POTENT NEUROLEPTIC AGENTS: SOME NEW AMINO ALCOHOLS OF THE 10-PIPERAZINODIBENZO[*b*,*f*]THIEPIN SERIES AND THEIR DERIVATIVES*

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Reactions of 8,10-dichloro-, 10-chloro-8-methoxy- and 10-chloro-8-methylthio derivatives of 10,11-dihydrodibenzo[*b*,*f*]thiepin with 1-(2-hydroxyethyl)piperazine and 1-(2-hydroxypropyl)-piperazine resulted in amino alcohols *Ib*, *Ic* and *IIIa*. Amino alcohol *IVa* was obtained by acylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin with 2-(ethoxycarbonyl)propionyl chloride and by reduction of the product with lithium aluminium hydride. Starting from the same compound and from the analogous 8-methylthio derivative, alkylation with 3-chloropropane-1,2-diol led to aminodiols *Va* and *Vc*. Acylation of *Ib*, *Ic* and *IIIa* with decanoyl chloride led to esters *VIb*, *VIc* and *VIIa*. Acid-catalyzed reactions of alcohols *Ia* and *IIc* with cyclododecanone dimethyl acetal resulted in the enol–ethers *VIIIa* and *IXc*. Oxidation of *Ia* and *Ic* gave rise to the S-oxides *X* and *Id* and to N-oxides *XIa* and *XId*. Heating of 8-chloro- and 8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*)-one with monotosylates of 1-(2-hydroxyethyl)piperazine and 1-(3-hydroxypropyl)piperazine *in vacuo* at 190°C resulted in enamines *XIIa* and *XIIIc*, the first of which was oxidized to the N-oxide *XIV*. Reduction of enamine *XIIIc* with zinc in acetic acid represents a preparative method for oxyprothepin (*IIc*). Amino alcohols *Ib*, *Ic*, *IIIa*, *IVa*, *Va* and *Vc* are powerful neuroleptics with a high degree of cataleptic and central depressant activity. With the N-oxides *XIa*, *XId* and *XIV* the cataleptic effect predominates over the sedative one; dissociation of both types of effect is displayed in the unstable compound *XIV*, the cataleptic effect of which is extremely high.

In several previous communications of this series[1–4] we reported on the high degree of central depressant and neuroleptic activity of N-(hydroxyalkyl) derivatives of 8-substituted 10-piperazinodibenzo[*b*,*f*]thiepins. Of these amino alcohols the greatest interest was aroused by noroxyclothepin[1,2] (*Ia*), oxyclothepin[1,2] (*IIa*), oxymetothepin[1,2] (*IIb*) and especially oxyprothepin[1,2,5–10] (*IIc*) which proved its antipsychotic efficacy in schizophrenia and manic syndromes[11–13]. Oxyprothepin (*IIc*) was recently examined for its molecular structure[14] by the X-ray method and studies of its metabolism were started[15–18]. The amino alcohols are investigated not only for their activity as such but especially as a basis for the preparation of depot ester

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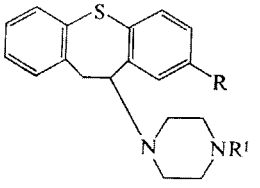
compounds[2]. Of these, the greatest interest was aroused by oxyprothepin decanoate (*IIc*-decanoate)[19–21]. In the present communication we describe several new amino alcohols of this series and some of their derivatives (esters, cyclic enol-ethers, sulfoxides, N-oxides and 10,11-dehydroanalogues).



Substituent R in formulae:
a, R = Cl
b, R = OCH_3
c, R = SCH_3
d, R = $SOCH_3$

I, $R^1 = CH_2CH_2OH$
II, $R^1 = (CH_2)_3OH$
III, $R^1 = CH_2CH(CH_3)OH$
IV, $R^1 = CH_2CH(CH_3)CH_2OH$
V, $R^1 = CH_2CH(OH)CH_2OH$

VI, $R^1 = (CH_2)_2OCO(CH_2)_8CH_3$
VII, $R^1 = CH_2CH(CH_3)OCO(CH_2)_8CH_3$
VIII, $R^1 = (CH_2)_2O-C(=CH)-(CH_2)_{10}$
IX, $R^1 = (CH_2)_3O-C(=CH)-(CH_2)_{10}$

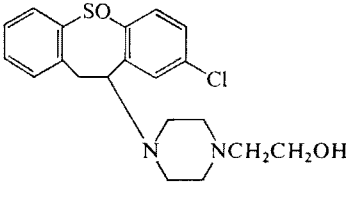
Substitution reactions of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[22], 10-chloro-8-methoxy- and 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[23] with 1-(2-hydroxyethyl)piperazine and 1-(2-hydroxypropyl)piperazine[24] in boiling chloroform (method *A*) led to new amino alcohols *Ib*, *Ic* and *IIIa*. For the preparation of amino alcohol *IVa*, the starting compound used was 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] which was acylated with 2-(ethoxycarbonyl)-propionyl chloride[25]. The resulting ester-amide was reduced without characterization in the crude state with lithium aluminium hydride. The aminodiols *Va* and *Vc* were obtained by alkylation of 8-chloro- and 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] with 3-chloropropane-1,2-diol in dimethylformamide in the presence of potassium hydroxide (method *B*). Amino alcohols *Ib*, *Ic* and *IIIa* were esterified with decanoyl chloride[26] in chloroform (method *C*, see ref.[2]) to esters *VIb*, *VIc* and *VIIa* which were purified by crystallization of the dimaleates. These esters are potential depot neuroleptics, the protracted effect of which is based on the fact that on intramuscular injection of their solutions in vegetable oils they are only slowly resorbed and the effective amine alcohol is liberated only then by serum and tissue hydrolases. A new type of potential neuroleptics prepared were the cyclododecanone enol-ethers *VIIIa* and *IXc* (for analogy see the series of steroid hormo-

nes[27]). They, too, are sufficiently lipophilic and suitable for intramuscular application in the form of oil solutions. As enol-ethers they are readily hydrolyzed in acid solutions when the active amino alcohols should be released. The preparation of these enol-ethers was effected by heating amino alcohols[1,2] *Ia* and *IIc* with cyclododecanone dimethyl acetal[28] in toluene in the presence of *p*-toluenesulfonic acid (method *D*, see ref.[27]); the crude bases obtained were purified by crystallization of the maleates.

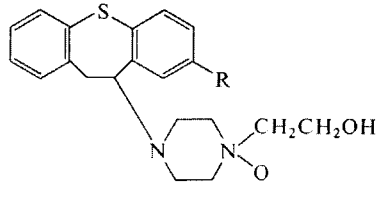
In analogy to an earlier work[15] we oxidized *Ia* and *Ic*. On oxidation of the methanesulfonate of *Ia* (ref.[1,2]) with excess hydrogen peroxide in an aqueous solution at room temperature sulfoxide *X* was obtained. Oxidation of the base of *Ia* (ref.[1]) with an equivalent of hydrogen peroxide in ethanol gave rise to N-oxide *XIa*. Compound *Ic* was oxidized in the form of hydrochloride with potassium bromate and bromide in acetic acid; the 8-(methanesulfinyl)compound *Id* was obtained. Oxidation of base *Ic* with 2 equivalents of hydrogen peroxide in boiling ethanol yielded a product which, according to polarography and IR spectra, has the structure of *XId*.

Heating of 8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[22] with mono-*4*-toluenesulfonate of 1-(2-hydroxyethyl)piperazine to 190°C *in vacuo* (method *E*; see ref.[29]) yielded 70% of enamine *XIIa* which had been prepared by a different method earlier[30]. In analogy, 8-methylthiodibenzo[*b*,*f*]thiepin-10(11*H*)-one[23] and mono-*p*-toluenesulfonate of 1-(3-hydroxypropyl)piperazine[31] yielded 75% of enamine *XIIIc*. The same compound was prepared by a reaction of the ketone named with 1-(3-hydroxypropyl)piperazine in boiling benzene in the presence of titanium tetrachloride (method[30,32]). Oxidation of enamine *XIIa* with an equivalent of hydrogen peroxide in ethanol resulted in enamine N-oxide *XIV*. Some other enamine N-oxides of the series were described before in a patent application[33]. Enamine *XIIIc* was reduced in two ways to the dihydro derivative *IIc*; whereas reduction with zinc in acetic acid (method[34,35]) gives a satisfactory yield and represents a realistic alternative to previous oxyprothepin preparation (*IIc*), the result of reduction with diborane (sodium borohydride and acetic acid in tetrahydrofuran (method[36]) is not satisfactory and the method appears as preparatively unsuitable.

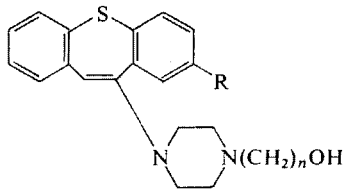
When preparing *IIc* in the usual substitution manner[1] the known elimination product[23] (*XVI*) was accompanied by a small amount of another neutral compound with a high melting point which, on the basis of analysis, was assigned the possible structure of *XV* (for an analogous



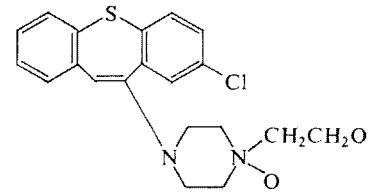
X



XI



XII, $n = 2$
XIII, $n = 3$

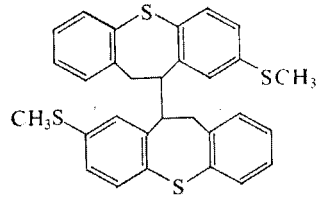


XIV

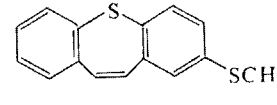
compound in the 8-unsubstituted series see[37]). The structure is taken into consideration in spite of the fact that the mass spectrum contains as the highest ion that of *m/e* 256, *i.e.* approximately half of the molecule, $C_{15}H_{12}S_2$. The composition is satisfied by the mentioned 2-methylthiodibenzo[*b*,*f*]thiepin[23] (*XVI*) which is clearly distinct from the substance now isolated. The discrepancy is possibly explained by the extreme stability of the ion *m/e* 256 (result of the high conjugation) and by the instability of the ion of *XV*. The ion of *m/e* 256 is thus considered a fragment of compound *XV*. Structure *XV* is obviously only a suggestion; the insolubility of the compound in common solvents prevented its further study by ^{1}H-NMR spectroscopy.

All the bases prepared here and their salts are summarized with the usual experimental data in Table I. The experimental section contains examples of preparations by methods *A* – *E* and descriptions of those preparations which cannot be included under the general methods.

Table II contains the results of orientation pharmacological screening of the compounds prepared which were applied in the form of the above salts intravenously (or *i.p.* in the catalepsy test) or *per os*, the values shown referring to the bases. Besides values of acute toxicity for mice (LD_{50}) the table shows the mean effective dose (ED_{50}) bringing about disturbance of motor coordination in mice using the rotating-rod test (the criterion of central depressant action) and finally the mean effective doses (ED_{50}) in the catalepsy test in rats (criterion of neuroleptic action) (on the methods used more details in[3]). The table includes octoclothepin[22] and chlorpromazine as standards and, of previously described compounds, noroxyclothepin[1,2] (*Ia*) (including novel data on its *p.o.* application), oxyclothepin[1,2] (*IIa*) (including novel data on *p.o.* application of its dimethanesulfonate; the previously reported relatively low cataleptic activity[1] of *p.o.* applied maleate was apparently due to the low solubility and incomplete resorption of the salt), oxyprothepin (*IIc*) as another standard and finally oxyclothepin N-oxide[15] (*IIa*—NO) (including novel data on activity on *p.o.*, application).



XV



XVI

TABLE I

Piperazine Derivatives and Their Salts

Compound[a] (Method / yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% N	% S	% Cl
Ia-2 M (*A*/78)[1,2]	152—153 (acetone–ethanol)	$C_{28}H_{31}ClN_2O_9S$ (607·1)	55·40 55·40	5·15 5·16	4·61 4·31	5·28 5·51	5·84 6·00
Ib (*A*/88)[b]	128—130 (benzene–light petroleum)	$C_{21}H_{26}N_2O_2S$ (370·5)	68·07 68·06	7·07 6·97	7·56 7·45	8·66 8·78	— —
Ib-2 MS[c]	210—212 (95% ethanol–ether)	$C_{23}H_{35}N_2O_{8\cdot5}S_3$ (571·7)	48·32 48·51	6·17 6·12	4·90 4·73	16·82 16·47	— —
Ic (*A*/50)	103—104[d] (acetone)	$C_{21}H_{26}N_2OS_2$ (386·6)	65·25 64·94	6·78 6·98	7·25 7·11	16·58 16·34	— —
Ic-2 MS	209—211 (ethanol)	$C_{23}H_{34}N_2O_7S_4$ (578·8)	47·73 47·85	5·92 6·39	4·84 4·82	22·16 22·19	— —
Id-2 HCl[e] *b*	166—170 (wet ethanol–ether)	$C_{21}H_{30}Cl_2N_2O_3S_2$ (493·5)	51·10 51·13	6·13 5·98	5·68 5·46	13·00 13·21	14·37 13·89
Id-2 HCl[c]	192—197 (aqueous ethanol)	$C_{21}H_{29}Cl_2N_2O_{2\cdot5}S_2$ (484·5)	52·06 52·45	6·03 6·03	5·78 5·97	13·24 13·25	14·64 14·77
IIIa (*A*/43)	153—154[f] (ethanol)	$C_{21}H_{25}ClN_2OS$ (388·9)	64·84 64·94	6·48 6·66	7·20 7·00	8·24 8·18	9·12 8·94
IIIa-2 MS[e]	201—203 (ethanol–ether)	$C_{23}H_{35}ClN_2O_8S_3$ (599·2)	46·10 46·66	5·89 5·85	4·64 4·78	16·06 16·04	5·92 6·18
IVa-2 M *b*	147—148 (ethanol)	$C_{30}H_{35}ClN_2O_9S$ (635·1)	56·73 56·55	5·56 5·82	4·41 4·57	5·05 5·28	5·58 5·62
Va[g] (*B*/92)[b]	88—90 (benzene)	$C_{24}H_{28}ClN_2O_2S$ (444·0)	64·92 64·57	6·36 6·31	6·30 5·94	7·22 7·11	7·99 8·15
Va-M[c]	129—131 (wet acetone–ether)	$C_{25}H_{30}ClN_2O_{6\cdot5}S$ (530·0)	56·65 56·52	5·71 5·64	5·28 4·96	6·05 5·95	6·69 6·53
Vc[g] (*B*/55)	85—87[h] (benzene–light petroleum)	$C_{25}H_{31}N_2O_2S_2$ (455·6)	65·90 65·68	6·86 6·95	6·15 6·16	14·07 14·32	— —
Vc-M	149—151 (ethanol)	$C_{26}H_{32}N_2O_6S_2$ (532·6)	58·62 58·60	6·06 6·21	5·26 5·15	12·04 12·26	— —
VIb-2 M (*C*/63)	123—125 (acetone)	$C_{39}H_{52}N_2O_{11}S$ (756·9)	61·89 61·19	6·92 6·85	3·70 3·91	4·24 4·58	— —
VIc-M (*C*/75)[b]	128—131 (aqueous acetone)	$C_{35}H_{48}N_2O_6S_2$ (656·9)	63·99 64·21	7·37 7·78	4·27 4·12	9·76 9·96	— —

TABLE I
(*Continued*)

Compound[a] (Method / yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% N	% S	% Cl
VIIa-2M	157—160	$C_{39}H_{51}ClN_2O_{10}S$	60·41	6·63	3·61	4·14	4·57
(*C*/80)	(acetone)	(775·3)	60·38	6·90	3·61	4·14	4·44
VIIIa-2 M	136—137	$C_{40}H_{51}ClN_2O_9S$	62·28	6·66	3·63	4·16	4·60
(*D*/87)[b]	(ethanol–ether)	(771·3)	61·85	6·37	3·78	4·51	5·13
VIIIa-M	120—122	$C_{36}H_{47}ClN_2O_5S$	65·98	7·23	4·28	4·89	5·41
	(ethanol–ether)	(655·3)	65·94	7·48	4·38	4·96	5·70
IXc-M[c]	109—112[i]	$C_{38}H_{53}N_2O_{5\cdot5}S_2$	66·15	7·74	4·06	—	—
(*D*/90)	(ethanol–ether)	(689·9)	65·98	7·76	4·32	—	—
X-M	167	$C_{24}H_{27}ClN_2O_6S$	56·85	5·37	5·53	6·32	6·99
b	(ethanol–ether)	(507·0)	56·94	5·44	5·54	6·37	6·88
XIa	187—190	$C_{20}H_{23}ClN_2O_2S$	61·45	5·93	7·16	8·21	9·07
b	(acetone)	(390·9)	61·29	6·20	7·11	8·34	9·24
XIa-2 HCl[c]	149—152	$C_{20}H_{26}Cl_3N_2O_{2\cdot5}S$	50·80	5·54	5·92	6·78	—
	(wet ethanol–ether)	(472·8)	50·62	5·26	5·67	6·72	—
XId-2 HCl[c]	168—171	$C_{21}H_{29}Cl_2N_2O_{3\cdot5}S_2$	50·39	5·84	5·59	12·82	14·17
b	(wet ethanol)	(500·5)	50·45	6·09	5·54	12·80	14·08
XIIa[g]	93—95[j]	$C_{23}H_{24}ClN_2OS$	67·05	5·87	6·80	7·78	8·61
(*E*/69)	(benzene–light petroleum)	(412·0)	66·63	6·43	6·88	7·85	8·78
XIIa-M	196 (decomp.)	$C_{24}H_{25}ClN_2O_5S$	58·95	5·15	5·73	6·56	7·25
	(ethanol)	(489·0)	58·85	5·41	6·01	6·42	7·21
XIIIc	109—110	$C_{22}H_{26}N_2OS_2$	66·29	6·58	7·03	16·09	—
b	(ethanol)	(398·6)	66·33	6·91	6·72	16·16	—
XIIIc[k]	96—100	$C_{23}H_{29}N_2O_{1\cdot5}S_2$	65·51	6·93	6·64	15·21	—
(*E*/75)[b]	(ethanol)	(421·6)	65·52	6·89	6·65	15·10	—
XIIIc-M	132—134	$C_{25}H_{30}N_2O_5S_2$	60·67	5·88	5·44	12·46	—
	(ethanol)	(514·6)	60·61	5·94	5·44	12·32	—
XIV	194—196	$C_{20}H_{21}ClN_2O_2S$	61·76	5·44	7·20	8·24	9·12
b	(acetone)	(388·9)	61·66	5·71	7·05	8·21	9·30
XIV-2 HCl[m]	125—130	$C_{20}H_{27}Cl_3N_2O_4S$	48·25	5·46	5·63		
	(wet ethanol)	(497·9)	48·74	5·45	6·16		
XIV-MS	181—183	$C_{21}H_{25}ClN_2O_5S_2$	52·00	5·20	5·78	13·22	7·31
	(ethanol)	(485·0)	52·09	5·68	5·70	13·14	7·19

The results shown in Table II permit to draw some conclusions on the structure--activity relationships in this group of compounds:

a) All the new amino alcohols, unless S- or N-oxidized, *i.e. Ib, Ic, IIIa, IVa, Va, Vc*, are highly effective neuroleptics which, in comparison with octoclothepin, display parenterally rather a cataleptic than a sedative activity. Compounds *Ib*, *Ic*, *IIIa* and *IVa* are 2–6 times more effective cataleptically than octoclothepin, being 1·5–3·5 times less effective as depressants. The same relationship is observed upon parenteral application in the trio of noroxyclothepin (*Ia*), oxyclothepin (*IIa*) and oxyprothepin (*IIc*), on the one hand, and octoclothepin, on the other. In comparison with octoclothepin, these amino alcohols thus display parenterally a clear dissociation between the two types of effect, in favour of the cataleptic one. This dissociation is obscured upon oral application, as shown by comparing the effects of *Ia*, *IIa* and *IIc* with octoclothepin; cataleptically, all the four compounds are identically effective while the amino alcohols are only 1·5–2 times weaker depressants than octoclothepin. Aminodiols *Va* and *Vc* which were applied only parenterally are nearly equivalent in the catalepsy test to octoclethepin and they are 4–5 times weaker as depressants. From the point of view of neuroleptic activity in the present series, we reported earlier[1] on the favourable effect of 2-hydroxyethyl, 3-hydroxypropyl, 3-hydroxybutyl and 4-hydroxybutyl as N-substituents; these are now joined by 2-hydroxypropyl, 3-hydroxy-2-methylpropyl and 2,3-dihydroxypropyl.

Explanation to table I

[a] M maleate, MS methanesulfonate, HCl hydrochloride. [b] See Experimental. [c] Hemihydrate. [d] IR spectrum: 762, 817, 860 (4 and 2 adjacent and solitary Ar—H), 1060 (CH_2OH), 3420 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 7·70 (mcs, J = 2·5 Hz, 1 H, aromatic 9-H), 7·50 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·06 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic 7-H), 7·20–7·60 (m, 4 H, remaining aromatic protons), 3·00–4·05 (m, 3 H, $ArCH_2CHAr$), 3·66 (t, J = 6·0 Hz, 2 H, CH_2O), c. 2·60 (m, 11 H, 5 NCH_2 and OH), 2·46 (s, 3 H, SCH_3). [e] Monohydrate. [f] IR spectrum: 770, 813, 837, 860, 880 (4 and 2 adjacent and solitary Ar—H), 1115 (CHOH), 1465, 1558, 1585 (Ar), 3420 cm^{-1} (OH). [g] Solvate with one-half molecule of benzene. [h] ^{1}H-NMR spectrum: δ 6·90–7·70 (m, aromatic protons), 3·00–4·00 (m, 4 H, $ArCH_2CHAr$ and CH—O), 3·09 (bs, 2 H, 2 OH), 2·50–264 (m, 12 H, 5 NCH_2 and CH_2O), 2·44 (s, 3 H, SCH_3). [i] IR spectrum (Nujol): 754, 820, 875 (4 and 2 adjacent and solitary Ar—H), 1117, 1354 (COOH), 1570, 1610 (Ar, COO^-), 1695 cm^{-1} (COOH of maleic acid); ^{1}H-NMR spectrum: δ 6·80–7·50 (m, 7 H, aromatic protons), 6·25 (s, 2 H, CH=CH of maleic acid), 4·25 (t, CH=C in a ring), 2·36 (s, 3 H, SCH_3), 1·70–4·00 (m, $ArCH_2CHAr$, 4 NCH_2 of piperazine and 3 CH_2 of propane chain), 1·29 (bs, 20 H, 10 CH_2 in a ring). [j] ^{1}H-NMR spectrum: δ 7·10–7·70 (m, 7 H, aromatic protons), 7·23 (s, C_6H_6), 6·33 (s, 1 H, ArCH=C), 3·61 (t, J = 6·0 Hz, 2 H, NCH_2 in a ring), 2·76 (s, after D_2O disappears, 1 H, OH), 2·98 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·61 (m, 6 H, $CH_2N^4CH_2$ of piperazine and CH_2O); patent[30] reports for a nonsolvated base prepared by the $TiCl_4$ method, a m.p. of 138–139°C and for the maleate a m.p. of 196–198°C. [k] Solvate with one-half molecule of ethanol. [m] Dihydrate.

b) S-Oxidation in the 8-substituent (comparison of *Ic* and *Id*) and in position 5 (comparison of *Ia* and *X*) results in a drop of cataleptic and depressant activity by about an order of magnitude.

c) N-Oxidation of *Ia* to *XIa* is accompanied by a drop of depressant activity to about one-fourth while the cataleptic activity is preserved (especially on oral application). The N-oxidation of *Id* to *XId* is accompanied by a remarkable doubling of activity in both directions, together with a decrease of toxicity to one-half. With the previously compared *IIa* and its N-oxide[15] the N-oxidation is associated, upon parenteral application, with a drop of depressant activity to 10% and of cataleptic activity to 50%; this was interpreted as a significant dissociation of both types of effect in the N-oxide of *IIa* as compared with octoclothepin in favour of cataleptic acivity. The newly reported data on activity on *p.o.* application obscure somewhat this dissociation; compound *IIa* and its N-oxide are practically equally effective as depressants and cataleptics.

d) Enamine N-oxide *XIV* surpasses in the catalepsy test all the previously tested compounds of the 10-piperazinodibenzo[*b*,*f*]thiepin series. Depending on the way of administration, it is 15–30 times more effective in this test than octoclothepin; if applied *i.v.*, it is 10 times weaker as depressant, if applied *p.o.* it is about equally effective. At any rate, it is a compound with a high degree of dissociation of the two types of effect in favour of the cataleptic effect. Its disadvantage lies in its instability in aqueous solutions; the methanesulfonate solution remains clear for only about 1 h, then becomes turbid due to precipitating 8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one.

Ester *VIIa* was evaluated as a depot neuroleptic using the test of apomorphine chewing and agitation in rats[3]. On intramuscular application of 25 mg/kg in the form of a 2·5% solution in sunflower oil the reaction to apomorphine is blocked for about 1 week. The effect slowly disappears during the subsequent week. As the same dose of fluphenazine oenanthate (for references see[2]) blocks apomorphine effects for 3 weeks, the ester *VIIa* appears to have only a relatively brief action.

Similarly, enol-ether *VIIIa* was applied to rats in an intramuscular dose of 25 mg/kg in the form of a 2·5% solution in sunflower oil and the intensity and duration of its antiapomorphine effect was examined (1·25 mg/kg apomorphine was applied *i.v.* 24 h after the neuroleptic which was repeated in daily intervals for 5 days). After 24 h since the application of *VIIIa* its significant antiapomorphine effect was observed which is more pronounced toward chewing than toward agitation (this suggests a relatively lower depressant action while the neuroleptic effect is preserved). At further time intervals the effect of the compound ceased to be apparent. On the other hand, the bases of octoclothepin[22] and oxyprothepin (*IIc*) at the same dose and in the same arrangement blocked the effects of apomorphine even four days after application. The enol-ether *VIIIa* thus does not have the character of a depot neuroleptic.

The compounds prepared were tested for antimicrobial activity *in vitro* (Dr J. Turinová, Dr A. Čapek); Table III shows the minimum inhibitory concentrations toward several typical microorganisms. The antimicrobial spectrum of *IIa* is rather broad while practically all the compounds tested are active against cocci and mycobacteria.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at room temperature or at a suitably raised temperature (not more than 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in an Infrascan (Hilger and Watts) or a Unicam SP 200G spectrophotometer. The ^{1}H-NMR spectra (in $CDCl_3$) were obtained in a ZKR 60 (Zeiss, Jena) spectrometer, the mass spectrum in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel or alumina. The analyses of all the bases prepared and of their salts are summarized in Table I.

10-[4-(2-Hydroxyethyl)piperazino]-8-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ib*) (Method *A*)

A mixture of 7·3 g 10-chloro-8-methoxy-10,11-dihydrodibenzo[*b*,*f*] thiepin[23], 20 ml 1-(2-hydroxyethyl)piperazine and 20 ml chloroform was refluxed for 6 h, diluted with 250 ml benzene and washed with water. The benzene solution was shaken with excess 5% hydrochloric acid, the precipitated solid hydrochloride was filtered, added to the acid aqueous phase of the filtrate, the suspension was made alkaline with 20% NaOH and the base was isolated by extraction with benzene: 8·6 g (88%), m.p. 128—130°C (benzene–light petroleum). IR spectrum: 758, 814, 873 (4 and 2 adjacent and solitary Ar—H), 1004 (CH_2OH), 1230 (Ar—O—R), 1595 (Ar), 2760 cm^{-1} (N—CH_2). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 6 H, aromatic protons in positions 1,2,3,4,6,9), 6·56 (mcd, J = 9·0; 3·0 Hz, 1 H, aromatic 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·65 (s, 3 H, OCH_3), 3·55 (t, J = 6·0 Hz, 2 H, CH_2O), c. 2·55 (m, 11 H, 5 NCH_2 and OH). Neutralization of the base with methanesulfonic acid in a mixture of 95% ethanol and ether yielded the dimethanesulfonate which crystallizes as hemihydrate and melts at 210—212°C.

8-Chloro-10-[4-(3-hydroxy-2-methylpropyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVa*)

Anhydrous Na_2CO_3 (10 g) was added to a solution of 13·25 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] in 120 ml benzene which was followed by a dropwise addition of a solution of 7·25 g 2-(ethoxycarbonyl)propionyl chloride[25] (b.p. 75—83°C/20 Torr) in 30 ml benzene. The mixture was stirred at room temperature for 3 h, filtered after standing overnight, washed with benzene and the filtrate was evaporated. The residue (18·8 g) was dissolved in 120 ml ether and the solution was added dropwise to 18·8 g $LiAlH_4$ in 120 ml ether. The mixture was refluxed for 7 h, left to stand overnight, decomposed under external cooling by gradually adding 20 ml water, 20 ml 15% NaOH and 60 ml water. The precipitate was filtered and washed with ether. The filtrate was dried with K_2CO_3 and evaporated. A total of 11·2 g (69%) oily base was obtained which was neutralized with maleic acid in ethanol and thus converted to dimaletate, melting at 147—148°C.

TABLE II

Pharmacological Properties of the Prepared Compounds (mg/kg)

Compound[a]	Code No VÚFB	Administration	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy[b] ED_{50}
Ia-M[c]	6·699	*i.v.*	30	0·21	0·85
Ia-MS[c]	9·501	*p.o.*	315	3·7	4·4
Ib-2 MS	10·044	*i.v.*	38	0·088	0·54
Ic-2 MS	10·045	*i.v.*	52	0·20	0·40
Id-2 HCl	10·053	*i.v.*	28·5	1·2	6·7
IIa-2 MS[d]	8·387	*i.v.*	49	0·18	1·0
		p.o.	135	3·3	4·5
IIc-MS[e]	8·334	*i.v.*	44	0·11	0·62
		p.o.	68	4·6	3·3
IIIa-2 MS	10·048	*i.v.*	53	0·15	1·2
IVa-2 M	10·078	*i.v.*	69	0·113	0·68
Va-M	9·474	*i.v.*	47	0·23	2·5
Vc-M	9·987	*i.v.*	45	0·33	3·2
X-M	10·047	*i.v.*	56	1·4	8·4
XIa-2 HCl	10 046	*i.v.*	94	0·85	1·6
		p.o.	—	11·5	5·0
IIa-NO—2 HCl	8 730	*i.v.*	80	2·1	2·0
		p.o.	—	4·8	5·4
XId-2 HCl	10·082	*i.v.*	64	0·7	3·1
XIIIc-M	12·254	*p.o.*	250	3·1	1·4
XIV-MS	10·513	*i.v.*	—	0·62	0·077
		p.o.	—	1·4	0·31
OCT[f]	—	*i.v.*	46·3	0·06	2·4
		p.o.	78·0	2·2	4·3
CPZ[g]	—	*i.v.*	52·2	0·585	8·6
		p.o.	198	8·2	16·0

[a] M maleate, MS methanesulfonate, HCl hydrochloride, NO N-Oxide. [b] When *i.v.* is indicated, *i.p.* application was used for the catalepsy test. [c] Noroxyclothepin. [d] Oxyclothepin. [e] Oxyprothepin. [f] Octoclothepin; parenterally as methanesulfonate, orally as maleate. [g] Chlorpromazine (hydrochloride).

TABLE III

Antimicrobial Activity of Prepared Compounds *in vitro* (μg/ml)

Compound[a]	Code No VÚFB-	Microorganism[b]					
		1	2	3	4	5	6
Ia-M	6·699	50	50	100	12·5	—	—
Ib-2 MS	10·044	—	—	—	50	—	—
Ic-2 MS	10·045	25	25	—	12·5	—	—
IIa-2 MS[c]	8·387	50	50	50	12·5	125	125
IIIa-2 MS	10·048	50	50	—	25	—	—
Va-M	9·474	25	25	—	3·1	—	125
Vc-M	9·987	25	25	—	12·5	—	—
IXc-M[d]	10·529	50	50	—	50	100	50
X-M	10·047	—	—	—	50	—	—
XIa-2 HCl	10·046	—	—	—	50	—	—

[a] M maleate, MS methanesulfonate, HCl hydrochloride. [b] 1 *Streptococcus* β-*haematicus*, 2 *Staphylococcus pyogenes aureus*, 3 *Klebsiella pneumoniae*, 4 *Mycobacterium tuberculosis* H37Rv, 5 *Saccharomyces pasterianus*, 6 *Trichophyton mentagrophytes*. [c] The compound is effective toward other microorganisms at the minimum concentrations shown in μg/ml: *Pseudomonas aeruginosa*, 100; *Escherichia coli*, 100; *Salmonella typhi abdominalis*, 100; *Proteus vulgaris*, 50. [d] The compound is effective toward other microorganisms at the minimum concentrations shown in μg/ml: *Streptococcus faecalis*, 50; *Candida albicans*, 100; *Aspergillus niger*, 100.

8-Chloro-10-[4-(2,3-dihydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Va*) (Method *B*)

3-Chloropropane-1,2-diol (5·1 g) and 3·1 g powdery KOH were added to a solution of 6·1 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] in 25 ml dimethylformamide and the mixture was refluxed for 10 h at 100°C. After cooling, it was diluted with 250 ml benzene, filtered and the filtrate was washed with water. After drying with K_2CO_3, benzene was evaporated. The residue crystallized on mixing with 7·5 ml benzene and 15 ml light petroleum; 6·8 g (92%) base, m.p. 88—90°C (benzene). According to analysis, we are dealing here with a solvate with 1/2 molecule of benzene. IR spectrum (Nujol): 680 (Ar—Cl), 758, 828, 860 (4 and 2 adjacent and solitary Ar—H), 1005 and 1045 (CH_2OH), 1110, 1130, 1155 (CHOH), 3240 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 7·40 (s, C_6H_6), 3·00—4·00 (m, 6 H, $ArCH_2CHAr$ and $OCHCH_2O$), 3·15 (s, 2 H, 2 OH), 2·60 (m, 10 H, 5 NCH_2). Neutralization with maleic acid in acetone yields maleate which crystallizes from a mixture of wet acetone and ether, as hemihydrate, m.p. 129—131°C.

10-[4-(2-Decanoyloxyethyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIc*) (Method *C*)

Decanoyl chloride[26] (13·4) g) was added to a solution of 11·6 g *Ic* (Table I) in 80 ml chloroform and the mixture was left at room temperature overnight. Then 80 ml chloroform was added and the mixture was quickly washed with ice-cold 5% NaOH and with water. After drying with K_2CO_3, it was evaporated and the inhomogeneous residue was chromatographed on a column of 400 g neutral alumina (activity II). Benzene eluted 12·3 g (75%) of an almost homogeneous ester base. Neutralization with maleic acid in acetone yielded the maleate which was purified by crystallization from aqueous acetone, m.p. 128–131°C. Decomposition of the pure salt with NH_4OH and extraction with ether yielded the pure base which was used for recording the spectra and for preparation of solution in sunflower oil for pharmacological testing. IR spectrum ($CHCl_3$): 1157, 1730 (COOR), 1575 (Ar), 2710 cm^{-1} (N—CH_2). ^{1}H-NMR spectrum: δ 7·50 (mcs, J = 3·0 Hz, 1 H, aromatic 9-H), 6·70–7·40 (m, 6 H, remaining aromatic protons), 4·13 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·55 (m, 10 H, 5 NCH_2), 2·35 (s, 3 H, SCH_3), c. 2·25 (2 H, $COCH_2$), 1·26 (bs, 14 H, 7 CH_2 in the chain), 0·85 (t, 3 H, C—CH_3).

8-Chloro-10-[4-(2-cyclododecenyloxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIIa*) (Method *D*)

p-Toluenesulfonic acid (1·8 g) and 4·5 g cyclododecanone dimethyl acetal[28] (b.p. 86–90°C/1 Torr) were added to a mixture of 3·84 g *Ia* (ref.[1]) in 500 ml toluene. Wet toluene was distilled from the mixture over a period of 10 h, being continuously replaced with anhydrous toluene, a total of 2 liters being thus substituted. After cooling, the toluene solution was washed with 5% NH_4OH and water, dried with K_2CO_3 and evaporated. The residue was dissolved in benzene and chromatographed on a column of 210 g alumina (activity II). After removing a small fraction of the least polar admixture, benzene eluted 4·7 g (87%) base which was neutralized by maleic acid in a mixture of ethanol and ether and thus converted to the dimaleate (m.p. 136–137°C) or to the monomaleate (m.p. 120–122°C), which was used for NMR spectrometry: δ 7·55 (mcs, J = 2·0 Hz, 1 H, aromatic 9-H), 6·90–7·50 (m, 6 H, remaining aromatic protons), 6·39 (s, 2 H, CH=CH of maleic acid), 4·30 (t, J = 7·5 Hz, 1 H, C=CH in a ring), 3·00–4·00 (m, 3 H, $ArCH_2$. .CHAr), 2·00–3·50 (m, 5 NCH_2 and CH_2O), 1·30 (bs, 20 H, 10 CH_2 in a ring). The base released from the salts with NH_4OH was isolated by extraction with ether and used both for pharmacological tests and for obtaining the IR spectrum ($CHCl_3$): 826, 872 (Ar—H), 1049 and 1246 (C=C—O—R), 1657 cm^{-1} (C=C).

8-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*X*)

A mixture of 11·5 g base[1] *Ia* and 3·24 g methanesulfonic acid was dissolved in 120 ml warm water, the solution was combined with 90 ml 27% H_2O_2 and the mixture was left for 24 h at room temperature. After filtration with charcoal, the solution was made alkaline with NH_4OH and the released base was isolated by extraction with benzene; 6·4 g (54%) oil. Neutralization with maleic acid in a mixture of ethanol and ether yielded the maleate, m.p. 167°C.

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

27% H_2O_2 (7 ml) was added to a solution of 15·0 g base[1] *Ia* in 85 ml 95% ethanol and the mixture was refluxed for 7 h. Excess H_2O_2 was removed by heating with a platinum foil for another hour.

After cooling, it was diluted with 50 ml water and ethanol was evaporated at reduced pressure. On standing in the refrigerator, 8·6 g (55%) anhydrous base crystallized from the aqueous solution; this was purified for analysis by recrystallization from acetone, m.p. 187–190°C. IR spectrum: 768, 820, 892 (4 and 2 adjacent and solitary Ar—H), 973 (N—O) 1063 (CH_2OH), 3440 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·75 (mcs, J = 2·5 Hz, 1 H, aromatic 9-H), 7·50 (d, J = 9·0 Hz, 1 H, aromatic 6-H), 7·15 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic 7-H), 7·20–7·65 (m, 4 H, remaining aromatic protons), 4·15 (t, 2 H, CH_2O), 2·50–4·00 (m, 14 H, $ArCH_2CHAr$, OH and 5 NCH_2). Treatment of the base in 95% ethanol with an ether solution of hydrogen chloride yields the dihydrochloride (hemihydrate) melting at 149–152;C.

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

20% hydrochloric acid (20 ml) was added to a solution of 7·73 g *Ic* (Table I) in 60 ml acetic acid, followed over 15 min by 45 ml 1M-$KBrO_3$ (100 ml of this solution contains 20 g KBr). The mixture was stirred for 1 h at room temperature and, after standing overnight, made alkaline with NH_4OH and the base isolated by extraction with benzene; 7·69 g (95%) oil. Neutralization of the solution of the base in ethanol with a solution of hydrogen chloride in ether and crystallization from a mixture of wet ethanol and ether yielded the dihydrochloride monohydrate, melting at 166 to 170°C. Polarography in 0·5M-HCl shows a single wave at −0·60 V against a saturated calomel electrode, corresponding to reduction of the Ar—SO—R group. IR spectrum: 742, 754, 830 (Ar—H), 1050 (SO and CH_2OH), 2480 (NH^+), 3380 cm^{-1} (OH). When crystallizing the dihydrochloride from aqueous ethanol, a compound melting at 192–197°C was obtained, according to analysis a hemihydrate. The possibility cannot be excluded that we are dealing here with different mixtures of stereoisomers, the existence of which is made possible by the presence of two centres of asymmetry ($C_{(10)}$ and the sulfoxide S).

10-[4-(2-Hydroxyethyl)piperazino]-8-(methanesulfinyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin N^4-Oxide (*XId*)

27% H_2O_2 (2·5 ml) was added to a solution of 3·86 g *Ic* (Table I) in 20 ml ethanol and the mixture was refluxed for 3 h, heated for 1 h with a platinum foil and then evaporated at reduced pressure. A total of 3·32 g (66%) deliquescent base was obtained, which was neutralized with hydrogen chloride in ethanol–ether to yield a dihydrochloride, crystallizing from ethanol as hemihydrate, m.p. 168–171°C. Polarography of the compound in 0·5M-HCl exhibits two waves at −0·27 and −0·60 V against a saturated calomel electrode, the first corresponding to the reduction of N-oxide, the other to the reduction of the Ar—SO—R group (see the previous sulfoxide). IR spectrum: 750, 767, 830 (Ar—H), 965 (N—O), 1046 (S—O and CH_2OH), 2480 (NH^+), 3380 cm^{-1} (OH).

10-[4-(3-Hydroxypropyl)piperazino]-8-(methylthio)-dibenzo[*b*,*f*]thiepin (*XIIIc*)

A. *Method* E: A mixture of 5·5 g 8-(methylthio)dibenzo[*b*,*f*]thiepin-10(11*H*)-one[23], 8·6 g 1-(3-hydroxypropyl)piperazine[31] and 10·3 g *p*-toluenesulfonic acid was heated for 1 h to 180–190°C at normal pressure and then for 3 h in water-pump vacuum. After cooling, the melt was divided between 150 ml benzene and 150 ml 10% NH_4OH. Evaporation of the benzene solution yielded 8.1 g residue which is the mixture of the desired compound and of the starting ketone. On chromatography on a column of 200 g neutral alumina (activity II), elution with benzene yielded first 1·12 g starting ketone and then, using benzene with 8% ethanol, 6·05 g (75%) homogeneous enamine *XIIIc* which crystallizes from ethanol as a solvate with one-half molecule of ethanol,

m.p. 96—100°C. UV spectrum: λ_{max} 225 nm (log ε 4·41), 265 nm (4·37), 275 nm (4·38), infl. 315 nm (3·96). IR spectrum: 756, 809, 884 (4 and 2 adjacent and solitary Ar—H), 1019 (CH_2OH), 1556, 1573, 1606 (Ar), 3430 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00—7·60 (m, 7 H, aromatic protons), 6·28 (s, 1 H, ArCH=C), 4.30 (bs, 1 H, OH), 3·74 (t, J = 6·0 Hz, CH_2O), 3·70 (q, CH_2O of ethanol), 3·00 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·60 (m, 6 H, remaining 3 NCH_2), 2·40 (s, 3 H, SCH_3), 1·72 (m, 2 H, middle CH_2 of the propanol residue), 1·20 (t, CH_3 of ethanol). In the usual procedure, the base forms a maleate which crystallizes from ethanol and melts at 132—134°C.

B. *By the* $TiCl_4$ *method*: 1-(3-Hydroxypropyl)piperazine[31] (39·7 g) was added to a solution of 15·0 g 8-(methylthio)dibenzo[*b*,*f*]thiepin-10(11*H*)-one[23] in 130 ml benzene and then, under stirring for 15 min, this was followed by a dropwise addition of 8·5 g $TiCl_4$ in 60 ml benzene. The mixture was refluxed under stirring for 30 h, cooled, decomposed with 25 ml saturated $NaHCO_3$ and 200 ml water. After 2 h of stirring, the solid was filtered and washed with benzene and chloroform. The filtrate was separated, the organic phase was washed with water, dried with $MgSO_4$ and evaporated. On crystallization after mixing with 20 ml light petroleum and 10 ml ethanol, the residue yielded 14·8 g product which was chromatographed on a column of 300 g alumina. Benzene eluted 7·4 g starting ketone, a mixture of benzene with 6% ethanol eluted 7·5 g enamine base (34% or 67% per conversion). This base crystallizes from a small volume of ethanol in the nonsolvated form and melts at 109—110°C. Its identity with the product according to *A* was demonstrated by recrystallization from a larger volume of ethanol when it is precipitated as an ethanol solvate melting at 96°C.

8-Chloro-10-[4-(2-hydroxyethyl)piperazino]dibenzo[*b*,*f*]thiepin N^4-Oxide (*XIV*)

25% H_2O_2 (1·8 g) was added to a solution of 5·10 g *XIIa* (with 0·5 C_6H_6) (Table I) in 35 ml ethanol. The mixture was refluxed for 3 h, then heated for 1 h with a platinum foil, diluted with water and evaporated at reduced pressure. The residue crystallized from 10 ml acetone to 3·10 g (64%) anhydrous base melting at 194—196°C. IR spectrum: 768, 830, 873 (4 and 2 adjacent and solitary Ar—H), 935 (N—O), the absence of bands in the region of 1025—1060 suggests the absence of sulfoxide, 1105 (CH_2OH), 1615 (Ar), 2800 cm^{-1} (OH···O—N in a six-membered ring). NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 6·48 (s, 1 H, ArCH=C), 5·85 (bs, disappears after D_2O, 1 H, OH), 4·15 (t, 2 H, CH_2O), 2·80—4·00 (m, 10 H, 5 NCH_2). Neutralization of the base with hydrogen chloride in ethanol–ether gives rise to dihydrochloride dihydrate (m.p. 125—130°C) which is poorly soluble in water and unstable even if solid. A somewhat greater stability was found in the conventionally prepared methanesulfonate (m.p. 181 to 183°C), a 2% solution of which in water remains clear for 1 h; then it begins to get turbit due to the ketone formed by decomposition.

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

A. Enamine *XIIIc* (3·0 g) was added to a stirred mixture of 50 ml acetic acid and 5·5 g powdery Zn at 100°C and the mixture was then refluxed for 2 h. After cooling, it was filtered and the filtrate was evaporated at reduced pressure. The residue was dissolved in 45 ml ethanol, 6 ml of a 35% solution of NaOH was added and the mixture was refluxed for 1 h. After evaporation *in vacuo*, the residue was divided between 100 ml water and 100 ml benzene and the benzene layer was shaken for 30 min with 70 ml 3M-HCl. The precipitated hydrochloride was filtered, suspended in water, made alkaline with NH_4OH which released the base which was then isolated by extraction with benzene; 1·90 g (63%) chromatographically homogeneous oil, the R_F of which is identical with the R_F of an authentic sample[1] of *IIc*. When dissolved in 3 ml benzene, it crystallizes on ad-

dition of some light petroleum and melts at 94—96°C. In mixture with the authentic product[1] it melts without depression.

B. Acetic acid (6·1 ml) was added dropwise under stirring over a period of 45 min to a mixture of 20 ml tetrahydrofuran, 3·0 g enamine *XIIIc* and 0·9 g $NaBH_4$ at 30°C. The mixture was refluxed for 3 h, evaporated at reduced pressure, the residue was combined with 10 ml 2M-NaOH and the product was extracted with 100 ml benzene. The benzene solution was shaken for 25 min with 80 ml 3M-HCl, the precipitated hydrochloride was filtrated and converted to the base according to *A*. A total of 0·55 g (18%) base *IIc* was obtained, m.p. 94—95°C, which is identical with the product according to *A*.

C. When repeating the preparation of *IIc* by a substitution reaction of 10-chloro-8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin (130 g) with 1-(3-hydroxypropyl)piperazine[31], there was obtained 74% base *IIc*, and processing of the benzene solution from which the basic portion was removed by shaking with hydrochloric acid, gave 17 g oily mixture of neutral compounds. The mixture was dissolved by boiling in 25 ml cyclohexane and the solution was left to stand for several days in the refrigerator. The small amount of precipitated substance was filtered; 0·40 g, m.p. 221—222°C (benzene). The compound is probably bis[8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl] (*XV*) in spite of the fact that the mass spectrum exhibits as the highest ion that of *m/e* 256, corresponding to an empirical formula of $C_{15}H_{12}S_2$. UV spectrum: λ_{max} 263·5 nm (log ε 4·27). IR spectrum (Nujol): 727, 744, 810, 813 cm^{-1} (Ar—H). For $C_{30}H_{26}S_4$ (514·7) calculated: 69·99% C, 5·09% H, 24·91% S; found: 70·36% C, 4·86% H, 24·49% S. The mother liquor of this substance was concentrated and crystallized from a mixture of benzene and light petroleum to yield 4·50 g 2-(methylthio)dibenzo[*b*,*f*]thiepin (*XVI*) melting at 89—91°C which is identical with the product prepared before[23].

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