POTENTIAL METABOLITES OF TRICYCLIC NEUROLEPTICS: 2,8-DIHYDROXY AND 3,8-DIHYDROXY DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

Miroslav PROTIVA, Karel ŠINDELÁŘ, Zdeněk ŠEDIVÝ and Josef POMYKÁČEK

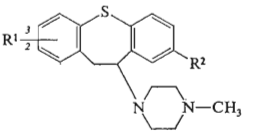
Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

Received February 6th, 1979

A synthesis of the title compounds *II* and *III*, potential metabolites of the neuroleptic agent perathiepin *I*, was carried out. A reaction of (2-iodo-5-methoxyphenyl)acetic acid with 4-methoxythiophenol afforded the acid *VI*. The isomeric acid *XI* was obtained from 2-iodo-4-methoxybenzoic acid by reaction with 4-methoxythiophenol and *via* intermediates *VIII*—*X*. Both acids (*VI*, *XI*) were cyclized with polyphosphoric acid to dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-ones *XIIab* which were transformed *via* the alcohols *XIIIab* to the chloro compounds *XIVab*. Substitution reactions with 1-methylpiperazine gave the piperazine derivatives *IV* and *V* and dimethoxydibenzo[*b*,*f*]thiepins *XVab*. The dimethoxy compounds *IV* and *V* were demethylated with boron tribromide to the diaminodiphenols *II* and *III*. The central depressant and cataleptic activity of compounds *II*—*V* is lower than that of the unsubstituted substance *I*.

10-(4-Methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (perathiepin, *I*) (ref.[1,2]) exhibited in animal tests a strong tranquilizing and clear neuroleptic activity[3,4] and became a basic substance of a new group of multipotent psychotropic agents[5]. When it appeared to be a clinically interesting tranquilizer, neuroleptic and antidepressant[6–10], a rather broad programme of investigating its biotransformation was started which led to the identification of several metabolites[11,12]. As standards for comparison with the metabolic products, some phenolic compounds were also prepared, *i.e.* perathiepin derivatives hydroxylated in the benzene nuclei: 2-hydroxy[13], 3-hydroxy[14], 6-hydroxy[15] and 8-hydroxy derivative[16]; unsuccessful were the attempts to prepare the 7-hydroxy derivative[17]. Out of the dihydroxy derivatives, only the 2,3-dihydroxy derivative[18] has been described until now. The present paper deals with the synthesis of two further dihydroxy derivatives of perathiepin *I* which were considered rather probable metabolites: the 2,8-dihydroxy (*II*) and 3,8-dihydroxy derivative (*III*).

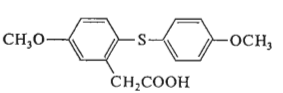
* Part CXXXIII in the series Neurotropic and Psychotropic Agents; Part CXXXII: This Journal *44*, 2689 (1979).



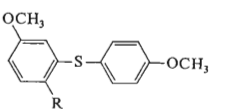
I, $R^1 = R^2 = H$ *III*, R^1 = 3-OH, $R^2 = OH$
II, R^1 = 2-OH, $R^2 = OH$ *IV*, R^1 = 2-OCH_3, $R^2 = OCH_3$
V, R^1 = 3-OCH_3, $R^2 = OCH_3$

The synthesis of compounds *II* and *III* made use of similar methods like in the preparation of the previously described hydroxy derivatives[13–18]. The first task was the synthesis of the diphenyl sulfide *o*-acetic acids *VI* and *XI* which were transformed in the second stage to the 2,8-dimethoxy and 3,8-dimethoxy derivatives of perathiepin (*IV* and *V*). The syntheses were concluded by demethylation of these ethers to the free phenols *II* and *III*.

The known (2-iodo-5-methoxyphenyl)acetic acid[19] was used as the starting material in the 2,8-disubstituted series. Its reaction with 4-methoxythiophenol[20] in a boiling potassium hydroxide solution and in the presence of copper resulted in [5-methoxy-2-(4-methoxyphenylthio)phenyl]acetic acid (*VI*). Treatment with polyphosphoric acid in boiling toluene effected the cyclization and 2,8-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIa*) was obtained in a good yield. Reduction with sodium borohydride in boiling aqueous ethanol gave the dimethoxy alcohol *XIIIa* which was transformed by treatment with hydrogen chloride in benzene to the chloro derivative *XIVa*. The substitution reaction with 1-methylpiperazine was carried out in boiling chloroform. The base *IV* was the main product; in a lower extent, elimination took place leading to 2,8-dimethoxydibenzo[*b*,*f*]thiepin (*XVa*). Demethylation of compound *IV* was carried out by treatment with boron tribromide in chloroform at room temperature. The primary product was hydrolyzed with boiling aqueous ethanol and the obtained crude hydrobromide of the product afforded by decomposition with a sodium carbonate solution the crude phenolic base *II*; its purification yielded only about 25% of the pure substance. The high melting point of this base and its IR spectrum confirmed its character of an inner salt.

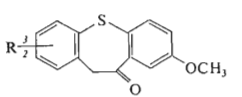


VI

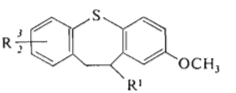


VII, R = COOH *IX*, R = CH_2Cl
VIII, R = CH_2OH *X*, R = CH_2CN
XI, R = CH_2COOH

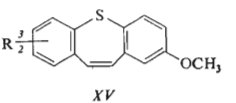
In the 3,8-disubstituted series, 2-iodo-4-methoxybenzoic acid[21] was condensed with 4-methoxythiophenol[20] similarly like in the preceding case and gave 4-methoxy--2-(4-methoxyphenylthio)benzoic acid (*VII*). Reduction with sodium dihydridobis-(2-methoxyethoxy)aluminate in benzene afforded the alcohol *VIII* which was transformed by treatment with thionyl chloride in the presence of pyridine to the substituted benzyl chloride *IX*. A reaction with sodium cyanide in dimethylformamide led to the nitrile *X* and its alkaline hydrolysis resulted in the homologous acid *XI*. The remaining steps had a similar course like in the preceding case: cyclization to the ketone *XIIb*, reduction to the alcohol *XIIIb*, conversion to the chloro compound *XIVb*. The substitution reaction with 1-methylpiperazine afforded the base *V* as the main product and 2,7-dimethoxydibenzo[*b*,*f*]thiepin (*XVb*) as the minor product of the simultaneously proceeding elimination reaction. Demethylation of compound *V* was carried out with boron tribromide in dichloromethane. The primary product was hydrolyzed in this case with aqueous sodium hydroxide. The high-melting phenolic base *III* was obtained in a low yield and its identity was corroborated by spectra. Neutralization with maleic acid gave a crystalline maleate.



XII



XIII, $R^1 = OH$
XIV, $R^1 = Cl$



XV

In formulae *XII*—*XV*: *a*, R = 2-OCH_3 *b*, R = 3-OCH_3

Compounds *III* (maleate sesquihydrate, VÚFB-12.425) and *IV* (maleate, VÚFB-12.424) were submitted to an orientation pharmacological evaluation from the point of view of the expected central depressant activity in the rota-rod test in mice and the neuroleptic activity in the test of catalepsy in rats. The compounds were evaluated in the form of the mentioned salts but the doses given were calculated for bases (Dr J. Metyšová, pharmacological department of this institute). Compounds *II* (base, VÚFB-12.494) and *V* (dimethanesulfonate monohydrate, VÚFB-12.393) were evaluated in a number of tests using the methods of the general pharmacological screening (Dr M. Bartošová, affiliated unit of this institute at Rosice n/L). For comparison, the medium lethal doses (LD_{50}, mice) and the medium effective doses of perathiepin *I* (ref.[3]) bringing about ataxia in mice and catalepsy in rats (ED_{50}) are given: LD_{50} 42·3 mg/kg *i.v.*, 63 mg/kg orally; ataxia, ED_{50} 0·187 mg/kg *i.v.*, 2·4 mg/kg orally; catalepsy, ED_{50} 10 mg/kg *i.p.*, 45 mg/kg orally.

Compound *II* is little toxic; its LD_{50} is higher than 1 500 mg/kg orally. On the rota-rod, a dose of 300 mg/kg orally was still practically without effect; it is inactive in the test of catalepsy. In an oral dose of 100 mg/kg, it decreases the spontaneous locomotor activity in mice to 50%.

Compound *III* showed some activity in the rota-rod test: ED_{50} = 0·73 mg/kg *i.v.* In the test of catalepsy, the ED_{50} is higher than 100 mg/kg *i.p.* (this dose brings about catalepsy in 40% rats).

Compound *IV* is less toxic than perathiepin: LD_{50} = 170 mg/kg orally. In both of the basic tests, it is less active. In the rota-rod test, the ED_{50} = 10 mg/kg orally. In the test of catalepsy, the ED_{50} is higher than 50 mg/kg orally (this dose brings about catalepsy in 40% animals).

Compound *V* is similarly toxic like perathiepin *I*, LD_{50} = 50 mg/kg *i.v.* In the rota-rod test, the ED_{50} = 1 mg/kg *i.v.*, and in the test of catalepsy, the ED_{50} is approximately 10 mg/kg *i.p.* The compound inhibits very efficiently the spontaneous locomotor activity in mice; ED_{50} = = 0·1 mg/kg *s.c.*. In a dose of 0·1—0·5 mg/kg *i.v.*, it prolongs the thiopental sleeping time to 200% of the control value (100%). On the other hand, a dose of 10 mg/kg *i.v.*, does not influence the body temperature of rats and has not anticonvulsant activity (pentetrazol). The same dose exhibits in more than 50% mice analgesia in the Haffner test. A dose of 1 mg/kg *i.v.* decreases the blood pressure of normotensive rats by 20% for more than 10 min; a dose of 0·1—1·0 mg/kg *i.v.* reduces the hypertensive epinephrine reaction in rats by 50%. The compound also exhibits spasmolytic activity: a concentration of 1—10 μg/ml decreases the acetylcholine contractions of the isolated rat duodenum by 50%; a concentration of 0·1—1·0 μg/ml inhibits similarly the barium chloride contractions. On the isolated atrium of the rabbit heart, the substance has a negative inotropic effect (in a concentration of 50 μg/ml, it decreases inotropy by 25%). Finally, a hyperglycaemic effect in rats was found (doses of 25—50 mg/kg orally bring about an increase of the blood sugar level by 20%).

In conclusion it may be stated that the dihydroxy derivatives *II* and *III* have some central depressant activity but neuroleptically are inactive. It is in agreement with our previous experience with dihydroxy compounds of this series of neuroleptics[18,22]. The dimethoxy compounds *IV* and *V* are a little more active but do not attain the activity of perathiepin *I*. A rather rich spectrum of activities was shown by the compound *V*, exhibiting also a significant adrenolytic and hypotensive effect which is typical for our series of neuroleptics.

Compounds *II*, *IV* and *V* in the form of the mentioned salts were also tested for antimicrobial activity *in vitro* towards a standard set of microorganisms (Dr J. Turinová and Dr A. Čapek, 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: *Staphylococcus pyogenes aureus*, *V* 100; *Escherichia coli*, *IV* 50; *Mycobacterium tuberculosis* H37Rv, *IV* 6·25, *V* 12·5; *Saccharomyces pasterianus*, *V* 50; *Trichophyton mentagrophytes*, *V* 50. The diol *II* is thus inactive, whereas the ethers *IV* and *V* have a rather high tuberculostatic activity.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at 67 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra

(in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

4-Methoxy-2-(4-methoxyphenylthio)benzoic Acid (*VII*)

4-Methoxythiophenol[20] (61 g), 121·5 g 2-iodo-4-methoxybenzoic acid[21] and 2 g "molecular" copper were successively added to a stirred solution of 106 g KOH in 1 l H_2O at 60°C and the mixture was refluxed for 10 h. It was then diluted with 3 l hot H_2O, the solution filtered with charcoal and the warm filtrate acidified with hydrochloric acid. After standing overnight, the product was filtered, washed with H_2O and dried *in vacuo*; 110 g (87%), m.p. 183–187°C. Analytical sample, m.p. 194–197°C (aqueous ethanol). UV spectrum: λ_{max} 235 nm (log ε 4·53), infl. 263 nm (4·17), infl. 301 nm (3·64). IR spectrum: 775, 825, 850, 880 (2 adjacent and solitary Ar—H), 932, 1235, 2550, (COOH), 1025, 1145, 1290 (ArOR), 1495, 1550, 1590 (Ar), 1675 cm^{-1} (Ar. .COOH). For $C_{15}H_{14}O_4S$ (290·3) calculated: 62·05% C, 4·86% H, 11·04% S; found: 62·13% C, 5·12% H, 11·05% S.

4-Methoxy-2-(4-methoxyphenylthio)benzyl Alcohol (*VIII*)

A suspension of 110 g *VII* in 880 ml benzene was stirred and treated at 35–40°C over 45 min with 235 ml 65% solution of sodium dihydridobis(2-methoxyethoxy)aluminate in benzene, added dropwise. The resulting solution was stirred for 4 h, allowed to stand overnight, decomposed under stirring with a 10% NaOH solution and the benzene layer was separated. It was washed with H_2O dried ($MgSO_4$) and evaporated; 83 g (79%) crude product which was used for further work. A sample for analysis was distilled, b.p. 185–190°C/0·13 kPa. IR spectrum (film): 829, 874, 882 (2 adjacent and solitary Ar—H), 1031, 1249, 1290 (ArOR), 1051 (CH_2OH), 1494, 1573, 1600, 3075, 3140 (Ar), 3480 cm^{-1} (OH). For $C_{15}H_{16}O_3S$ (276·3) calculated: 65·19% C, 5·84% H, 11·60% S; found: 64·96% C, 6·21% H, 11·66% S.

4-Methoxy-2-(4-methoxyphenylthio)benzyl Chloride (*IX*)

A mixture of 74 g crude *VIII* and 25 g pyridine was stirred and treated at 10°C over 25 min with a solution of 37 g $SOCl_2$ in 500 ml benzene. The mixture was allowed to stand overnight, then stirred for 45 min at 40°C, cooled to 10°C and decomposed by addition of 160 ml H_2O. The benzene layer was washed with dilute hydrochloric acid and H_2O, dried with $MgSO_4$ and evaporated; 71 g (90%), m.p. 55–60°C. Analytical sample, m.p. 66–67°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 7·35 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in the methoxyphenylthio group), 7·26 (d, J = 8·5 Hz, 1 H, 6-H), 6·85 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in the methoxyphenylthio group), 6·64 (mcd, J = 8·5; 3·0 Hz, 1 H, 5-H), 6·50 (mcs, J = 3·0 Hz, 1 H, 3-H), 4·71 (s, 2 H, $ArCH_2Cl$), 3·78 and 3·61 (2 s, 6 H, 2 OCH_3). For $C_{15}H_{15}ClO_2S$ (294·8) calculated: 61·11% C, 5·13% H, 12·03% Cl, 10·88% S; found: 61·38% C, 5·34% H, 12·03% Cl, 10·79% S.

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

A solution of 71 g *IX* in 160 ml dimethylformamide was treated with 35·5 g NaCN, the mixture stirred and heated for 8 h to 105–110°C and evaporated *in vacuo*, the residue treated with 600 ml H_2O and the mixture extracted with benzene. The extract was washed with H_2O, dried with $MgSO_4$, filtered with charcoal and evaporated. The residue was crystallized from a mixture of benzene and light petroleum; 44 g (64%), m.p. 82–84°C. Analytical sample, m.p. 89–90°C

(benzene–light petroleum). IR spectrum: 810, 830, 860 (2 adjacent and solitary Ar-H), 1030, 1048, 1230, 1252, 1290 ($ArOCH_3$), 1482, 1496, 1573, 1590, 1600 (Ar), 2264 cm^{-1} (R—CN). For $C_{16}H_{15}NO_2S$ (285·4) calculated: 67·34% C, 5·30% H, 4·91% N, 11·23% S; found: 67·73% C, 5·54% H, 4·95% N, 11·60% S.

[5-Methoxy-2-(4-methoxyphenylthio)phenyl]acetic Acid (*VI*)

4-Methoxythiophenol[20] (42 g), 87 g (2-iodo-5-methoxyphenyl)acetic acid[19] and 1 g Cu were successively added to a stirred solution of 69 g KOH in 700 ml H_2O at 55°C. The mixture was stirred and refluxed for 14 h. After cooling, it was filtered with charcoal and the filtrate acidified with dilute hydrochloric acid. The oily product was extracted with benzene, the extract was dried with $MgSO_4$ and evaporated; 61 g (68%), m.p. 69—73°C. Analytical sample, m.p. 79—81°C (aqueous ethanol). IR spectrum: 809, 826, 836, 857 (2 adjacent and solitary Ar—H), 960, 1240, 1709, 2555, 2625, 2740 (COOH), 1029, 1310 ($ArOCH_3$), 1500, 1576, 1596, 3010, 3090, 3100 cm^{-1} (Ar). For $C_{16}H_{16}O_4S$ (304·4) calculated: 63·14% C, 5·30% H, 10·53% S; found: 63·52% C, 5·52% H, 10·61% S.

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

A warm solution of 43 g *X* in 230 ml ethanol was added to a warm solution of 42 g KOH in 200 ml H_2O and the mixture was refluxed for 12 h. Ethanol was evaporated, the precipitated potassium salt was dissolved in 650 ml warm H_2O, the solution was washed with benzene, filtered with charcoal and the filtrate acidified with 1 : 1 dilute hydrochloric acid. After standing overnight at 0°C, the product was filtered, washed with H_2O and dried *in vacuo*; 44·7 g (98%), m.p. 114 to 116°C. Analytical sample, m.p. 119—121°C (aqueous ethanol). IR spectrum: 788, 818, 830, 861 (2 adjacent and solitary Ar—H), 950, 1173, 1239, 1280, 1300, 1689, 2640 (COOH), 1030, 1051 ($ArOCH_3$), 1490, 1563, 1601 cm^{-1} (Ar). For $C_{16}H_{16}O_4S$ (304·4) calculated: 63·14% C, 5·30% H, 10·53% S; found: 63·24% C, 5·62% H, 10·53% S.

2,8-Dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIa*)

A mixture of 30 g *VI*, 300 g polyphosphoric acid and 130 ml toluene was stirred and refluxed for 1·5 h (bath temperature of 125°C). After cooling, it was decomposed with 700 g ice and water and the product extracted with benzene. The extract was washed with H_2O, 5% NaOH and H_2O, dried with $MgSO_4$, filtered with charcoal and the filtrate was evaporated *in vacuo*; 23 g (82%) residue, m.p. 122—127°C. Analytical sample, m.p. 142—143°C (benzene). UV spectrum: λ_{max} 235 nm (log ε 4·43), infl. 260 nm (4·15), 352 nm (3·64). IR spectrum: 816, 887, 898 (2 adjacent and solitary Ar—H), 1020, 1030, 1290 ($ArOCH_3$), 1560, 1572, 1598, 3050 (Ar), 1670 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 6·50—7·70 (m, 6 H, Ar—H), 4·30 (s, 2 H, $ArCH_2CO$), 3·75 (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: 66·61% C, 5·01% H, 11·39% S.

3,8-Dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIb*)

XI (40 g) was cyclized with 400 g polyphosphoric acid in 150 ml toluene like in the preceding case; 30·2 g (81%) crude ketone, m.p. 102—103°C. Analytical sample, m.p. 106—108°C (benzene–light petroleum). UV spectrum: λ_{max} 236 nm (log ε 4·45), infl. 259 nm (4·11), 292·5 nm (3·59), 347 nm (3·64). IR spectrum (KBr): 800, 811, 821, 855, 874, 899 (2 adjacent and solitary Ar—H), 1030, 1055, 1226, 1240, 1269, 1287, 1292 ($ArOCH_3$), 1490, 1560, 1600, 3000, 3067 (Ar), 1675

cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·72 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·47 (d, J = 8·0 Hz, 1 H, 6-H), 7·30 (d, J = 8·0 Hz, 1 H, 1-H), 7·17 (mcs, J = 2·5 Hz, 1 H, 4-H), 6·96 (mcd, J = 8·0 3·0 Hz, 1 H, 7-H), 6·85 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 4·28 (s, 2 H, $ArCH_2CO$), 3·78 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{14}O_3S$ (286·3) calculated: 67·11% C, 4·92% H, 11·20% S; found: 67·44% C, 5·10% H, 10·93% S.

2,8-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIIa*)

A suspension of 18·4 g *XIIa* in 300 ml ethanol was stirred and treated at 70°C dropwise with a solution of 0·85 g $NaBH_4$ in 9 ml H_2O containing 0·25 ml 20% NaOH. The mixture was refluxed for 5 h. After cooling, it was filtered and the filtrate evaporated *in vacuo*. The residue was treated with 200 ml H_2O and extracted with benzene. The extract was washed with 3% NaOH and H_2O, dried ($MgSO_4$), filtered with charcoal and evaporated under reduced pressure; 16·4 g (89%), m.p. 90—93°C. Analytical sample, m.p. 97—98°C (benzene–light petroleum). IR spectrum: 818, 885 (2 adjacent and solitary Ar—H), 1035, 1061 (CHOH in a cycle), 1239, 1281 ($ArOCH_3$), 1480, 1527, 1573, 1602 (Ar), 3400 cm^{-1} (OH). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 66·71% C, 5·66% H, 11·10% S.

3,8-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIIb*)

XIIb (31 g) was reduced with 1·46 g $NaBH_4$ in 500 ml ethanol and 15 ml H_2O similarly like in the preceding case. There were obtained 31 g (100%) of the oily product which was crystallized from a mixture of benzene and light petroleum; 19 g (61%), m.p. 77—79°C. Analytical sample, m.p. 81—83°C (cyclohexane). IR spectrum (KBr): 806, 850, 872, 891, 900 (2 adjacent and solitary Ar—H), 1030, 1050 (CHOH in a cycle), 1253, 1270 ($ArOCH_3$), 1498, 1567, 1602, 3020 (Ar), 2850 (OCH_3), 3405 cm^{-1} (OH). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 66·88% C, 5·75% H, 10·92% S.

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

A solution of 13·3 g *XIIIa* in 180 ml benzene was saturated in the presence of 10 g $CaCl_2$ for 2·5 h with anhydrous HCl at 20°C. The mixture was allowed to stand overnight, filtered with charcoal and the filtrate evaporated *in vacuo*; 14·0 g (98%), m.p. 147—150°C. Analytical sample, m.p. 148—151°C (benzene). ^{1}H-NMR spectrum: δ 7·40 and 7·32 (2 d, J = 8·0 Hz, 4,6-H_2), 7·05 (mcs, J = 3·0 Hz, 1 H, 9-H), 6·81 (mcs, J = 3·0 Hz, 1 H, 1-H), 6·68 (mcd, J = 8·0; 3·0 Hz, 2 H, 3,7-H_2), 5·80 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—Cl), *c.* 3·75 (m, 2 H, $ArCH_2$), 3·74 (s, 6 H, 2 OCH_3). For $C_{16}H_{15}ClO_2S$ (306·8) calculated: 62·63% C, 4·93% H, 11·56% Cl, 10·45% S; found: 62·86% C, 4·97% H, 11·66% Cl, 10·28% S.

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

XIIIb (20·0 g) was processed similarly like in the preceding case. There were obtained 20·0 g (94%) crude product, m.p. 106—110°C. Analytical sample, m.p. 116—118°C (benzene). ^{1}H-NMR spectrum: δ 7·34 (d, J = 8·5 Hz, 1 H, 6-H), 7·14 (d, J = 8·5 Hz, 1 H, 1-H), 7·08 and 7·04 (2 mcs, J = 2·5 Hz, 2 H, 4,9-H_2), 6·75 and 6·70 (2 mcd, J = 8·5; 2·5 Hz, 2 H, 2,7-H_2), 5·80 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·72 (s, 6 H, 2 OCH_3). For $C_{16}H_{15}ClO_2S$ (306·8) calculated: 62·63% C, 4·93% H, 11·56% Cl, 10·45% S; found: 63·14% C, 5·10% H, 11·38% Cl, 10·48% S.

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

A solution of 13·2 g *XIVa* and 12·9 g 1-methylpiperazine in 35 ml chloroform was refluxed for 6 h. Chloroform was evaporated *in vacuo*, the residue treated with 70 ml 3% NaOH and extracted with benzene. The extract was washed with H_2O and shaken with an excess of 1·25M-H_2SO_4. The solid sulfate was filtered off, combined with the aqueous layer of the filtrate and the suspension was made alkaline with NH_4OH. The base was extracted with benzene, the extract was dried ($MgSO_4$), filtered with charcoal and evaporated *in vacuo*; 12·3 g (78%) oily base. Neutralization with maleic acid in ethanol gave the maleate, m.p. 166—168°C (ethanol–ether). For $C_{25}H_{30}N_2O_6S$ (486·6) calculated: 61·71% C, 6·21% H, 5·76% N, 6·59% S; found: 62·13% C, 6·36% H, 5·65% N, 6·53% S.

The pure maleate was decomposed with NH_4OH and the base, isolated by extraction with ether, was used for recording the ^{1}H-NMR spectrum: δ 7·40 and 7·30 (2 d, J = 8·0 Hz, 2 H, 4,6-H_2), 7·20 (mcs, J = 3·0 Hz, 1 H, 9-H), 6·80 (mcs, J = 3·0 Hz, 1 H, 1-H), 6·60 (mcd, J = 8·0; 3·0 Hz, 2 H, 3,7-H_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·88 and 3·85 (2 s, 6 H, 2 OCH_3), 2·70 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3).

The benzene layer after the extraction of the base with dilute H_2SO_4 was washed with H_2O, dried and evaporated; 1·8 g crude 2,8-dimethoxydibenzo[*b,f*]thiepin (*XVa*), m.p. 117—119°C (benzene). UV spectrum: λ_{max} 228 nm (log ε 4·45), 262 nm (4·47), 305 nm (3·83), 359 nm (2·76). IR spectrum (KBr): 785, 832, 864 (2 adjacent and solitary Ar—H), 1034, 1239 ($ArOCH_3$), 1472, 1561, 1591, 3018 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·60—7·40 (m, 8 H, Ar—H and CH=CH), 3·69 (s, 6 H, 2 OCH_3). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 71·36% C, 5·43% H, 11·90% S.

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

The reaction of 14·8 g *XIVb* with 14·5 g 1-methylpiperazine in 40 ml chloroform was carried out like in the preceding case. The oily base was obtained in a yield of 14·0 g (79%). It crystallized after mixing with light petroleum, m.p. 114—116°C. Analytical sample, m.p. 117—118°C (benzene–light petroleum). IR spectrum: 814, 822, 856, 882, 899 (2 adjacent and solitary Ar—H), 1021, 1033, 1230, 1252 ($ArOCH_3$), 1469, 1483, 1500, 1602, 3012 (Ar), 2805 cm^{-1} (OCH_3, NCH_3). ^{1}H-NMR spectrum: δ 7·30 and 7·12 (2 d, J = 8·5 Hz, 2 H, 1,6-H_2), 7·20 and 7·04 (2 mcs, J = 3·0 Hz, 2 H, 4,9-H_2), 6·80 and 6·60 (2 mcd, J = 8·5; 3·0 Hz, 2 H, 3,7-H_2), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (s, 6 H, 2 OCH_3), 2·66 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{21}H_{26}N_2O_2S$ (370·5) calculated: 68·07% C, 7·07% H, 7·56% N, 8·65% S; found: 68·14% C, 7·23% H, 7·39% N, 8·61% S.

Dimethanesulfonate monohydrate, m.p. 171—174°C (95% ethanol). For $C_{23}H_{34}N_2O_8S_3 + H_2O$ (580·7) calculated: 47·57% C, 6·25% H, 4·82% N, 16·56% S; found: 47·86% C, 6·16% H, 4·76% N, 16·74% S.

The neutral product was obtained in a yield of 2·4 g and was identified as 2,7-dimethoxydibenzo[*b,f*]thiepin (*XVb*) crystallizing from a mixture of benzene and light petroleum, m.p. 99—101°C. UV spectrum: λ_{max} 227 nm (log ε 4·50), 269 nm (4·12), 303 nm (3·90), infl. 340 nm (3·34). IR spectrum (KBr): 784 (*cis*-CH=CH), 827, 848, 866, 898 (2 adjacent and solitary Ar—H), 1030, 1218, 1250 ($ArOCH_3$), 1498, 1591, 1600, 3028, 3078 (Ar), 2855 cm^{-1} (OCH_3). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 70·64% C, 5·27% H, 11·58% S.

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

A solution of 3·7 g *IV* in 40 ml chloroform was stirred and treated at 15°C with a solution of 15·0 g BBr_3 in 60 ml chloroform over 20 min. The mixture was stirred for 4 h at 22°C. Chloroform was evaporated *in vacuo*, the residue dissolved in a mixture of 150 ml ethanol and 50 ml H_2O and the solution was refluxed for 5 h. Ethanol was then evaporated *in vacuo* and the residue was treated with 120 ml 10% Na_2CO_3 solution. The precipitate was filtered and dried *in vacuo*; 3·45 g (m.p. 190—210°C). It was purified by extraction with boiling water and by crystallization from acetone; 0·9 g (26%), m.p. 247—249°C. UV spectrum: λ_{max} 260 nm infl. (log ε 4·01), infl. 295 nm (3·52). IR spectrum: 792, 812, 881, 907 (2 adjacent and solitary Ar—H), 1153 (ArOH), 1478, 1581, 1610 (Ar), 2520 (NH^+), 3380 cm^{-1} (OH in a H bond). For $C_{19}H_{22}N_2O_2S$ (342·4) calculated: 66·64% C, 6·48% H, 8·18% N, 9·36% S; found: 66·02% C, 6·66% H, 8·13% N, 9·68% S.

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

A solution of 4·2 g *V* in 20 ml dichloromethane was stirred and treated dropwise with a solution of 11·3 g BBr_3 in 10 ml dichloromethane. The mixture was stirred for 5 h at room temperature and allowed to stand overnight. Dichloromethane was evaporated, the residue was treated with 25 ml 20% NaOH and 20 ml H_2O and the mixture stirred for 30 min at 90°C. After cooling, it was neutralized with acetic acid, the solid was extracted with dilute hydrochloric acid and the acid solution neutralized with 5% $NaHCO_3$ solution. The precipitated product was crystallized from a mixture of benzene and ethanol; 0·60 g (14%) of a benzene solvate, m.p. 235—239°C. Mass spectrum, *m/e*: 342·1398 (M^+ corresponding to $C_{19}H_{22}N_2O_2S$). IR spectrum (KBr): 826, 869 (2 adjacent and solitary Ar—H), 1235, 1292 (ArOH), 1471, 1578, 1601 (Ar), 2830 (NCH_3), 3400 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·40 (bs, 2 H, 2 OH), 7·30 (s, 2 H, 1/3 C_6H_6), 7·14 (d, J = 8·0 Hz, 1 H, 6-H), 7·08 (d, J = 8·0 Hz, 1 H, 1-H), 6·97 and 6·80 (2 mcs, J = 3·0 Hz, 2 H, 4,9-H_2), 6·59 and 6·50 (2 mcd, J = 8·0; 3·00 Hz, 2 H, 2,7-H_2), 2·80 to 4·00 (m, 3 H, $ArCH_2CHAr$), 2·50 (bs, 4 H, $CH_2N^1CH_2$ of piperazine), 2·20 (bs, 4 H, $CH_2N^4CH_2$ of piperazine), 2·10 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2O_2S$ + 1/3 C_6H_6 (368·5) calculated: 68·45% C, 6·56% H, 7·60% N, 8·70% S; found: 67·55% C, 6·51% H, 7·22% N, 8·64% S.

Maleate sesquihydrate, m.p. 176—179°C (aqueous acetone–ether). Mass spectrum, *m/e* (%): 342·1421 (M^+ corresponding to $C_{19}H_{22}N_2O_2S$, 10), 299 (5), 285 (10), 271 (6), 257 (8), 242 (45), 181 (25), 99 (80), 70 (100), 58 (100). For $C_{23}H_{26}N_2O_6S$ + 1·5 H_2O (485·6) calculated: 56·89% C, 6·02% H, 5·77% N, 6·60% S; found: 57·00% C, 5·83% H, 5·76% N, 6·32% S.

The authors are indebted to Drs J. Holubek, E. Svátek and M. Ryska (department of physical chemistry of this institute) for recording and interpreting the spectra reported, and to Mrs J. Komancová, Mrs V. Šmídová and Mrs J. Kropáčová (department of analytical chemistry of this institute) for carrying out the analyses.

REFERENCES

1. Jílek J. O., Seidlová V., Svátek E., Protiva M., Pomykáček J., Šedivý Z.: Monatsh. Chem. *96*, 182 (1965).
2. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
3. Metyšová J.: Activ. Nerv. Super. *8*, 388 (1966).
4. Benešová O., Bohdanecký Z.: Activ. Nerv. Super. *8*, 390 (1966).
5. Protiva M., Jílek J. O., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I., Pelz K., Pomykáček J.: Farm. Sci. Tec. (Pavia) *20*, 721 (1965).

6. Vinař O., Taussigová D.: Activ. Nerv. Super. *8*, 394 (1966).
7. Náhunek K., Švestka J.: Activ. Nerv. Super. *8*, 392 (1966).
8. Vinař O., Ledererová E., Baštecký J.: Activ. Nerv. Super. *9*, 429 (1967).
9. Náhunek K., Švestka J., Rodová A., Mišurec J.: Activ. Nerv. Super. *9*, 430 (1967).
10. Náhunek K.: Activ. Nerv. Super. *12*, 93 (1970).
11. Queisnerová M., Svátek E., Macek K., Metyšová J.: Activ. Nerv. Super. *10*, 335 (1968).
12. Queisnerová M., Svátek E., Macek K., Metyšová J.: Česk. Farm. *17*, 248 (1968).
13. Šindelář K., Holubek J., Dlabač A., Bartošová M., Protiva M.: This Journal *42*, 2231 (1977).
14. Protiva M., Šindelář K., Šedivý Z., Metyšová J.: This Journal *44*, 2108 (1979).
15. Protiva M., Šedivý Z., Metyšová J.: This Journal *40*, 2667 (1975).
16. Šindelář K., Kakáč B., Svátek E., Metyšová J., Protiva M.: This Journal *38*, 1579 (1973).
17. Valenta V., Bártl V., Dlabač A., Metyšová J., Protiva M.: This Journal *41*, 3607 (1976).
18. Šindelář K., Kakáč B., Holubek J., Svátek E., Ryska M., Metyšová J., Protiva M.: This Journal *41*, 1396 (1976).
19. Archer S. (Sterling Drug, Inc.): U.S. 2 548 852 (17. 04. 51); Chem. Abstr. *46*, 1042 (1952).
20. Wagner A. W.: Chem. Ber. *99*, 375 (1966).
21. Šindelář K., Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *39*, 3548 (1974).
22. Šindelář K., Kopicová Z., Metyšová J., Protiva M.: This Journal *40*, 3530 (1975).

Translated by the author (M.P.).