NONCATALEPTIC POTENTIAL NEUROLEPTICS: 2-NITRO AND 2-HYDROXY DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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Acid *IV* obtained by nitration of (2-chlorophenyl)acetic acid reacts with thiophenol in boiling water solution in the presence of potassium hydroxide and copper and yields acid *V*. *Via* intermediates *VI*, *X* and *XI*, the synthesis of the 2-nitro derivative of perathiepin (*I*) was completed. Reduction of nitro ketone *VI* yielded the amino ketone *VII* which was converted *via* the diazonium salt to hydroxy ketone *VIII*. Methylation resulted in methoxy ketone *IX*, the transformation of which to the 2-methoxy derivative of perathiepin (*III*) is known. Demethylation of *III* to the 2-hydroxy-analogue *II* was done with boron tribromide. Compounds *I* and *II* are ineffective cataleptically and are relatively weak central depressants.

In a previous communication of this series[1] we mentioned unfinished attempts to synthesize the 2-nitro derivative of perathiepin (*I*) which was expected to possess the properties of a noncataleptic neuroleptic or tranquilizer. Difficulties were encountered in the transformation of 5-nitro-2-(phenylthio)benzyl chloride to the corresponding nitrile; a nonhomogeneous product was formed and was hydrolyzed under acid conditions to [5-nitro-2-(phenylthio)phenyl]acetic acid (*V*) in a very low yield. Attempts at direct nitration of dibenzo[*b*,*f*]thiepin-10(11*H*)-one did not yield a useful intermediate, *i.e.* ketone *VI*. After interruption of our experiments, synthesis of intermediates *V*, *VI*, *X* and *XI* was described. Ziering[2] reports in a patent application the oxidation of a previously prepared[3] 3-(5-nitro-2-phenylthio)-2-oxopropanoic acid (method in[4]) to acid *V* and cyclization of this acid to 2-nitrodibenzo[*b*,*f*]thiepin-10(11*H*)-one with polyphosphoric acid. Gerecke and coworkers[5,6], in their patent application, describe the transformation of 5-nitro-2-(phenylthio)benzyl chloride with the aid of potassium cyanide in a boiling mixture of ethanol, dioxane and water to an uncharacterized nitrile which was acid-hydrolyzed to acid *V* (without mentioning the yield). They cyclized it further with polyphosphoric acid to ketone *VI* which was reduced with sodium borohydride in aqueous dioxane to alcohol *X*.

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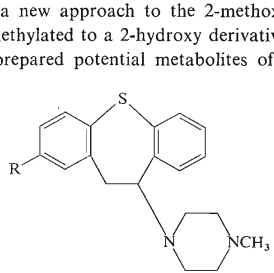
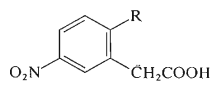
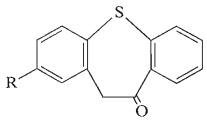
This was converted with thionyl chloride in a mixture of benzene and chloroform in the presence of pyridine to a product designated as chloride *XI*. Finally, Kyburz[7] in a lecture mentioned a scheme suggesting a way from (2-chlorophenyl)acetic acid[8] to 2-chloro-5-nitrophenyl acetic acid (*IV*) and further *via* acid *V* to ketone *VI*. In our synthesis of *I* we used the last-named procedure and employed the intermediate *VI* for a new approach to the 2-methoxy derivative of perathiepin[9] (*III*) which was demethylated to a 2-hydroxy derivative of perathiepin (*II*). In this way, the number of prepared potential metabolites of perathiepin (see[10,11]) was further increased.



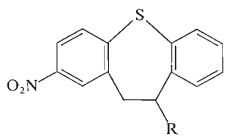
I, R = NO_2
II, R = OH
III, R = OCH_3



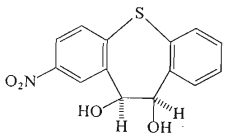
IV, R = Cl
V, R = SC_6H_5



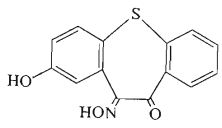
VI, R = NO_2
VII, R = NH_2
VIII, R = OH
IX, R = OCH_3



X, R = OH
XI, R = Cl



XII



XIII

Nitration of (2-chlorophenyl)acetic acid[8] produced a fine yield of (2-chloro-5-nitrophenyl)acetic acid (*IV*) (mentioned in [7,12]), the identity of which was established

by spectra and by the high reactivity of its chlorine atom. Its potassium salt reacts smoothly with the potassium salt of thiophenol in a boiling aqueous solution in the presence of copper and yields 5-nitro-2-(phenylthio)phenylacetic acid (*V*) (other methods of preparation see in[1,2,5,6]). Cyclization to 2-nitrodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VI*) was done by a modification of the described method[2,5,6] by treatment with polyphosphoric acid in the presence of boiling toluene. Reduction of ketone *VI* to alcohol *X* was done according to literature data[5,6] but for the transformation of alcohol *X* to chloride *XI* hydrogen chloride in chloroform in the presence of anhydrous calcium chloride was used at room temperature. A product was obtained which melted differently from the report of other authors[5,6]. While the identity of our compound *XI* is supported by spectra as well as by the course of subsequent reaction, the identity of the mentioned product[5,6] is not clear. Substitution reaction of chloride *XI* with excess 1-methylpiperazine in boiling chloroform produced a high yield of base *I* which was converted to dimethanesulfonate. The by-products of the reaction were two neutral substances. The first of these was highly polar and was identified as *cis*-2-nitro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10,11-diol (*XII*). Products of this type were encountered before[13,14], always as by-products of the reduction of dibenzo[*b*,*f*]thiepin-10(11*H*)-ones to the corresponding 10,11-dihydro-10-ols. Their formation was explained by contamination of the starting ketones with a small amount of the corresponding 10,11-diketone which is reduced to a diol. In the present case it is somewhat surprising that the intact diol appears only after two further steps of the synthesis, *i.e.* it must have passed intact through the reaction with hydrogen chloride. The formation of these *cis*-glycols is thus unclear. Another by-product of the substitution reaction is more appreciable as to its quantity and it is the product of the usual parallel elimination, *i.e.* 2-nitrodibenzo[*b*,*f*]thiepin[3,15].

Reduction of nitro ketone *VI* with stannous chloride produced amino ketone *VII* which had been described before[1,5,6] and obtained by cyclization of 5-amino-2-(phenylthio)phenyl acetic acid. Diazotization of amino ketone *VII* and subsequent decomposition of the diazonium salt yielded ketone *VIII*. A by-product was identified as oximino ketone *XIII*. Methylation of *VIII* with methyl iodide in acetone in the presence of anhydrous potassium carbonate resulted in methoxy ketone *IX*, prepared before by cyclization of 5-methoxy-2-(phenylthio)phenylacetic acid[9,16]. Its transformation to the 2-methoxy derivative of perathiepin (*III*) was done as described before.[9] The final demethylation was done by the action of boron tribromide in chloroform at room temperature; the primary product had to be hydrolyzed with boiling aqueous–ethanolic sodium hydroxide (for analogy see[17]). Phenolic base *II* was obtained in a low yield and was converted to a salt with methanesulfonic acid.

Compounds *I* and *III* (VÚFB-12.284 and 12.285) were evaluated pharmacologically in the form of dimethanesulfonates primarily for their expected tranquilizing effect on oral application. The acute toxicity for mice LD_{50} (*I*, 400 mg/kg; *III*, 550 mg/kg) and the mean effective dose causing ataxia in the rotating-rod test ED_{50} (*I*, 11·5

mg/kg; *III* 15·5 mg/kg) were determined. In the catalepsy test in rats both compounds were ineffective; at a high oral dose of 100 mg/kg they do not cause catalepsy in any animal of a group of ten. The shift of the "neuroleptic" substituent from position 8 (8-substituted isomers see[15,18]) to the quasi-symmetrical position 2 (for a working hypothesis see[9]) abolishes thus the cataleptic activity but the compounds prepared are relatively weak even from the point of view of central depressant activity (somewhat weaker than chlorpromazine, the ED_{50} of which in the rotating-rod test is 8·2 mg/kg *p.o.*). All the doses shown refer to the base.

Compound *I* was also tested after parenteral administration using general screening methods. Acute toxicity for mice after *i.v.* application was LD_{50} = 75 mg/kg; in most tests *in vivo* the compound was applied at a dose D = 15 mg/kg *i.v.* At doses greater than D the compound increases activity and reactivity of mice at first but this is followed by an inhibition after 15 min. At dose D it causes ataxia in mice (ED_{50} about 10 mg/kg *i.v.*), it prolongs significantly thiopental sleep in mice (doses of 5 – 10 mg/kg *i.v.* prolong to twice the control value) and cause a significant decrease of body temperature of rats (by 1°C) *in recto*. At a 1% concentration the solutions of the substance cause complete anaesthesia in 50% animals, both in the infiltration anaesthesia test in guinea-pigs and in the corneal anaesthesia test in rabbits. At a dose of 15 mg/kg *i.p.* it dilates the mouse eye pupil by 100% (mydriatic effect). At a dose of D/2 *i.v.* it decreases the blood pressure of normotensive rats by 20% (for at least 10 min) and the adrenaline pressor response by 50% (adrenolytic effect). At a concentration of 1 μg/ml it inhibits acetylcholine contractions of isolated rat duodenum by 50% (about 5% spasmolytic activity of atropine) and, at a concentration of 10 μg/ml it causes a similar inhibition of barium chloride contractions (about 50% activity of papaverine). It has an antihistamine effect in the detoxication test in guinea-pigs. At a dose of 5 mg/kg *s.c.* it protects 50% animals from a lethal dose of 5 mg/kg histamine, applied intrajugularly. At a dose of 1 – 5 mg/kg *i.v.* it has a significant antiarrhythmic effect in rats toward aconitine arrhythmias. In an isolated rabbit atrium it has a negatively inotropic effect (concentration of 25 – 50 μg/ml brings about a drop of heart inotropy by 25%). At an oral dose of 25 – 50 mg/kg it increases the blood sugar level in rats by 20% and at a dose of 75 mg/kg it has an anorectic effect in rats (it depresses the intake of food by 50% of the control) with signs of a general depression. The overall spectrum of effects resembles the activity profile of major tranquilizers of the chlorpromazine and thioridazine type.

In tests *in vitro* compound *I* has a slight antimicrobial effect (Dr J. Turinová and Dr A. Čapek, microbiological department of this institute; the microorganisms and the minimum inhibitory concentrations of *I* in μg/ml are shown): *Streptococcus β-haemolyticus*, 50; *Staphylococcus pyogenes aureus*, 100; *Mycobacterium tuberculosis* H37Rv, 25; *Saccharomyces pasterianus*, 50; *Trichophyton mentagrophytes*, 50.

EXPERIMENTAL

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

(2-Chloro-5-nitrophenyl)acetic Acid (*IV*)

A mixture of 37 ml 96% HNO_3 and 80 ml H_2SO_4 was added dropwise under stirring at −10°C over a period of 2 h to a solution of 132 g (2-chlorophenyl)acetic acid[8] (m.p. 92−95°C) in 350 ml H_2SO_4. The mixture was stirred for 3 h and poured into excess ice and water. The precipitated product was filtered and recrystallized from aqueous acetic acid; 154 g (92%), m.p. 171−173°C. The analytical sample melts at 174−175°C. UV spectrum: λ_{max} 272 nm (log ε 4·00). IR spectrum: 825, 837 (Ar—H), 921, 1245, *1715*, 2560, 2655, 2740 (COOH), 1351, 1521 (Ar—NO_2), 1580, 1612 cm^{-1} (Ar). ^{1}H-NMR-spectrum: δ 8·26 (mcs, J = 3·0 Hz, 1 H, 6-H), 8·05 (mcd, J = 8·0; 3·0 Hz, 1 H, 4-H), 7·64 (d, J = 8·0 Hz, 1 H, 3-H), 3·80 (s, 2 H, $ArCH_2COO$). For $C_8H_6ClNO_4$ (215·6) calculated: 44·57% C, 2·81% H, 16·45% Cl, 6·50% N; found: 43·97% C, 2·71% H, 16·27% Cl, 6·79% N.

[5-Nitro-2-(phenylthio)phenyl]acetic Acid (*V*)

A solution of 39·5 g KOH in 400 ml water was combined one by one with 40·5 g thiophenol, 71 g *IV* and 4·0 g "molecular" copper and the mixture was refluxed for 5 h. It was filtered while hot, the filtrate was acidified with hydrochloric acid and the precipitated product was filtered. Crystallization from aqueous ethanol with some charcoal yielded 63·8 g (67%) product melting at 138−141°C; analytical product, m.p. 141−145°C (aqueous ethanol). For $C_{14}H_{11}NO_4S$ (289·2) calculated: 58·13% C, 3·83% H, 4·84% N, 11·08% S; found: 58·34% C, 3·92% H, 4·72% N, 11·00% S. For a compound prepared by different procedures ref.[1,2,5,6] report m.p. of 143−145, 136−138 and 138−140°C.

2-Nitrodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VI*)

A mixture of polyphosphoric acid (180 g P_2O_5 and 90 ml 85% H_3PO_4), 63·8 g *V* and 600 ml toluene was refluxed for 16 h. The toluene layer was separated by decanting while hot and the residue was extracted with further 500 ml boiling toluene. Combined toluene solutions were washed with 5% NaOH; crystallization and concentration of mother liquors yielded a total of 46·2 g (84% per conversion; 5·2 g *V* was recovered by acidification of the alkaline aqueous solution) of product melting at 169−173°C. Ref.[2,5,6] describe a similar cyclization without using toluene as solvent and they do not report the yield (m.p. 172−173, and 171−172°C, respectively). In an attempt to achieve cyclization without toluene at 105−110°C a substantially lower yield of the desired product was obtained.

10-Chloro-2-nitro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XI*)

During reduction of 10·0 g *VI* with 1·4 g $NaBH_4$ in 150 ml dioxane according to ref.[5,6], 10·0 g (almost the theoretical yield) of crude 2-nitro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*X*) melting

at 139—143°C was obtained. Ref.[5,6] report for a pure product a m.p. of 144—146°C. The total amount of *X* obtained was dissolved in 250 ml chloroform, 5·0 g powdered $CaCl_2$ was added and the suspension was saturated for 2 h with anhydrous hydrogen chloride. After 48 h of standing, it was filtered and the filtrate was evaporated at reduced pressure; 10·5 g (98%) m.p. 106 to 110°C. Analytical product, m.p. 108·5—110·5°C (benzene–light petroleum). Since ref.[5,6] report a m.p. of 74—77°C for a product obtained with the aid of $SOCl_2$ we checked the identity of compound *XI* by analysis and spectra. UV spectrum: λ_{max} 247 nm (log ε 4·00), 338 nm (3·76). IR spectrum: 745, 760, 775, 788, 824, 838, 910, 921 (4 and 2 adjacent and solitary Ar—H), 1345, 1520 (Ar—NO_2), 1582, 1606 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·08 (mcs, *J* = 2·5 Hz, 1 H, 1-H), 7·98 (mcd, *J* = 8·0; 2·5 Hz, 1 H, 3-H), 7·57 (d, *J* = 8·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 4 H, 6,7,8,9-H_4), 5·79 (dd, *J* = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·02 and 3·60 (2 dd, *J* = = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, ArCH_2). For $C_{14}H_{10}ClNO_2S$ (291·8) calculated: 57·63% C, 3·46% H, 12·15% Cl, 4·80% N, 10·99% S; found: 58·15% C, 3·53% H, 11·99% Cl, 4·61% N, 10·63% S.

10-(4-Methylpiperazino)-2-nitro-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

A mixture of 10·0 g *XI*, 20 ml 1-methylpiperazine and 20 ml chloroform was refluxed for 8 h, cooled and diluted with 200 ml benzene and washed with water. The benzene solution was shaken with excess 5% hydrochloric acid. After separation, standing of the benzene solution yielded 0·1 g substance which was twice crystallized from a mixture of benzene and ethanol and melted at 217 to 220°C. It was identified as *cis*-2-nitro-10,11-dihydrodibenzo[*b,f*]thiepin-10,11-diol (*XII*). IR spectrum: 719, 752, 779, 832, 902 (4 and 2 adjacent and solitary Ar—H), 1029, 1057, 1077 (CHOH in a ring), 1343, 1520 (Ar—NO_2), 1581, 1606 (Ar), 3190, 3385 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 8·25 (mcs, *J* = 2·0 Hz, 1 H, 1-H), 7·90 (mcd, *J* = 8·0; 2·0 Hz, 1 H, 3-H), 7·55 (d, *J* = = 8·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 4 H, 6,7,8,9-H_4), 5·90 and 5·60 (2 bs, 2 H, 2 OH), 5·20 and 5·08 (2s, 2 H, Ar—CH—CH—Ar). The mass spectrum agrees with the suggested structure (molecular ion at *m/e* 289); the fragments indicate the presence of NO_2 and OH groups. For $C_{14}H_{11}NO_4S$ (289·3) calculated: 58·13% C, 3·83% H, 4·84% N, 11·06% S; found: 58·12% C, 4·04% H, 4·80% N, 10·60% S.

Evaporation of the benzene filtrate and crystallization of the residue from ethanol yielded 2·60 g (30%) 2-nitrodibenzo[*b,f*]thiepin melting at 109·5—111·5°C. Ref.[3,15] report a m.p. of 110°C and 111—112°C, respectively.

The acid aqueous layer was made alkaline with 20% NaOH and base *I* was isolated by extraction with benzene; 8·5 g (70%). It crystallizes from a mixture of ethanol and benzene, m.p. 185 to 188°C. IR spectrum: 751, 810, 832, 840, 903 (4 and 2 adjacent and solitary Ar—H), 1350, 1518 (NO_2), 1579 and 1603 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·06 (mcs, *J* = 2·0 Hz, 1 H, 1-H), 7·90 (mcd, *J* = 8·0; 2·0 Hz, 1 H, 3-H), 7·55 (d, *J* = 8·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 4 H, 6,7,8,9-H_4), 3·00—4·00 (m, 3 H, ArCH_2CHAr), 2·60 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·22 (s, 3 H, NCH_3). For $C_{19}H_{21}N_3O_2S$ 355·4) calculated: 64·21% C, 5·96% H, 11·83% N, 9·01% S; found: 64·41% C, 6·17% H, 11·61% N, 9·09% S.

Dimethanesulfonate crystallizes from a mixture of ethanol and ether as solvate with a molecule of ethanol and melts at 182—184°C. For $C_{21}H_{29}N_3O_8S_3+C_2H_6O$ (593·8) calculated: 46·53% C, 5·94% H, 7·08% N, 16·20% S; found: 47·11% C, 5·72% H, 7·10% N, 15·91% S.

2-Aminodibenzo[*b,f*]thiepin-10(11*H*)-one (*VII*)

Hydrochloric acid (175 ml) was added dropwise under stirring to a mixture of 40·7 g *VI*, 450 ml acetic acid and 135·5 g $SnCl_2.2\,H_2O$ and the mixture was refluxed for 3 h. After cooling, the

precipitated solid was filtered, stirred with 300 ml 10% NaOH, left to stand overnight, filtered, washed with water and dried in air; 33·7 g (93%) m.p. 194—195°C. Ref.[1,5,6] report for a product obtained by cyclization of 5-amino-2-(phenylthio)phenyl acetic acid a m.p. of 193—195°C and 191—193°C, respectively.

2-Hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one (*VIII*)

A solution of 16·0 g *VII* in dilute sulfuric acid (30 ml H_2SO_4 and 600 ml water) was diazotized at 0°C with a solution of 5·6 g $NaNO_2$ in 20 ml water, the mixture was stirred for 2 h under cooling and then added dropwise over a period of 1 h to a mixture of 1 litre water and 30 ml H_2SO_4. After 5 min of boiling, it was cooled and the product was extracted with chloroform. The extract was evaporated, the residue was dissolved in benzene and, by shaking with 10% NaOH, the acid nonhomogeneous product was transferred to the aqueous phase. After separation, it was acidified with hydrochloric acid and extracted with chloroform. The extract was placed on a column of 500 g silica gel and eluted with chloroform. The product was obtained from the less polar component by evaporation of the chloroform eluates; 9·95 g (62%), m.p. 195—197·5°C (benzene). UV spectrum (C_2H_5OH): λ_{max} 233 nm (log ε 4·33), 249 nm (4·26), 338 nm (3·57). IR spectrum (KBr): 764, 828, 861 (4 and 2 adjacent and solitary Ar—H), 1173, 1230, 1251 (C—O), 1296, 1306 (Ar—OH), 1591, 1604 (Ar), 1663 (Ar—CO...HO), 3330 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 9·90 (s, 1 H, OH), 7·94 (mcd, 1 H, 9-H), 7·10—7·60 (m, 4 H, 4,6,7,8-H_4), 6·82 (mcs, J = 3·0 Hz, 1 H, 1-H), 6·58 (mcd, J = 8·0; 3·0 Hz, 1 H, 3-H), 4·12 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}O_2S$ (242·2) calculated: 69·42% C, 4·16% H, 13·22% S; found: 69·56% C, 4·29% H, 12·90% S.

Continuation of chromatography, using elution with a mixture of chloroform and ethanol, yielded 2·0 g more polar substance which crystallizes from a mixture of benzene and ethanol, m.p. 226—228·5°C (decomp.). It was identified as 2-hydroxy-11-oximinodibenzo[*b,f*]thiepin-10(11*H*)-one (*XIII*). UV spectrum: λ_{max} 239 nm (log ε 4·44), infl. 265 nm (4·17), infl. 345 nm (3·25). IR spectrum: 743, 820, 844, 867 (4 and 2 adjacent and solitary Ar—H), 1234, 1279 (Ar—OH), 1589 (Ar), 1642 (CO—C=N), 3220 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 13·90 (bs, 1 H, NOH), 10·00 (bs, 1 H, OH), 7·88 (m, 1 H, 9-H), c. 7·40 (m, 4 H, 4,6,7,8-H_4), c. 6·70 (m, 2 H, 1,3-H_2). For $C_{14}H_9NO_3S$ (271·3) calculated: 61·98% C, 3·34% H, 5·16% N, 11·82% S; found: 62·44% C, 3·60% H, 5·05% N, 11·60% S.

2-Methoxydibenzo[*b,f*]thiepin-10(11*H*)-one *IX*)

A mixture of 4·5 g *VIII*, 30 ml acetone, 4·2 g methyl iodide and 2·7 g K_2CO_3 was refluxed under stirring for 24 h, diluted with benzene and washed with water, 10% NaOH, with water again, dried with $MgSO_4$ and evaporated. The crude product obtained in a nearly theoretical yield (4·57 g) was recrystallized from ethanol, m.p. 126—132·5°C. For a pure product, obtained by cyclization of 5-methoxy-2-(phenylthio)phenylacetic acid, ref.[9,16] report m.p. of 131·5—132·5 and 131·5°C, respectively.

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

A solution of 10 g BBr_3 in 8 ml chloroform was added dropwise under stirring and cooling with water to a solution of 4·4 g 2-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[9] (*III*) in 15 ml chloroform. The mixture was stirred for 7 h at room temperature and left to stand overnight. Ethanol (15 ml) was then added and the mixture stirred for 8 h at room temperature. Addition of 60 ml ether resulted in the precipitation of hydrobromides of the basic pro-

ducts which were then filtered. They were mixed with 50 ml ethanol, 5 ml 20% NaOH was then added and the mixture refluxed for 3 h. Ethanol was evaporated *in vacuo*, the residue was dissolved in water, the solution was neutralized with acetic acid and the precipitated product was isolated by extraction with dichloromethane. After evaporation of the extract, 1·8 g nonhomogeneous substance was obtained which was dissolved in ethanol and the solution was combined with 1·6 g methanesulfonic acid and ether until turbidity formed. A total of 0·80 g dimethanesulfonate of base *II* was formed. It crystallized from a mixture of 95% ethanol and ether as a monohydrate melting at 187—188°C. For $C_{21}H_{30}N_2O_7S_3 + H_2O$ (536·7) calculated: 47·00% C, 6·01% H, 5·22% N, 17·92% S; found: 46·82% C, 5·67% H, 5·00% N, 17·58% S.

The mother liquors were evaporated, the residue dissolved in water, insoluble contaminants were removed by extraction with benzene and the aqueous solution was made alkaline with 10% Na_2CO_3. Base *II* was obtained in a yield of 0·42 g; it was dried in air and crystallized from benzene to melt at 223—226°C. IR spectrum: 751, 822, 863 (4 and 2 adjacent and solitary Ar—H), 1 245 (Ar—OH), 1 590 (Ar), 2 700 cm^{-1} (OH···N). ^{1}H-NMR spectrum: δ 7·50 (mcd, 1 H, 6-H), 6·90—7·40 (m, 4 H, 4,7,8,9-H_4), 6·78 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·48 (mcd, J = 8·0; 2·5 Hz, 1 H, 3-H), 2·80—4·00 (m, 3 H, $ArCH_2CHAr$), 2·50 and 2·20 (2 m, 4 CH_2 groups of piperazine), 2·10 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2OS$ (326·4) calculated: 69·92% C, 6·79% H, 8·58% N, 9·82% S; found: 70·06% C, 6·70% H, 8·24% N, 9·88% S.

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