NEUROLEPTICS OF THE 8-METHYLTHIO-10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN SERIES: NEW COMPOUNDS AND NEW PROCEDURES*

Jiří JÍLEK, Josef POMYKÁČEK, Antonín DLABAČ, Marie BARTOŠOVÁ**
and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

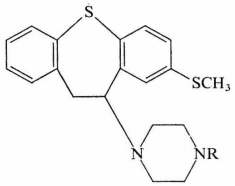
Received May 23th, 1979

Heating of 8-methylthiodibenzo[*b,f*]thiepin-10(11*H*)-one with mono-*p*-toluenesulfonates of 1-methylpiperazine and piperazine *in vacuo* led in good yields to the enamines *IX*—*XI*, the first of which was reduced with zinc and acetic acid to the base *I* (methiothepin). The ester *III* (oxyprothepin decanoate) was obtained by reaction of the amino alcohol *II* (oxyprothepin) with decanoic acid in the presence of N,N'-carbonyldiimidazole and by substitution of 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin with 1-(3-decanoyloxypropyl)piperazine. The substitution reaction of the same chloro compound with piperazine gave two stereoisomeric 1,4-disubstituted piperazines *V*. Reaction of the amino alcohol *II* with octyl isocyanate afforded the carbamate *VI*, an isoster of oxyprothepin decanoate (*III*). This substance showed in the test of antiapomorphine activity in dogs the properties of a long-acting antiemetic. Two new potential metabolites (*XII*, *XIII*) of compounds *I*—*III* were synthesized and new pharmacological data are given for two further potential metabolites (*XIV*, *XV*) of oxyprothepin (*II*).

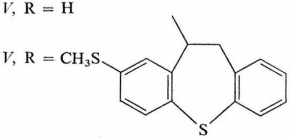
The sub-group of neuroleptics of the 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin series, represented by methiothepin (*I*), oxyprothepin (*II*) and oxyprothepin decanoate (*III*), continues to attract the interest of psychopharmacologists and psychiatrists. Whereas *I* (ref.[1]) is an experimental agent used mainly in neuropharmacological investigations, *II* as an oral agent (in the form of methanesulfonate) proved very successful in the treatment of schizophrenic psychoses[2–4], manic syndrome[5,6] and endogenic depression[7]. *III* is a depot neuroleptic agent, the usefulness of which in the maintenance therapy of schizophrenic patients was reported in a preliminary manner[8,9]. Likewise the chemical knowledge of these compounds and of some related substances is increasing and a report on the synthesis of some new compounds and on some new synthetic procedures forms the object of the present communication.

* Part CXXXVIII in the series Neurotropic and Psychotropic Agents; Part CXXXVII: This Journal *44*, 491 (1979).

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

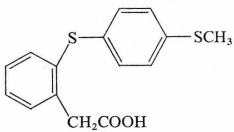


I, R = CH_3
II, R = $(CH_2)_3OH$
III, R = $(CH_2)_3OCO(CH_2)_8CH_3$
IV, R = H

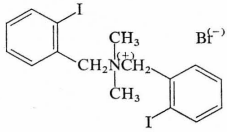


VI, R = $(CH_2)_3OCONH(CH_2)_7CH_3$

The syntheses of compounds *I*–*III* proceed *via* 8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*)-one[10] which is obtained by cyclization of [2-(4-methylthiophenylthio)phenyl]acetic acid (*VII*). Until now, this acid has been prepared only by the reaction of 2-iodobenzoic acid with 4-(methylthio)thiophenol and by the following four-step homologation sequence[10]. Now, it has also been prepared by a reaction of (2-iodophenyl)acetic acid[11] with 4-(methylthio)thiophenol[12] in a boiling aqueous potassium hydroxide solution in the presence of copper. (2-Iodophenyl)acetonitrile, the synthetic precursor of (2-iodophenyl)acetic acid[11], was obtained in a yield of 80% by reaction of 2-iodobenzyl bromide[11] with sodium cyanide in dimethylformamide at 100°C. This reaction gave in a yield of 8·5% a crystalline by-product, corresponding on the basis of analysis to the composition of $C_{16}H_{18}BrI_2N$. Its mass spectrum appears like one of a mixture of three compounds $C_{15}H_{15}I_2N$, $C_9H_{12}IN$ and C_7H_6BrI. The product, however, is a homogeneous one and the mixture found could only be formed by its thermic degradation. It has the character of a quaternary ammonium bromide and evidently the structure *VIII*; the products of the thermic cleavage are then N,N-bis(2-iodobenzyl)methylamine, N-(2-iodobenzyl)dimethylamine and 2-iodobenzyl bromide. Dimethylformamide, used as the reaction medium, is the only possible source of the dimethylamino group present in compound *VIII*; it is thus necessary to consider its participation in similar reactions in every case.

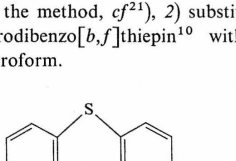


VII



VIII

The preparation of 8-methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo-[*b*,*f*]thiepin (*I*) was described on the one hand by a substitution reaction of 10-chloro--8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin with 1-methylpiperazine[10,12], on the other by reduction of the enamine *IX* (ref.[13]) with diborane, generated from sodium borohydride and acetic acid in tetrahydrofuran[14]. Enamine *IX* has now been obtained by a new method consisting in heating 8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*) -one[10] with 1-methylpiperazine mono-*p*-toluenesulfonate *in vacuo* to 180–190°C (for analogy, *cf.*[15]). A similar reaction with piperazine mono-*p*-toluenesulfonate gave new enamines *X* and *XI*; the excess of the piperazine salt used determined the course of the reaction. The enamine *IX* afforded by reduction with zinc in acetic acid 82% of the base *I* (for analogy, *cf.*[16]). The Experimental presents the preparation of several new salts of the base *II* (ref.[17–19]). Until now, the ester *III* has been prepared on the one hand by reaction of the alcohol *II* with decanoyl chloride[18] (the reaction accompanied by an important side reaction[20]), and by azeotropic esterification[20] of the alcohol *II* with decanoic acid in xylene on the ether. Two new procedures for preparing this ester are being described now: *1*) esterification of the alcohol *II* with decanoic acid in dichloromethane in the presence of N,N'-carbonyldiimidazole (for the method, *cf*[21]), *2*) substitution reaction of 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[10] with 1-(3-decanoyloxypropyl)piperazine[20] in boiling chloroform.

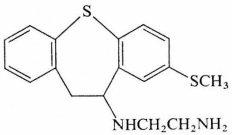


IX, R = CH_3
X, R = H
XI, R = CH_3S

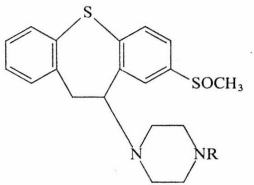
The secondary amine *IV* (ref.[12,17,22]) was previously prepared in the form of the almost insoluble maleate which probably caused an unexpected result of the pharmacological testing[17]. For enabling the testing under more favourable conditions, the soluble methanesulfonate has now been prepared. A substitution reaction of 10--chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[10] with anhydrous piperazine in boiling chloroform gave a mixture of almost equal amounts of two stereoisomeric bases *V*. Whereas the lower melting and benzene-soluble isomer exhibits in the mass spectrum the expected molecular ion corresponding to the formula $C_{34}H_{34}N_2S_4$, the higher melting and benzene-insoluble isomer appears to be unstable under elevated temperatures and the mass spectrum indicated as the molecular ion a species $C_{19}H_{22}N_2S_2$, corresponding to the amine *IV*; the base peak of *m*/*e* 256 corresponds

to the radical cation of 2-methylthiodibenzo[*b*,*f*]thiepin. In this connection it is necessary to mention the mass spectrum of methiothepin (*I*), ref.[23]. Our lower melting isomer seems to be identical (TLC comparison) with an impurity which was separated by column chromatography from one batch of oxyprothepin (*II*), prepared by the substitution reaction of 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin with 1-(3-hydroxypropyl)piperazine[17]. The presence of this impurity is easily to be explicated by the presence of piperazine in the used 1-(3-hydroxypropyl)piperazine which was obtained by a reaction of piperazine with 3-chloropropanol[24].

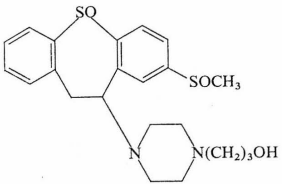
Ho and coworkers[25] prepared fluphenazine adamantylcarbamate which was investigated for its acute neuroleptic activity and for the potential antiparkinsonic activity. We were interested in the substitution of the α-methylene group of the decanoyl residue in the molecule of oxyprothepin decanoate (*III*) with an NH group especially from the standpoint of having the opportunity to study the properties of the compound as a depot neuroleptic. For this reason, oxyprothepin octylcarbamate (*VI*), an isoster of the ester *III*, has been prepared by a reaction of the base *II* with octyl isocyanate[26,27] in boiling toluene.



XII



XIII, R = H
XIV, R = $(CH_2)_3OH$



XV

Metabolic studies with oxyprothepin in rats and humans[28-30] required the synthesis of further compounds as standards for comparison. In the first line, the diamine *XII* was prepared by a substitution reaction of 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[10] with ethylenediamine; the product *XII* is to be considered a potential metabolite of substances *I*—*III* on the basis of investigations of Breyer and coworkers[31] on the metabolism of phenothiazine series neuroleptics with piperazine side chains[32]. Selective oxidation of the methanesulfonate of the secondary amine *IV* with a solution of potassium bromate and bromide in the presence of hydrochloric acid at room temperature[33] afforded the monosulfoxide *XIII*. The oxidation is accompanied by the introduction of a second centre of chirality and only repeated crystallization resulted in one homogeneous racemate.

Out of the compounds prepared, the following ones were pharmacologically tested: *III* [bis-(hydrogen maleate), VÚFB-12·452], *IV* (methanesulfonate, VÚFB-12·343), *VI* (VÚFB-12·497), *XII* [bis(hydrogen maleate), VÚFB-12·316], *XIII* (methanesulfonate, VÚFB-12·342), *XIV* (dihydrochloride, VÚFB-9472), *XV* (VÚFB-12·368). The data are summarized in Table I (acute toxicity in mice, incoordinating activity in the rota-rod test in mice, cataleptic activity in rats); with compounds *IV*, *XIII* and *XIV*, the data given were calculated for bases. The Table includes as standards methiothepin (*I*) (ref.[1]) and oxyprothepin (*II*) (ref.[17,18,34]).

Pharmacology and biochemical pharmacology of oxyprothepin decanoate (*III*) as an intramuscularly administered depot neuroleptic (a solution of the base in the sunflower oil or in miglyol) in rats and dogs was reported in a preliminary manner[35-39]. The effects of the orally administered maleate of this agent have been investigated now. The Table I shows that in this form, the agent appears as little toxic and centrally weakly active (results of the acute study). It shows, however, a series of further neurotropic and different activities: in doses of 10—50 mg/kg analgesia in the Haffner test in 50% mice; in doses of 25—50 mg/kg increase of the blood sugar level in rats by 20%; doses of 50—100 mg/kg prolong significantly the latency of clonic convulsion in mice elicited by pentetrazole; doses of 50—100 mg/kg antagonize with statistical significance the development of oedema of the rat paw after a subplantarly administered kaolin suspension (antiinflammatory effect); doses of 50—100 mg/kg bring about a decrease of the rectal temperature of rats by 1°C; a dose of 5 mg/kg protects 50% guinea-pigs from the lethal action of 5 mg/kg histamine, given intrajugularly; doses of 10—50 mg/kg prolong the duration of the thiopental sleeping time in mice to 200% of the control value; doses of 10—50 mg/kg prolong with statistical significance the latency of ventricular extrasystoles in rats elicited with aconitine (antiarrhythmic effect); doses of 10—25 mg/kg inhibit significantly the motility of mice in known, as well as unknown surroundings (central depressant effect); doses of 5—10 mg/kg protect 50% mice from the lethal effect of a standard dose of amphetamine.

Desmethyl-methiothepin (*IV*) was previously tested in the form of maleate[17] which was practically insoluble in water; this fact was probably the reason of a negative finding in the rota-rod test. Repeating of the test with the more soluble methanesulfonate (*cf.* Table I) showed a mild incoordinating activity on oral administration and a relatively high cataleptic activity on intraperitoneal administration (the cataleptic activity on oral administration is low).

Oxyprothepin octylcarbamate (*VI*) was tested as a potential depot neuroleptic for the anti-apomorphine activity in dogs and rats, and was administered intramuscularly in the form of a 2·5% solution of the base in miglyol. In the test of apomorphine emesis in dogs, the compound was administered in a single dose of 5 mg/kg *i.m.* Though a 100% blockade of emesis was not attained in the first interval after the administration, *i.e.* after 7 days, the blockade of emesis lasted

in a part of the animals longer than for 4 weeks and with 1 dog (out of the group of 6 animals), it lasted even longer than for 6 weeks. On the other hand, a dose of 25 mg/kg *i.m.* in rats did not show any inhibiting action against the apomorphine stereotypies when evaluated after 24 and 48 hours.

The ethylenediamine derivative *XII* brings about central effects only after high doses in the orientation test of toxicity in mice: inhibition of activity, ataxia, convulsions. In a dose of 15 mg/kg *i.v.* it is already free of the central effects. At this dose, it decreases the blood pressure of normotensive rats by 20% for at least 10 minutes and in a dose of 1 mg/kg *i.v.* it inhibits the adrenaline pressor reaction in rats by 50%. It has a musculotropic spasmolytic action *in vitro*: a concentration of 10 μg/ml brings about a reduction of barium chloride contractions of the isolated rat duodenum by 50% (near to the papaverine activity). In a dose of 5—15 mg/kg *i.v.* it has antiarrhythmic activity towards aconitine in rats.

Desmethylmethiothepin 8-sulfoxide (*XIII*) is rather highly toxic on the *i.v.* administration, is midly central depressant and cataleptic only in toxic doses. Oxyprothepin 8-sulfoxide (*XIV*) was previously tested on parenteral administration[33] and showed a surprissingly high acute toxicity. For this reason, the toxicity has now been determined on oral administration and was

TABLE I

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

Compound[a]	Administration[b]	Acute toxicity LD_{50}	Rotating rod ED_{50}[e]	Catalepsy ED_{50}[f]
I (ref.[1])	*p.o.*	94[c]	1·9	10·5
I (ref.[1])	*i.v./i.p.*	51[c]	0·09	2·0
II (ref.[18])	*p.o.*	68[c]	4·6	3·3
II (ref.[18])	*i.v./i.p.*	28[c]	0·03	0·33
III	*p.o.*	675[d]	30	30
IV	*p.o.*	94[c]	—	40
IV	*i.v./i.p.*	—	13·4	3
XII	*i.v.*	75[d]	>15	—
XIII	*i.v./i.p.*	21[c]	7·0	>20 (30%)
XIV (ref.[33])	*p.o.*	160[c]	—	—
XV (ref.[33])	*p.o.*	380[c]	68	>50 (10%)

[a] The compounds were tested in the form of salts described in the Experimental. [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] Orientation acute toxicity was determined in mice, 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] Medium effective dose eliciting ataxia in mice at the time of maximum effect. [f] Medium effective dose eliciting catalepsy in rats; in cases when the ED_{50} could not be attained, per cent of cataleptic animals corresponding to the dose used are given.

found to be lower than that of oxyprothepin (Table I). It is a further case of discrepancy between toxicities of sulfoxides of this series on intravenous and oral administration (for clorothepin S-oxide, *cf.*[40]).

Oxyprothepin 5,8-disulfoxide (*XV*) was prepared previously[33] but pharmacological data were not published. The Table I shows that it is little toxic and almost inactive in the tests of ataxia and catalepsy. The following data relate exclusively to oral administration: doses of 25—50 mg/kg have a similar hyperglycaemic effect like with compound *III*; hypothermic effect in rats after doses of 100—150 mg/kg; antihistamine effect in guinea-pigs after a dose of 150 mg/kg; potentiation of the thiopental sleeping time in mice after doses of 50—100 mg/kg; inhibition of motility of mice in known as well as unknown surroundings after 25—150 mg/kg; a dose of 150 mg/kg protects 100% mice from the lethal action of amphetamine. There was a preliminary report[41] on the pharmacology of this compound.

Some of the compounds prepared were also tested (in the form of the salts described in the Experimental) for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). Tested microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *IV* 6·25, *XII* 50, *XV* 100; *Streptococcus faecalis*, *IV* 25, *XII* 50; *Staphylococcus pyogenes aureus*, *IV* 12·5, *XII* 50; *Pseudomonas aeruginosa*, *XV* 100; *Escherichia coli*, *IV* 100, *XII* 100; *Mycobacterium tuberculosis* H37Rv, *III* 25, *IV* 3·12, *XII* 25, *XV* 100; *Saccharomyces pasterianus*, *IV* 25; *Trichophyton mentagrophytes*, *III* 50, *IV* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined 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, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$) 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 chromatography on thin layers of alumina or silica gel (Silufol). For column chromatography, neutral Al_2O_3 (activity II) was used.

N,N-Bis(2-iodobenzyl)dimethylammonium Bromide (*VIII*)

A mixture of 2·71 kg 2-iodobenzyl bromide[11], 4·5 l dimethylformamide and 0·76 kg NaCN was processed like in our previous work[11]. The benzene extract deposited on standing overnight 215 g (8·5%) solid, m.p. 109—113°C. The filtrate yielded by distillation 1·75 kg (79%) of (2-iodophenyl)acetonitrile, b.p. 125—130°C/330 Pa. The solid was crystallized from ethanol for analysis; m.p. 111—113°C. Mass spectrum, *m/e* (corresponding to): 463 (M^+, $C_{15}H_{15}I_2N$), 261 (M^+, $C_9H_{12}IN$), 297 (M^+, C_7H_6BrI). UV spectrum: λ_{max} 268·5 nm infl. (log ε 3·25), 275 nm (3·33), 282 nm (3·30). IR spectrum: 757, 771 (4 adjacent Ar—H), 1569, 1590, 1621, 3010, 3035 cm^{-1} (Ar). For $C_{16}H_{18}BrI_2N$ (558·1) calculated: 34·43% C, 3·25% H, 14·32% Br, 45·49% I, 2·51% N; found: 34·38% C, 3·29% H, 14·76% Br, 45·51% I, 2·48% N.

[2-(4-Methylthiophenylthio)phenyl]acetic Acid (*VII*)

4-(Methylthio)thiophenol[12] (156 g) was dissolved in a solution of 224 g KOH in 3 l water, 262 g (2-iodophenyl)acetic acid[11] and 10 g Cu catalyst were added and the mixture was stirred and refluxed for 18 h. After cooling, it was filtered and the filtrate acidified under stirring with 1 : 1

dilute hydrochloric acid. After standing overnight, the product was filtered, washed with water and dried *in vacuo*; 280 g (96%) crude acid *VII*, m.p. 70–80°C, containing some starting (2-iodophenyl)acetic acid. For further work, the product was used in this form. Recrystallization of a sample from a mixture of benzene and light petroleum gave a substance melting at 117–119°C, identical with the product obtained by hydrolysis of the nitrile[10].

8-Methylthio-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*IX*)

A mixture of 10·9 g 8-methylthiodibenzo[*b,f*]thiepin-10(11*H*)-one[10], 12·0 g 1-methylpiperazine and 20·6 g 4-toluenesulfonic acid was heated in a bath of 180–190°C for 1 h at atmospheric pressure and for 3 h *in vacuo*. After cooling, the melt was diluted with 150 ml 1 : 3 dilute NH_4OH and the mixture was extracted with benzene. The extract was washed with dilute NH_4OH, dried and evaporated. The residue (14·3 g mixture of the starting ketone and the product) was dissolved in benzene and chromatographed on a column of 250 g Al_2O_3. Elution with benzene gave first 2·5 g of the starting ketone, m.p. 83–88°C. This was followed by 8·5 g (78% per conversion) enamine *IX*, m.p. 152–154°C (benzene). The product is identical with a compound obtained using the $TiCl_4$ procedure (m.p. 152–154°C) (ref.[13]).

8-Methylthio-10-piperazinodibenzo[*b,f*]thiepin (*X*)

A mixture of 1·35 g 8-methylthiodibenzo[*b,f*]thiepin-10(11*H*)-one[10], 14·5 g piperazine hexahydrate and 13·0 g 4-toluenesulfonic acid was heated for 2 h to 170–180°C and then for 2 h *in vacuo* to 190°C. The cooled melt was diluted with 70 ml 1 : 1 dilute NH_4OH and extracted with benzene. The undissolved solid was filtered off; 0·25 g (17%) crude *XI*, m.p. 305°C (*cf.* the following experiment). The benzene extract was evaporated under reduced pressure and the residue crystallized from 5 ml ethanol; 0·75 g (42%) *X* solvated with 0·5 C_2H_5OH, m.p. 78–82°C. UV spectrum: λ_{max} 275 nm ($\log \varepsilon$ 4·38), 311 nm (3·96). IR spectrum: 752, 809, 825, 871, 884 (4 and 2 adjacent and solitary Ar—H), 1542, 1552, 1571, 1600 (Ar), 3285 cm^{-1} (NH and OH). For $C_{19}H_{20}N_2S_2 + 0{\cdot}5\ C_2H_5OH$ (363·5) calculated: 66·07% C, 6·38% H, 7·70% N, 17·64% S; found: 66·59% C, 6·26% H, 7·81% N, 18·04% S.

Maleate, m.p. 183–185°C with decomposition (ethanol). For $C_{23}H_{24}N_2O_4S_2$ (456·6) calculated: 60·50% C, 5·30% H, 6·14% N, 14·04% S; found: 60·88% C, 5·58% H, 6·06% N, 13·75% S.

1,4-Bis(8-methylthiodibenzo[*b,f*]thiepin-10-yl)piperazine (*XI*)

A mixture of 5·5 g 8-methylthiodibenzo[*b,f*]thiepin-10(11*H*)-one[10], 11·7 g piperazine hexahydrate and 10·3 g 4-toluenesulfonic acid was heated for 2 h to 180–190°C and then for 2 h *in vacuo* to 230–240°C. The product was cooled, made alkaline with dilute NH_4OH and the suspension shaken with 150 ml benzene. The undissolved solid product was filtered, washed with water and dried *in vacuo*; 3·7 g (62%), m.p. 300–302°C. Analytical sample, m.p. 307–310°C (dimethyl sulfoxide). The substance is almost insoluble in most of the common solvents. Mass spectrum, *m/e*: 594 (M^+, $C_{34}H_{30}N_2S_4$). For $C_{34}H_{30}N_2S_4$ (594·6) calculated: 68·67% C, 5·08% H, 4·71% N, 21·53% S; found: 68·30% C, 5·19% H, 4·52% N, 21·66% S.

8-Methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

IX (3·50 g) was added to a stirred mixture of 6·0 g Zn and 60 ml acetic acid at 100°C. The mixture was stirred and refluxed for 2 h. After cooling, it was filtered and the filtrate evaporated *in vacuo*. The residue was made alkaline with 60 ml 1 : 1 dilute NH_4OH and extracted with

benzene. The extract was shaken for 1 h with 50 ml 3M-HCl, the precipitated hydrochloride was filtered, decomposed with 60 ml 1 : 1 dilute NH_4OH and the base isolated by extraction with benzene; 2·9 g (82%), m.p. 80–82°C (ethanol). This melting point remained unchanged on repeated crystallization and the product was considered to be a crystal modification of the base *I*, described previously[10] (m.p. 88–89°C). UV spectrum: λ_{max} 274·5 nm (log ε 4·25). IR spectrum: 765, 810, 880 (4 and 2 adjacent and solitary Ar—H), 1470, 1574, 1580, 3050 (Ar), 2753, 2770 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 6·80–7·60 (m, 7 H, Ar—H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·69 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·44 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·43 (s, 3 H, SCH_3), 2·28 (s, 3 H, NCH_3). For $C_{20}H_{24}N_2S_2$ (356·5) calculated: 67·38% C, 6·78% H, 7·85% N, 17·99% S; found: 67·07% C, 6·81% H, 7·94% N, 17·65% S.

Monomethanesulfonate, m.p. 191–192°C (ethanol). For $C_{21}H_{28}N_2O_3S_3$ (452·6) calculated: 55·72% C, 6·23% H, 6·19% N, 21·25% S; found: 55·74% C, 6·22% H, 6·15% N, 21·17% S.

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

II . C_6H_6 (ref.[18]) (2·39 g) was neutralized with 1·16 g maleic acid in ethanol to give 2·9 g bis-(hydrogen maleate), m.p. 137°C (ethanol). For $C_{30}H_{36}N_2O_9S_2$ (632·7) calculated: 56·94% C, 5·74% H, 4·43% N, 10·13% S; found: 57·32% C, 6·02% H, 4·32% N, 10·30% S.

Monomaleate hemihydrate, m.p. 83–85°C (95% ethanol–ether). For $C_{26}H_{32}N_2O_5S_2 + 0{\cdot}5\ H_2O$ (525·7) calculated: 59·40% C, 6·33% H, 5·33% N, 12·20% S; found: 59·52% C, 6·25% H, 5·35% N, 12·46% S.

Basic (+)-tartrate, m.p. 159–160°C (90% ethanol), $[\alpha]_D^{20}$ +9·9° (1%, CH_3OH). For $C_{48}H_{62}N_4O_8S_4$ (951·3) calculated: 60·60% C, 6·57% H, 5·89% N, 13·48% S; found: 59·83% C, 6·58% H, 5·75% N, 13·12% S.

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

A) A solution of 1·4 g N,N′-carbonyldiimidazole in 15 ml dichloromethane was stirred under nitrogen and treated dropwise with a solution of 1·3 g decanoic acid in 5 ml dichloromethane. The mixture was stirred for 15 min at room temperature and treated dropwise with a solution of 3·0 g *II* in 5 ml dichloromethane. It was stirred for 2 h, allowed to stand for 16 h, evaporated and the residue dissolved in benzene. The solution was washed with water, dried with K_2CO_3 and evaporated. The residue (3·74 g) was dissolved in benzene and chromatographed on a column of 100 g Al_2O_3. Elution with benzene gave 2·60 g (63%) almost pure *III*, identified by comparison with an authentic sample[20] by means of TLC. Neutralization with oxalic acid yielded the bis-(hydrogen oxalate) melting at 173–175°C (aqueous ethanol), identical with a product prepared previously[20].

B) A mixture of 2·3 g 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin[10], 4·8 g 1-(3-decanoyloxypropyl)piperazine[20] and 3 ml chloroform was refluxed for 7 h. The mixture was diluted with 50 ml benzene, the solution washed with 10% NaOH and water, dried with K_2CO_3 and evaporated. The residue was dissolved in benzene and the solution chromatographed on a column of 140 g Al_2O_3. The elution with benzene gave first 0·15 g 2-methylthiodibenzo-[*b,f*]thiepin[10] and then 1·40 g (32%) ester *III*, identical with the product prepared according to *A*.

Mono-oxalate was obtained by neutralization of 0·50 g *III* with 0·11 g oxalic acid in 5 m acetone; m.p. 136°C (aqueous ethanol). For $C_{34}H_{48}N_2O_6S_2$ (644·9) calculated: 63·32% C 7·50% H, 4·34% N, 9·94% S; found: 63·20% C, 7·47% H, 4·12% N, 9·99% S.

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

Mono-methanesulfonate was obtained from 6·8 g base *IV* (ref.[17]) and 2·3 g methanesulonic acid in 70 ml water; 5·7 g, m.p. 203–204°C (first melting and resolidification at 151–154°C) (water). For $C_{20}H_{26}N_2O_3S_3$ (438·6) calculated: 54·77% C, 5·98% H, 6·39% N, 21·92% S; found: 54·31% C, 5·98% H, 6·29% N, 21·64% S,

1,4-Bis(8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*V*)

A) A mixture of 13·7 g 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin[10], 2·7 g anhydrous piperazine and 15 ml chloroform was refluxed for 7·5 h. Chloroform was evaporated and the residue stirred with 150 ml benzene and 100 ml water. The undissolved solid was filtered off, washed with benzene and dried in *vacuo*; 3·6 g (26%) isomer *A*, m.p. 276–278°C (xylene). The mass spectrum showed as the molecular ion a product of thermic decomposition: *m/e* 342·1228 (corresponding to $C_{19}H_{22}N_2S_2$); fragments with *m/e* 257 and 256. For $C_{34}H_{34}N_2S_4$ (598·9) calculated: 68·19% C, 5·72% H, 4·68% N, 21·41% S; found: 68·17% C, 5·90% H, 4·88% N, 20·40% S.

The filtrate after *V-A* was separated and the benzene layer shaken with 50 ml 3M-HCl. The precipitated hydrochloride was filtered, washed with benzene, decomposed with NH_4OH and the base isolated by extraction with benzene. The extract was washed with water, dried and evaporated. The residue was dissolved in benzene and chromatographed on a column of 80 g neutral Al_2O_3. A mixture of benzene and 10% chloroform eluted 2·35 g (17%) isomer *B*, m.p. 217–219°C (benzene). Mass spectrum, *m/e* (corresponding to): 598·16 (M^+, $C_{34}H_{34}N_2S_4$) 341, 257. For $C_{34}H_{34}N_2S_4$ (598·9) calculated: 68·19% C, 5·72% H, 4·68% N, 21·41% S; found: 68·84% C, 5·71% H, 4·78% N, 21·33% S.

Maleate of isomer B, m.p. 138–139°C (acetone–benzene). For $C_{38}H_{38}N_2O_4S_4$ (714·9) calculated:63·84% C, 5·36% H, 3·92% N, 17·93% S; found: 64·20% C, 5·76% H, 3·64% N, 17·67% S.

B) A batch of the base *II* prepared according to [17] was found to contain a small amount of a different basic component. A sample of 10 g crude substance was chromatographed on a column of 250 g Al_2O_3. Benzene and its mixture with 1% ethanol eluted 270 mg of the mentioned impurity; elution with benzene containing 3% ethanol gave 7·1 g pure *II*. The less polar component was oily and its comparison with *V–B* (TLC) indicated identity. Neutralization with maleic acid in acetone gave 230 mg maleate containing 1 mol.crystal acetone, m.p. 97–98°C (acetone–ether). For $C_{38}H_{38}N_2O_4S_4 + CH_3COCH_3$ (773·0) calculated: 63·70% C, 5·74% H, 3·62% N, 16·59 S; found: 63·62% C, 5·92% H, 3·63% N, 16·48% S.

3-[4-(8-Methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazino]propyl N-Octylcarbamate (*VI*)

A mixture of 9·5 g *II* . C_6H_6 (ref.[18]), 80 ml toluene and 5·0 g octyl isocyanate (b.p. 96–100°C : : 3 KPa) (ref.[26]) was refluxed for 3 h and evaporated *in vacuo*. The residue was dissolved in 70 ml 80% aqueous ethanol and neutralized with 6·3 g oxalic acid dihydrate; 8·4 g (58%) bis(hydrogen oxalate), m.p. 143–148°C (ethanol). For $C_{35}H_{49}N_3O_{10}S_2$ (735·9) calculated: 57·12% C, 6·71% H, 5·71% N, 8·71% S; found: 56·99% C, 6·57% H, 5·72% N, 8·83% S.

A sample of the oxalate was decomposed with NH_4OH, the oily base isolated by extraction with benzene and used for recording the spectra. IR spectrum (film): 759, 817, 897 (4 and 2 adjacent and solitary Ar–H), 1154, 1258 (COOR), 1525, 1715 (R'NHCOOR), 2820, 2860 (CH_2N), 3063 (Ar), 3350 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·55 (mcs, J = 2·5 Hz, 1 H, 9-H), 6·80–7·50 (m, 6 H, remaining Ar–H), 4·65 (bs, 1 H, CONH), 4·10 (t, J = 7·0 Hz, 2 H, OCH_2),

3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·10 (t, 2 H, CH_2N in the octylamino residue), 2·65 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (2 t, 6 H, $(CH_2)_2N^1CH_2$ of piperazine and the chain), 2·40 (s, 3 H, SCH_3), 1·50—2·20 (m, 4 H, CH_2 in the middle of the aminopropanol residue and CH_2 adjacent to the terminal methyl), 1·25 (bs, 10 H, remaining 5 CH_2 in the octyl), 0·88 (t, 3 H, terminal CH_3).

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

A mixture of 4·50 g 10-chloro-8-methylthio-10,11-dihydrodibenzo-[*b,f*]thiepin[10] and 18 g ethylenediamine was heated for 6 h to 120°C. After cooling, the mixture was diluted with 150 ml water and extracted with benzene. The extract was washed with water and shaken with 150 ml 3M-HCl. The oily hydrochloride and the acid aqueous layer were made alkaline with NH_4OH and the base isolated by extraction with benzene; 3·10 g (66%) oily base. Neutralization with maleic acid in ethanol gave bis(hydrogen maleate) solvated with 1 mol. ethanol, m.p. 125—128°C (90% aqueous ethanol). For $C_{25}H_{28}N_2O_8S_2 + C_2H_6O$ (594·7) calculated: 54·53% C, 5·76% H, 4·71% N, 10·78% S; found: 54·71% C, 5·73% H, 4·59% N, 10·87% S.

8-(Methylsulfinyl)-10-piperazino-10,11-dihydrodibenzo [*b,f*]-thiepin (*XIII*)

A solution of 5·0 g *IV* (ref.[17]) and 1·5 g methanesulfonic acid in 50 ml 50% acetic acid was treated with 5 ml 1 : 1 dilute hydrochloric acid and then under stirring with 29 ml 1N-$KBrO_3$ (containing 20 g KBr in 100 ml) added dropwise. The mixture was allowed to stand overnight at room temperature, made alkaline with NH_4OH and the base isolated by extraction with benzene; 5·2 g (almost 100%) inhomogeneous solid (mixture of racemates). Repeated crystallization from benzene gave one homogeneous racemate m.p. 167—168·5°C. IR spectrum: 751, 797, 818, 892 (4 and 2 adjacent and solitary Ar—H), 1047 (S—O), 3325 cm^{-1} (NH). The polarographic reduction at $E_{1/2}$ −0·645 V (towards a saturated calomel electrode) in 0·5M-HCl proves the presence of the sulfoxide group. ^{1}H-NMR spectrum: δ 8·00 (mcs, J = 2·5 Hz, 1 H, 9-H), 7·00—7·80 (m, 6 H, remaining Ar—H), 3·00—4·00 (m, 3H, $ArCH_2CHAr$), 2·82 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·62 (s, 3 H, $SOCH_3$), 2·60 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·60 (bs, 1 H, NH).

The mother liquors were combined and transformed by neutralization with methanesulfonic acid in ethanol–ether to a methanesulfonate sesquihydrate (mixture of racemates), m.p. 158 to 162°C (95% ethanol–ether). For $C_{20}H_{26}N_2O_4S_3 + 1·5\,H_2O$ (481·7) calculated: 49·87% C, 6·06% H, 5·81% N, 19·97% S; found: 49·70% C, 5·62% H, 6·04% N, 20·18% 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, to Mr Z. Šedivý for technical assistance with the syntheses and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs Z. Volková (department of analytical chemistry of this Institute) for carrying out the analyses.

REFERENCES

1. Protiva M.: Drugs of the Future *2*, 250 (1977).
2. Náhunek K., Švestka J., Rodová A., Mišurec J., Výborová L.: Česk. Psychiat. *72*, 32 (1976).
3. Vinař O., Taussigová D., Baštecký J., Vinařová E.: Activ. Nerv. Super. *18*, 212 (1976).

4. Švestka J., Náhunek K., Rodová A.: Farmakoterap. Zprávy *22*, 209 (1976).
5. Švestka J., Náhunek K., Rodová A.: Activ. Nerv. Super. *16*, 162 (1974).
6. Švestka J., Náhunek K., Rodová A.: Scr. Med. (Brno) *49*, 209 (1976).
7. Náhunek K., Švestka J., Rodová A., Češková E., Kulísková O.: Activ. Nerv. Super. *17*, 211 (1975).
8. Molčan J., Čaplová T., Heretík A., Kolibáš E.: 11th CINP Congr., Vienna, July 1978; Abstr. p. 50.
9. Švestka J., Náhunek K., Češková E.: 11th CINP Congr., Vienna, July 1978; Abstr. p. 455.
10. Pelz K., Jirkovský I., Adlerová E , Metyšová J., Protiva M.: This Journal *33*, 1895 (1968).
11. Šindelář K., Metyšová J., Protiva M.: This Journal *37*, 1734 (1972).
12. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *39*, 3338 (1974).
13. Jílek J. O., Šindelář K., Metyšová J., Metyš J., Pomykáček J., Protiva M.: This Journal *35*, 3721 (1970).
14. Kaplan J. P., Kyburz E. (F. Hoffmann-La Roche & Co., A. G.): Ger. Offen 2 216 883 (Swiss Appl. 04.05.71); U.S. 3 811 026; Neth. Appl. 72/4168; Chem. Abstr. *78*, 72 211 (1973).
15. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
16. Ueda I., Sato Y., Maeno S., Umio S.: Chem. Pharm. Bull. *23*, 2223 (1975).
17. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
18. Jílek J. O., Šindelář K., Dlabač A., Kazdová E., Pomykáček J., Šedivý Z., Protiva M.: This Journal *38*, 1190 (1973).
19. Jílek J. O., Červená I., Kopicová Z., Šindelář K., Svátek E., Metyšová J., Dlabač A., Pomykáček J., Protiva M.: This Journal *41*, 443 (1976).
20. Červená I., Jílek J. O., Dlabač A., Protiva M.: This Journal *41*, 3437 (1976).
21. Staab A., Mannschreck A.: Chem. Ber. *95*, 1284 (1962).
22. Schindler W., Schmid E., Züst A. (J. R. Geigy A. G.): Swiss 501 664; U.S. 3 563 993; Neth. Appl. 69/2286; Fr. Demande 2 002 327 (Swiss Appl. 21.02.68—04.12.68); Chem. Abstr. *73*, 25 520 (1970).
23. Eschenhof E., Meister W., Oesterhelt G., Vetter W.: Arzneim.-Forsch. *26*, 262 (1976).
24. Zawisza T., Machoń Z., Kuczyński L.: Acta Pol. Pharm. *22*, 477 (1965).
25. Ho B. T., Englert L. F., McKenna M. L.: J. Med. Chem. *19*, 850 (1976).
26. Voloshin A. I., Kuzmina O. P., Danilov S. N.: Zh. Prikl. Khim. (Leningrad) *37*, 1578 (1964); Chem. Abstr. *61*, 9662 (1964).
27. Allen C. F. H., Bell A.: Org. Syn., Coll. Vol. *3*, 846 (1955).
28. Queisnerová M., Svátek E., Metyšová J.: Activ. Nerv. Super. *15*, 99 (1973).
29. Queisnerová M., Svátek E., Metyšová J.: Activ. Nerv. Super. *17*, 211 (1975).
30. Queisnerová M., Svátek E., Metyšová J.: 6th Xenobiochem. Symp., Hradec Králové, June 1977; Abstr. p. 27.
31. Breyer U., Muller-Oerlinghausen B., Mauruschat W. in the book: *Psychopharmacology Series*, Vol. 2, *Psychotherapeutic Drugs* (E. Usdin, I. S. Forrest, Eds), Part II, p. 755. Dekker, New York 1977.
32. Bártl V., Holubek J., Němec J., Bartošová M., Protiva M.: This Journal *43*, 2427 (1978).
33. Jílek J. O., Metyšová J., Svátek E., Jančik F., Pomykáček J., Protiva M.: This Journal *38*, 599 (1973).
34. Metyšová J., Metyš J.: Activ. Nerv. Super. *13*, 185 (1971).
35. Dlabač A.: Psychopharmacology *26*, Suppl., 106 (1972).
36. Dlabač A.: Česk. Fysiol. *22*, 356 (1973).
37. Dlabač A., Kazdová E.: Activ. Nerv. Super. *16*, 166 (1974); Chem. Abstr. *82*, 68 230 (1975).
38. Dlabač A., Kazdová E.: Česk. Fysiol. *23*, 336 (1974).

39. Dlabač A.: J. Pharmacol. (Paris) *5*, Suppl. 2, 26 (1974).
40. Jílek J., Holubek J., Svátek E., Bartošová M., Metyšová J., Pomykáček J., Protiva M.: This Journal *43*, 3092 (1978).
41. Bartošová M., Protiva M.: Česk. Fysiol. *26*, 214 (1977).

Translated by the author (M. P.).