POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENTS BELONGING TO THE 8-METHYLTHIO-10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN SERIES; SYNTHESIS OF 2-HYDROXY AND 3-HYDROXY DERIVATIVES

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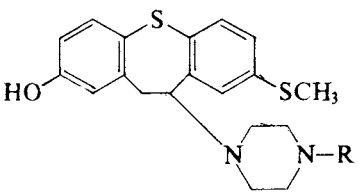
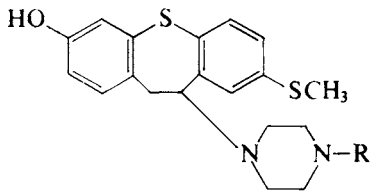
The acid *VI*, prepared by reaction of potassium salts of (2-iodo-5-methoxyphenyl)acetic acid and 4-(methylthio)thiophenol in the presence of copper, was transformed *via* intermediates *VII*—*IX* to 2-methoxy-8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins *X* and *XI*. Their demethylation with boron tribromide afforded 2-hydroxy derivatives of the neuroleptic agents methiothepin and oxyprothepin *I* and *II*. 11-Chloro-7-methoxy-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin was subjected to substitution reactions with 1-methylpiperazine and 1-(ethoxycarbonyl)piperazine and gave piperazine derivatives *XIII* and *XIV*, out of which the latter gave the secondary amine *XV* by alkaline hydrolysis. The ethers *XIII* and *XV* were also cleaved with boron tribromide and gave 3-hydroxy derivatives of methiothepin (*III*) and its demethyl derivative *IV*. The phenols *I*, *II*, and *IV* are potential metabolites of the mentioned neuroleptic agents; compound *III*, which already was identified as a metabolite, disclosed properties of a strong and cataleptic neuroleptic agent with prolonged duration of the effects. The methoxy compounds *X*, *XI*, and *XIII* are practically devoid of the neuroleptic activity.

2-Hydroxy-8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins *I* and *II* have to be considered potential metabolites of the neuroleptic agents methiothepin[1] and oxyprothepin[2,3] (in this way also of oxyprothepin decanoate[4]). For this reason, it was useful to carry out the synthesis of compounds *I* and *II* as standards for studies of biotransformation of the mentioned neuroleptics. The metabolic study of methiothepin[5] led to the finding of the 3-hydroxy derivative *III* as the main metabolite in rat faeces and in the same material there was found a "hydroxy demethyl derivative" which could not be precisely identified due to the lack of the synthetic standard for comparison. In the mentioned paper[5], compound *III* was presented among synthetic standards which were at disposal and enabled the reliable identification of the corresponding metabolites (R_F values in two systems were given as the only characteristics). Synthesis of this compound or its more detailed characterization have not been described. It is now disclosed in the present communication together with the synthesis of compound *IV* which could be the mentioned "hydroxy demethyl

derivative". 3-Hydroxy derivative of oxyprothepin (*V*) was identified in human urine as the metabolite[6,7]; its synthesis was described previously[8]. In a recent metabolic study with 10-^{14}C-oxyprothepin[9] it did succeed, however, to identify this compound neither in rat urine, nor in faeces.



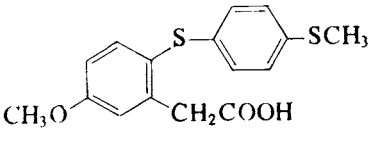
I, R = CH_3
II, R = $(CH_2)_3OH$



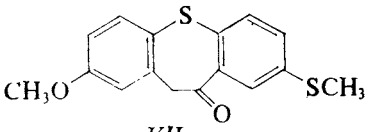
III, R = CH_3
IV, R = H
V, R = $(CH_2)_3OH$

In the synthesis of compounds *I* and *II* the acid *VI* was obtained in satisfactory yield by reaction of (2-iodo-5-methoxyphenyl)acetic acid[10] with 4-(methylthio)-thiophenol[11] in a boiling aqueous solution of potassium hydroxide in the presence of copper. The same compound was mentioned in patents[12] as having been prepared by hydrolysis of the corresponding nitrile; the melting point value is the only form of characterization. In the same patents[12] there also were named the further intermediates of our synthesis, *i.e.* compounds *VII*–*X*; no experimental details are given for their preparation and regarding their characterization, analyses and spectra are lacking and only melting points are given. In the Experimental we describe briefly the course of our preparations and complete the data about the characterization of these compounds. The acid *VI* was cyclized with polyphosphoric acid in the presence of boiling toluene to 2-methoxy-8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VII*) with a yield of 61%. Its reduction to the alcohol *VIII* with sodium borohydride in a boiling solution in aqueous ethanol proceeded with a yield of 88%. The transformation of the alcohol *VIII* to the chloro compound *IX* was carried out by the treatment with hydrogen chloride in benzene and the yield was almost theoretical. The substitution reaction of the chloro derivative *IX* with 1-methylpiperazine in boiling chloroform afforded a mixture of a basic and a neutral product which was separated by isolating the base as the solid sulfate. Its decomposition gave the oily base *X* in a yield of 79% which was transformed to the maleate. The homogeneous base *X* was released from the pure maleate and used on the one hand for recording the ^{1}H NMR spectrum, and to processing to compound *I* on the other. The neutral product was obtained in a yield of 20% and identified as 2-methoxy-8-methylthiodibenzo[*b*,*f*]thiepin (*XII*). A similar substitution reaction of the chloro derivative *IX* with 1-(3-hydroxypropyl)piperazine[13] afforded the oily base *XI* which

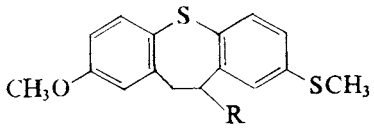
was transformed to the dimethanesulfonate and purified by crystallization in this form. This salt was used for pharmacological testing and its decomposition gave the homogeneous base which was used for recording the ^{1}H NMR spectrum and processing to compound *II*. Demethylations of compounds *X* and *XI* were carried out with boron tribromide at room temperature (method[14,15]). In the first case, chlorobenzene proved a suitable medium and the primary product was hydrolyzed with a boiling dilute solution of sodium hydroxide in aqueous ethanol. The phenolic product *I* was a solid substance which was transformed to the bis(hydrogen maleate); its identity was corroborated by spectra. In the other case, demethylation proceeded in dichloromethane and after hydrolysis, analogous like in the preceding case, the crystalline base *II* was obtained and its structure was also confirmed by spectra.



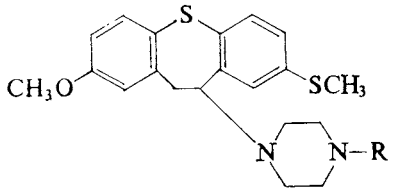
VI



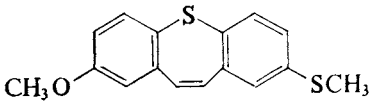
VII



VIII, R= OH
IX, R= Cl



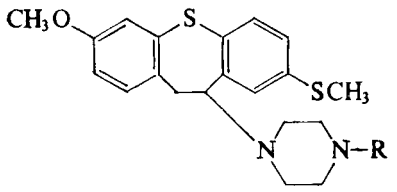
X, R= CH_3
XI, R= $(CH_2)_3OH$



XII

Substitution reactions of 11-chloro-7-methoxy-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[8,12] with 1-methylpiperazine and 1-(4-ethoxycarbonyl)piperazine gave the bases *XIII* and *XIV* which were transformed for characterization to maleates. The first of them (*XIII*) was described in the patent[12] already mentioned. The secondary base *XV* was obtained by hydrolysis of the carbamate *XIV* with a boiling concentrated solution of potassium hydroxide in ethanol; it was also transformed to the maleate. Compounds *XIII* and *XV* were demethylated with boron tribromide. In the first case, the reaction was carried out in dichloromethane and the base *III* was directly

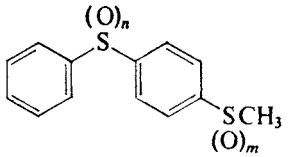
isolated as the product. Spectra confirmed the structure and the compound was transformed to the maleate for pharmacological testing. In the other case, the reaction proceeded in chlorobenzene and the hydrobromide was obtained as the primary product; the mass spectrum and IR spectrum confirmed structure *IV*. It was surprising that this hydrobromide crystallized even from alkaline solutions which only contained the bromide ions. Preparation of the free base *IV* did not succeed but the hydrobromide could be transformed to the dimethanesulfonate. Attempts at oxidizing this salt with hydrogen peroxide in aqueous solution as well as attempts to oxidize an aqueous solution of the methanesulfonate of compound *V* (ref.[8]) with periodic acid to sulfoxides led to mixtures of oxidation products (in the first case, the sulfone, *i.e.* methylsulfonyl derivative, was partly formed) from which homogeneous compounds were not obtained. The corresponding monosulfoxide would be very desirable with regard to the indications obtained in the mentioned metabolic studies with methiothepin[5] ("dioxy demethyl metabolite") and oxyprothepin[6] ("hydroxylated S-oxide").



XIII, R = CH_3
XIV, R = $COOC_2H_5$
XV, R = H

As model compounds for metabolic studies of compounds of the methiothepin and oxyprothepin type there were required 4-(methylthio)diphenyl sulfide (*XVI*) and its oxidation products. The sulfide *XVI* was obtained by reaction of 4-(methylthio)thiophenol[11] with iodobenzene in boiling dimethylformamide in the presence of potassium carbonate and copper, while the literature[16,17] described its synthesis by more complicated ways. Oxidation of the disulfide *XVI* with a mixture of potassium bromate and potassium bromide in a mixture of acetic and hydrochloric acid (method[18]) led selectively to the monosulfoxide *XVII*. The same compound was obtained in attempts at preparing the corresponding disulfoxide[17,19] on the one hand as the main product in a reaction of the sulfide *XVI* with hydrogen peroxide in acetic acid at 0–5°C, and as a by-product of a similar reaction carried out in a mixture of acetic acid and dimethyl sulfoxide (in this case the main product is an oily substance whose analysis indicates the presence of one oxygen atom more than calculated for the desired disulfoxide; its IR spectrum, however, does not show the band of the

sulfone group). By oxidation of the disulfide *XVI* under severe conditions, *i.e.* with hydrogen peroxide in boiling acetic acid, the disulfone *XVIII* was obtained. Its preparation by a similar method was described previously[20].



XVI, $m = n = 0$
XVII, $m = 1$, $n = 0$
XVIII, $m = n = 2$

Compounds *III*, *X*, *XI*, and *XIII* were tested in the form of salts, described in the Experimental, as potential neuroleptic agents. They were administered orally and the doses (in mg/kg) were calculated for the bases. Acute toxicity in mice was determined only for compound *III*; LD_{50} = 136 mg/kg. Discoordinating activity in the rotarod test in mice, ED_{50}: *III*, 1·7 (in 24 h after the administration the effect is over); *X*, 30; *XI*, 48; *XII*, 6·3 (the effect is prolonged and disappears only in 72 h after the administration). Discoordinating activity in the rotarod test in rats, ED_{50}: *III*, 0·8. Inhibition of the spontaneous motility of mice followed by the photo-cell method (Dews), D_{50}: *III*, 2·1 (after 24 h D_{50} is still 3·1 mg/kg). Cataleptic activity in rats, ED_{50}: *III*, 74 (in 24 h after the administration the dose of 25 mg/kg is still cataleptic for 40% animals; in the interval of 48 h the effect is over); *X* and *XI*, doses of 50 mg/kg are inactive. Antiapomorphine activity in rats: *X* and *XI* in doses of 40 mg/kg are without effect in the interval of 4 h after the administration. The results indicate that only the 3-hydroxy derivative of methiothepin (*III*) is a potent neuroleptic. This finding is a new contribution to the question of the influence of nuclear hydroxylation on activity and of the relation between polarity and neuroleptic activity in the series of tricyclic neuroleptic agents[21]. The discrepancy between the activity of compound *III* and inactivity of compound *V* (refs[8,21]) is a further proof of the correctness of our earlier hypothesis according to which the amassing of hydrophilic groups in the molecule leads to exceeding of structural limits for neuroleptic activity since transport to the receptor site is made difficult or impossible[21]: on the other hand we consider very probable that the receptor affinities of compounds *III* and *V* are very similar.

Compounds *X*, *XI*, and *XIII* were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in $\mu g\ ml^{-1}$, unless they exceed 100 $\mu g\ ml^{-1}$, are given): *Streptococcus β-haemolyticus*, *X* 6·25, *XI* 12·5, *XIII* 25; *Streptococcus faecalis*, *X* 12·5, *XI* 25, *XIII* 50; *Staphylococcus pyogenes aureus*, *X* 12·5, *XI* 25, *XIII* 100; *Escherichia coli*, *X* 25, *XI* 25; *Proteus vulgaris*, *X* 50, *XI* 100; *Trichophyton mentagrophytes*, *X* 25, *XI* 50, *XIII* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined partly in Kofler's block (are not corrected), partly in an automatic Mettler FP-5 melting point recorder; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and mass spectra with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel. The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure.

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

4-(Methylthio)thiophenol[11] (101 g) was added to a solution of 138 g 85% KOH in 1·4 l water and the mixture was stirred for 30 min at 55–60°C. It was treated with 184 g (2-iodo-5-methoxyphenyl)acetic acid[10] and 3 g Cu and the mixture was stirred and refluxed for 23 h, cooled and filtered with charcoal. The solid on the filtre was washed with 150 ml boiling water and the filtrate was acidified with 250 ml hydrochloric acid. The separated oily product crystallized after 1 h stirring, was filtered, washed with water, dried and crystallized from a mixture of benzene and light petroleum; 141 g (70%), m.p. 93–96°C. Analytical sample, m.p. 104–105°C (aqueous methanol). IR spectrum: 805, 853 (2 adjacent and solitary Ar—H), 944, 1 240, **1 698**, 2 550, 2 620, 2 730, infl. 3 140 (COOH), 1 240, 1 310 ($ArOCH_3$), 1 480, 1 596 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 10·80 (bs, 1 H, COOH), 6·70–7·50 (m, 7 H, ArH), 3·80 (s, 5 H, OCH_3 and $ArCH_2CO$), 2·40 (s, 3 H, SCH_3). Ref.[12], m.p. 100–101°C (prepared differently).

2-Methoxy-8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*)one (*VII*)

A mixture of 7·6 g *VI*, 76 g polyphosphoric acid and 50 ml toluene was stirred and refluxed for 4 h, and then decomposed by pouring into 500 ml ice-cold water. The product was extracted with benzene, the extract was washed with water and 5% NaOH, dried and evaporated; 4·4 g (61%) crystalline residue, m.p. 112–117°C. Analytical sample, m.p. 128–129°C (benzene). UV spectrum: λ_{max} 207·5 nm (log ε 4·52), 235 nm (4·45), 251 nm (4·40), 282 nm (4·29), 364 nm (3·57). IR spectrum: 819, 880, 890 (2 adjacent and solitary Ar—H), 1 248, 1 313 ($ArOCH_3$), 1 490, 1 580, 1 594, 3 060 (Ar), 1 659 (ArCO), 2 840 cm^{-1} (OCH_3). ^{1}H NMR spectrum: δ 8·00 (d, J = 2·5 Hz, 1 H, 9-H), 7·49 (d, J = 8·0 Hz, 1 H, 4-H), 7·45 (d, J = 8·0 Hz, 1 H, 6-H), 7·20 (q, J = 8·0; 2·5 Hz, 1 H, 7-H), 6·94 (d, J = 2·5 Hz, 1 H, 1-H), 6·68 (q, J = 8·0; 2·5 Hz, 1 H, 3-H), 4·30 (s, 2 H, $ArCH_2CO$), 3·79 (s, 3 H, OCH_3), 2·48 (s, 3 H, SCH_3). Ref.[12], m.p. 129°C.

2-Methoxy-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*VIII*)

A mixture of 21·0 g *VII* and 300 ml ethanol was heated to 75°C and treated under stirring with a solution of 13·2 g $NaBH_4$ in 130 ml water containing 2 ml 20% NaOH, added dropwise over 15 min. The resulting solution was refluxed for 5 h, evaporated and the residue was distributed between water and benzene. The benzene extract was washed with 2% NaOH and water, dried and evaporated; 18·7 g (88%), m.p. 88–90°C. Analytical sample, m.p. 89–91°C (benzene–light petroleum). IR spectrum: 808, 880, 890 (2 adjacent and solitary Ar—H), 1 029, 1 220, 1 306 ($ArOCH_3$), 1 050 (CHOH in the ring), 1 478, 1 570, 1 598 (Ar), 3 300, 3 375 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·42 (d, J = 8·0 Hz, 1 H, 4-H), 7·40 (d, J = 2·0 Hz, 1 H, 9-H), 7·36 d, J = = 8·0 Hz, 1 H, 6-H), 7·00 (q, J = 8·0; 2·0 Hz, 1 H, 7-H), 6·84 (d, J = 2·5 Hz, 1 H, 1-H), 6·65 (q, J = 8·0; 2·5 Hz, 1 H, 3-H), 5·28 (bm, 1 H, Ar—CH—O). 3·86 (s, 3 H, OCH_3), 3·72 and 3·30

(2 dd, $J = 14{\cdot}0$ Hz, 1 + 1 H, $ArCH_2$), 2·42 (s, 3 H, SCH_3), 2·20 (bd, $J = 8{\cdot}0$ Hz, 1 H, OH). Ref.[12], m.p. 95°C.

10-Chloro-2-methoxy-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IX*)

A solution of 50 g *VIII* in 900 ml benzene was treated with 70 g powdered $CaCl_2$ and saturated for 7 h with HCl at 20°C. After standing overnight the mixture was filtered, the solid washed with benzene and the filtrate evaporated; 50 g (94%), m.p. 94–98°C. Analytical sample, m.p. 106–110°C (benzene). ^{1}H NMR spectrum: δ 7·48 (d, $J = 8{\cdot}0$ Hz, 1 H, 4-H), 7·40 (d, 1 H, 9-H), 7·36 (d, $J = 8{\cdot}0$ Hz, 1 H, 6-H), 7·00 (q, $J = 8{\cdot}0$; 2·0 Hz, 1 H, 7-H), 6·87 (d, $J = 2{\cdot}5$ Hz, 1 H, 1-H), 6·70 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, 3-H), 5·75 (dd, 1 H, Ar—CH—O), 3·88 and 3·59 (2 dd, $J = 14{\cdot}0$ Hz, 1 + 1 H, $ArCH_2$), 3·80 (s, 3 H, OCH_3), 2·45 (s, 3 H, SCH_3). Ref.[12], m.p. 105°C.

2-Methoxy-10-(4-methylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*X*)

A mixture of 15·8 g *IX*, 40 ml chloroform and 14·7 g 1-methylpiperazine was refluxed for 6 h and evaporated. The residue was dissolved in 150 ml benzene, the solution was washed with 3% NaOH and water, and shaken with 1·25M-H_2SO_4. The solid sulfate was filtered, combined with the aqueous layer of the filtrate and the suspension was treated with NH_4OH. The base was extracted with benzene, the extract was dried and evaporated; 15·0 g (79%) oily *X*. Neutralization of 14·6 g base with 4·4 g maleic acid in 30 ml warm ethanol, cooling, addition of 20 ml ether and standing overnight resulted in 19·0 g maleate, m.p. 173–174°C (ethanol). For $C_{25}H_{30}N_2O_5S_2$ (502·6) calculated: 59·73% C, 6·01% H, 5·57% N, 12·76% S; found: 59·51% C, 5·95% H, 5·41% N, 12·47% S. Ref.[12], m.p. 169°C. The homogeneous base, released from the maleate with NH_4OH and isolated by extraction with ether, remained oily and was used for recording the ^{1}H NMR spectrum: δ 7·60 (d, $J = 2{\cdot}0$ Hz, 1 H, 9-H), 7·43 (d, $J = 9{\cdot}0$ Hz, 1 H, 4-H), 7·36 (d, $J = 8{\cdot}0$ Hz, 1 H, 6-H), 6·96 (q, $J = 8{\cdot}0$; 2·0 Hz, 1 H, 7-H), 6·88 (d, $J = 2{\cdot}5$ Hz, 1 H, 1-H), 6·62 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, 3-H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·80 (s, 3 H, OCH_3), 2·70 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·42 (s, 3 H, SCH_3), 2·28 (s, 3 H, NCH_3).

The benzene solution, from which the base was removed as sulfate, was washed with water, dried and evaporated; 2·8 g (20%) 2-methoxy-8-methylthiodibenzo[*b*,*f*]thiepin (*XII*), m.p. 112–114°C (benzene). UV spectrum: λ_{max} 269 nm (log ε 4·65), 228 nm (4·41). IR spectrum: 811, 821, 866, 887 (2 adjacent and solitary Ar—H), 782 (CH=CH), 1 030, 1 242, 1 272 ($ArOCH_3$), 1 480, 1 572, 1 590, 3 013 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·60–7·40 (m, 8 H, ArH and CH=CH), 3·62 (s, 3 H, OCH_3), 2·30 (s, 3 H, SCH_3). For $C_{16}H_{14}OS_2$ (286·4) calculated: 67·09% C, 4·93% H, 22·39% S; found: 67·57% C, 5·08% H, 22·20% S.

10-[4-(3-Hydroxypropyl)piperazino]-2-methoxy-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]-thiepin (*XI*)

A similar reaction of 30 g *IX* and 26·8 g 1-(3-hydroxypropyl)piperazine[13] in 90 ml chloroform gave 22·4 g (56%) oily *XI* which was transformed to 26·0 g dimethanesulfonate, m.p. 126–129°C (ethanol–ether). Analytical sample, m.p. 132–134°C (ethanol). For $C_{25}H_{38}N_2O_8S_4$ (622·8) calculated: 48·21% C, 6·15% H, 4·50% N, 20·59% S; found: 48·02% C, 6·15% H, 4·15% N, 20·14% S. The released oily base was used for recording the ^{1}H NMR spectrum: δ 7·48 (d, $J = 2{\cdot}5$ Hz, 1 H, 9-H), 7·30 (d, $J = 8{\cdot}0$ Hz, 1 H, 6-H), 7·22 (d, $J = 8{\cdot}0$ Hz, 1 H, 4-H), 6·85 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, 7-H), 6·70 (d, $J = 2{\cdot}5$ Hz, 1 H, 1-H), 6·50 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, 3-H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (t, 2 H, CH_2O), 3·70 (s, 3 H, OCH_3), c. 2·50 (bm, 11 H, 5 CH_2N, and OH), 2·30 (s, 3 H, SCH_3), 1·65 (m, 2 H, CH_2 in the middle of the propane chain).

7-Methoxy-11-(4-methylpiperazino)-2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin (*XIII*)

A mixture of 15 g 11-chloro-7-methoxy-2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin[8], 15 g 1-methylpiperazine and 20 ml chloroform was refluxed for 6 h and evaporated. The residue was distributed between 150 ml water and 200 ml benzene, the benzene layer was washed with water and shaken with 130 ml 3M-HCl. The precipitated hydrochloride was filtered after 1 h standing, washed with benzene, suspended in water and decomposed with NH_4OH. The released base was extracted with benzene, the extract was dried and evaporated, and the residue was chromatographed on 300 g neutral Al_2O_3 (activity II). Elution with benzene gave 9·75 g (54%) homogeneous oily *XIII*. Maleate, m.p. 117–119°C (ethanol). Ref.[12], m.p. 117–119°C.

11-(4-Ethoxycarbonylpiperazino)-7-methoxy-2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin (*XIV*)

A mixture of 21 g 11-chloro-7-methoxy-2-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin[8] and 40 g 1-(ethoxycarbonyl)piperazine was stirred and heated to 110°C for 4·5 h, allowed to stand overnight, diluted with 200 ml water and extracted with benzene. The benzene layer was washed with water, dried and evaporated. The residue was dissolved in 200 ml ether and the solution was treated with a solution of HCl in ether. The precipitated hydrochloride was filtered, washed with ether, suspended in 200 ml water and decomposed by treatment with 25 ml NH_4OH. The base was isolated by extraction with benzene; 20·9 g (72%) oily *XIV*. A sample (1·0 g) was transformed for characterization by neutralization with 0·26 g maleic acid in 7 ml ethanol to the maleate (0·6 g), m.p. 134–135°C (acetone). For $C_{27}H_{32}N_2O_7S_2$ (560·7) calculated: 57·84% C, 5·75% H, 5·00% N, 11·43% S; found: 57·82% C, 5·90% H, 4·80% N, 11·56% S.

7-Methoxy-2-methylthio-11-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin (*XV*)

A mixture of 19·9 g *XIV*, 10 g KOH and 20 ml ethanol was stirred and refluxed for 3 h in a bath of 120°C, allowed to stand overnight and distributed between 200 ml water and 200 ml benzene. The benzene layer was washed with water and shaken with 3M-HCl. The precipitated hydrochloride was filtered, washed with benzene and decomposed with dilute NH_4OH. The base was isolated by extraction with benzene; 14·2 g (86%), m.p. 118–121°C (ether–light petroleum). Without purification it was transformed to the maleate, m.p. 166–167°C (acetone). For $C_{24}H_{28}N_2O_5S_2$ (488·6) calculated: 59·00% C, 5·78% H, 5·73% N, 13·12% S; found: 59·02% C, 5·92% H, 5·80% N, 13·24% S.

10-(4-Methylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-2-ol (*I*)

A stirred solution of 5·7 g *X* in 70 ml chlorobenzene was treated at 15–20°C with a solution of 11·1 g PBr_3 in 30 ml chlorobenzene, added dropwise over 15 min. The mixture was stirred for 6 h at room temperature, allowed to stand overnight and treated under stirring with a solution of 3·0 g methanesulfonic acid in 60 ml water. The precipitated methanesulfonate was filtered after 15 min stirring, washed with 20 ml water and added to a mixture of 180 ml ethanol and 80 ml 3% NaOH. The mixture was refluxed for 8 h, evaporated *in vacuo*, the residue was diluted with 60 ml water and the solution was neutralized with acetic acid. The separated product was extracted with chloroform, the extract was dried and evaporated; 1·75 g (32%), m.p. 170–178°C (ether–light petroleum). UV spectrum: λ_{max} 279 nm (log ε 4·27). IR spectrum (KBr): 780, 800, 819, 862 (2 adjacent and solitary Ar—H), 1 112, 1 145, 1 160 (ArOH), 1 230 (C—N), 1 567 (Ar), inflexes at 2 520 and 3 050 cm^{-1} (NH^+). ^1H NMR spectrum: δ 7·58 (d, J = 2·5 Hz, 1 H, 9-H), 6·40–7·40 (m, 5 H, remaining ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·65 (bm, 4 H, CH_2N^1.

.CH_2 of piperazine), 2·50 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·39 (s, 3 H, SCH_3), 2·28 (s, 3 H, NCH_3). For $C_{20}H_{24}N_2OS_2$ (372·5) calculated: 64·47% C, 6·50% H, 7·51% N; found: 64·17% C, 6·51% H, 6·91% N.

Bis(hydrogen maleate), m.p. 158—159°C (ethanol–ether). For $C_{28}H_{32}N_2O_9S_2$ (604·7) calculated: 55·61% C, 5·34% H, 4·63% N, 10·60% S; found: 55·19% C, 5·44% H, 4·56% N, 10·48% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-ol (*II*)

A solution of 6·3 g *XI* in 100 ml dichloromethane was stirred and treated over 15 min with a solution of 11·04 g PBr_3 in 50 ml dichloromethane, the mixture was stirred for 6 h at room temperature, allowed to stand overnight and evaporated. The residue was dissolved in a mixture of 100 ml ethanol and 75 ml 5% NaOH, the solution was stirred for 8 h at room temperature and evaporated after standing overnight. The residue was treated with 100 ml 5% Na_2CO_3 and extracted with chloroform, the extract was washed with water, dried and evaporated. The residue crystallized from 15 ml acetone; 2·5 g (41%), m.p. 186—190°C. Analytical sample, m.p. 192°C (acetone). Mass spectrum, *m/z* (%): 416 (M^+ corresponding to $C_{22}H_{28}N_2O_2S_2$, 6·5%), 272 (63), 225 (52), 116 (100), 70 (76), 58 (47), 56 (58). IR spectrum (KBr): 822, 842, 874 (2 adjacent and solitary Ar—H), 1 069, 1 242, 1 294 (CH_2OH), 1 170 (ArOH), 1 481, 1 579, 1 604 (Ar), 2 675, 2 770 (NH^+), 3 030 cm^{-1} (O—H...N). ^1H NMR spectrum ($C^2H_3SOC^2H_3$, 60°C): δ 7·48 (d, J = 2·5 Hz, 1 H, 9-H), 7·20 (d, J = 8·0 Hz, 2 H, 4,6-H_2), 6·98 (q, J = 8·0; 2·5 Hz, 1 H, 7-H), 6·82 (d, J = 2·5 Hz, 1 H, 1-H), 6·55 (q, J = 8·0; 2·5 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 3·48 (t, 2 H, CH_2O), c. 2·50 (bm, 5 NCH_2), 2·40 (s, 3 H, SCH_3). 1·65 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{22}H_{28}N_2O_2S_2$ (416·6) calculated: 63·43% C, 6·78% H, 6·72% N, 15·39% S; found: 63·64% C, 7·04% H, 6·73% N, 15·37% S.

10-(4-Methylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-3-ol (*III*)

XIII (6·0 g) was demethylated with 11·7 g BBr_3 in 100 ml dichloromethane similarly like in the preceding case and the mixture was similarly processed; 2·4 g (42%) *III*, m.p. 199—200°C (ethanol). UV spectrum: λ_{max} 278·5 nm (log ε 4·25), infl. 235 nm (4·21). IR spectrum: 805, 835, 850, 896 (2 adjacent and solitary Ar—H), 1 007, 1 258 (ArOH), 1 495, 1 575, 1 600, 3 000, 3 025 (Ar), 2 535, 2 630 (NH^+), 2 725, 2 800 (CH_3—N), infl. 3 100 cm^{-1} (O—H...N). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·40 (bs, OH), 7·50 (d, J = 2·5 Hz, 1 H, 9-H), 7·35 (d, J = 8·5 Hz, 1 H, 6-H), 7·20 (d, J = 8·5 Hz, 1 H, 1-H), 7·00 (q, J = 8·5; 2·5 Hz, 1 H, 7-H), 6·95 (d, J = 2·5 Hz, 1 H, 4-H), 6·70 (q, J = 8·5; 2·5 Hz, 1 H, 2-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (bm and s, 4 + 3 H, $CH_2N^4CH_2$ of piperazine and CH_3S), 2·20 (s, 3 H, CH_3N). For $C_{20}H_{24}N_2OS_2$ (372·5) calculated: 64·48% C, 6·49% H, 7·52% N, 17·21% S; found: 64·32% C, 6·35% H, 7·47% N, 16·93% S.

Maleate, m.p. 177—178°C (ethanol). For $C_{24}H_{28}N_2O_5S_2$ (488·6) calculated: 59·00% C, 5·78% H, 5·73% N, 13·12% S; found: 58·92% C, 5·96% H, 5·46% N, 12·91% S.

8-Methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin-3-ol (*IV*)

A solution of 3·0 g *XV* in 50 ml chlorobenzene was stirred and treated over 15 min with a solution of 6·02 g BBr_3 in 30 ml chlorobenzene at 15°C, it was stirred for 6 h at room temperature, allowed to stand overnight and shaken with a solution of 1·5 g methanesulfonic acid in 30 ml water. The precipitated solid was filtered, combined with the aqueous layer of the filtrate, the suspension was made alkaline (pH c. 8) with 30% NaOH, treated with 60 ml ethanol and refluxed for 5 h. Ethanol was evaporated *in vacuo*, the residue diluted with water and neutralized with

acetic acid. The separated oil, which was insoluble in benzene and chloroform, was isolated by decantation and induced to crystallize by dissolving in 10 ml ethanol and treatment with ether; 0·7 g (20%) *IV* hydrobromide, m.p. 146–148°C (ethanol). Mass spectrum, *m/z* (%): 358 (M^+ corresponding to $C_{19}H_{22}N_2OS_2$, 22%), 301 (21), 273 (48), 272 (83, $C_{15}H_{12}OS_2$), 259 (30), 240 (22), 227 (23), 226 (48), 225 (30), 194 (36), 165 (22), 85 (74, $C_4H_9N_2$), 56 (100, C_3H_6N). IR spectrum: 826, 863 (2 adjacent and solitary Ar—H), 1 171, 1 223 (ArOH), 1 480, 1 570, 1 597 (Ar), 2 450, 2 640, 2 695, 2 765 (NH_2^+), 3 180, 3 360 cm^{-1} (OH). For $C_{19}H_{23}$·.BrN_2OS_2 (439·4) calculated: 51·93% C, 5·28% H, 18·19% Br, 6·37% N, 14·59% S; found: 52·19% C, 5·44% H, 17·88% Br, 6·47% N, 14·03% S.

Dimethanesulfonate was obtained by treatment of the solution of hydrobromide in ethanol with methanesulfonic acid and crystallized from aqueous ethanol as the hemihydrate, m.p. 173·5°C. For $C_{21}H_{30}N_2O_7S_4 + 0{\cdot}5\ H_2O$ (559·7) calculated: 45·06% C, 5·58% H, 5·01% N, 22·91% S; found: 44·79% C, 5·51% H, 5·04% N, 22·51% S.

4-Methylthiodiphenyl Sulfide (*XVI*)

A mixture of 10·0 g iodobenzene, 7·8 g 4-(methylthio)thiophenol[11], 30 ml dimethylformamide, 9·7 g K_2CO_3 and 0·5 g Cu was stirred and refluxed (bath temperature 150–160°C) for 6 h. After cooling the solid components were filtered off and washed with 20 ml dimethylformamide. The filtrate was evaporated *in vacuo* and the residue was distributed between water and benzene. The organic layer was dried and evaporated, and the residue was distilled; 10·2 g (89%), b.p. 155–160°C/0·4 kPa. For $C_{13}H_{12}S_2$ (232·4) calculated: 67·19% C, 5·20% H, 27·60% S; found: 67·47% C, 5·25% H, 27·22% S. Refs[16,17] (different synthetic procedures), b.p. 194–196°C/0·9 kPa, and 187°C/6 kPa, respectively.

4-(Methylsulfinyl)diphenyl Sulfide (*XVII*)

A) A solution of 5·0 g *XVI* in 130 ml acetic acid was treated with a solution of 5·0 KBr in 25 ml water and 10 ml 20% hydrochloric acid and then under stirring slowly with a solution of 1·20 g $KBrO_3$ in 40 ml water. The mixture was allowed to stand overnight, poured into 1·5 l water and the product was extracted with benzene. The extract was washed with a saturated solution of $NaHCO_3$ and with water, dried and evaporated. The residue, which crystallized on standing, was recrystallized from a mixture of 6·5 ml benzene and 6·5 ml light petroleum; 4·1 g (77%), m.p. 67–69°C. Analytical sample, m.p. 72–73°C (hexane–ethanol). Mass spectrum, *m/z* (%): 248 (M^+ corresponding to $C_{13}H_{12}OS_2$, 25%), 233 (100, $C_{12}H_9OS_2$), 217 (4, $C_{12}H_9S_2$), 201 (11), 184 (30). IR spectrum (KBr): 695, 750 (5 and 2 adjacent Ar—H), 1 030, 1 063 (ArSOR), 1 570 cm^{-1} (Ar). Polarographic reduction in 0·5M-HCl (towards a saturated calomel electrode), $E_{1/2}$ −0·61 V (SO). For $C_{13}H_{12}OS_2$ (248·4) calculated: 62·86% C, 4·87% H, 25·82% S; found: 62·62% C, 4·89% H, 25·53% S.

B) A solution of 2·32 g *XVI* in 25 ml acetic acid was stirred and slowly treated with a solution of 1·0 g 35% H_2O_2 in 25 ml acetic acid at 3°C. The mixture was allowed to stand for 2 h at 0–5°, poured into 400 ml water and extracted with chloroform. The extract was washed with water, dried and evaporated. Crystallization of the residue from a mixture of 20 ml hexane and 5 ml benzene gave 2·0 g (81%) *XVII*, m.p. 71·5–73°C. Comparison with the product, obtained under *A*, proved identity (TLC, mixed melting point).

C) A solution of 6·6 g *XVI* in a mixture of 100 ml dimethyl sulfoxide, 100 ml acetic acid and 100 ml water was stirred and treated with 23·6 ml 35% H_2O_2. The mixture was stirred for 5 h at room temperature and for 4 h at 80°C, cooled, diluted with 500 ml water and extracted with

dichloromethane. The extract was washed with water, dried and evaporated. The residue was chromatographed on 70 g silica gel. Chloroform eluted 1·3 g *XVII*, m.p. 71—72°C, and then 5·0 g more polar oily product which was not identified.

4-(Methylsulfonyl)diphenyl Sulfone (*XVIII*)

A solution of 10·0 g *XVI* in 50 ml acetic acid was treated with 26 ml 30% H_2O_2; the mixture was refluxed for 6 h, cooled and poured into 1 l water. The precipitated product was filtered, washed with water, dried and crystallized from 300 ml ethanol; 8·4 g (67%) *XVIII*, m.p. 152 to 153°C. UV spectrum: λ_{max} 238 nm (log ε 4·27), inflexes at 265 nm (3·52), 270 nm (3·47) and 277 nm (3·22). IR spectrum: 690, 729, 749, 760, 849 (5 and 2 adjacent Ar—H), 1 162, 1 290, 1 320 (SO_2), 1 583, 3 018, 3 055 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·12 (s, 4 H, ArH of 1,4-phenylene), 8·00 (m, 2 H, 2,6-H_2 of phenyl), 7·60 (m, 3 H, remaining ArH), 3·10 (s, 3 H, $CH_3.SO_2$). Ref.[20], m.p. 150—151°C.

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