10-[4-(3-HYDROXYPROPYL)PIPERAZINO]-8-METHYLSULFONYL--10,11-DIHYDRODIBENZO[*b,f*]THIEPIN AND SOME RELATED POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENTS OXYPROTHEPIN AND METHIOTHEPIN*

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Received June 22nd, 1979

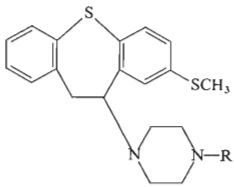
Substitution reaction of 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin with 1-(3--hydroxypropyl)piperazine afforded the title compound *IV* which was transformed by selective oxidation reactions to the sulfoxide *X*, N-oxide *XII* and N,S-dioxide *XIII*. The secondary amine *VII* was prepared *via* the carbamate *VI* and oxidized to the sulfoxide *XI*. Reaction of 10-chloro--8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin with ethylenediamine gave the diamine *XIV* which was oxidized to the corresponding sulfoxide *XV*. Compounds *IV*, *VII* and *X—XV* are potential metabolites of the neuroleptic agent oxyprothepin (*II*); compounds *VII*, *XI*, *XIV* and *XV* are potential metabolites of methiothepin (*I*). Out of the compounds prepared, only the title compound *IV* preserves the neuroleptic character.

An investigation of the metabolism of the neuroleptic agent methiothepin[1] (*I*) which used a combination of gas chromatography and mass spectrometry for the characterization and identification of metabolites[2], proved the formation of the following 8-sulfones as metabolites: 8-sulfone *III*, 5-sulfoxide 8-sulfone, N-demethyl-8-sulfone *VII* and N-demethyl-5-sulfoxide 8-sulfone *XI*. Out of these compounds, the 8-sulfone *III* has already been prepared by our group[3]. It has been stated[2] that as further synthetic standards, the 5-sulfoxide 8-sulfone, 5,8-disulfone and N-demethyl-5,8--disulfone were at disposal; the preparation and properties of these compounds (with the exception of the R_F values) have not been described. In connection with our studies of the metabolism[4-12] of the neuroleptic agent oxyprothepin (*II*) (ref.[7,11,13]), we also carried out the synthesis of a series of 8-methylsulfonyl derivatives as standards for the purpose of comparison which is described in the present communication.

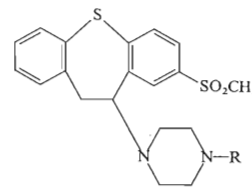
* Part CXL in the series Neurotropic and Psychotropic Agents; Part CXXXIX: This Journal *45*, 517 (1980).

** Affiliated unit of this Institute at Rosice n/L.

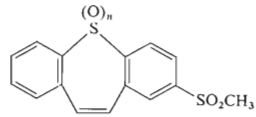
The starting compound of the whole study was 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] giving by a substitution reaction with 1-(3-hydroxypropyl)piperazine[14] in boiling chloroform the title compound *IV* in a high yield. In a small amount, 2-methylsulfonyldibenzo[*b*,*f*]thiepin (*VIII*) (ref.[14]) was isolated as the neutral by-product formed by the parallel elimination. Analogous substitution reactions with 1-(2-hydroxyethyl)piperazine and 1-(ethoxycarbonyl)piperazine resulted in bases *V* and *VI*. The alkaline hydrolysis of the carbamate *VI* yielded the secondary amine *VII*.



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



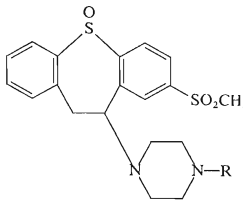
III, R = CH_3
IV, R = $(CH_2)_3OH$
V, R = $(CH_2)_2OH$
VI, R = $COOC_2H_5$
VII, R = H



VIII, *n* = 0
IX, *n* = 1

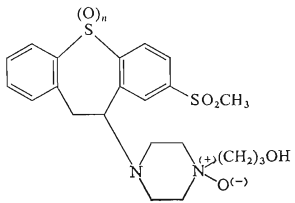
The oxidation of compound *IV* in the form of monomethanesulfonate with hydrogen peroxide in aqueous solution and at room temperature gave the sulfoxide *X* as the main product. The olefinic sulfoxide *IX* was isolated as an important by-product, formed by S-oxidation and elimination of 1-(3-hydroxypropyl)piperazine. This oxidation-elimination becomes the main reaction in acid solutions (*e.g.* in acetic acid) and at elevated temperatures. In these cases, it seems unlikely that the olefinic sulfoxide *IX* would be formed by a sequence of S^5-oxidation, followed by N^1-oxidation and a Cope elimination (*cf.*[15,16]); it is more probable that the sulfoxide *X* is unstable under the conditions mentioned and easily cleaves the piperazine fragment. The secondary amine *VII* was oxidized in the form of dimethanesulfonate in acetic

acid by a mild excess of hydrogen peroxide at 25°C; the sulfoxide *XI* was obtained in a high yield and the elimination was not observed at all.



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

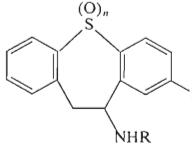
The oxidation of the base *IV* with hydrogen peroxide in ethanol proceeds selectively as N-oxidation, shown by the IR spectrum of the product *XII* and its polarographic reduction in comparison with the properties of the sulfoxide *X*. The analogous oxidation of the sulfoxide *X* results in the N,S-dioxide *XIII*; its IR spectrum exhibits absorption bands of N—O bond (968 cm^{-1}), as well as S—O bond (1032 cm^{-1}). Polarographic reduction, unfortunately, does not differentiate both oxygen functions; both processes appear as a single long wave at $E_{1/2}$ −0·48 V.



XII, *n* = 0
XIII, *n* = 1

Likewise in the case of 8-sulfones, the possibility of metabolic degradation of the piperazine ring according to the findings of Breyer and coworkers[17] (*cf.*[11,18]) was considered: a substitution reaction of 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] with ethylenediamine was used to prepare the diamine *XIV*, the dimethanesulfonate of which was oxidized in aqueous solution with an excess of hydrogen peroxide to the sulfoxide *XV*. 10-Formamido-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVI*) was prepared by Leuckart reaction of 8-methylsulfonyldibenzo[*b*,*f*]thiepin-10(11*H*)-one[3] (treatment with formamide and formic acid at 190−200°C) as an intermediate for further work.

Out of the compounds prepared, *IV*, *VII* and *X*–*XV* are potential metabolites of the neuroleptic agent oxyprothepin (*II*); until now none of them has been proven as a real metabolite[4-6]. Compounds *VII*, *XI*, *XIV* and *XV* are simultaneously potential metabolites of methiothepin (*I*) (ref.[1]) out of which *VII* and *XI* were really identified as metabolites[2]; this happened without the use of synthetic standards which were not available at that time.



XIV, R = $CH_2CH_2NH_2$, $n = 0$
XV, R = $CH_2CH_2NH_2$, $n = 1$
XVI, R = CHO, $n = 0$

Most of the compounds prepared were pharmacologically tested as potential neuroleptics on the one hand, and by methods of the general pharmacological screening on the other. They were tested in the form of salts (or bases) described in the Experimental. The basic data are summarized in Table I including methiothepin (*I*) and oxyprothepin (*II*) as standards for comparison. The acute toxicity was estimated in mice and the LD_{50} values are given. The rotating-rod test in mice was used to investigate the influence of the compounds on the motor coordination (used as one of the criteria of central depressant activity); the ED_{50} values given are medium effective doses eliciting ataxia at the time of maximum effect. Cataleptic activity was invesitgated in rats and the ED_{50} are medium effective doses eliciting catalepsy. The data in the Table show that only compound *IV* has a clear neuroleptic character; in comparison with oxyprothepin, it is less toxic but also significantly less active in both of the tests used. This compound was also tested for the antiapomorphine activity in rats but found practically inactive: a dose of 25 mg/kg did influence neither the apomorphine chewing, nor the agitation; a dose of 50 mg/kg *p.o.* inhibited only the agitation which corresponds to central depression. A preliminary report on the pharmacology of compounds *X*, *XI* and *XIII*–*XV* has been published[12].

The following further effects of the compounds prepared were found within the general screening programme: Antiamphetamine activity (doses in mg/kg protecting 100% mice from the lethal effect of a standard dose of amphetamine): *X*, 300 *p.o.*; *XIII*, 80 *i.v.* Anticonvulsant effect (a dose *p.o.* in mg/kg prolonging significantly the latency of clonic convulsions in mice elicited by pentetrazole): *XIII*, 100—300. Antihistamine activity (doses in mg/kg protecting 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly): *X*, <300 *p.o.*; *XI*, 0·1 *s.c.*; *XIII*, 0·25—1·0 *s.c.* Hypotensive effect (doses *i.v.* in mg/kg decreasing the blood pressure

of normotensive rats by 20% for at least 10 min): *XI*, 5; *XIII*, 80; *XIV*, 25. Adrenolytic effect (doses *i.v.* in mg/kg inhibiting the adrenaline pressor reaction in rats by 50%): *XI*, 0·01; *XIII*, 2·5; *XIV*, 0·5. Antiarrhythmic activity (a dose in mg/kg prolonging with statistical significance the latency of ventricular extrasystoles in rats elicited with aconitine): *XI*, 1—5. Positive inotropic and chronotropic effect (concentration in μg/ml exhibiting an increase of inotropy and frequency in the isolated rabbit atria by 25%): *XI*, 50.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). The microorganisms used, number of the compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *X* 100, *XIII* 100; *Pseudomonas aeruginosa*, *X* 100; *Mycobacterium tuberculosis* H37Rv, *IV* 50, *X* 100, *XIII* 100; *Saccharomyces pasterianus*, *IV* 50; *Trichophyton mentagrophytes*, *IV* 50, *X* 50, *XV* 50; *Aspergillus niger*, *XIV* 50.

TABLE I

Pharmacological Properties of 8-Methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin Derivatives and of the 8-Methylthio Standards (doses in mg/kg)

Compound[a]	Code number or name	Administration[b]	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
I (ref.[1])	methiothepin	*p.o.*	94[c]	1·9	10·5
I (ref.[1])	methiothepin	*i.v./i.p.*	51[c]	0·09	2·0
II (ref.[13])	oxyprothepin	*p.o.*	68[c]	4·6	3·3
II (ref.[13])	oxyprothepin	*i.v./i.p.*	28[c]	0·03	0·33
III (ref.[3])	VÚFB- 6·284	*i.v.*	47[c]	0·215	—
IV	VÚFB-12.337	*p.o./i.p.*	170[c]	21	7·4
X	VÚFB-12.370	*p.o.*	2 000[d]	>300	225
XI	VÚFB-12.356	*i.v./i.p.*	105[d]	15	>20
XII	VÚFB-12.357	*p.o.*	320[c]	43	>50[e]
XIII	VÚFB-12.373	*i.v./i.p.*	400[d]	>80	50
XIII	VÚFB-12.373	*p.o.*	—	—	150
XIV	VÚFB-12.501	*i.v./i.p.*	125[d]	>25	>25
XV	VÚFB-12.503	*i.v./i.p.*	55[d]	>10	>10

[a] The compounds were tested in the form of salts or bases described in the Experimental; the doses of compounds *I*—*IV* and *XII* were calculated for bases. [b] Intraperitoneal administration was used only in the test of catalepsy. [c] The toxicity was estimated in groups by 10 animals (mice) and the survival was followed for a period of 7 days. [d] Acute toxicity (mice) was determined in groups by 5 animals; the survival was followed for the *i.v.* administered compounds for 3 days and for the orally administered ones for 5 days. [e] The dose given brought about catalepsy in 10% rats.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 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 KBr unless stated otherwise) with a Unicam SP 200G spectrophotometer and the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 HMz) spectrometer. The homogeneity of the compounds and composition of the reaction mixtures was checked by chromatography on thin layers of silica gel (Silufol).

10-[4-(3-Hydroxypropyl)piperazino]-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IV*)

A mixture of 32·0 g 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], 56 g 1-(3-hydroxypropyl)piperazine[14] and 40 ml chloroform was stirred and refluxed for 14 h. It was then diluted with 300 ml chloroform and washed with water. The base was extracted from the chloroform solution into 500 ml 2M-H_2SO_4, the acid aqueous solution was filtered with charcoal, the filtrate made alkaline with NH_4OH and the base extracted with chloroform. The extract was dried with K_2CO_3 and evaporated; 37·9 g (88%), m.p. 90—100°C. Analytical sample, m.p. 115—117°C (benzene–cyclohexane). IR spectrum (Nujol): 762, 821, 900 (4 and 2 adjacent and solitary Ar—H), 1052 (CH_2OH), 1146, 1309 (SO_2), 1552, 1582 (Ar), 3220 cm^{-1} (OH). For $C_{22}H_{28}N_2O_3S_2$ (432·6) calculated: 61·08% C, 6·52% H, 6·48% N, 14·82% S; found: 61·31% C, 6·59% H, 6·33% N, 14·61% S.

Dimethanesulfonate monohydrate, m.p. 135—138°C (95% ethanol–ether). For $C_{24}H_{36}N_2O_9S_4 + H_2O$ (642·8) calculated: 44·84% C, 5·95% H, 4·35% N, 19·95% S; found: 45·07% C, 5·74% H, 4·31% N, 20·15% S.

Evaporation of the chloroform solution after the extraction with dilute H_2SO_4 gave 3·6 g (12%) 2-methylsulfonyldibenzo[*b*,*f*]thiepin (*VIII*), m.p. 135—138°C. Our group[3] reported earlier for the pure substance a m.p. of 138—140°C.

10-[4-(2-Hydroxyethyl)piperazino]-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*V*)

A mixture of 6·5 g 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], 13 g 1-(2-hydroxyethyl)piperazine and 10 ml chloroform was refluxed for 8 h and processed similarly like in the precesing case; 6·8 g (81%) base, m.p. 70—74°C. Analytical sample, m.p. 77—78°C (benzene–light petroleum); the compound is a solvate with 1 molecule of benzene. IR spectrum (Nujol): 687 (C_6H_6), 750, 768, 830, 883 (4 and 2 adjacent and solitary Ar—H), 1050 (CH_2OH), 1146, 1309 (SO_2), 1520, 1557, 1582 (Ar), 3190 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 8·28 (s, 1 H, 9-H), 7·50 (s, 2 H, 6,7-H_2), 6·90—7·50 (m, 4 H, remaining Ar—H), 7·23 (s, 6 H, C_6H_6), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·52 (t, 2 H, CH_2O), 2·92 (s, 3 H, SO_2CH_3), 2·70 (s, 1 H, OH), c. 2·50 (m, 10 H, 5 NCH_2). For $C_{21}H_{26}N_2O_3S_2 + C_6H_6$ (496·7) calculated: 65·28% C, 6·49% H, 5·64% N, 12·92% S; found: 65·03% C, 6·63% H, 5·58% N, 13·10% S.

Bis(hydrogen oxalate), m.p. 128—130°C (ethanol–ether). For $C_{25}H_{30}N_2O_{11}S_2$ (598·7) calculated: 50·15% C, 5·05% H, 4·68% N, 10·71% S; found: 50·48% C, 5·62% H, 4·27% N, 10·27% S.

10-(4-Ethoxycarbonylpiperazino)-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VI*)

A mixture of 32·5 g 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], 40 g 1-(ethoxycarbonyl)piperazine and 40 ml chloroform was refluxed for 5 h. Similar processing like in the

preceding cases gave 31·3 g (70%) crude base which crystallized from a mixture of benzene and light petroleum, m.p. 133—140°C. Analytical sample, m.p. 136·5—137·5°C (benzene–light petroleum). IR spectrum (Nujol): 760, 769, 812, 826, 879 (4 and 2 adjacent and solitary Ar—H), 1 143, 1 302 (SO_2), 1 248, 1 713 (NCOOR), 1 486, 1 557, 1 581 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·30 (s, 1 H, 9-H), 7·55 (s, 2 H, 6,7-H_2), 7·00—7·50 (m, 4 H, remaining Ar—H), 4·10 (q, J = = 7·0 Hz, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·55 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·98 (s, 3 H, SO_2CH_3), 1·21 (t, J = 7·0 Hz, 3 H, CH_3 in ethyl). For $C_{22}H_{26}N_2O_4S_2$ (446·6) calculated: 59·16% C, 5·87% H, 6·27% N, 14·36% S; found: 59·34% C, 6·00% H, 6·29% N, 14·10% S.

Hydrogen maleate, m.p. 168—170°C (ethanol–ether). For $C_{26}H_{30}N_2O_8S_2$ (562·7) calculated: 55·50% C, 5·37% H, 4·98% N, 11·40% S; found: 55·76% C, 5·62% H, 4·88% N, 11·34% S.

Hydrochloride hemihydrate, m.p. 214—215°C (95% ethanol–chloroform). For $C_{22}H_{27}ClN_2 . O_4S_2 + 0{\cdot}5\ H_2O$ (492·1) calculated: 53·70% C, 5·74% H, 7·20% Cl, 5·69% N, 13·03% S; found: 53·29% C, 5·62% H, 7·08% Cl, 5·54% N, 12·72% S.

8-Methylsulfonyl-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VII*)

A mixture of 19·2 g *VI*, 20 ml ethanol and 18 g KOH was stirred and refluxed for 4 h. After cooling, it was diluted with 100 ml water and the base extracted with ether. Evaporation of the extract gave 11·8 g (73%) crude base. Crystallization from a mixture of benzene and cyclohexane gave a pure substance, m.p. 158—161°C. ^{1}H-NMR spectrum: δ 8·30 (bs, 1 H, 9-H), 7·00—7·70 (m, 6 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·95 (s, 3 H, SO_2CH_3), 2·78 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·55 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·78 (bs, 1 H, NH). For $C_{19}H_{22}N_2O_2S_2$ (374·5) calculated: 60·93% C, 5·92% H, 7·48% N, 17·12% S; found: 60·96% C, 5·81% H, 7·22% N, 17·19% S.

Dimethanesulfonate monohydrate, m.p. 211—212·5°C (95% ethanol–ether). For $C_{21}H_{30} . N_2O_8S_4 + H_2O$ (584·8) calculated: 43·13% C, 5·51% H, 4·79% N, 21·94% S; found: 43·07% C, 5·28% H, 4·83% N, 21·62% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin S^5-Oxide (*X*)

IV (8·6 g) was dissolved in a solution of 1·92 g methanesulfonic acid in 40 ml water, 50 ml 30% H_2O_2 were added and the mixture allowed to stand for 40 h at room temperature. The precipitated solid was filtered and identified to be 2-methylsulfonyldibenzo[*b*,*f*]thiepin S^5-oxide (*IX*), 1·85 g (31%), m.p. 182—186°C. Analytical sample, m.p. 188—189°C (benzene). It is reduced polarographically in 0·5M-HCl at $E_{1/2}$ —0·80 V (against a saturated calomel electrode). UV spectrum: λ_{max} 251 nm infl. (log ε 4·30), 284 nm (3·82). IR spectrum: 756, 794, 828, 883 (4 and 2 adjacent and solitary Ar—H), 1 046 (S—O), 1 139, 1 304 (SO_2), 1 555, 1 585, 3 015, 3 080 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·00—8·20 (m, 9 H, Ar—H) and CH=CH), 3·04 (s, 3 H, SO_2CH_3). For $C_{15}H_{12}N_3S_2$ (304·4) calculated: 59·18% C, 3·98% H, 21·07% S; found: 59·24% C, 4·05% H, 20·86% S.

The aqueous filtrate was made alkaline with NH_4OH, the product extracted with chloroform, the extract was dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in a hot 1 : 1 mixture of benzene and acetone and the product crystallized on standing; 5·1 g (57%) crude *X*, m.p. 178—185°C. Analytical sample, m.p. 189—191°C (benzene–acetone), probably still a mixture of two racemates. The compound is reduced polarographically in 0·5M-

-HCl at $E_{1/2}$ —0·545 V which indicates the presence of S—O group. UV spectrum: λ_{max} 235 nm (log ε 4·19), infl. 270 nm (3·58). IR spectrum: 768, 832, 862 (4 and 2 adjacent and solitary Ar—H), 1050, 1072 (S—O and CH_2OH), 1144, 1320, (SO_2), 1570, 3013, 3065, 3090 (Ar), 2790, 2820 (NCH_2), 3440 cm^{-1} (OH). For $C_{22}H_{28}N_2O_4S_2$ (448·6) calculated: 58·90% C, 6·29% H, 6·24% N, 14·30% S; found: 58·66% C, 6·35% H, 5·95% N, 14·16% S.

Oxalate, m.p. 174—176°C (ethanol). For $C_{24}H_{30}N_2O_8S_2$ (538·6) calculated: 53·51% C, 5·61% H, 5·20% N, 11·91% S; found: 52·98% C, 5·86% H, 5·04% N, 11·57% S.

8-Methylsulfonyl-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin S^5-Oxide (*XI*)

A solution of 5·8 g *VII*-dimethanesulfonate monohydrate in 45 ml acetic acid was treated at 25°C with 1·75 ml 29% H_2O_2 and the mixture allowed to stand for 48 h at room temperature. It was then diluted with 250 ml water, made alkaline with NH_4OH and extracted with chloroform. Processing of the extract and crystallization of the crude product from a mixture of benzene, cyclohexane and ethanol gave 3·9 g (100%) *XI*. The analytical sample of m.p. 201—203°C represents probably one homogeneous racemate. It is reduced polarographically in 0·5M-HCl at $E_{1/2}$ —0·50 V (presence of S—O). IR spectrum: 768, 839, 858 (4 and 2 adjacent and solitary Ar—H), 1035 (S—O), 1143, 1310 (SO_2), 3015, 3050, 3070 (Ar), 3310 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 8·50 (s, 1 H, 9-H), 7·70—8·00 (m, 3 H, 4,6,7-H_3), *c.* 7·25 (m, 3 H, 1,2,3-H_3), 4·30 (m, 1 H, Ar—CH—N), 3·20—3·80 (m, 2 H, $ArCH_2$), 3·05 (s, 3 H, SO_2CH_3), 3·00 (bs, 4 H, $CH_2N^4CH_2$ of piperazine), 2·65 (bs, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (bs, 1 H, NH). For $C_{19}H_{22}N_2O_3S_2$ (390·5) calculated: 58·43% C, 5·68% H, 7·19% N, 16·42% S; found: 58·06% C, 5·65% H, 6·62% N, 16·05% S.

Dimenthanesulfonate hemihydrate, m.p. 157—158°C (95% ethanol–ether). For $C_{21}H_{30}N_2O_9S_4 + 0{\cdot}5\ H_2O$ (591·7) calculated: 42·62% C, 5·28% H, 4·73% N, 21·67% S; found: 42·73% C, 5·31% H, 4·55% N, 20·90% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin N^4-Oxide (*XII*)

A solution of 4·3 g *IV* in 25 ml 95% ethanol was stirred and treated dropwise with 4·75 ml 28% H_2O_2 at room temperature and the mixture was allowed to stand for 48 h. It was filtered with charcoal, the filtrate evaporated partly *in vacuo* (30°C), the residue diluted with 100 ml water and extracted with chloroform. The extract was dried with K_2CO_3 and evaporated; 4·0 g (89%), m.p. 165—168°C. Analytical sample, m.p. 165·5—167·5°C (benzene–acetone). It is reduced polarographically in 0·5M-HCl at $E_{1/2}$ —0·49 V (presence of N—O). UV spectrum: λ_{max} 227 nm (log ε 4·11), 288 nm (4·00). IR spectrum: 760, 818, 900 (4 and 2 adjacent and solitary Ar—H), 955 (N—O), 1052, 1060 (CH_2OH), 1145, 1315 (SO_2), 1555, 1572, 3000, 3068 (Ar), 3435 cm^{-1} (OH). For $C_{22}H_{28}N_2O_4S_2$ (448·6) calculated: 58·90% C, 6·29% H, 6·24% N, 14·30% S; found: 58·44% C, 6·38% H, 6·06% N, 13·88% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-methylsulfonyl-10,11-dihydrodibenzo[*b*,*f*]thiepin N^4,S^5-Dioxide (*XIII*)

A solution of 4·48 g *X* in 100 ml ethanol was treated with 20 ml 29% H_2O_2, the mixture was heated for a short time to 75°C and allowed to stand for 48 h at room temperature. It was then processed similarly like in the preceding case and yielded 3·9 g (84%) crude base, m.p. 185—190°C. The analytical sample, corresponding to a hemihydrate, melted at 192—193°C (acetone–methanol) and represented probably a mixture of two racemates. It is reduced polarographically in 0·5M-HCl

in a single and long wave of $E_{1/2}$ —0·48 V (N—O and S—O). IR spectrum: 768, 840, 858 (4 and 2 adjacent and solitary Ar—H), 968 (N—O), 1032, 1062, 1073 (S—O and CH_2OH), 1140, 1310 (SO_2), 3200 (OH...N), 3440 cm^{-1} (OH, H_2O). For $C_{22}H_{28}N_2O_5S_2 + 0{\cdot}5\ H_2O$ (473·6) calculated: 55·79% C, 6·17% H, 5·91% N, 13·54% S; found: 56·32% C, 6·17% H, 5·68% N, 13·38% S.

10-(2-Aminoethylamino)-8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XIV*)

A mixture of 9·75 g 10-chloro-8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin[3] and 27 g ethylenediamine was stirred and heated under reflux for 6 h to 105—110°C. It was then diluted with 100 ml chloroform and washed with water. The base was extracted from the chloroform solution into 200 ml 2M-H_2SO_4, the aqueous solution filtered with charcoal and the filtrate made alkaline with NH_4OH. The base was extracted with chloroform, the extract was dried with K_2CO_3 and evaporated under reduced pressure; 6·9 g (66%) oil. Neutralization with 5·0 g maleic acid in 80 ml ethanol yielded 8·8 g salt of m.p. 102—104°C. Analytical sample, m.p. 107—109°C (ethanol–ether), corresponds analytically to sesquimaleate. For $C_{23}H_{26}N_2O_8S_2$ (522·6) calculated: 52·86% C, 5·01% H, 5·36% N, 12·27% S; found: 53·20% C, 4·81% H, 5·03% N, 11·52% S.

Dipicrate, m.p. 238—240°C with decomposition (dimethylformamide–ethanol–water). For $C_{29}H_{26}N_8O_{16}S_2$ (806·7) calculated: 43·18% C, 3·24% H, 13·89% N, 7·95% S; found: 43·31% C, 3·39% H, 14·14% N, 8·13% S.

10-(2-Aminoethylamino)-8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin S^5-Oxide (*XV*)

XIV (5·8 g, released from the maleate) was dissolved in a solution of 3·2 g methanesulfonic acid in 100 ml H_2O, the solution was filtered with charcoal, the filtrate treated with 80 ml 29% H_2O_2 and the mixture allowed to stand for 5 days at room temperature. It was then made alkaline with NH_4OH and the product extracted with chloroform. Processing of the extract gave 2·7 g (45%) oily base *XV*. Neutralization with maleic acid in ethanol gave the sesquimaleate, m.p. 126—129°C (aqueous ethanol). For $C_{25}H_{32}N_2O_{10}S_2$ (584·7) calculated: 51·35% C, 5·52% H, 4·79% N; found: 51·26% C, 5·39% H, 4·56% N.

Dipicrate, m.p. 213·5—214·5°C (dimethylformamide–ethanol–acetone). For $C_{29}H_{26}N_8O_{17}S_2$ (822·7) calculated: 42·33% C, 3·19% H, 13·62% N, 7·79% S; found: 42·87% C, 3·16% H, 13·40% N, 8·02% S.

10-Formamido-8-methylsulfonyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XVI*)

A mixture of 12·2 g 8-methylsulfonyldibenzo[*b,f*]thiepin-10(11*H*)-one[3], 75 ml formamide and 8 ml formic acid was slowly heated to 190—200°C and maintained at that temperature for 24 h. After cooling to 100°C it was diluted with 200 ml water, and the solid was filtered after cooling. It was extracted with a boiling mixture of 150 ml ethanol and 45 ml dimethylformamide; the insoluble solid was removed by filtration. The filtrate was evaporated *in vacuo* and the residue diluted with aqueous ethanol; 8·8 g (66%), m.p. 190—206°C. Analytical sample, m.p. 216 to 218°C (ethanol–dimethylformamide). IR spectrum (Nujol): 750, 762, 830, 899 (4 and 2 adjacent and solitary Ar—H), 1149, 1261 (SO_2), 1480, 1599, 3015, 3060 (Ar), 1540, 1652 (NHCHO), 3290 cm^{-1} (NH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·55 (bd, 1 H, NH), 7·00—8·00 (m, 8 H, Ar-H and CHO), 5·60 (m, 1 H, Ar—CH—N), 3·35 (m, 2 H, $ArCH_2$), 3·10 (s, 3 H, SO_2CH_3). For $C_{16}H_{15}NO_3S_2$ (333·4) calculated: 57·63% C, 4·53% H, 4·20% N, 19·23% S; found: 58·14% C, 4·54% H, 4·09% N, 19·04% S.

The authors are indebted to Dr J. Holubek (department of physical chemistry of this Institute) for recording and interpreting the ^{1}H-NMR *spectra, to Mrs M. Vlková for technical assistance with the synthesis of intermediates, and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech, Mrs J. Kropáčová and Mrs Z. Volková (department of analytical chemistry of this Institute) for carrying out the analyses.*

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Translated by author (M. P.).