NONCATALEPTIC NEUROLEPTICS: POTENTIAL METABOLITES OF 2-CHLORO-10-[4-(2-HYDROXYETHYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

Vladimír VALENTA, Emil SVÁTEK, Antonín DLABAČ, Marie BARTOŠOVÁ** and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

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The synthesis of nine potential metabolites of the title compound is being described. Using oxidation reactions, compound *I* was transformed to the S-oxide *VII*, N-oxide *IX* and N,S-dioxide *X*. Substitution reactions of 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin with 1-ethoxycarbonylpiperazine, piperazine and ethylenediamine afforded the amines *II*, *III*, *IV* and *XIII*. Leuckart reaction of 2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one led in addition to the expected formamido derivative *XI* to the heptacyclic pyridine derivative *XIV*. Hydrolysis of compounds *II* and *XI* gave the secondary amine *III* and the primary amine *XII*. Oxidation of substances *III*, *XII* and *XIII* afforded the sulfoxides *VIII*, *XV* and *XVI*. Most of the prepared piperazine derivatives exhibit some central depressant, adrenolytic and antihistamine activity.

In previous communications of this series[1,2], we described the synthesis of 2-chloro--10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*), characterized in the form of succinate (VÚFB-10.032) as a noncataleptic neuroleptic agent[3-6] which received recently[7] the nonofficial generic name of "docloxythepin". More detailed investigations of this substance requested the synthesis of potential metabolites from which until present only the 8-hydroxy derivative[8] has been described. In the present paper, the synthesis of nine further potential metabolites is being described, designed and prepared on the basis of our previous experiences with related neuroleptic agents[9-11].

A substitution reaction of 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12] with 1-ethoxycarbonylpiperazine in boiling chloroform gave the carbamate *II* affording by alkaline hydrolysis the secondary amine *III*. The same compound was obtained directly by the substitution reaction of the mentioned chloro compound with an excess of piperazine; the use of 1 mol piperazine per 2 mol chloro compound resulted in the 1,4-disubstituted piperazine *IV*, the identity of which was confirmed by the mass spectrum.

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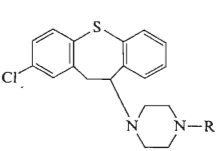
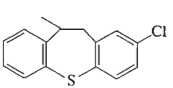
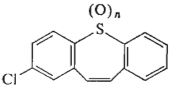
** Affiliated unit of this Institute, Rosice n/L.



I, R = CH_2CH_2OH
II, R = $COOC_2H_5$
III, R = H
IV, R =

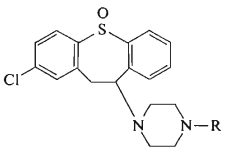




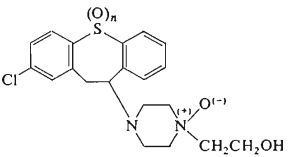
V, $n = 0$
VI, $n = 1$

The amine *III* was used as the starting compound for preparing docloxythepin *I* by new procedures. Successful was the addition of ethylene oxide in ethanol or methanol, as well as the alkylation with 2-chloroethanol in the presence of potassium carbonate. With regard to the yields, these methods are less advantageous than the direct substitution reaction of 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12] with 1-(2-hydroxyethyl)piperazine (ref.[1]). Base *I* was also obtained by reaction of 2-chloro--10,11-dihydrodibenzo[*b*,*f*]-thiepin-10-ol[12] with methanesulfonyl chloride in pyridine, followed by a substitution reaction of the formed (not isolated) methanesulfonic ester with 1-(2-hydroxyethyl)piperazine; a by-product was 2-chlorodibenzo[*b*,*f*]-thiepin (*V*) (ref.[13]) formed by a simultaneous elimination reaction. In an attempt at reacting 2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol[12] with 1-(2-hydroxyethyl)piperazine dihydrochloride and aluminium chloride in chloroform, 2-chlorodibenzo[*b*,*f*]thiepin (*V*) (ref.[13]) was the only product.

Oxidation of compound *I* in the form of methanesulfonate with hydrogen peroxide in aqueous solution at room temperature gave the sulfoxide *VII*; its identity was confirmed not only by analysis and the IR spectrum but also by polarography. As an important by-product, a neutral substance was simultaneously formed which was identified as 2-chlorodibenzo[*b*,*f*]thiepin S-oxide (*VI*), obtained previously[14] by oxidation of compound *V* with hydrogen peroxide. In our case, this substance was formed by an elimination reaction, mentioned previously in our oxidation experiments with 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin and hydrogen peroxide in acetic acid[15]. The mechanism of this elimination reaction is not clear but the Cope elimination[16] of the primarily formed N^1-oxide has to be considered. An aqueous solution of methanesulfonate of compound *III* was similarly transformed to the sulfoxide *VIII*; elimination reaction did not take place.



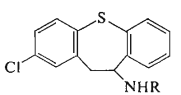
VII, R = CH_2CH_2OH
VIII, R = H



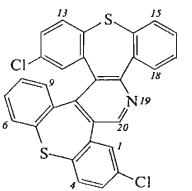
IX, $n = 0$
X, $n = 1$

Oxidation of the bases *I* and *VII* with hydrogen peroxide in ethanol at room temperature gave the N-oxides *IX* and *X*; polarographic reductions of both products display reduction waves typical for N-oxides and compound *X* shows in addition a sulfoxide reduction wave.

In order to prepare potential metabolites of docloxythepin *I*, designed according to the metabolic studies of Breyer[17] in the series of phenothiazine neuroleptics with a piperazine residue in the side chain, it was necessary to investigate the Leuckart reaction of 2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[12] with formamide in the presence of formic acid. Two products were obtained, separated on the basis of different solubility in ethanol. The soluble fraction (56%) was identified as the desired 2-chloro-10-formamido-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XI*). The insoluble substance has a very high melting point and is oxygen-free; the mass spectrum in agreement with analysis estimated for it the empirical formula $C_{29}H_{15}Cl_2NS_2$. The IR spectrum comprises a band corresponding to the C=N fragment (1651 cm^{-1}) and the UV spectrum indicates the presence of conjugation like in Ar—C=C—Ar. All of the experimental data are compatible with formulating the substance as 2,11-dichlorobisdibenzo[2,3; 6,7]thiepino[4,5-*b*; 4′,5′-*d*]pyridine (*XIV*). Similar compounds containing the dibenzo[*b*,*f*]oxepin moiety were obtained under similar conditions by Kametani and coworkers[18,19] who presented a plausible explanation of their formation.

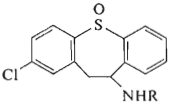


XI, R = CHO
XII, R = H
XIII, R = $CH_2CH_2NH_2$



XIV

Alkaline hydrolysis of the amide *XI* afforded the primary amine *XII*. A substitution reaction of 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12] with anhydrous ethylenediamine at 110°C gave the diamine *XIII*. Oxidation of compounds *XII* and *XIII* in the form of aqueous solutions of methanesulfonates with hydrogen peroxide gave the sulfoxides *XV* and *XVI*. The polarographic reduction of the first of them exhibits two waves corresponding probably to two racemates present (the S-oxidation introduced a second centre of chirality). The mass spectrum with a characteristic fragment $M-OH$ contributed to the identification of the sulfoxide *XVI*.



XV, R = H
XVI, R = $CH_2CH_2NH_2$

Out of the compounds prepared, *III*, *VII*, *VIII*, *IX*, *X*, *XII*, *XIII*, *XV* and *XVI* were considered potential metabolites of docloxythepin *I*. Compounds *III*, *VIII*, *XII*, *XIII*, *XV* and *XVI* are simulteneously potential metabolites of doclothepin, *i.e.* 2-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[1,12,20]. During a preliminary investigation of pharmacokinetics and metabolism of docloxythepin *I* in rats[21], compounds *VII*, *VIII*, *IX* and *X* were identified as metabolites in the urine and feces using the just described standards. An additional metabolite has the R_F identical with that of compound *XII* but the proof of identity was not unequivocal. Some of these metabolites were also mentioned in a study[22] comparing the levels of docloxythepin *I* and oxyprothepin[23] in the blood and gall of rats.

The compounds prepared were pharmacologically evaluated for a number of effects within a general screening programme. They were tested in the form of salts described in the Experimental under the following code numbers: *I* (docloxythepin, VÚFB-10.032) (ref.[1]) as a standard, *III* (VÚFB-12.353), *IV* (base VÚFB-12.352), *VII* (VÚFB-12.397), *VIII* (VÚFB-12.374), *IX* (base VÚFB-12.421), *XI* (VÚFB-12.347), *XII* (VÚFB-12.340), *XIII* (VÚFB-12.437), *XIV* (base VÚFB-13.720), *XV* (VÚFB-12.396), *XVI* (VÚFB-12.504). The compounds were administered intravenously (unless stated otherwise) and the doses are given in mg/kg.

Acute toxicity (mice, medium lethal doses LD_{50}; survival followed for 3 days, with the orally administered compounds for 7 days): *I*, 84 orally; *III*, 58 (after an oral dose of 50 mg/kg, 90% animals perish until the 5th day and 100% until the 6th day); *IV*, >2500 orally; *VII*, 40; *VIII*, 70; *IX*, 205 orally; *X*, 80; *XI*, >2500 orally; *XII*, 1000 orally; *XIII*, 30; *XIV*, >2500 orally; *XV*, 40; *XVI*, 150. Basic dose D used in most of the tests: *III*, 12; *IV*, 300 orally; *VII*, 8; *VIII*, 16; *X*, 16; *XI*, 300 orally; *XII*, 200 orally; *XIII*, 6; *XIV*, 300 orally; *XV*, 8; *XVI*, 30.

Incoordinating effect in the rota-rod test in mice; effective dose (ED_{50}) exhibiting ataxia in 50% animals: *I*, 0·8 orally; *III*, 0·75, 2·25 orally; *IV*, inactive; *VII*, 2·5; *VIII*, 2·5; *IX*, 2·7 orally; *X*, 13; *XI*–*XVI*, inactive. Thiopental potentiation in mice; a dose prolonging the duration

of the thiopental sleeping time to 200% of the control value (for chlorpromazine ED = 0·5 *i.v.*, 1·0 orally): *III*, 0·75; *VII*, 0·3; *VIII*, 1; *X*, 13; *XII*, 75 orally; *IV*, *XI*, *XIII*—*XV*, inactive. Inhibition of spontaneous motility in mice; effective dose (for chlorpromazine ED = 1·0 *s.c.*): *III*, 0·5 *s.c.*; *VII*, 8·0 *s.c.*; *VIII*, 1·0 *s.c.*; *X*, 13·0 *s.c.*; *XIII* and *XVI*, CNS depressant effect in doses higher than D. Hypothermic effect in rats was observed only with compound *X*, ED = 16 (dose decreasing the rectal temperature by 1°C; for chlorpromazine ED = 0·75). Catalepsy in rats: *I*, 50 mg/kg orally bring about catalepsy in 20% animals; *III*, the same effect; *VIII*, an indication of effect at 16 mg/kg *i.p.*; *IX*, an oral dose of 50 mg/kg was cataleptic for 10% animals; *XV*, an indication of effect at 8 mg/kg *i.p.* Anticonvulsant effect in mice; a dose inhibiting significantly convulsions elicited by pentetrazole (for phenytoine ED = 100 mg/kg orally): *VII*, 25 orally. Analgetic activity (Haffner test) in mice; a dose exhibiting complete analgesia in 50% animals: *III*, 2·5 (*i.e.* pethidine effect); *VIII*, 3·75. Hypotensive effect; a dose decreasing the blood pressure of normotensive rats by 10% for at least 10 min: *VIII*, 16; *XI*, 300 orally. Adrenolytic effect in rats; a dose reducing the epinephrine hypertensive reaction by 50%: *III*, 0·1; *VII*, 0·1; *VIII*, 0·01; *X*, 0·1; *XIII*, 6; *XV*, 8; *XVI*, 5. Local anaesthetic effect; a concentration bringing about a complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia: *III*, 0·3%; *VII*, 0·3%. Spasmolytic (parasympatholytic) effect; a concentration in μg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50% (for atropine ED = 0·05 μg/ml): *III*, 1—10; *VII*, 1—10; *VIII*, 1—10. Spasmolytic (musculotropic) effect; a concentration in μg/ml inhibiting similarly the barium chloride contractions (for papaverine ED = 5 μg/ml): *III*, 1—10; *VII*, 10. Antihistamine effect; an *s.c.* dose protecting 50% guinea-pigs from the lethal effect of histamine in a dose of 5 mg/kg (for mebrophenhydramine ED = 0·25 mg/kg *s.c.*): *III*, 0·5 to 1·0; *VII*, 0·1—1·0; *VIII*, 0·25—1·0; *X*, 0·1—1·0. Antiarrhythmic effect; a dose prolonging significantly the latency of ventricular extrasystoles, elicited by the infusion of aconitine (for quinidine ED = 7·5 mg/kg *i.v.*): *III*, 0·25—1·0; *VII*, 1—8; *VIII*, <16. Hyperglycaemic effect; an oral dose effecting an increase of blood sugar level in rats by 20%: *III*, 25; *VII*, 10—25; *VIII*, 10—25; *X*, 50. Inhibition of diuresis in mice was observed after the doses D with compounds *VII*, *VIII* and *X*. Frequency of the isolated rabbit heart atrium was decreased by 25% by a concentration of 50 μg/ml of compounds *VII* and *XV*.

In conclusion, some central effects are shown only by the piperazine derivatives *III*, *VII*, *VIII* and *IX*, all of them being, however, weaker central depressants than *I*. In the test of catalepsy, they show only indications of effectiveness. Their adrenolytic activity is typical being especially very high with *VIII*. The local anaesthetic and antiarrhythmic activity of *III* and *VII* is also worth mentioning. The piperazines *III*, *VII*, *VIII* and *X* have rather important antihistamine activity. The amines *XII*, *XIII*, *XV* and *XVI* differ distinctly from the piperazines and are almost devoid of pharmacodynamic activities. The insoluble compounds *IV*, *XI* and *XIV* are nontoxic and completely inactive.

The prepared compounds were also tested in the form of the salts described for antimicrobial activity *in vitro* (Dr A. Čapek and Dr J. Turinová, bacteriological department of this institute). The microorganisms used, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *III* 25, *VIII* 25, *IX* 25, *XII* 25, *XIII* 6·25; *Streptococcus faecalis*, *III* 25, *VIII* 50, *IX* 50, *XII* 50, *XIII* 50; *Staphylococcus pyogenes aureus*, *III* 25, *VIII* 50, *IX* 25, *XII* 50, *XIII* 50; *Escherichia coli*, *III* 50, *IX* 25, *XII* 100, *XIII* 50; *Proteus vulgaris*, *VIII* 100; *Mycobacterium tuberculosis* H37Rv, *III* 6·2, *VII* 50, *VIII* 12·5, *IX* 12·5, *XII* 12·5, *XIII* 25, *XV* 25; *Saccharomyces pasterianus*, *VII* 50, *X* 50; *Trichophyton*

mentagrophytes, *VIII* 50, *IX* 50, *X* 50, *XI* 50, *XII* 50, *XV* 50, *XVI* 50. The compounds are inactive towards *Pseudomonas aeruginosa*, *Aspergillus niger* and *Candida albicans*.

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 70 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in CD_3SOCD_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the MS 902 (AEI) and MAT 311 (Varian) spectrometers. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

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

A mixture of 13·3 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12], 24 g 1-ethoxycarbonylpiperazine and 24 ml chloroform was stirred and refluxed for 5 h. It was then diluted with 150 ml benzene, washed with H_2O and extracted with an excess of 2M-H_2SO_4. The separated aqueous layer with some precipitated sulfate was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with K_2CO_3 and evaporated under reduced pressure; 17·1 g (90%) oily base. Neutralization with maleic acid in ethanol and addition of ether gave the hydrogen maleate, m.p. 142—144°C (ethanol). For $C_{25}H_{27}ClN_2O_6S$ (519·0) calculated: 57·85% C, 5·24% H, 6·83% Cl, 5·40% N, 6·18% S; found: 58·25% C, 5·41% H, 7·00% Cl, 5·42% N, 6·13% S.

2-Chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*III*)

A. A mixture of 17·0 g *II*, 25 g KOH and 30 ml ethanol was stirred and refluxed for 3 h. It was then diluted with 150 ml H_2O and extracted with chloroform. Processing of the extract gave 13·1 g (93%) base, m.p. 120—126°C. Analytical sample, m.p. 126—128°C (cyclohexane). For $C_{18}H_{19}ClN_2S$ (330·9) calculated: 65·33% C, 5·79% H, 10·72% Cl, 8·47% N, 9·69% S; found: 64·75% C, 5·89% H, 10·73% Cl, 8·27% N, 9·62% S.

The dimethanesulfonate crystallized from aqueous ethanol as a hemihydrate, m.p. 209·5—210°C. For $C_{20}H_{27}ClN_2O_6S_3 + 0{\cdot}5\ H_2O$ (532·1) calculated: 45·14% C, 5·30% H, 6·66% Cl, 5·27% N, 18·08% S; found: 45·26% C, 5·24% H, 6·69% Cl, 5·11% N, 17·94% S.

B. A mixture of 4·0 g piperazine hexahydrate and 100 ml benzene was distilled at normal pressure for removing the crystal water. The residue was treated with 15 ml chloroform and 1·4 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12] and the mixture refluxed for 2 h. It was then diluted with 100 ml chloroform, washed with H_2O and the basic product extracted with 2M-H_2SO_4. The separated aqueous solution was filtered with charcoal, the filtrate made alkaline with NH_4OH and the product isolated by extraction with chloroform; 0·7 (41%) crude base *III*. The dimethanesulfonate hemihydrate melted at 207·5—208·5° (ethanol–ether) and was identical with the compound prepared according to *A*.

1,4-Bis(2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (*IV*)

A mixture of 11·5 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[12], 1·8 g anhydrous piperazine, 3·3 g pyridine and 6 ml chloroform was stirred and refluxed for 14 h. The mixture was

diluted with 100 ml boiling chloroform, washed with water, dried and partly evaporated under reduced pressure. The residue was diluted with benzene; 4·3 g (37%) crude base *IV* crystallized, m.p. 272—274°C. Analytical sample, m.p. 277°C (0·2 g from 20 ml benzene). Mass spectrum, *m/e*: 574 (M^+ corresponding to $C_{32}H_{28}Cl_2N_2S_2$), 329, 245, For $C_{32}H_{28}Cl_2N_2S_2$ (575·6) calculated: 66·77% C, 4·90% H, 12·32% Cl, 4·87% N, 11·14% S; found: 66·30% C, 4·82% H, 12·24% Cl, 4·68% N, 10·98% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

A. A solution of 19 g *III* in 200 ml methanol was stirred and treated over 3 h with 8·8 g ethylene oxide at 36—40°C. After standing overnight, methanol was evaporated under reduced pressure, the residue was dissolved in 100 ml chloroform and the product extracted with 2M-H_2SO_4. The aqueous solution was filtered with charcoal and the filtrate made alkaline with NH_4OH. The base was extracted with chloroform, the extract dried with K_2CO_3 and evaporated. There were obtained 14·0 g (75%) oily *I* which did not crystallize but a comparison with an authentic sample of *I* (ref.[1]) by means of TLC proved identity of both samples. Neutralization with succinic acid in ethanol gave 10·5 g crude succinate, m.p. 158—160°C. Recrystallization from ethanol gave the pure salt melting at 166—168°C, identical with the product prepared previously[1].

B. A stirred mixture of 19·3 g *III*, 100 ml ethanol and 16·8 g K_2CO_3 was treated over 30 min with a solution of 8·1 g 2-chloroethanol in 10 ml ethanol at 70°C. The mixture was stirred for 5 h at 70°C, cooled, filtered, and the filtrate was processed similarly like in the preceding case; 15·0 g (80%) crude base *I* giving 16·9 g succinate, m.p. 157—160°C. Crystallization from ethanol gave the pure salt melting at 166—168°C.

C. A solution of 26 g 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol[12] in 80 ml pyridine was stirred and treated at 0—5°C with 11·4 h methanesulfonyl chloride, added dropwise. The mixture was stirred for 1 h at room temperature, treated with 52 g 1-(2-hydroxyethyl)piperazine, stirred for 1 h and allowed to stand for 48 h at room temperature. It was then decomposed with H_2O and extracted with chloroform. The extract was washed with H_2O and the basic product transferred into the aqueous layer by shaking with an excess of 2M-H_2SO_4. Processing of the chloroform layer gave 6·0 g (25%) 2-chlorodibenzo[*b,f*]thiepin (*V*), m.p. 68—72°C. Crystallization from methanol gave the pure compound melting at 78—79°C, identical with the product prepared previously[13]. Processing of the acid aqueous layer like in the preceding cases gave 19 g (51%) oily *I* which crystallized slowly, m.p. 94—98°C. The pure base melted at 102—103° (acetone) and was identical with the product prepared previously[1].

2-Chlorodibenzo[*b,f*]thiepin (*V*)

A stirred mixture of 2·6 g 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol[12], 3·1 g 1-(2-hydroxyethyl)piperazine dihydrochloride[24] and 20 ml chloroform was treated with 3·3 g $AlCl_3$ in small portions. After the exothermic reaction was over, the mixture was cooled to 20°C and stirred for 2 h at room temperature. It was diluted with 25 ml chloroform, washed with H_2O, dried and evaporated. There were obtained 2·4 g (100%) crude *V*, m.p. 68—70°C. Crystallization from methanol gave the pure substance, m.p. 78—79°C, identical with the product prepared previously[13].

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

A mixture of 14·0 g 2-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one[12], 36·5 g formamide and 7·4 g formic acid was stirred and heated for 17 h under reflux in a bath of 190°C. The hot melt was

decomposed with 500 ml warm H_2O and the precipitated inhomogeneous solid was filtered. It was separated by extraction with 300 ml boiling ethanol. The insoluble product was filtered off, washed with ethanol and dried; 4·5 g (33%) 2,11-dichlorobisdibenzo[2,3; 6,7]thiepino-[4,5-*b*; 4',5'-*d*]pyridine (*XIV*), m.p. 343—348°C. Analytical sample, m.p. 351·5—352·5°C (dimethylformamide–methanol). Mass spectrum, *m/e* (%): 511·0006 (M^+ corresponding to $C_{29}H_{15}Cl_2NS_2$, 100), 478 (48, M—SH), 447 (30, M—S_2), 407 (10), 400 (8). UV spectrum (saturated solution): λ_{max} 252 nm, infl. 287 nm, infl. 310 nm. IR spectrum: 741, 756, 760, 792, 820, 876 (4 and 2 adjacent and solitary Ar-H), 1 021, 1 111, 1 529, 1 558, 1 580, 1 610 (Ar), 1 651 $c.^{-1}$(C=N). For $C_{29}H_{15}Cl_2NS_2$ (512·5) calculated: 67·96% C, 2·95% H, 13·84% Cl, 2·73% N, 12·52% S; found: 68·13% C, 3·20% H, 13·89% Cl, 2·86% N, 12·46% S.

The ethanolic solution was partly evaporated under reduced pressure and the residue allowed to stand overnight; there crystallized 8·7 g (56%) *XI*, m.p. 170—173°C, representing one homogeneous crystal modification. Crystallization from benzene gave another crystal modification melting at 196·5—197·5°C. IR spectrum: 759, 826, 885 (4 and 2 adjacent and solitary Ar—H), 1 493, 1 561, 1 580, 1 589 (Ar), 1 650 (NHCHO), 3 360 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 8·55 (d, J = 7·0 Hz, 1 H, NH), 8·05 (s, 1 H, CHO), 7·00—7·60 (m, 7 H, Ar—H), 5·65 (m, 1 H, Ar—CH—N), *c.* 3·30 (m, 2 H, $ArCH_2$). For $C_{15}H_{12}ClNOS$ (289·8) calculated: 62·17% C, 4·18% H, 12·24% Cl, 4·83% N, 11·06% S; found: 62·04% C, 4·18% H, 12·32% Cl, 4·71% N, 11·23% S.

10-Amino-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XII*)

A mixture of 17·9 g *XI*, 20 ml ethanol and 20 g KOH was refluxed for 4·5 h, diluted with 120 ml H_2O and the product extracted with chloroform. Processing of the extract gave 14·9 g (93%) oily *XII*.

Hydrogen maleate, m.p. 165—167°C (ethanol). For $C_{18}H_{16}ClNO_4S$ (377·8) calculated: 57·22% C, 4·27% H, 9·38% Cl, 3·70% N, 8·48% S; found: 57·37% C, 4·28% H, 9·56% Cl, 3·62% N, 8·80% S.

Hydrogen oxalate monohydrate, m.p. 208—209°C (95% ethanol). For $C_{16}H_{14}ClNO_4S$ — H_2O (369·8) calculated: 51·96% C, 4·36% H, 3·79% N; found: 52·54% C, 4·01% H, 3·69% N.

10-(2-Aminoethylamino)-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIII*)

A mixture of 5·6 g 2,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[12] and 18 g anhydrous ethylenediamine was stirred for 8 h under reflux at 100—110°C. It was then diluted with 100 ml chloroform, the solution washed with H_2O and extracted with 100 ml 2M-H_2SO_4. The aqueous layer was filtered with charcoal, the filtrate made alkaline with NH_4OH and the base extracted with chloroform. Processing of the extract gave 3·9 g (64%) oily *XIII*.

Bis(hydrogen maleate), m.p. 156—157°C (ethanol). ^{1}H-NMR spectrum: δ 8·72 (bs, 3 H, NH and NH_2), 7·00—7·60 (m, 7 H, Ar—H), 6·04 (s, 4 H, 2 CH=CH of maleic acid), 4·88 (m, 1 H, Ar—CH—N), 3·35 (m, 2 H, $ArCH_2$), 2·98 (bs, 4 H, NCH_2CH_2N). For $C_{24}H_{25}ClN_2O_8S$ (537·0) calculated: 53·67% C, 4·69% H, 6·60% Cl, 5·21% N, 5·97% S; found: 53·17% C, 4·88% H, 6·47% Cl, 5·15% N, 5·97% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin S-Oxide (*VII*)

I (9·4 g) was dissolved in a solution of 2·4 g methanesulfonic acid in 50 ml H_2O, the solution was treated with 50 ml 29% H_2O_2 and the mixture allowed to stand for 40 h at room temperature. The precipitated solid was filtered off, washed with H_2O and dried *in vacuo*; 1·4 g (22%) 2-chlorodibenzo[*b,f*]thiepin S-oxide (*VI*), m.p. 152—155°C. Analytical sample, m.p. 156·5—158·5°C

(benzene). It is polarographically reduced in 0·5M-HCl containing 30% ethanol at $E_{1/2}$ —0·95 V (towards a saturated calomel electrode) which corresponds to the behaviour of the sulfoxide. UV spectrum: λ_{max} 248 nm (log ε 4·38), 292 nm (3·77). IR spectrum: 749, 765, 800, 819, 830, 873, 889, 900 (4 and 2 adjacent, solitary Ar—H and CH=CH), 1030, 1036, 1070 (S—O), 1552, 1582, 3025 and 3080 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 6·80—8·00 (m, Ar—H and CH=CH). For $C_{14}H_9ClOS$ (260·7) calculated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·03% C, 3·58% H, 13·64% Cl, 12·05% S. The literature[14] reported a m.p. of 153 to 156°C for this substance prepared differently.

The filtrate was made alkaline with NH_4OH and extracted with chloroform. Processing of the extract gave 6·6 g (67%) crude *VII*, m.p. 155—170°C. Analytical sample, m.p. 166—169°C (acetone–benzene). It is reduced polarographically in 0·5M-HCl at $E_{1/2}$ —0·52 V (S—O) IR spectrum: 760, 770, 829, 879 (4 and 2 adjacent and solitary Ar—H), 1010, 1035, 1060, 1073 (CH_2OH, S—O), 1553, 1587, 3067, 3087 cm^{-1} (Ar). For $C_{20}H_{23}ClN_2O_2S$ (390·9) calculated: 61·44% C, 5·93% H, 9·07% Cl, 7·17% N, 8·20% S; found: 61·55% C, 6·21% H, 9·14% Cl, 7·10% N, 8·08% S.

Succinate monohydrate, m.p. 152—153°C with decomposition (95% ethanol–ether). For $C_{24}H_{29}ClN_2O_6S + H_2O$ (527·0) calculated: 54·69% C, 5·93% H, 6·73% Cl, 5·31% N, 6·08% S; found: 54·76% C, 5·71% H, 6·46% Cl, 4·96% N, 5·79% S.

2-Chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin S-Oxide (*VIII*)

A solution of 5·25 g *III* and 2·9 g methanesulfonic acid in 30 ml H_2O was oxidized with 6·0 ml 28% H_2O_2 at room temperature for 48 h. It was made alkaline with NH_4OH and the base isolated by extraction with chloroform; 4·9 g (94%) oil. Neutralization with methanesulfonic acid in 95% ethanol gave 5·9 g dimethanesulfonate hemihydrate, m.p. 215—220°C. Analytical sample, m.p. 223·5°C (95% ethanol). Polarographic reduction in 0·5M-HCl at $E1_{/2}$ —0·80 V (S—O). UV spectrum: $\lambda_{Infl.}$ 250 nm (log ε 3·87). IR spectrum: 759, 769, 780, 835, 895, 904 (4 and 2 adjacent and solitary Ar—H), 1035 (S—O), 1570, 1590 (Ar), 2535, 2600, 2740 (NH^+ and NH_2^+), 3200 cm^{-1} (OH, H_2O). For $C_{20}H_{27}ClN_2O_7S_3 + 0{\cdot}5\ H_2O$ (548·1) calculated: 43·82% C, 5·15% H, 6·47% Cl, 5·11% N, 17·55% S; found: 43·53% C, 5·25% H, 6·78% Cl, 5·04% N, 18·02% S.

10-Amino-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin S-Oxide (*XV*)

A solution of 5·6 g *XII* and 1·92 g methanesulfonic acid in a mixture of 160 ml H_2O and 40 ml acetic acid was oxidized with 80 ml 28% H_2O_2 at 40°C for 60 h. The solution was filtered, the filtrate made alkaline with NH_4OH and the base isolated by extraction with chloroform; 4·4 g (79%), m.p. 148—153°C. Analytical sample, m.p. 148—153°C (benzene–light petroleum). Polarographic reduction in 0·5M-HCl at $E_{1/2}$ —0·61 and —0·86 V (two sulfoxides). IR spectrum: 760, 784, 825, 875 (4 and 2 adjacent and solitary Ar—H), 1035, 1079 (S—O), 1570, 1593 (Ar), 1612 cm^{-1} (NH_2). For $C_{14}H_{12}ClNOS$ (277·8) calculated: 60·53% C, 4·35% H, 12·77% Cl, 5·04% N, 11·54% S; found: 60·35% C, 4·37% H, 12·60% Cl, 5·06% N, 11·71% S.

Methanesulfonate, m.p. 231—232°C (ethanol–ether). For $C_{15}H_{16}ClNO_4S_2$ (373·9) calculated: 48·18% C, 4·31% H, 9·48% Cl, 3·75% N, 17·15% S; found: 48·50% C, 4·44% H, 9·28% Cl, 3·84% N, 17·38% S.

10-(2-Aminoethylamino)-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin S-Oxide (*XVI*)

A solution of 3·7 g *XIII* and 2·32 g methanesulfonic acid in 15 ml H_2O was oxidized with 8 ml 25% H_2O_2 for 60 h at 25°C. Processing like in the preceding cases gave 3·8 g (99%) oily base.

Neutralization with maleic acid in ethanol gave 4·6 g bis(hydrogen maleate), m.p. 136—144°C. Analytical sample, m.p. 153—154°C (ethanol). Polarographic reduction on 0·5M-HCl at $E_{1/2}$ —0·88 V (S—O). IR spectrum: 764 (4 adjacent Ar—H), 1077, 1085 (S—O), 1518, 1624, 1707 (COOH and COO^-), 2490, 2640 (NH_2^+ and NH_3^+, COOH), 3065, 3088 (Ar), 3410 cm^{-1} (NH). Mass spectrum, *m/e*: 320 (M^+ corresponding to $C_{16}H_{17}ClN_2OS$), 303 (M—OH). For $C_{24}H_{25}ClN_2O_9S$ (553·0) calculated: 52·12% C, 4·56% H, 6·41% Cl, 5·06% N, 5·80% S; found: 51·77% C, 4·66% H, 6·58% Cl, 5·06% N, 5·60% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin N^4-Oxide (*IX*)

A solution of 7·5 g *I* in 35 ml ethanol was treated with 2·5 ml 28% H_2O_2 and the mixture allowed to stand for 20 h at room temperature. It was diluted with 250 ml H_2O and extracted with chloroform. The extract was dried with K_2CO_3 and evaporated under reduced pressure. The oily residue crystallized after dissolution in 15 ml benzene and addition of light petroleum; 5·9 g (76%) base, m.p. 168—175°C. Analytical sample, m.p. 172—174°C (toluene). Polarographic reduction in 0·5M-HCl at $E_{1/2}$ —0·35 V (N—O). IR spectrum: 753, 822, 896 (4 and 2 adjacent and solitary Ar—H), 1080, 1097 (CH_2OH), 1563, 1580 cm^{-1} (Ar).

Maleate, m.p. 108—110°C (acetone–methanol–ether). For $C_{24}H_{27}ClN_2O_6S$ (507·0) calculated, 56·85% C, 5·37% H, 6·99% Cl, 5·53% N, 6·32% S; found: 56·79% C, 5·24% H, 6·91% Cl, 5·61% N, 6·23% S.

2-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin N^4,S-Dioxide (*X*)

A mixture of 4·5 g *VII*, 50 ml ethanol and 25 ml 29% H_2O_2 was heated to 70°C and then allowed to stand for 3 days at room temperature. It was partly evaporated under reduced pressure, diluted with H_2O and extracted with chloroform. Processing gave 4·3 g (68%) base, m.p. 188—198°C (acetone). Analytical sample, m.p. 205—206°C (ethanol–acetone). Polarographic reduction in 0·5M-HCl at $E_{1/2}$ —0·35 V (N—O) and —0·65 V (S—O). IR spectrum (KBr): 760, 840, 870 (4 and 2 adjacent and solitary Ar—H), 977 (N—O), 1080 (S—O), 1550, 1581, 3010, 3060, 3095 cm^{-1} (Ar). For $C_{20}H_{23}ClN_2O_3S$ (406·9) calculated: 59·03% C, 5·70% H, 8·71% Cl, 6·88% N, 7·88% S; found: 59·30% C, 5·89% H, 8·84% Cl, 6·82% N, 7·61% S.

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