixture was stirred and refluxed for 4·5 h, diluted with 110 ml water and refluxed for 1 h. After cooling the solid was filtered off, the filtrate was diluted with 800 ml water and extracted with benzene. The extract was dried with $MgSO_4$ and processed by distillation in a stream of nitrogen; 121 g (81%), b.p. 150—155°C/2·27 kPa. Lit.[14], b.p. 138°C/1·87 kPa.

4-Methoxy-2-(3-methoxyphenylthio)benzoic Acid (*II*)

3-Methoxythiophenol[9] (100 g), 181 g 2-iodo-4-methoxybenzoic acid[8] and 3 g Cu were added to a stirred solution of 156 g 85% KOH in 1·5 l water at 50—60°C and the mixture was refluxed for 14 h. After cooling, the mixture was filtered with charcoal and the filtrate was acidified with dilute hydrochloric acid. After standing overnight, the crude product was filtered, washed with water and crystallized from aqueous ethanol; 145 g (77%), m.p. 158—160°C. Analytical sample m.p. 164—165°C (ethanol). UV spectrum: inflexes at 261 nm (log ε 4·11), 288 nm (3·86), 305 nm (3·68). IR spectrum: 697, 782, 834, 870, 882 (3 and 2 adjacent and solitary Ar—H), 1 049, 1 290 ($ArOCH_3$), 958, 1 240, 1 675, 1 680, 2 558, 2 603, 2 680 (ArCOOH), 1 480, 1 554, 1 583, 1 600, 3 080 cm^{-1} (Ar). For $C_{15}H_{14}O_4S$ (290·3) calculated: 62·05% C, 4·86% H, 11·05% S; found: 61·52% C, 4·62% H, 10·72% S.

4-Methoxy-2-(3-methoxyphenylthio)benzyl Alcohol (*III*)

A stirred suspension of 29 g *II* in 23 ml benzene was treated over 45 min at 35—40°C with 62 ml 65% $NaAlH_2(OCH_2CH_2OCH_3)_2$ solution in benzene. The solution formed was stirred for 4 h at 20°C and allowed to stand overnight. It was then decomposed by a slow addition of 290 ml 10% NaOH, the benzene layer was separated, washed with water, dried with $MgSO_4$ and distiled; 24·4 g (88%), b.p. 188—191°C/0·13 kPa. A sample for analysis was redistilled, b.p. 190°C : : 0·13 kPa. IR spectrum (film): 693, 779, 831, 863 (3 and 2 adjacent and solitary Ar—H), 1 046 (CH_2OH), 1 236, 1 250 ($ArOCH_3$), 1 482, 1 579, 1 591, 3 008, 3 070 (Ar), 2 840 (OCH_3), 3 400 cm^{-1} (OH). For $C_{15}H_{16}O_3S$ (276·3) calculated: 65·19% C, 5·84% H, 11·60% S; found: 65·25% C, 5·96% H, 11·56% S.

[4-Methoxy-2-(3-methoxyphenylthio)phenyl]acetonitrile (*IV*)

The alcohol *III* (55 g) was vigorously stirred with 55 ml hydrochloric acid at room temperature for 15 min and the chloride formed was extracted with benzene. The extract was dried with $CaCl_2$ and evaporated under reduced pressure. The oily residue was dissolved in 120 ml acetone and 12·5 g 98% NaCN and 2·0 g NaI were added. The mixture was stirred and refluxed for 20 h (acetone was added for substituting the evaporated part). After cooling, the inorganic salts were filtered off and washed with acetone, the filtrate was evaporated, the residue was dissolved in 250 ml benzene, the solution was washed with warm (45°C) water, dried with $MgSO_4$ and evaporated; 55 g (97%) crude oily *IV* which could be used for hydrolysis without purification. A sample for analysis was distilled, b.p. 205—210°C/0·2 kPa. IR spectrum (film): 690, 780, 820, 863 (3 and 2 adjacent and solitary Ar—H), 1 045, 1 246, 1 250, 2 850 ($ArOCH_3$), 1 483, 1 579, 1 592, 3 018, 3 078 (Ar), 2 262 cm^{-1} (R—CN). For $C_{16}H_{15}NO_2S$ (285·4) calculated: 67·34% C, 5·30% H, 4·91% N, 11·24% S; found: 67·59% C, 5·27% H, 4·63% N, 11·25% S.

[4-Methoxy-2-(3-methoxyphenylthio)phenyl]acetic Acid (*V*)

A solution of 28·5 g crude *IV* in 140 ml ethanol was treated with a solution of 27·7 g KOH in 135 ml water and the mixture was stirred and refluxed for 12 h. Ethanol was evaporated under reduced pressure, the residue was dissolved in 500 ml warm water, the solution was washed with benzene and filtered with charcoal. The filtrate was cooled and acidified with dilute hydrochloric acid. The product was filtered, washed with water and dried *in vacuo*; 20·0 g (66%), m.p. 109—112°C. Analytical sample, m.p. 112—113°C (70% ethanol). IR spectrum: 692, 778, 800, 829, 880, 900 (3 and 2 adjacent and solitary Ar—H), 936, 1 290, 1 713, 2 562, 2 640, 2 735 (RCOOH), 1 050, 1 242 ($ArOCH_3$), 1 480, 1 488, 1 573, 1 590, 3 020, 3 060 cm^{-1} (Ar). For $C_{16}H_{16}O_4S$ (304·4) calculated: 63·14% C, 5·30% H, 10·53% S; found: 63·54% C, 5·20% H, 10·60% S.

[2-(3,4-Dimethoxyphenylthio)phenyl]acetic Acid (*XI*)

3,4-Dimethoxythiophenol (62 g), 91 g (2-iodophenyl)acetic acid[13] and 2 g Cu were added to a solution of 78 g 85% KOH in 700 ml water and the mixture was stirred and refluxed for 9 h. It was filtered while warm with charcoal and the filtrate was acidified after cooling with dilute hydrochloric acid. The product separated as an oil which did not crystallize on standing and cooling. It was, therefore, isolated by extraction with benzene. Processing of the extract gave 100 g (95%) oily product which was used for cyclization without characterization.

3,7-Dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIa*)

A mixture of 18·3 g *V*, 180 g polyphosphoric acid and 75 ml toluene was stirred and refluxed for 1 h (bath of 120°C). After partial cooling it was decomposed with ice-cold water and the separated product was extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$, filtered with charcoal and the filtrate evaporated under reduced pressure; 17·0 g (99%) crude product, m.p. 145—147°C. Analytical sample, m.p. 147—148°C (benzene). UV spectrum: λ_{max} 259 nm ($\log \varepsilon = 4{\cdot}41$), infl. 282 nm (4·13), infl. 315 nm (3·62). IR spectrum: 882, 860, 880 (2 adjacent and solitary Ar—H), 1 036, 1 228, 1 267 ($ArOCH_3$), 1 483, 1 497, 1 594, 3 015, 3 080 (Ar), 1 660 cm^{-1} (ArCO), ^{1}H-NMR spectrum: δ 8·12 (d, $J = 8{\cdot}0$ Hz, 1 H, 9-H), 7·28 (d, $J = 8{\cdot}0$ Hz, 1 H, 1-H), 7·10 and 7·00 (2 mcs, $J = 2{\cdot}5$ Hz, 2 H, 4,6-H_2), 6·82 and 6·76 (2 mcd, $J = 8{\cdot}0$; 2·5 Hz, 2 H, 2,8-H_2), 4·20 (s, 2 H, $ArCH_2CO$), 3·80 and 3·72 (2 s,

6 H, 2 OCH_3). For $C_{16}H_{14}O_3S$ (286·3) calculated: 67·11% C, 4·93% H, 11·20% S; found: 67·50% C, 5·13% H, 11·10% S.

7,8-Dimethoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VIb*)

The oily *XI* (7·5 g) was cyclized by refluxing with 75 g polyphosphoric acid and 30 ml toluene under vigorous stirring for 1·5 h. The mixture was processed similarly like in the preceding case; 4·2 g (60%), m.p. 155—160°C. Analytical sample, m.p. 161—162°C (benzene). UV spectrum: λ_{max} 242·5 nm (log ε 4·36), 257 nm (4·25), infl. 267 nm (4·22), 334 nm (3·73). IR spectrum: 750, 759, 856, 887 (4 adjacent and solitary Ar—H), 1 038, 1 216, 1 257, 1 274 ($ArOCH_3$), 1 506, 1 515, 1 594, 3 025, 3 080 (Ar), 1 660 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·71 (s, 1 H, 9-H), 7·63 (mcd, 1 H, 4-H), 7·10—7·50 (m, 3 H, 1,2,3-H_3), 7·03 (s, 1 H, 6-H), 4·35 (s, 2 H, $ArCH_2CO$), 3·97 and 3·89 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{14}O_3S$ (286·3) calculated: 67·11% C, 4·93% H, 11·20% S; found: 67·26% C, 5·07% H, 11·29% S.

3,7-Dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*VIIa*)

A suspension of 20 g *VIa* in 300 ml ethanol was stirred and treated at 70°C with a solution of 2·0 $NaBH_4$ in 20 ml water containing 0·3 ml 20% NaOH over 20 min. The mixture was stirred and refluxed for 5 h, filtered while warm and the filtrate was evaporated under reduced pressure. The residue was diluted with 20 ml water and the product was extracted with benzene. The extract was washed with 2% NaOH and water, dried with $MgSO_4$, filtered with charcoal and evaporated; 16·0 g (79%), m.p. 122—124°C. Analytical sample, m.p. 124—125°C (ethanol). IR spectrum: 816, 838, 859, 894 (2 adjacent and solitary Ar—H), 1 040, 1 054 (CHOH), 1 240, 1 252 ($ArOCH_3$), 1 499, 1 573, 1 600, 3 065 (Ar), 3 345 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·40 and 7·20 (2 d, J = 8·5 Hz, 2 H, 1,8-H_2), 7·08 and 6·98 (2 mcs, J = 3·0 Hz, 2 H, 4,6-H_2), 6·79 (mcd, J = 8·5; 3·0 Hz, 2 H, 2,8-H_2), 5·11 (m, after ^2H_2O dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·90 and 3·88 (2 s, 6 H, 2 OCH_3), 3·68 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·12 (bd, disappears after ^2H_2O, J = 8·0 Hz, 1 H, OH). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 66·68% C, 5·78% H, 11·36% S.

7,8-Dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*VIIb*)

The ketone *VIb* (44 g) was reduced similarly with 2·1 g $NaBH_4$ in a mixture of 700 ml ethanol and 20 ml water; 41 g (93%), m.p. 130—133°C. Analytical sample, m.p. 136—137°C (benzene). IR spectrum: 759, 868, 877 (4 adjacent and solitary Ar—H), 1 050 (CHOH), 1 251 ($ArOCH_3$), 1 514, 1 602, 3 013, 3 080 (Ar), 3 508 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·50 (m, 1 H, 4-H), 7·00—7·30 (m, 3 H, 1,2,3-H_3), 7·00 and 6·89 (2 s, 2 H, 6·9-H_2), 5·18 (bs, 1 H, Ar—CH—O), 3·81 and 3·79 (2 s, 6 H, 2 OCH_3), *c* 3·50 (m, 2 H, $ArCH_2$), 2·08 (bs, 1 H, OH). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 66·64% C, 5·69% H, 11·08% S.

2,3-Dimethoxydibenzo[*b,f*]thiepin (*VIIIb*)

The alcohol *VIIb* (40 g) was dissolved in 1 300 ml benzene at 55—60°C, the heating was discontinued and the solution was saturated with hydrogen chloride for 8 h in the presence of 50 g $CaCl_2$ (powder). The mixture was allowed to stand overnight at room temperature, filtered and the filtrate was evaporated. The residue was crystallized from a mixture of benzene and light petroleum; 29·4 g (78%), m.p. 120—121°C. Analytical sample, m.p. 121—122°C (benzene). IR spec-

trum: 763, 789, 860, 872 (4 adjacent and solitary Ar—H, olefinic CH=CH), 1 056, 1 256 ($ArOCH_3$), 1 498, 1 509, 1 512, 1 559, 1 596, 3 005, 3 060, 3 085 cm^{-1} (Ar). Lit.[18], m.p. 123 to 124°C.

3,7-Dimethoxy-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IXa*)

A solution of 4·3 g *VIa* in 90 ml benzene was treated at 70°C with 7·5 g 1-methylpiperazine and a solution of 1·45 g $TiCl_4$ in 15 ml benzene and the mixture was stirred and refluxed for 24 h. After cooling it was decomposed with 60 ml water, the mixture was stirred for 10 min, the solid was filtered off and washed with benzene. The benzene layer of the filtrate was separated, washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated under reduced pressure. The oily residue crystallized from ethanol; 3·9 g (71%), m.p. 154—155°C. Analytical sample, m.p. 157—159°C (benzene). UV spectrum: λ_{max} 243 nm (log ε 4·44), 270 nm (4·31), infl. 310 nm (3·96), IR spectrum (KBr): 834, 847, 858 (2 adjacent and solitary Ar—H), 1 026, 1 054, 1 240 ($ArOCH_3$), 1 495, 1 556, 1 599, 3 015, 3 065 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·50 (d, J = = 8·5 Hz, 1 H, 9-H), 7·10 (d, J = 8·5 Hz, 1 H, 1-H), 7·00 and 6·98 (2 mcs, J = 2·5 Hz, 2 H, 4,6-H_2), 6·80 and 6·72 (2 mcd, J = 8·5; 2·5 Hz, 2 H, 2,8-H_2), 6·19 (s, 1 H, ArCH=C), 3·71 and 3·69 (2 s, 6 H, 2 OCH_3), 2·90 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·29 (s, 3 H, NCH_3). For $C_{21}H_{24}N_2O_2S$ (368·5) calculated: 68·45% C, 6·57% H, 7·60% N, 8·70% S; found: 68·70% C, 6·60% H, 7·64% N, 8·91% S.

Maleate, m.p. 221—223°C (ethanol. For $C_{25}H_{28}N_2O_6S$ (484·6) calculated: 61·97% C, 5·82% H, 5·78% N, 6·62% S; found: 61·52% C, 5·83% H, 5·83% N, 6·76% S.

2,3-Dimethoxy-11-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IXb*)

A similar reaction of 25 g *VIb*, 44 g 1-methylpiperazine and 8·4 g $TiCl_4$ in 570 ml boiling benzene gave 27·6 g (86%) product, m.p. 153—157°C. Analytical sample, m.p. 162—163°C (benzene–light petroleum). UV spectrum: λ_{max} 224 nm (log ε 4·43), 241 nm (4·36), infl. 252 nm (4·34), 275 nm (4·21), 303 nm (3·95). IR spectrum (KBr): 760, 890 (4 adjacent and solitary Ar—H), 1 060, 1 200, 1 255 ($ArOCH_3$), 1 504, 1 555, 1 605. 3 029, 3 055, 3 085 cm^{-1} (Ar). For $C_{21}H_{24}N_2O_2S$ (368·5) calculated: 68·45% C, 6·57% H, 7·60% N, 8·70% S; found: 68·96% C, 6·49% H, 7·47% N, 8·54% S.

Maleate, m.p. 200—201°C (ethanol). For $C_{25}H_{28}N_2O_6S$ (484·6) calculated: 61·97% C, 5·82% H, 5·78% N, 6·62% S; found: 62·18% C, 5·81% H, 5·83% N, 6·48% S.

3,7-Dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*)

A stirred solution of 9·7 g *IXa* in 75 ml tetrahydrofuran in a nitrogen atmosphere was treated with 2·8 g $NaBH_4$ and then with 18 ml acetic acid, added dropwise without cooling. The mixture was refluxed for 6 h, decomposed with 70 ml 10% hydrochloric acid, 70 ml ethanol were added and the mixture was stirred for 30 min. The precipitated hydrochloride was filtered, combined with the aqueous layer of the filtrate, the suspension was made alkaline with 20% NaOH and the base extracted with benzene. The extract was dried with K_2CO_3 and evaporated. The residue was crystallized from methanol; 4·4 g (45%), m.p. 97—100°C. Analytical sample, m.p. 99—101°C (methanol). IR spectrum (KBr): 821, 836, 846, 877, 897 (2 adjacent and solitary Ar—H), 1 011, 1 042, 1 052, 1 150, 1 248, 1 253 ($ArOCH_3$), 1 495, 1 600, 3 000 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·49 (d, J = 8·5 Hz, 1 H, 9-H), 7·12 (d, J = 8·5 Hz, 1 H, 1-H), 7·02 and 6·88 (2 mcs, J = 3·0 Hz, 2 H, 4,6-H_2), 6·70 and 6·64 (2 mcd, J = 8·5; 3·0 Hz, 2 H, 2,8-H_2), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 3·72 and 3·71 (2 s, 6 H, 2 OCH_3), 2·62 (def. t, 4 H, $CH_2N^{(1)}CH_2$ of piperazine), 2·38

(def. t, 4 H, $CH_2N^{(4)}CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). For $C_{21}H_{26}N_2O_2S$ (370·6) calculated: 68·07% C, 7·07% N, 7·56% N, 8·65% S; found: 67·78% C, 7·12% H, 7·41% N, 8·82% S.

Maleate, m.p. 112—116°C (ethanol). For $C_{25}H_{30}N_2O_6S$ (486·6) calculated: 61·71% C, 6·21% H, 5·76% N, 6·59% S; found: 62·28% C, 6·49% H, 5·50% N, 6·41% S.

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

Similar reduction of 18·4 g *IXb* with 5·7 g $NaBH_4$ and 36 ml acetic acid in 150 ml tetrahydrofuran gave 12·9 g (70%) base, m.p. 124—126°C. Analytical sample, m.p. 130—132°C (methanol). IR spectrum: 752, 760, 875 (4 adjacent and solitary Ar—H), 1 040, 1 152, 1 210, 1 250 ($ArOCH_3$), 1 505, 1 513, 1 600, 3 000, 3 060 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·45 (mcd, 1 H, 6-H), *c.* 7·18 (m, 3 H, 7,8,9-H_3), 7·20 and 6·81 (2 s, 2 H, 1,4-H_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·83 and 3·79 (2 s, 6 H, 2 OCH_3), 2·65 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (def. t, 4 H, $CH_2N^4.CH_2$ of piperazine), 2·22 (s, 3 H, NCH_3). For $C_{21}H_{26}N_2O_2S$ (370·6) calculated: 68·07% C, 7·07% H, 7·56% N, 8·65% S; found: 68·47% C, 7·34% H, 7·52% N, 8·64% S.

Maleate monohydrate, m.p. 102—105 and 112—115°C (95% ethanol). For $C_{25}H_{30}N_2O_6S + H_2O$ (504·6) calculated: 59·51% C, 6·39% H, 5·55% N, 6·35% S; found: 59·58% C, 6·51% H, 5·30% N, 6·20% S.

Neutralization of 3·5 g *Ib* with 2·0 g methanesulfonic acid in a mixture of ethanol and acetone gave a salt which was recrystallized from ethanol–ether; 2·9 g 1-methylpiperazine dimethanesulfonate, m.p. 151—152°C. For $C_7H_{20}N_2O_6S_2$ (292·4) calculated: 28·75% C, 6·90% H, 9·58% N, 21·93% S; found: 29·60% C, 7·19% H, 9·38% N, 22·04% S. Methanesulfonic acid effected evidently a cleavage of *Ib*.

3,7-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Xa*)

A mixture of 60 ml acetic acid and 6·8 g Zn was heated to 90—100°C and under stirring there were added 3·7 g *IXa* over 10 min. The mixture was stirred and refluxed for 3 h. After cooling it was filtered and the solid washed with acetic acid. The filtrate was evaporated and the oily residue was diluted with 80 ml benzene. The solution was washed with diluted NH_4OH and water, dried with $MgSO_4$ and evaporated. The residue was crystallized from ethanol to give 2·2 g 1 : 1 mixture of *Xa* and 3,7-dimethoxydibenzo[*b*,*f*]thiepin (*VIIIa*), m.p. 84—86°C. Mass spectrum, *m/z*: 272 (M^+ corresponding to $C_{16}H_{16}O_2S$) and 270 (M^+ corresponding to $C_{16}H_{14}O_2S$). The product was chromatographed on a column of neutral Al_2O_3 (activity II). The first product eluted with light petroleum containing 5% benzene melted at 75—76°C (ethanol). According to the ^{1}H-NMR spectrum, the product is still a mixture of 86% *Xa* and 14% *VIIIa*: δ 6·50—7·20 (m, *c.* 6·3 H, Ar—H and ArCH=CHAr), 3·75 (s, 6 H, 2 OCH_3, basis for the integration), 3·20 (s, 86% of 4 H, $ArCH_2CH_2Ar$). For $C_{16}H_{16}O_2S$ (272·4) calculated: 70·55% C, 5·92% H, 11·77% S; found: 70·75% C, 6·02% H, 11·96% S.

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

Similar reaction of 3·7 g *IXb* with 6·8 g Zn and 60 ml acetic acid gave 2·4 g product, m.p. 97 to 99°C. The spectra identified it to be a mixture of *Xb* and *VIIIb*. Mass spectrum, *m/z*: 272 (M^+ corresponding to $C_{16}H_{16}O_2S$) and 270 (M^+ corresponding to $C_{16}H_{14}O_2S$). IR spectrum: 780, 810, 860 (4 adjacent and solitary Ar—H and olefinic CH=CH), 1 058, 1 217, 1 250 ($ArOCH_3$) 1 514, 1 595, 1 600, 3 000, 3 055 cm^{-1} (Ar). The ^{1}H-NMR spectrum characterized the mixture as consisting of 66% *Xb* and 34% *VIIIb*: δ 7·40 (m, 1 H, 6-H), 6·80—7·20 (m, 4·7 H, 4,7,8,9-H_4 and 34% ArCH=CHAr), 6·65 (s, 0·34 H, 1-H in *VIIIb*), 6·59 (s, 0·66 H, 1-H in *Xb*), 3·80 and 3·73

(2 s, 6 H, 2 OCH_3 — basis for the integration), 3·20 (s, 66% of 4 H, $ArCH_2CH_2Ar$). For $C_{16}H_{16}O_2S$ (372·4) calculated: 70·55% C. 5·92% H, 11·77% S; found: 70·62% C, 5·90% H, 11·66% S.

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