8-CHLORO-3-HYDROXY-10-PIPERAZINO--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS, THEIR O-METHYL DERIVATIVES AND FURTHER POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENT OCTOCLOTHEPIN*

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Several potential metabolites of octoclothepin (*III*), having an oxygen function in position 3 were synthesized. 8,10-Dichloro-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin was transformed *via* the ethoxycarbonylpiperazine derivative *VI* to the 3-methoxy derivative of noroctoclothepin (*VII*) which was demethylated to afford the 3-hydroxy derivative *X*. Methanesulfonates of noroctoclothepin (*XVI*), 3-hydroxy (*IV*) and 3-methoxy derivative of octoclothepin (*V*) and compound *VII* were oxidized with hydrogen peroxide in aqueous solution to the sulfoxides *XII*—*XV*. Sulfoxides *XIV* and *XV* are typical by a rather high toxicity on intravenous administration; in comparison with octoclothepin, all the new substances are considerably weaker in tests for central depressant and cataleptic activity. The adrenolytic activity is mostly preserved (*VII*, *X*, *XIV*, *XV*). *X* was the relatively most active compound from the point of viev of central effects.

The extensive knowledge of the metabolism of the neuroleptic agent chlorpromazine (*I*) (75 metabolites detected, at least 33 of them identified by the help of synthetic standards[1]) is a steady lead for our own studies of biotransformation of the chemically somewhat related neuroleptic octoclothepin (*III*) (ref.[2-4]). With regard to the fact that the 7-hydroxy derivative (*II*) (ref.[5]) of chlorpromazine (*I*) is an important metabolite of *I*, some time ago, we carried out a synthesis of the corresponding 3-hydroxy derivative of octoclothepin (*IV*) (ref.[6]) and could establish that this compound, when administered orally, is significantly less toxic than octoclothepin and at the same time approximately twice as active in the tests of ataxia and catalepsy. The literature[1] reports that during the biotransformation of chlorpromazine (*I*), the common S-oxidation and N-demethylation take place in addition to the hydroxylation of the aromatic nucleus leading to the monodemethyl and didemethyl analogues of compound *II* and to all the three corresponding sulfoxides as metabolites. The main object of the present paper is to describe the synthesis of some new derivatives

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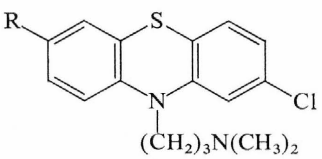
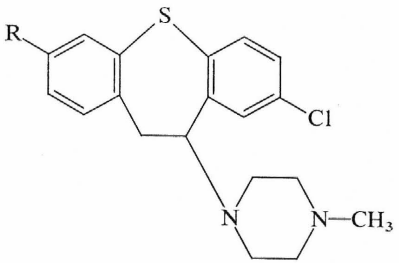
of octoclothepin (*III*) and its demethyl analogue *XVI* having an oxygen function (methoxyl or hydroxyl) in position 3 and of the corresponding sulfoxides. From these products, compounds with the free phenolic function in position 3 may be considered very probable potential metabolites; because of the fact that O-methylation of the phenolic compounds was also identified as one of the metabolic routes in the chlorpromazine complex[7,8], our 3-methoxy derivatives can also be considered potential metabolites of octoclothepin.



I; R = H
II; R = OH

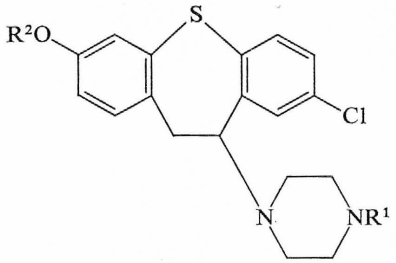


III; R = H
IV; R = OH
V; R = OCH_3

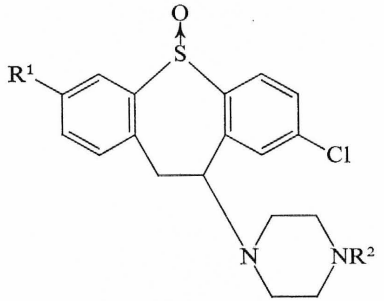
Reaction of 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin[6] with 1-(ethoxycarbonyl)piperazine yielded the carbamate *VI* which was transformed by alkaline hydrolysis to the secondary amine *VII*. Its formylation with ethyl formate in the autoclave at 120–130°C, and acetylation with acetic anhydride in acetic acid, led to amides *VIII* and *IX*. The formamido compound *VIII* was reduced with lithium aluminium hydride to the N-methyl derivative *V* (ref.[6]) which represents a new way of formation of this compound. Its demethylation with boron tribromide to the phenolic compound *IV* was repeated (*cf.*[6]); there were some differences in comparison with the previous work which are mentioned in the Experimental. The ^{1}H-NMR spectrum of the actually obtained product (the maleate of compound *IV*) confirmed, however, the absence of the O-methyl group and thus the desired course of the demethylation reaction. Similar demethylation of compound *VII* afforded the phenolic secondary amine *X*.

The sulfides *XVI*, *IV*, *V* and *VII* were oxidized in the form of methanesulfonates with hydrogen peroxide in aqueous solutions to the sulfoxides *XII*–*XV*; this method was used for the first time for the preparation of the sulfoxide *XI* by oxidation of octoclothepin (*III*) (ref.[9]). The sulfoxide *XII* has already been prepared by oxidation of the sulfide *XVI* with sodium periodate in aqueous methanol[9]. The band at 1060 to 1070 cm^{-1} in the infrared spectra on the one hand and the typical polarographic reduction on the other were used for the identification of the sulfoxides prepared. The low yields of the individual sulfoxides are to be explained by the fact that the

S-oxidation is connected with the formation of a second centre of chirality; the purification procedures represent thus in fact separation of mixtures of stereoisomers.



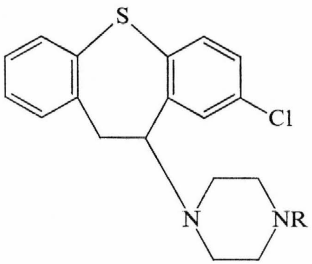
VI; $R^1 = COOC_2H_5$, $R^2 = CH_3$
VII; $R^1 = H$, $R^2 = CH_3$
VIII; $R^1 = CHO$, $R^2 = CH_3$
IX; $R^1 = COCH_3$, $R^2 = CH_3$
X; $R^1 = R^2 = H$



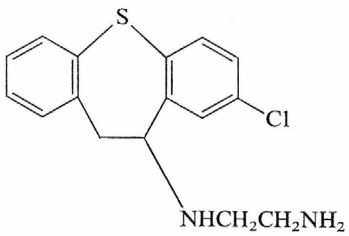
XI; $R^1 = H$, $R^2 = CH_3$
XII; $R^1 = R^2 = H$
XIII; $R^1 = OH$, $R^2 = CH_3$
XIV; $R^1 = OCH_3$, $R^2 = CH_3$
XV; $R^1 = OCH_3$, $R^2 = H$

In one of the preceding communications[10] we described the synthesis of the hydroxylamine derivative *XVIII* as a potential metabolite of octoclothepin (*III*); it was obtained by oxidation of noroctoclothepin (*XVI*) (ref.[11]) with benzoyl peroxide in a mixture of chloroform and ether and by the following alkaline hydrolysis of the benzoyloxy derivative *XVII*. For getting a sample for pharmacological evaluation and spectral characterization of compound *XVIII*, we repeated its preparation in a somewhat larger scale. In the first line, it has been found by means of TLC that the intermediate *XVII*, in the form used for the hydrolysis, was not completely homogeneous and was contaminated by more polar components. The alkaline hydrolysis afforded a mixture from which the base *XVIII* was easily isolated in a rather low yield, being evidently identical with the product obtained earlier[10]. Its identity was now corroborated by recording the mass and infrared spectra. Neutralization with maleic acid yielded a maleate, distinctly different from the salt described in our mentioned paper[10] and designated as the di(hydrogen maleate). The identity of the salt and its relation to the base *XVIII* was confirmed by the mass spectrum. Mother liquors after the base *XVIII* were also neutralized with maleic acid and another maleate was obtained, having a melting point very close to that of the salt described in our preceding paper[10]. Decomposition of this maleate with alkali afforded a homogeneous oily base, being according to the TLC significantly more polar than the base *XVIII*. The ^{1}H-NMR spectrum identified this base unequivocally as the ethylenediamine derivative *XIX* which was in agreement with the infrared spectrum. The mass spectrum of the maleate showed the molecular ion *m/e* 304, corresponding

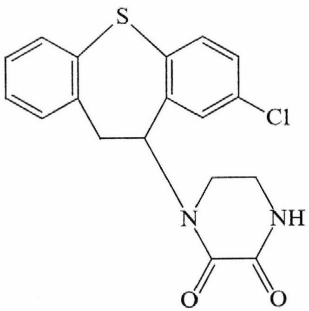
to $C_{16}H_{17}ClN_2S$, *i.e.* the empirical formula of the base *XIX*. The analysis of the maleate indicated it to be the ethanol solvate of the bis(hydrogen maleate) of base *XIX*. The ethylenediamine derivative *XIX* has recently been prepared by us[12] by a substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] with ethylenediamine. Comparison of the ^{1}H-NMR spectra of the authentic base *XIX* and of the product now having been isolated proved the identity of both substances. Direct comparing of the bis(hydrogen maleates) proved more difficult because of the formation of various solvates. Anyway, it is necessary to accept the formation of compound *XIX* as a by-product of oxidation of the secondary amine *XVI* with benzoyl peroxide and of the following alkaline hydrolysis. The consequence is the question about the origin of this rather surprising by-product.* We suppose that oxidation of the amine *XVI* to the N-benzoyloxy derivative *XVII* is accompanied



XVI; R = H
XVII; R = $OCOC_6H_5$
XVIII; R = OH



XIX



XX

* *Note added in proof*: In a discussion on this reaction, Prof. J. P. Kutney, Department of Chemistry, University of British Columbia, Vancouver, Canada, suggested to consider a Polonovski-type fragmentation (*cf.* ref.[13] and references cited therein).

TABLE I

Pharmacological Properties of 8-Chloro-3-hydroxy-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]-thiepins, Their O-Methyl Derivatives and Some Related Compounds (doses in mg/kg)

Compound[a]	Code number	Administration	Acute toxicity LD_{50}[b]	Basic dose D[c]	Rotating rod ED_{50}[d]	Catalepsy ED_{50}[e]	Further effects
I	—	*i.p.*	—	—	—	4·0	—
II (ref.[5])	—	*i.p.*	—	—	—	8·6	—
III (ref.[4])	—	oral	78	—	2·2	4·3	—
III (ref.[4])	—	*i.v.*	46	—	0·06	2·4	—
IV (ref.[6])	—	oral	350	—	0·84	2·4	—
V (ref.[6])	—	oral	185	—	2·1	7·2	—
VII	VÚFB-10.688	*i.v.*	25	5	>5	>5	[f]
X	VÚFB-10.704	*i.v.*	35	8	5·2	>8	[g]
XI[3,9]	VÚFB- 6·290	oral	72	—	—	—	—
XIV	VÚFB-10.706	*i.v.*	8	2	>2	[h]	[i]
XV	VÚFB-10.705	*i.v.*	17·5	3	>3	[h]	[j]
XVIII	VÚFB-12.502	oral	[h]	—	10·2	22·0	—

[a] The compounds were tested in the form of salts but the doses given were calculated for bases. [b] Acute toxicity was determined in mice in groups by 10 animals (in the cases of *VII*, *X*, *XIV*, and *XV* in groups by 5 animals). [c] Dose in which the compound was administered in the *in vivo* tests in the general screening. [d] Mean effective dose bringing about ataxia in mice. [e] Mean effective doses bringing about catalepsy in rats; intraperitoneal administration was used as the parenteral route. [f] Weak central depressant effect at doses higher than D; sign of cataleptic activity at the dose given; hypotensive effect in normotensive anaesthetized (pentobarbital) rats (a dose of 5 mg/kg brings about a drop of blood pressure by 20% for at least 10 min); adrenolytic effect in rats (a dose of 2·5 mg/kg reduces the adrenalinehypertensive reaction to 50%); diminishes the heart inotropy in the isolated rabbit atrium (a concentration of 10—50 μg/ml reduces the inotropy by 25%); anticonvulsant effect (oral dose of 25 mg/kg) in mice towards pentetrazole; spasmolytic effect on the isolated rat duodenum towards barium chloride contractions (a concentration of 1—10 μg/ml inhibits the contractions by 50%, *i.e.* approximately the intensity of the effect of papaverine). [g] Significant central depressant activity in mice (doses of 1·0—2·5 mg/kg *s.c.* inhibit the motility in known or unknown surroundings by 50%); sign of cataleptic effect in the dose given; potentiation of the thiopental sleeping time in mice (a dose of 0·5—1·0 mg/kg prolongs the sleeping time by 100%); antihistamine effect in guinea pigs in the test of histamine detoxication (the dose D, administered subcutaneously, protects 100% animals from the lethal effect of 5 mg/kg histamine administered intrajugularly); antiamphetamine effect in mice (the dose D protects 100% animals from the lethal effect of 30 mg/kg amphetamine *i.p.*); analgetic effect in the Haffner test in mice (a dose of 2·5—5·0 mg/kg brings about analgesia in 50% animals, *i.e.* almost full intensity of the pethidine effect); hypotensive effect in rats (ED = 2 mg/kg); very strong adrenolytic effect in rats (ED = 0·1 μg/kg); antiarrhythmic effect in rats towards aconitine infusion. [h] Was not estimated. [i] In doses higher than D in mice first excitation followed

by a parallel oxidation to the cyclic oxalamide *XX* which is the precursor of the diamine *XIX*, formed by alkaline hydrolysis. Unfortunately, we have neither experimental evidence, nor analogy from the literature for supporting this hypothesis. The identity of the maleate, described earlier[10] as being derived from the base *XVIII*, has to be considered as dubious; we were dealing here rather with the maleate of the base *XIX*.

The substances prepared were subjected to a preliminary pharmacological evaluation with regard to their structural relationship to octoclothepin (*III*), *i.e.*, in the first line, as potential neuroleptics. The information was completed by methods of the general pharmacological screening. The results are summarized in Table I including as standards octoclothepin (*III*) (ref.[4]) (data for oral as well as for parenteral administration), its 3-hydroxy derivative *IV* and 3-methoxy derivative *V* (ref.[6]). It is apparent that the compounds with an oxygen function in position 3 (*VII*, *X*, *XIV*, *XV*), all administered parenterally, are rather weak from the point of view of central effects. In this line, the relatively most effective is the 3-hydroxy derivative of noroctoclothepin (*X*), which inhibits spontaneous motility, brings about ataxia, potentiates thiopental narcosis, has antiamphetamine, antihistamine and analgesic activity and a very significant adrenolytic effect. This last named effect in various intensity is a common property of the substances prepared. The sulfoxides *XIV* and *XV* were shown to have a weaker spasmolytic activity of the anticholinergic type; on the other hand, the myotropic antispasmodic activity attains by the intensity in some cases the activity of papaverine (*VII*, *XIV*). With *VII* and *XIV*, an anticonvulsant effect towards pentetrazole was noted and in two other cases (*X*, *XV*) an antiarrhythmic effect towards aconitine. The sulfoxides *XIV* and *XV* are typical by the rather high toxicity after intravenous administration. In connection with this phenomenon, mentioned earlier[3,9], the oral toxicity of octoclothepin-S-oxide (*XI*) has now been determined. The values in Table I show that upon oral administration, there is almost no difference between the toxicity of octoclothepin (*III*) and its S-oxide (*XI*). An increase of toxicity by S-oxidation is thus probably limited only to parenteral administration. The hydroxylamine derivative *XVIII*, appearing also in Table I, has only mild incoordinating and cataleptic activity; in both lines, it is about five times weaker than octoclothepin and equals approximately chlorpromazine.

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by a mild depression; anticonvulsant effect (oral dose of 10 mg/kg) in mice against pentetrazole; adrenolytic effect in rats (ED = 2 mg/kg); negative inotropic effect in the isolated rabbit atrium (concentration of 25–50 μg/ml); spasmolytic effect on the isolated rat duodenum towards acetylcholine, as well as barium chloride contractions (concentration of 1–10 μg/ml, *i.e.* 1% of the atropine effect and the full papaverine effect). [j] Inhibits the spontaneous motility of mice in known surrounding (ED = 3 mg/kg *s.c.*); adrenolytic effect in rats (ED = 0·5 mg/kg); antiarrhythmic effect in rats against aconitine (ED = 3 mg/kg); spasmolytic effect on the isolated rat duodenum towards acetylcholine (1% of the atropine effect).

In our foregoing paper[6] we mentioned literature data about pharmacological properties of the 7-hydroxy derivative of chlorpromazine (*II*) among which the information on cataleptic activity was missing. This gap has now been filled by our own estimation of this effect and the result is given in Table I in comparison with the cataleptic activity of chlorpromazine (*I*). It is apparent that upon intraperitoneal administration, 7-hydroxy derivative *II* preserves approximately 50% of the cataleptic activity of chlorpromazine. Even in this test, it has thus been shown that the hydroxylated metabolite is neuroleptically significantly more active than the corresponding sulfoxide; it is a further contribution to the topic discussed in the mentioned paper[6].

Compounds *VII*, *X* and *XIV* were also tested for antimicrobial activity *in vitro* towards a series of typical microorganisms (carried out by Dr J. Turinová and Dr A. Čapek, bacteriological department of this institute). Microorganisms, numbers of compounds (tested in the form of salts described in the Experimental) and finally the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *VII* 50, *X* 25; *Streptococcus faecalis*, *VII* 25, *X* 25; *Staphylococcus pyogenes aureus*, *VII* 25, *X* 25; *Mycobacterium tuberculosis* H37Rv, *VII* 12·5, *X* 12·5, *XIV* 25; *Escherichia coli*, *X* 100; *Saccharomyces pasterianus*, *VII* 50, *X* 100, *XIV* 100; *Trichophyton mentagrophytes*, *VII* 50, *X* 50, *XIV* 100; *Candida albicans*, *VII* 100, *X* 100, *XIV* 100; *Aspergillus niger*, *VII* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder. The samples were dried at about 0·5 Torr 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 CD_3SOCD_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) or a Varian MAT 311 spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of alumina.

8-Chloro-10-(4-ethoxycarbonylpiperazino)-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VI*)

A mixture of 62 g 8,10-dichloro-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]-thiepin[6] and 130 g 1-(ethoxycarbonyl)piperazine was stirred and heated to 105—110°C for 5 h. After cooling, the mixture was diluted with 150 ml water and extracted with benzene. The extract was washed with water and then shaken with 250 ml 1 : 1 dilute hydrochloric acid. The oily hydrochloride separated was combined with the aqueous layer, made alkaline with NH_4OH and the oily base was isolated by extraction with benzene; 63 g (73%). The oily product was used for further work. A sample was neutralized with maleic acid in ethanol and gave the hydrogen maleate, m.p. 127—128°C (acetone–light petroleum). For $C_{26}H_{29}ClN_2O_7S$ (549·0) calculated: 56·88% C, 5·32% H, 6·46% Cl, 5·10% N, 5·84% S; found: 56·70% C, 5·34% H, 6·31% Cl, 5·01% N, 6·00% S.

8-Chloro-3-methoxy-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VII*)

A mixture of 63 g crude *VI*, 32 g KOH and 65 ml ethanol was stirred and refluxed (bath temperature 120°C) for 3 h. After cooling, the mixture was diluted with 250 ml water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated *in vacuo*;

49 g (93%) oily base suitable for further work. A sample was neutralized with maleic acid in acetone giving the maleate, m.p. 171°C (ethanol). ^{1}H-NMR spectrum: δ 7·55 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·48 (d, J = 8·0 Hz, 1 H, 6-H), 7·32 (d, J = 8·0 Hz, 1 H, 1-H), 7·15 (mcd, J = 8·0; 2·0 Hz, 1 H, 7-H), 7·02 (mcs, J = 3·0 Hz, 1 H, 4-H), 6·82 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 6·00 (s, 2 H, CH=CH of maleic acid), 3·68 (s, 3 H, OCH_3), 2·50—4·20 (m, $ArCH_2CHAr$ and 4 NCH_2 of piperazine). For $C_{23}H_{25}ClN_2O_5S$ (477·0) calculated: 57·92% C, 5·28% H, 7·43% Cl, 5·87% N, 6·72% S; found: 58·07% C, 5·43% H, 7·79% Cl, 5·74% N, 6·80% S.

8-Chloro-10-(4-formylpiperazino)-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIII*)

A solution of 10·0 g crude *VII* in 70 ml ethyl formate was heated in an autoclave to 120—130°C for 5 h. After cooling, the excess of ethyl formate was evaporated. The amorphous and homogeneous amide *VIII* was obtained in the theoretical yield (10·7 g). Neutralization with maleic acid in a mixture of ethanol and ether produced the crystalline hydrogen maleate, m.p. 107 to 108°C (acetone–light petroleum). IR spectrum: 1 680, 3 590 cm^{-1} (N—CHO). For $C_{24}H_{25}$·$.ClN_2O_6S$ (505·0) calculated: 57·08% C, 4·99% H, 7·02% Cl, 5·55% N, 6·35% S; found: 56·38% C, 5·05% H, 7·06% Cl, 5·62% N, 6·45% S.

10-(4-Acetylpiperazino)-8-chloro-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IX*)

A mixture of 3·0 g *VII*, 20 ml acetic acid and 2·0 g acetic anhydride was refluxed for 3 h. Volatile fractions were evaporated *in vacuo*, the residue dissolved in 30 ml benzene and the solution shaken with 30 ml 3M-HCl. The separated oily hydrochloride was combined with the aqueous layer, the mixture was made alkaline with NH_4OH and the base isolated by extraction with benzene. The extract was dried and evaporated under reduced pressure. The residue was dissolved in 5 ml methanol and the solution left for 2 days at room temperature; 2·12 g (64%), m.p. 154—156°C. Analytical sample, m.p. 157°C (methanol). IR spectrum 809, 829, 841, 889, 893 (2 adjacent and solitary Ar—H), 1 003, 1 254, 1 270 (Ar—O—CH_3), 1 495, 1 601 (Ar), 1 650 cm^{-1} (NCOR). ^{1}H-NMR spectrum ($CDCl_3$) δ 7·58 (mcs, J = 2·5 Hz, 1 H, 9-H), 7·30 (d, J = 8·0 Hz, 1 H, 6-H), 7·12 (d, J = 8·0 Hz, 1 H, 1-H), 7·02 (mcs, J = 2·5Hz, 1 H, 4-H), 7·00 (mcd, J = 8·0; 2·5 Hz, 1 H, 7-H), 6·72 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 3·70 (s, 3 H, OCH_3), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), *c.* 3·50 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·05 (s, 3 H, $COCH_3$). For $C_{21}H_{23}ClN_2O_2S$ (402·9) calculated: 62·60% C, 5·75% H, 8·80% Cl, 6·95% N, 7·96% S; found: 62·67% C, 5·89% H, 8·76% Cl, 6·75% N, 7·70% S.

8-Chloro-3-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*V*)

A solution of 22 g *VIII* in 150 ml ether and 100 ml tetrahydrofuran was added dropwise over 1 h to a stirred suspension o 8·9 g $LiAlH_4$ in 250 ml ether. The mixture was then refluxed for 8 h. After standing overnight, it was decomposed by gradual addition of 8·8 ml water, 8·8 ml 15% NaOH and 26 ml water. After 30 min of stirring, the precipitated solid was removed by filtration, the filtrate dried and evaporated. The residue (17·4 g, 82%) crystallized from a mixture of 25 ml ethanol and 25 ml light petroleum; 10·0 g (47%), m.p. 124—127°C. For the same substance, prepared previously[6] by a different method, we reported a m.p. of 130—131°C. The identity was proven by TLC and the mixed melting point determination.

8-Chloro-3-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IV*)

The demethylation of 7·9 g *V* with 15·8 g BBr_3 in 135 ml chloroform was repeated according to our previous paper[6]. The final product was crystallized from aqueous ethanol giving 4·8 g

substance melting at 106—108°C (the value reported previously[6] was 222—223°C). Evidently, we are dealing here with a solvate of *IV*. It was transformed to the maleate, m.p. 206°C (aqueous ethanol). Its ^{1}H-NMR spectrum proved the absence of the methoxyl group: δ 7·50 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·38 (d, J = 8·0 Hz, 1 H, 6-H), *c.* 7·15 (m, 2 H, 1,7-H_2), 6·85 (mcs, J = 3·0 Hz, 1 H, 4-H), 6·64 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 6·00 (s, 2 H, CH=CH of maleic acid), 2·50 to 4·00 (m, $ArCH_2CHAr$ and 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{23}H_{25}ClN_2O_5S$ (476·9) calculated: 57·92% C, 5·28% H, 7·43% Cl, 5·87% N, 6·72% S; found: 58·03% C, 5·23% H, 7·43% Cl, 5·79% N, 6·88% S.

8-Chloro-3-hydroxy-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*X*)

A solution of 7·2 g oily *VII* in 80 ml chloroform was treated dropwise at 15°C with a solution of 5·64 ml BBr_3 in 60 ml chloroform. The mixture was stirred for 4 h, chloroform was evaporated *in vacuo* and the residue dissolved in a mixture of 220 ml ethanol and 80 ml water. The mixture was stirred and refluxed for 5 h, evaporated *in vacuo*, the residue diluted with 150 ml 10% Na_2CO_3 and extracted with chloroform. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue (5·7 g) was dissolved in a mixture of 185 ml ethanol and 100 ml 3% NaOH and refluxed for 3 h. After the evaporation of ethanol *in vacuo*, the residue was diluted with 160 ml water and the solution treated with 3·5 ml acetic acid. The precipitated product (4·7 g) was filtered after standing overnight, washed with water and dried, m.p. 123—127°C. It was transformed by neutralization with maleic acid in ethanol to the maleate; 3·5 g (56%), m.p. 189°C (ethanol–ether). ^{1}H-NMR spectrum δ 7·53 (mcs, J = 2·5 Hz, 1 H, 9-H), 7·39 (d, J = 8·0 Hz, 1 H, 6-H), 7·17 (d, J = 8·0 Hz, 1 H, 1-H), 7·15 (mcd, J = 8·0; 2·5 Hz, 1 H, 7-H), 6·87 (mcs, J = 2·0 Hz, 1 H, 4-H), 6·65 (mcd, J = 8·0; 2·0 Hz, 1 H, 2-H), 6·00 (s, 2 H, CH=CH of maleic acid), 2·50—4·00 (m, $ArCH_2CHAr$, 4 NCH_2 of piperazine). For $C_{22}H_{23}ClN_2O_5S$ (462·9) calculated: 57·08% C, 5·01% H, 7·66% Cl, 6·05% N, 6·92% S; found: 57·04% C, 4·93% H, 7·66% Cl, 5·75% N, 7·01% S.

8-Chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*XII*)

8-Chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[11] (*XVI*, 25 g) and 7·26 g methanesulfonic acid were dissolved in 250 ml warm water, the cooled solution was treated with 96 ml 26% H_2O_2 and the mixture was left for 24 h at room temperature. It was filtered with charcoal, the filtrate was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with $MgSO_4$ and evaporated giving 20·5 g amorphous base (homogeneous according to TLC). Neutralization with 6·86 g maleic acid in 70 ml ethanol and addition of ether gave 25 g crude maleate melting unsharply at 148—158°C. Two crystallizations from ethanol yielded 8·3 g maleate, m.p. 174°C, identical with the compound described previously[9] using a different method of oxidation. Its polarography in 0·5M-HCl showed a single wave at −0·53 V against a saturated calomel electrode, corresponding to reduction of the sulfoxide group.

8-Chloro-3-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*XIII*)

Like in the preceding case, 1·7 g *IV* and 0·55 g methanesulfonic acid were dissolved in 25 ml water and the solution was oxidized with 12 ml 27% H_2O_2 at room temperature. Processing of the mixture gave 0·80 g (45%) of base, m.p. 211—215°C. Analytical sample, m.p. 235—236°C (acetone). IR spectrum 815, 833, 851, 872, 892 (2 adjacent and solitary Ar—H), 1066, 1088 (Ar—SO—Ar), 1159, 1280 (Ar—OH), 1502, 1615 (Ar), 2795 (N—CH_3), 3305 cm^{-1} (OH). For $C_{19}H_{21}ClN_2O_2S$ (376·9) calculated: 60·55% C, 5·62% H, 9·41% Cl, 7·43% N, 8·50% S; found: 60·86% C, 5·75% H, 9·51% Cl, 7·41% N, 8·49% S.

Maleate, m.p. 199°C (acetone–ether). For $C_{23}H_{25}ClN_2O_6S$ (492·9) calculated: 56·04% C, 5·11% H, 7·19% Cl, 5·68% N, 6·50% S; found: 56·17% C, 5·39% H, 7·15% Cl, 5·47% N, 6·60% S.

8-Chloro-3-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*XIV*)

Like in the preceding cases, 4·50 g *V* (ref.[6]) and 1·50 g methanesulfonic acid in 40 ml water were treated at room temperature with 10 ml 26% H_2O_2. Processing of the mixture produced 4·2 g (91%) amorphous base which was transformed to the maleate, m.p. 170—171°C (ethanol). IR spectrum: 1065 cm^{-1} (Ar—SO—Ar). For $C_{24}H_{27}ClN_2O_6S$ (507·0) calculated: 56·85% C, 5·36% H, 6·99% Cl, 5·52% N, 6·32% S; found: 56·90% C, 5·58% H, 7·03% Cl, 5·83% N, 6·29% S.

8-Chloro-3-methoxy-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*XV*)

Like in the preceding cases, a solution of 5·0 g *VII* and 1·7 g methanesulfonic acid in 50 ml water was oxidized with 11 ml 26% H_2O_2. Processing of the mixture gave 2·6 g amorphous base which was neutralized with maleic acid to afford 2·5 g (49%) crude maleate, m.p. 152—160°C. Analytical sample, m.p. 177—179°C (ethanol). IR spectrum (KBr): 1042, 1069 cm^{-1} (SO). ^{1}H-NMR spectrum δ 7·75 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·62 (d, J = 8·0 Hz, 1 H, 6-H), 7·44 (mcd, J = 8·0; 2·0 Hz, 1 H, 7-H), 7·20 (d, J = 8·0 Hz, 1 H, 1-H), 7·10 (mcs, J = 3·0 Hz, 1 H, 4-H), 6·88 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 6·00 (s, 2 H, CH=CH of maleic acid), 3·70 (s, 3 H, OCH_3), 2·50 to 4·40 (m, $ArCH_2CHAr$, 4 NCH_2 of piperazine). For $C_{23}H_{25}ClN_2O_6S$ (493·0) calculated: 56·03% C, 5·11% H, 7·19% Cl, 5·68% N, 6·50% S; found: 55·86% C, 5·42% H, 6·99% Cl, 5·52% N, 6·60% S.

8-Chloro-10-(4-hydroxypiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIII*)

A mixture of 4·5 g crude 10-(4-benzoyloxypiperazino)-8-chloro10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVII*) (ref.[10]), 1·5 g KOH, 120 ml ethanol and 8 ml water was refluxed for 1 h. Standing and cooling produced 0·90 g substance, melting unsharply at 183—192°C, which was identical with the hemihydrate of base *XVIII*, obtained previously[10]. Its characterization has now been completed by recording the spectra. IR spectrum (KBr): 771, 812, 836, 898 (4 and 2 adjacent and solitary Ar—H), 3062 (Ar), 3220, 3430 cm^{-1} (OH). The mass spectrum exhibits a molecular ion *m/e* 346·0892 (7·5%), corresponding to the expected $C_{18}H_{19}ClN_2OS$; main fragments: 329 (15), 273 (17), 245 (100), 210 (43).

Neutralization of the base *XVIII* with maleic acid in ethanol yielded the maleate of m.p. 174—175°C with decomposition (equeous ethanol). The mass spectrum demonstrated the relation of this salt to the base *XVIII* : *m/e* 346·0919 (M^+, 12%), 329 (10), 245 (100), 210 (32), 167 (15). UV spectrum: λ_{max} 266 nm (log ε 3·98). For $C_{22}H_{23}ClN_2O_5S$ (462·9) calculated: 57·07% C, 5·00% H, 7·66% Cl, 6·05% N, 6·93% S; found: 57·01% C, 5·10% H, 7·50% Cl, 6·02% N, 6·90% S.

The mother liquor after the base *XVIII* was partly evaporated and left for 10 days at room temperature; 0·60 g separated solid was filtered off, the filtrate was evaporated *in vacuo* and the residue (2·6 g) was transformed by neutralization with 1·65 g maleic acid to a maleate (1·0 g) which was identified as the ethanol solvate of 10-(2-aminoethylamino)-8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIX*) bis(hydrogen maleate), m.p. 124—130°C (aqueous ethanol). Mass spectrum: *m/e* 304 (M^+, 10%, corresponds to $C_{16}H_{17}ClN_2S$), 274 (24), 245 (100), 210 (50), 178 (20), 165 (30). For $C_{24}H_{25}ClN_2O_8S + C_2H_6O$ (583·0) calculated: 53·55% C, 5·36% H, 6·08% Cl, 4·81% N, 5·50% S; found: 53·51% C, 5·44% H, 6·02% Cl, 4·81% N, 5·38% S. This salt is very probably identical with the hydrogen maleate (m.p. 126—128°C), prepared by us[10] from the mother liquors after the base *XVIII* and erroneously considered to be derived from this base. In another paper[12] we described the maleate of the authentic base *XIX* and reported the m.p. of 129—131°C with decomposition; this salt, howewer, was a hemihydrate.

The maleate of base *XIX* now obtained was decomposed with NH_4OH, the oily base was isolated by extraction with benzene and used for recording the spectra. IR spectrum (film): 758, 822, 890 (4 and 2 adjacent and solitary Ar—H), 1469, 1570, 1586, 3020, 3073 (Ar), 3310, 3378 cm^{-1} (NH, NH_2). ^{1}H-NMR spectrum ($CDCl_3$): δ 6·90—7·50 (m, 7 H, Ar—H), 4·62 (dd, J = = 4·0; 8·0 Hz, 1 H, Ar—CH—N), 3·45 and 3·25 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·72 (m, 4 H, N—CH_2CH_2—N), 1·62 (s, disappears after D_2O, 3 H, NH and NH_2). These spectra are identical with those of the authentic *XIX* (ref.[12]).

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