NEUROTROPIC AND PSYCHOTROPIC SUBSTANCES. XLV.*

FURTHER 8-SUBSTITUTED 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS AND RELATED COMPOUNDS. THE NOR-ANALOGUE OF OCTOCLOTHEPIN AND ITS N-SUBSTITUTION DERIVATIVES

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A greater number of N-substitution derivatives of 8-chloro-10-piperazino-10,11-dihydrodibenzo-[*b*,*f*]thiepin (*III*) was prepared *1.* by a substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin with the corresponding N-monosubstituted piperazines, *2.* from free secondary amine *III* ("noroctoclothepin") by alkylation, addition, acylation and other reactions, *3.* from N,N-bis(2-chloroethyl)amino derivative *XLIX* by a reaction with primary amines and *4.* by other transformations of compounds prepared by methods (*1*) to (*3*). A similar procedure was used for preparing some 8-methoxy- and 8-methylthio-analogues (*XXXIX*, *XLIII*–*XLVI*). The piperazino derivative *L* and morpholines *LI*–*LIII* were obtained by an analogy of method (*1*). A number of products showed a high degree of neuroleptic activity; in tests for central depressant and cataleptic activity compounds *VII*, *XIV*, *XIX*, *XXI*, *XXVIII*, *XLIII* and *XLV* are equal to or better than octoclothepin (*1*).

After having demonstrated the high degree of central depressant and neuroleptic activity of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*, octoclothepin)[1–3] we set out to study its analogues derived by substitution of the terminal methyl group with other residues. The aim of the work was to discover more active or less toxic compounds and further to define in more detail the relationships between structure and activity in this new group of neuroleptics. A similar, even if not so extensive, study was earlier devoted to the 8-unsubstituted series, *i.e.* to the N-substitution derivatives of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[4] which made it possible to draw first conclusions on the relationship between structure and activity and which defined the most promissing approaches to be used in the study described here. In the 8-chloro series we described so far[2] only the N-phenyl and the N-benzyl analogues of compound *I*. In the present communication

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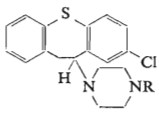
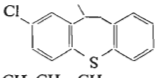
we include also* several N-substitution analogues of the basic compounds of the 8-methylthio series (*XXXVII*, "methiothepin") and of the 8-methoxy series (*XXXVIII*, "octometothepin")[5] because of the high activity of the parent compounds.

The principal synthetic method for the compounds described here was the substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2] or of its 8-methylthio- and 8-methoxy analogue[5], with the correspondingly N-substituted piperazines. The reaction was carried out in part without solvent at temperatures of 100–125°C (method *A*), in part in boiling chloroform (method *B*). In both cases we used excess substituted piperazine (at least 2·5 mol per mol chloride). Method *A* was used with



I, R = CH_3
II, R = $COOC_2H_5$
III, R = H

XX, R = $CO(CH_2)_2COOH$
XXI, R = $CH_2CH_2CH_2CH_2OH$
XXII, R = $CH_2CH_2OCOCH_3$

IV, R = 

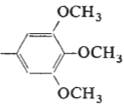
V, R = $CH_2CH{=}CH_2$
VI, R = $CH_2C{\equiv}CH$

VII, R = 

VIII, R = 

IX, R = CH_2– 

X, R = $CH_2C_6H_4OCH_3$-*p*
XI, R = $CH_2CH_2N(C_2H_5)_2$
XII, R = $CH_2CH_2N(CH_3)_2$
XIII, R = CH_2CH_2CN
XIV, R = $CH_2CH_2CONH_2$
XV, R = $CH_2CH_2COOCH_3$
XVI, R = $CH_2CH_2COCH_3$
XVII, R = CH_2CH_2OH
XVIII, R = $CH_2CH_2CH_2OH$
XIX, R = $CH_2CH_2CHCH_3$ (OH)

XXIII, R = CH_2CH_2OCO– 

XXIV, R = $(CH_2)_3OCOCH_3$
XXV, R = $(CH_2)_3OCOC_2H_5$
XXVI, R = CH_2CH_2COOH
XXVII, R = $(CH_2)_3NH_2$
XXVIII, R = $CH_2CH_2C(=NOH)NH_2$
XXIX, R = $CH_2CH_2C(=NOH)CH_3$
XXX, R = $C(=NH)NH_2$
XXXI, R = $(CH_2)_3NHC(=NH)NH_2$
XXXII, R = $CH_2COOC_2H_5$
XXXIII, R = $CONH_2$
XXXIV, R = SO_2CH_3
XXXV, R = $SO_2C_6H_5$

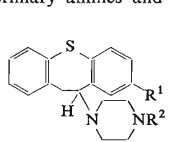
XXXVI, R = $SO_2C_6H_4CH_3$-*p*

* Some of the compounds were prepared by Dr K. Šindelář, Dr K. Pelz, Dr E. Adlerová and Dr Z. Šedivý of this laboratory.

1-(ethoxycarbonyl)piperazine[6] to obtain *II*, *XXXIX* and *XL* which were subjected to alkaline hydrolysis (method *C*) to yield secondary amines *III*, *XLI* and *XLII* (nor-analogues of octoclothepin, methiothepin and octometothepin). These secondary amines are interesting as intermediates of other preparations and as metabolites or potential metabolites of octoclothepin[7,8], methiothepin and octometothepin. The procedure for their preparation followed from our previous work in the 8-unsubstituted series[1,4,9] which suggested the probability of the substantially lower pharmacodynamic activity of compounds *III*, *XLI* and *XLII* in comparison with the methyl derivatives *I*, *XXXVII* and *XXXVIII*. It is thus rather surprising that the firm Geigy[10,11] has requested a patent protection of the preparation of these secondary amines which are clearly within the range of interest of this work team.

The secondary amines *III*, *XLI* and *XLII* are accessible also by the substitution reaction of the corresponding 10-chloroderivatives with excess piperazine (see already[12]). Method *B* was applied in this case (a five-fold excess of piperazine) to prepare noroctoclothepin (*III*) in a 68% yield. On the other hand, when using excess 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin one can obtain analogously the corresponding symmetrically 1,4-disubstituted piperazine *IV*.

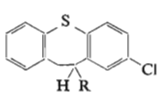
Alkylation of noroctoclothepin *III* with allyl bromide or with propargyl bromide in 1-butanol at 110–120°C and in the presence of anhydrous potassium carbonate (method *D*) yielded amines *V* and *VI*. A principally different procedure was used for the preparation of the cyclopropyl derivative *VII*. The procedure consists in the reaction of cyclopropylamine with 8-chloro-10-[bis(2-chloroethyl)amino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XLIX*) in 1-butanol in an autoclave at 150°C (method *E*). It is generally applicable to primary amines and it is further demonstrated here



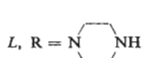
XXXVII, $R^1 = SCH_3$, $R^2 = CH_3$
XXXVIII, $R^1 = OCH_3$, $R^2 = CH_3$
XXXIX, $R^1 = SCH_3$, $R^2 = COOC_2H_5$
XL, $R^1 = OCH_3$, $R^2 = COOC_2H_5$
XLI, $R^1 = SCH_3$, $R^2 = H$
XLII, $R^1 = OCH_3$, $R^2 = H$
XLIII, $R^1 = SCH_3$, $R^2 = (CH_2)_3OH$
XLIV, $R^1 = SCH_3$, $R^2 = (CH_2)_2COOCH_3$
XLV, $R^1 = OCH_3$, $R^2 = (CH_2)_3OH$
XLVI, $R^1 = SCH_3$, $R^2 = (CH_2)_3OCOC_2H_5$
XLVII, $R^1 = H$, $R^2 = NHC(=NH)NH_2$

on the example of the cyclohexyl derivative *VIII*. The required chloro derivative *XLIX* was obtained from the diethanolamine derivative *XLVIII* which was prepared by an analogy of method *A* using diethanolamine. The cyclopropylmethyl derivative *IX* was obtained by alkylation of amine *III* with cyclopropylmethyl bromide applying the method *D*, while the 4-methoxybenzyl derivative *X* was obtained by a substitution reaction using 1-(4-methoxybenzyl)-piperazine[13], *i.e.* by method *A*. This last-named compound is mentioned in the patents of Rhone-Poulenc[14] but our priority is guaranteed by a corresponding patent[15]. Similarly, the 2-diethylaminoethyl derivative *XI* and the 2-dimethylaminoethyl derivative *XII* were obtained by method *A*. The required starting 1-(2-diethylaminoethyl)piperazine was prepared as described before[16] and 1-(2-dimethylaminoethyl)piperazine (*LV*)[17] was obtained analogously *via* the ethoxycarbonyl derivative *LIV*.

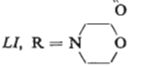
Another general method of preparing the N-substitution derivatives of noroctoclothepin was the addition of acrylonitrile, acrylamide, methylacrylate and methylvinyl ketone to the amine *III*. The additions were carried out in anhydrous tertiary butanol in the presence of triethylbenzylamonium hydroxide in methanol (method *F*) and they resulted in compounds *XIII*–*XVI* and further in the 8-methylthio series resulting in compound *XLIV*. Reduction of the methyl acrylate adducts *XV* and *XLIV* with lithium aluminium hydride (method *G*) resulted in 3-hydroxypropyl



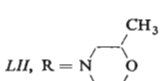
XLVIII, R = $N(CH_2CH_2OH)_2$
XLIX, R = $N(CH_2CH_2Cl)_2$



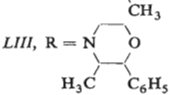
L, R = NH



LI, R = O

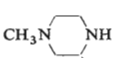


LII, R = O

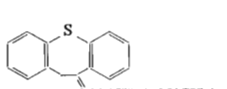


LIII, R = O

LIV, R = $COOC_2H_5$
LV, R = H



LVI



LVII

derivatives *XVIII* and *XLIII*, available, together with the methoxy analogue *XLV* and the 2-hydroxyethyl derivative *XVII* also by applying method *B* to 1-(2-hydroxyethyl)piperazine[6] and 1-(3-hydroxypropyl)piperazine[18]. The 3-hydroxybutyl derivative *XIX* was obtained by a reduction of ketone *XVI* with sodium borohydride. The base was obtained as two different crystalline forms with identical IR spectra. It is difficult to decide whether we are dealing here with a case of dimorphism or with two different racemates, the possibility of their existence being given by the presence of two asymmetric centers in the molecule of *XIX*. Reaction of amine *III* with succinic anhydride in boiling chloroform yielded the 3-carboxypropionyl derivative *XX* which was reduced with lithium aluminium hydride to the 4-hydroxybutyl derivative *XXI*. Acylation of alcohols *XVII*, *XVIII* and *XLIII* with acetyl chloride, propionyl chloride and 3,4,5-trimethoxybenzoyl chloride[19] in a boiling mixture of benzene and chloroform (method *H*) gave rise to esters *XXII*–*XXV* and *XLVI*.

Transformation of the nitrile group in *XIII* made the preparation of other compounds possible: alkaline hydrolysis yielded the carboxylic acid *XXVI*, reduction with lithium aluminium hydride resulted in the amine *XXVII* and reaction with hydroxylamine[20] (methods in ref.[21–23]) gave rise to the amidoxime *XXVIII*. The attempt to convert the nitrile *XIII* to the corresponding 2-imidazoline by heating with ethylenediamine mono-*p*-toluenesulfonate (for methods see ref.[24]) was not successful: the acrylonitrile fragment was split off and the only isolated product was noroctoclothepin *III*. The usual procedure was applied to the ketone *XVI* for preparing the oxime *XXIX*. Reaction of the secondary amine *III* with S-methylisothiourea sulfate in aqueous ethanol resulted in the guanidine derivative *XXX* in the form of a crystalline hemisulfate. Similarly, we obtained the aminoguanidine derivative *XLVII* from the previously prepared 10-(4-aminopiperazino)-10,11-dihydrodibenzo[*b*,*f*]-thiepin[4] and further the guanidine derivative *XXXI* from the primary amine *XXVII* described here. Alkylation of amine *III* with ethyl bromoacetate according to method *D* resulted in the ethoxycarbonylmethyl derivative *XXXII*. Reaction of amine *III* with potassium cyanate in aqueous acetic acid (for methods see ref.[25]) was used for preparing the asymmetric urea *XXXIII*. Finally, the amine *III* was used for the preparation of sulfonamides *XXXIV*–*XXXVI* by a reaction with methanesulfonyl chloride, benzenesulfonyl chloride and 4-toluenesulfonyl chloride in pyridine (method *J*).

Application of method *B* to 2-piperazinone[26] yielded the 10-(3-oxopiperazino) derivative *L*. For a planned preparation of the corresponding 2-oxo-4-methylpiperazino derivative we prepared the required 4-methyl-2-piperazinone (*LVI*) by methylation of 2-piperazinone with methyl iodide. The reaction of this compound with sodium hydride and with 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin in dimethylformamide did not result in the desired product.* Similarly, method *B* applied to mor-

* This section was carried out by Dr K. Pelz of this laboratory.

TABLE I

Dibenzo[*b*,*f*]thiepin Derivatives Prepared by Methods *A* to *J*

Compound[a]	Method	M.p., °C solvent	Formula (m.w.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
II	*A*	113—115 ethanol	$C_{21}H_{23}ClN_2O_2S$ (402·9)	62·60 62·61	5·75 5·77	8·80 8·99	6·96 6·80	7·96 7·79
II-HM	—	190 ethanol	$C_{25}H_{27}ClN_2O_6S$ (519·0)	57·85 57·73	5·24 5·34	6·83 7·14	5·39 5·46	6·17 6·72
III	*C*	135 acetone	$C_{18}H_{19}ClN_2S$ (330·9)	65·34 65·27	5·78 6·05	10·72 10·31	8·47 8·32	9·69 9·75
III-M[b]	—	140—148 ethanol	$C_{24}H_{29}ClN_2O_5S$ (493·0)	58·47 58·73	5·93 5·70	7·19 7·63	5·68 5·32	6·50 6·89
V	*D*	44—47 ethanol	$C_{21}H_{23}ClN_2S$ (370·9)	67·99 67·38	6·25 6·59	9·56 9·75	7·55 7·36	8·64 8·72
V-M	—	192—193 ethanol	$C_{25}H_{27}ClN_2O_4S$ (487·0)	61·65 61·80	5·59 5·63	7·28 7·30	5·74 5·88	6·58 6·91
VI[c]	*D*	120—122 ethanol	$C_{21}H_{21}ClN_2S$ (368·9)	68·37 68·27	5·73 5·88	9·61 9·61	7·59 7·53	8·69 8·43
VI-M	—	172—174 ethanol	$C_{25}H_{25}ClN_2O_4S$ (485·0)	61·91 61·51	5·19 5·37	7·31 7·28	5·77 5·72	6·61 6·21
VII-M	*E*	175—176 ethanol	$C_{25}H_{27}ClN_2O_4S$ (487·0)	61·65 61·15	5·59 5·70	7·28 7·54	5·74 5·65	6·58 6·47
VIII-M	*E*	184—185 ethanol	$C_{28}H_{33}ClN_2O_4S$ (529·1)	63·56 63·17	6·29 6·63	6·70 7·19	5·29 4·98	6·06 6·42
IX[b]	*D*	60—63 ethanol	$C_{24}H_{31}ClN_2OS$ (431·0)	66·87 67·00	7·25 6·87	8·23 8·50	6·50 6·99	7·44 7·39
IX-M	—	153—155 ethanol–ether	$C_{26}H_{29}ClN_2O_4S$ (501·0)	62·32 62·62	5·83 5·69	7·08 7·05	5·59 5·82	6·40 6·47
X-M[b]	*A*	160—165 ethanol	$C_{32}H_{37}ClN_2O_6S$ (613·2)	62·68 62·11	6·08 5·53	5·78 5·77	4·57 4·60	5·23 5·16
X-MS	—	211—212 ethanol–ether	$C_{27}H_{31}ClN_2O_4S_2$ (547·1)	59·27 59·38	5·71 5·85	6·48 6·69	5·12 5·29	11·72 11·67

TABLE I
(*Continued*)

Compound[a]	Method	M.p., °C solvent	Formula (m.w.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
XI-2 M	*A*	197—199 aqueous ethanol	$C_{32}H_{40}ClN_3O_8S$ (662·2)	58·04 58·13	6·09 5·81	5·35 5·54	6·34 6·52	4·85 5·30
XII-2 M	*A*	192—194 aqueous ethanol	$C_{30}H_{36}ClN_3O_8S$ (634·1)	56·82 56·81	5·72 5·85	5·59 5·54	6·63 6·42	5·05 5·30
XIII	*F*	111—112 ethanol	$C_{21}H_{22}ClN_3S$ (383·9)	65·69 65·71	5·78 5·88	9·23 9·44	10·95 10·93	8·35 8·62
XIII-M	—	170—171 ethanol	$C_{25}H_{26}ClN_3O_4S$ (500·0)	60·05 60·03	5·24 5·30	7·09 7·21	8·41 8·31	6·41 6·72
XIV[d]	*F*	210—211 ethanol	$C_{21}H_{24}ClN_3OS$ (401·9)	62·74 63·04	6·02 6·09	8·82 8·98	10·46 10·70	7·98 8·04
XIV-M	—	169—170 aqueous ethanol	$C_{25}H_{28}ClN_3O_5$ (518·0)	57·95 58·15	5·44 5·65	6·85 7·11	8·12 8·07	6·19 6·33
XV	*F*	100—101 ethanol	$C_{22}H_{25}ClN_2O_2S$ (416·9)	63·37 63·38	6·04 6·09	8·50 8·62	6·72 6·77	7·69 7·71
XV-M	—	144—145 ethanol	$C_{26}H_{29}ClN_2O_6S$ (533·0)	58·58 58·30	5·48 5·43	6·65 6·80	5·26 5·31	6·02 6·24
XVI[e]	*F*	126—128 ethanol	$C_{22}H_{25}ClN_2OS$ (401·1)	65·90 66·16	6·28 6·59	8·84 9·01	6·99 6·84	7·99 7·87
XVI-M	—	122—125 ethanol	$C_{26}H_{29}ClN_2O_5S$ (517·0)	60·40 60·35	5·65 5·71	6·86 6·73	5·42 5·21	6·20 6·13
XVII[f]	*B*	103—105 aqueous ethanol	$C_{20}H_{23}ClN_2OS + 0{\cdot}5\ H_2O$ (383·9)	62·56 62·39	6·30 6·33	9·23 9·52	7·30 7·61	8·35 8·31
XVII-M	—	165—166 ethanol	$C_{24}H_{27}ClN_2O_5S$ (491·0)	58·70 58·71	5·54 5·59	7·22 7·50	5·70 5·74	6·53 6·69
XVIII	*B*	114—116 aqueous ethanol	$C_{21}H_{25}ClN_2OS$ (388·9)	64·85 64·92	6·48 6·52	9·11 9·25	7·20 7·08	8·24 8·44
XVIII-2 MS[g]	—	166—167 ethanol–ether	$C_{23}H_{35}ClN_2O_8S_3$ (599·2)	46·10 46·32	5·88 5·88	—	4·68 4·43	16·06 16·06

TABLE I
(*Continued*)

Compound[a]	Method	M.p., °C solvent	Formula (m.w.)	Calculated/Found % C	% H	% Cl	% N	% S
XVIII-2 HM	—	139—140 ethanol	$C_{29}H_{33}ClN_2O_9S$ (621·1)	56·08 56·33	5·35 5·51	5·71 5·96	4·51 4·66	5·16 5·10
XXII-2 HM	*H*	160—161 aqueous acetone	$C_{30}H_{33}ClN_2O_{10}S$ (649·1)	55·51 55·91	5·12 5·27	5·46 5·59	4·32 4·16	4·94 5·21
XXIII-2 HM	*H*[h]	154—156 aqueous acetone	$C_{38}H_{41}ClN_2O_{13}S$ (801·3)	56·96 56·95	5·16 5·21	4·42 4·52	3·49 3·93	4·00 4·29
XXIV-2 HM	*H*	163—164 aqueous acetone	$C_{31}H_{35}ClN_2O_{10}S$ (663·1)	56·15 56·11	5·32 5·33	5·34 5·60	4·22 4·35	4·84 5·05
XXV-2 HM	*H*	159 aqueous acetone	$C_{32}H_{37}ClN_2O_{10}S$ (677·2)	56·75 56·49	5·51 5·59	5·24 5·50	4·14 4·10	4·73 4·93
XXXII-M	*D*	134—136 ethanol	$C_{26}H_{29}ClN_2O_6S$ (533·0)	58·58 58·37	5·48 5·56	6·65 6·71	5·25 5·35	6·02 6·17
XXXII-2 MS	—	195—196 ethanol	$C_{24}H_{33}ClN_2O_8S_3$ (609·2)	47·32 47·70	5·46 5·49	5·82 5·79	4·60 4·47	15·79 15·83
XXXIV	*J*	190—192 ethanol–benzene	$C_{19}H_{21}ClN_2O_2S_2$ (409·0)	55·80 55·91	5·18 5·29	8·67 8·87	— —	15·68 15·45
XXXIV-MS	—	217—218 aqueous ethanol	$C_{20}H_{25}ClN_2O_5S_3$ (505·1)	47·56 47·94	4·99 5·02	7·02 7·34	5·54 5·65	19·05 18·80
XXXV	*J*	194—195 benzene–ethanol	$C_{23}H_{23}ClN_2O_2S_2$ (471·0)	61·20 61·83	4·92 4·96	7·53 7·58	5·95 5·52	13·61 13·74
XXXVI	*J*	185—186 benzene	$C_{25}H_{25}ClN_2O_2S_2$ (485·1)	61·90 62·05	5·20 5·23	7·31 7·03	5·77 5·60	13·22 13·31
XXXIX	*B*	112—115 benzene–light petroleum	$C_{22}H_{26}N_2O_2S_2$ (414·6)	63·75 63·79	6·32 6·39	— —	6·76 6·78	15·46 15·46
XXXIX-HM	—	181—182 ethanol–acetone	$C_{26}H_{30}N_2O_6S_2$ (530·7)	58·86 58·77	5·70 5·74	— —	5·28 5·20	12·06 12·19
XLI[i]	*C*	94—96 acetone	$C_{19}H_{22}N_2S_2$ (342·4)	66·65 66·20	6·48 6·51	— —	8·18 8·30	18·70 18·53

TABLE I
(*Continued*)

Compound[a]	Method	M.p., °C solvent	Formula (m.w.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
XLI-M	—	162—163 ethanol–ether	$C_{23}H_{26}N_2O_4S_2$ (458·5)	60·25 60·08	5·72 5·80	— —	6·11 5·88	13·98 13·81
XLII-2 HM	*C*[j]	155—157 ethanol–ether	$C_{27}H_{30}N_2O_9S$ (558·6)	58·05 57·57	5·41 5·52	— —	— —	5·74 5·56
XLIII	*B*, *G*	93—95 benzene–light petroleum	$C_{22}H_{28}N_2OS_2$ (400·6)	65·98 65·58	7·05 7·07	— —	7·00 6·80	16·00 15·92
XLIII-2HCl[k]	—	223—226 ethanol–ether	$C_{22}H_{34}Cl_2N_2O_3S_2$ (509·6)	51·85 51·76	6·72 6·51	13·92 14·10	5·50 5·63	12·59 12·56
XLIII-MS	—	194—196 ethanol	$C_{23}H_{32}N_2O_4S_3$ (496·7)	55·61 55·70	6·49 6·56	— —	5·64 5·76	19·37 19·30
XLIV[m]	*F*	117—119 acetone	$C_{23}H_{28}N_2O_2S_2$ (428·6)	64·46 64·71	6·58 6·72	— —	6·53 6·28	14·97 15·16
XLV-2 HM	*B*	115—118 ethanol	$C_{30}H_{36}N_2O_{10}S$ (616·6)	58·43 58·46	5·89 6·20	— —	4·54 4·53	5·19 5·38
XLV-2 MS[g]	—	205—207 ethanol–ether	$C_{24}H_{38}N_2O_9S_3$ (594·8)	48·47 48·63	6·44 6·49	— —	4·71 4·88	16·17 15·88
XLVI-2 HM	*H*	130—131 acetone–ether	$C_{33}H_{40}N_2O_{10}S_2$ (688·8)	57·54 57·09	5·85 5·92	— —	— —	9·31 9·62
L[n]	*B*	176—178 aqueous ethanol	$C_{18}H_{17}ClN_2OS$ (344·9)	62·69 62·38	4·97 5·28	10·28 10·52	8·13 8·07	9·30 9·55
L-MS	—	218—219 ethanol–ether	$C_{19}H_{21}ClN_2O_4S_2$ (441·0)	51·75 51·67	4·80 4·87	8·04 8·08	6·35 6·16	14·55 14·54
LI	*B*	150—151 benzene–ethanol	$C_{18}H_{18}ClNOS$ (331·9)	65·14 65·22	5·47 5·44	10·69 10·52	4·22 4·16	9·66 9·72
LI-HCl	—	200—204 benzene–ether	$C_{18}H_{19}Cl_2NOS$ (368·3)	58·70 58·68	5·20 5·14	19·26 19·28	3·80 4·01	8·70 8·76
LI-HM	—	154—155 aqueous ethanol	$C_{22}H_{22}ClNO_5S$ (447·9)	58·99 59·17	4·95 5·24	7·91 7·96	3·13 3·20	7·16 7·24

TABLE I
(*Continued*)

Compound[a]	Method	M.p., °C solvent	Formula (m.w.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
LII[o]	*B*	116—118 methanol	$C_{20}H_{22}ClNOS$ (359·9)	66·74 66·70	6·16 6·27	9·85 9·93	3·89 3·62	8·91 8·74
LII-HCl	—	200—202 aqueous ethanol	$C_{20}H_{23}Cl_2NOS$ (396·4)	60·60 60·45	5·85 5·90	17·90 17·83	3·53 3·56	8·08 8·20
LIII[p]	*B*	210—212 benzene–ethanol	$C_{25}H_{24}ClNOS$ (422·0)	71·16 71·05	5·73 5·87	8·40 8·43	3·32 3·16	7·60 7·52
LIII-HCl	—	184—192 ethanol	$C_{25}H_{25}Cl_2NOS$ (458·4)	65·50 64·81	5·50 5·62	15·47 15·31	3·05 3·01	6·99 7·04
LIII-A-HCl[r]	—	214—216 ethanol	$C_{25}H_{25}Cl_2NOS$ (458·4)	65·50 65·65	5·50 5·50	15·47 15·49	3·05 3·20	6·99 7·17

[a] M maleate, HM hydrogen maleate, MS methanesulfonate. [b] Solvate with 1 molecule of ethanol. [c] UV spectrum: λ_{max} 213 nm (log ε 4·382), 256 nm (3·948), 266 nm (3·959). IR spectrum: 762 (1,2-disubstituted benzene), 820 and 900 (1,2,4-trisubstituted benzene), 1 580 (Ar), 3 286 (CH≡) cm^{-1}. [d] UV spectrum: λ_{max} 226 nm (log ε 3·920). IR spectrum: 759 (1,2-disubstituted benzene), 809, 830 and 872 (1,2,4-trisubstituted benzene), 1 694 (CONH), 3 140 and 3 260 (NH) cm^{-1}. [e] UV spectrum λ_{max} 265 nm (log ε 3·930). IR spectrum: 760 (1,2-disubstituted benzene), 807 and 891 (1,2,4-trisubstituted benzene), 1 703 cm^{-1} (RCOR'). NMR spectrum: δ 6·85—7·80 (mult., 7 H, aromatic protons), 3·0—4·0 (mult., 3 H, CH_2—CH), 2·56 and 2·68 (deformed doublet, 12 H, CH_2 groups of the piperazine ring and of the side chain), 2·20 (singlet, 3 H, CH_3). [f] Hemihydrate. [g] Monohydrate. [h] Reaction mixture was refluxed for 8 h. [i] UV spectrum: λ_{max} 214·5 nm (log ε 4·416), 275·5 nm (4·230). IR spectrum: 759 (1,2-disubstituted benzene), 795, 831 and 886 (1,2,4-trisubstituted benzene), 1 580 cm^{-1} (Ar). [j] The compound was prepared from an uncharacterized (crude) carbethoxy derivative (*XL*). [k] Dihydrate. [m] NMR spectrum: δ 6·8 to 7·70 (mult., 7 H, aromatic protons), 3·85 (split singlet, 2 H, CH_2 in position 11), 3·68 (singlet, 3 H, ester CH_3), 3·20 (triplet, 1 H, CH in position 10), 2·45—3·0 (multiplet, 12 H, CH_2 groups in the piperazine ring and in the side chain), 2·44 (singlet, 3 H, CH_3 of the methylthio group). [n] UV spectrum: λ_{max} 257 nm (log ε 3·917), 266 nm (3·923). IR spectrum: 759 (1,2-disubstituted benzene), 820, 831, 871 (1,2,4-trisubstituted benzene), 1 680 (CON in a ring) cm^{-1}. [o] UV spectrum: λ_{max} 265 nm (log ε 4·024). IR spectrum: 752, 759 (1,2-disubstituted benzene), 807 and 887 (1,2,4-trisubstituted benzene), 1 086 (cyclic ether), 1 580 (Ar) cm^{-1}. [p] Racemate mixture. UV spectrum: λ_{max} 233·5 nm (log ε 4·011), 264·5 nm (3·944). IR spectrum: 698 (monosubstituted benzene), 756 and 768 (monosubstituted and 1,2-disubstituted benzene), 810, 828 and 892 (1,2,4-trisubstituted benzene), 1 116 (ether) cm^{-1}. NMR spectrum: δ 6·85—7·90 (mult., 12 H, aromatic protons), from this a singlet at 7·35 (monosubstituted benzene) and a singlet at 7·83 (1 H in position 9), 2·2—4·45 (multiplet, 9 H, CH_2 and CH in rings), 1·0 (doublet, 3 H, C-methyl). [r] Probably one individual racemate.

pholine 2,6-dimethylmorpholine[27] and 2-phenyl-3-methylmorpholine[28], was used to prepare the morpholine derivatives *LI – LIII*; the last-named was obtained in two crystalline forms, one of which representing probably an individual racemate. In supplement to our previous work, the oxime of 11*H*-dibenzo[*b*,*f*]thiepin-10-one[29] was converted by aminoalkylation to the O-(2-dimethylaminoethyl) derivative *LVII*.

In the experimental section we present one example of each of the preparations corresponding to methods *A* – *J*. The other compounds prepared by these methods are shown with the usual experimental data in Table I. The table does not include compounds prepared by methods other than *A* – *J*.

Most of the compounds prepared here were tested pharmacologically in the form of salts, using the selection of tests employed for the evaluation of potential neuroleptics. The results are summarized in Table II, the values referring to the corresponding bases. The Table shows the values of acute toxicity (LD_{50}) for mice upon intravenous or oral application, the mean effective doses (ED_{50}) bringing about disturbances of motor coordination in the rotating-rod test in mice at the period of maximum effect (again after intravenous or oral application), indexes expressing the ratio of LD_{50} and ED_{50}, threshold doses of compounds significantly prolonging the narcotic effect of thiopental in mice after previous intravenous (30 min) or oral (60 min) application and finally the mean effective doses (ED_{50}) in the catalepsy test in rats after intraperitoneal or oral application. Of the previously described compounds, the table includes octoclothepin (*I*)[2], methiothepin (*XXXVII*)[5] and octometothepin (*XXXVIII*)[5], and chlorpromazine as standard.

Table II confirms some of the previously derived relationships[2,4] and demonstrates some relationships unknown before: *1.* Replacement of N-methyl in the octoclothepin (*I*) molecule and in similar compounds with a hydrogen atom (see compounds *III* and *XLI*) results in a substantial decrease of the depressant and particularly cataleptic activity. *2.* Replacement of N-methyl with unsaturated residue (allyl, propargyl – compounds *V, VI*) and with cycloalkyls (compounds *VIII, IX*) has a similar effect. The lowest unfavourable effect is found upon replacement with the lowest cycloalkyl, *i.e.* cyclopropyl. Compound *VII* resembles octoclothepin in its depressant and cataleptic activity. *3.* Replacement of N-methyl with 4-methoxybenzyl (compound *X*) brings about also a decrease of activity but, at the same time, a shift in the ratio of depressant and cataleptic acitivity. While in its depressant activity the compound is by two orders of magnitude less effective than octoclothepin and by one order of magnitude than chlorpromazine, in the cataleptic test it is only three times weaker than octoclothepin and it actually exceeds somewhat chlorpromazine in its activity. *4.* Replacement of N-methyl with aminoalkyl (compounds *XI, XII, XXVII*) results in a marked decrease of depressant as well as cataleptic activity. *5.* The high degree of activity is maintained upon replacement of N-methyl with hydroxyalkyl (see compounds *XVII – XIX, XXI, XLIII* and *XLV*). Only one of the compounds thus derived (*XLV*) exceeds somewhat octoclothepin in activity in the rotating-rod

test. On the other hand, four of these (*XIX*, *XXI*, *XLIII* and *XLV*) exceed it in the cataleptic test. In this test, a special place is held by the 3-hydroxypropyl analogues of methiothepin (*XLIII*, "oxyprothepin") and octometothepin (*XLV*, "oxymetothepin") which deserve special attention. *6.* Considerable activity is displayed by esters of the hydroxyalkyl derivatives just mentioned (*XXII–XXV*, *XLVI*) although they do not attain them in any single case. *7.* Of compounds with other functional groups in the N-alkyl (*XIII–XVI*, *XXVI*, *XXVIII*, *XXIX*, *XXXII*) mention should be made of 2-aminocarbonylethyl derivative *XIV* and the corresponding amidoxime *XXVIII* which, upon oral application, are practically equal to octoclothepin in both fundamental tests. Other compounds (*XIII*, *XV*, *XVI*, *XXIX*) are weaker but in the cataleptic test they are still about twice more effective than chlorpromazine.

Compounds shown in Table II were tested partly for other types of activity. It can be stated generally that they do not affect reserpine ptosis in mice and that they potentiate more or less the ulcerogenic effect of reserpine in rats. A general property of compounds of this group is their antiserotonin effect demonstrated in the *in vivo* test in rats. Compounds *XI* and *XII* antagonize the effect of serotonin in the intraperitoneal dose of 5 mg/kg, compound *IX* displaying the same effect in the same oral dose. "Oxyprothepin" *XLIII* is highly effective, showing an antiserotonin effect starting at 0·1 mg/kg *i.p.* Similarly, the hypothermic effect (in a test on mice) seems to be a general phenomenon in this group of compounds although it was demonstrated only in several selected cases; *e.g.* compounds *XXV* and *XLI* decrease with statistical significance the body temperature of mice starting with an oral dose of 0·5 mg/kg (they are more effective than chlorpromazine by an order of magnitude) and compound *XXII* displays this effect from the intravenous threshold dose of 0·25 mg/kg.

Some compounds were not included in the table because their central depressant activity, if demonstrated at all, is so low that the compounds appear to be uninteresting from the pharmacological point of view. This holds first for all the N-acyl derivatives (compounds *II*, *XX*, *XXXIII* and *L*), further for the N-methanesulfonyl derivative *XXXIV* and for the symmetrically disubstituted piperazine derivative *IV*. Similarly, no central depressant effect was found with the O-(aminoalkyl)-oxime *LVII* which was also ineffective against reserpine ptosis in mice. Among the guanidine derivatives *XXX*, *XXXI* and *XLVII*, their potential sympatholytic and hypotensive activity stands in the foreground, as was studied at the pharmacological department of this Institute by Dr A. Dlabač and Dr M. Vaněček. It was found that compound *XXX* at a dose of 42 mg/kg brings about a mild relaxation of the nictitating membrane in rats which sets in 1 h after application and persists for 2–3 h. The same dose of this compound was without effect on the pressor reaction to an intravenous infusion of hypertensin in monkeys under conditions, where guanethidine depresses the reaction at a dose of 25 mg/kg *p.o.*

Finally, the remaining compounds (*XLVIII*, *XLIX*, *LI–LIII*) were subjected

TABLE II

Pharmacological Properties of Derivatives of 10-Piperazino-11,11-dihydrodibenzo[*b*,*f*]thiepin

Compound	Application	Acute toxicity LD_{50} mg/kg	Rotating rod ED_{50} mg/kg	Index LD_{50}/ED_{50}	Potentiation of thiopental narcosis threshold dose mg/kg	Catalepsy[a] ED_{50} mg/kg
I	*i.v.*	46·3	0·06	780	0·05	2·4
I	*p.o.*	78·0	2·2	35	0·25	4·3
III	*p.o.*	120	5·6	21	5·0	30·0
V	*p.o.*	220	6·4	34	1·0	24·5
VI	*p.o.*	110	25·0	4	2·5	25·0
VII	*p.o.*	—	3·8	—	—	5·1
VIII	*p.o.*	155	6·2	25	—	7·8
IX	*p.o.*	88	5·7	15	1·0	13·0
X	*i.v.*	152	5·1	30		7·3
XI	*i.v.*	57·0	1·9	30	5·0	11·5
XII	*i.v.*	58·0	1·5	39	1·0	>10
XIII	*p.o.*	420	27·0	16	—	9·2
XIV	*p.o.*	128	2·8	46	—	3·3
XV	*p.o.*	72	2·0	36	—	9·5
XVI	*p.o.*	>150	5·9	—	—	7·8
XVII	*i.v.*	> 50	0·21	—	0·05	—
XVIII	*p.o.*	145	3·4	43	2·5	12·0
XIX	*i.v.*	59	0·195	302	—	1·6
XXI	*i.v.*	50	0·165	303	0·1	1·2
XXII	*i.v.*	66	0·42	157	0·05	2·8
XXIII	*p.o.*	420	19·0	22	1·0	inact.[b]
XXIV	*i.v.*	56	0·17	329	0·1	3·0
XXV	*p.o.*	155	3·0	52	1·0	16·0
XXVI	*p.o.*	82	1·4	59	—	20·0
XXVII	*i.v.*	49·4	>30	—	10·0	13·5
XXVIII	*p.o.*	210	4·7	45	—	2·2
XXIX	*p.o.*	300	7·4	40	—	8·8
XXXII	*i.v.*	~100	4·1	—	—	>10
XXXVII	*i.v.*	51	0·094	542	0·01	2·0
XXXVII	*p.o.*	94	1·9	50	1·0	10·5
XXXVIII	*i.v.*	38	0·049	775	0·01	1·3
XXXVIII	*p.o.*	36	1·5	24	0·25	4·0
XLI	*p.o.*	68	inact.	—	1·0	—
XLIII	*i.v.*	44	0·11	400	0·025	0·62
XLIII	*p.o.*	—	4·6	—	—	3·3
XLV	*i.v.*	37	0·052	712	—	0·5
XLVI	*i.v.*	—	0·185	—	0·1	3·6
XLVI	*p.o.*	175	—	—	—	—

TABLE II
(*Continued*)

Compound	Application	Acute toxicity LD_{50} mg/kg	Rotating rod ED_{50} mg/kg	Index LD_{50}/ED_{50}	Potentiation of thiopental narcosis threshold dose mg/kg	Catalepsy[a] ED_{50} mg/kg
Chlorpromazine	*i.v.*	52·2	0·585	89	0·25	8·6
	p.o.	198	8·2	24·2	2·5	16·0

[a] Application either *i.p.* or *p.o.* [b] Applied dose 50 mg/kg *p.o.*

to a wider spectrum of tests of general pharmacological screening under the direction of Dr F. Hradil at the affiliated unit of this Institute at Rosice n/L. With the exception of compound *XLVIII* (LD_{50} 150 mg/kg *i.v.*) which showed a considerable degree of spasmolytic effect on isolated rat duodenum toward barium chloride spasms, the compounds show low toxicity ($LD_{50} > 2·5$ g/kg *p.o.*) and do not show any pronounced effects.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block. The samples were dried for 8 h in oil-pump vacuum (about 0·2 Torr) over phosphorus pentoxide at a temperature adequate to the melting point of the substance (at most 100°C). The UV spectra in methanol were recorded on a Unicam SP 700 spectrophotometer, IR spectra in Nujol on a Unicam SP 200 G spectrophotometer and NMR spectra in deuteriochloroform in a ZKR 60 (Zeiss Jena) apparatus.

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

A homogeneous mixture of 56·0 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] and 80 g 1-ethoxycarbonylpiperazine[6] was heated for 5 h to 110°C. After cooling, the mixture was separated between 200 ml benzene and 200 ml water, the benzene layer was washed with further 200 ml water and then shaken with 250 ml 3M-HCl. The mixture was left to stand for 12 h at room temperature and the product hydrochloride was then separated by filtration and, after washing with benzene, it was suspended in 300 ml water, decomposed with excess aqueous ammonia and the liberated base was isolated by extraction with benzene: 66 g (82%), m.p. 113–115°C (ethanol). Neutralization with maleic acid in ethanol yielded a hydrogen maleate melting at 190°C (ethanol). The analysis of the base as well as of the hydrogen maleate is shown in Table I.

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

A. *By substitution reaction of the* 8,10-*dichloro derivative with piperazine* (Method *B*): A solution of 14·0 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] and 21·5 g anhydrous piperazine

in 30 ml chloroform was refluxed for 6 h in a water bath. Chloroform was then evaporated at reduced pressure and the residue divided by shaking between 150 ml benzene and 150 ml water. The benzene solution was washed with water and shaken with 100 ml 3M-HCl. The precipitated hydrochloride was filtered after 2 h of standing at room temperature. The benzene layer was separated from the filtrate, evaporated and 3·4 g elimination product was obtained, *i.e.* 2-chlorodibenzo[*b*,*f*]thiepin[2] (m.p. 76—78°C after recrystallization from methanol). The filtered hydrochloride was suspended in the aqueous phase of the filtrate, the suspension was made alkaline with excess aqueous ammonia and the released base was isolated by extraction with benzene; 11·3 g (68%), m.p. 132—134°C (acetone). In a mixture with the product obtained as described below, the melting point is without depression.*

B. *By alkaline hydrolysis of* II (Method *C*): A mixture of 6·0 g ethoxycarbonyl derivative *II*, 3·0 g potassium hydroxide and 6 ml ethanol was refluxed for 3 h on a 120—130°C bath. After cooling, the mixture was divided by shaking between 150 ml water and 150 ml benzene and the benzene phase was used to obtain (via the hydrochloride) the desired product as described before: 4·8 g (98%), m.p. 135°C (acetone). UV spectrum: λ_{max} 265 and 236·6 nm. IR spectrum: 759 (1,2-disubstituted benzene), 809 (1,2,4-trisubstituted benzene), 1 578 (Ar) cm^{-1}. Neutralization with maleic acid in ethanol yielded the maleate, crystallizing with 1 molecule of ethanol, m.p. 140—148°C (decomp.). The analyses of the base as well as of the maleate are shown in Table I.

C. *From nitrile* XIII *when attempting to prepare the imidazoline*: A mixture of 10·0 g nitrile *XIII* and 6·05 g ethylenediamine mono-*p*-toluenesulfonate was heated for 3 h to 200—205°C; after cooling, the solid melt was recrystallized from 150 ml ethanol. A total of 4·4 g p-*toluenesulfonate* of *III* was obtained, m.p. 270—271°C. For $C_{25}H_{27}ClN_2O_3S_2$ (503·1) calculated: 59·69% C, 5·41% H, 7·05% Cl, 5·57% N, 12·74% S; found: 60·22% C, 5·61% H, 7·35% Cl, 5·73% N, 12·85% S. Decomposition of the *p*-toluenesulfonate with aqueous ammonia released a base which, by neutralization with maleic acid and by crystallization from ethanol, yielded the *maleate*, this time free of the crystal solvent, m.p. 169—171°C. For $C_{22}H_{23}ClN_2O_4S$ (446·8) calculated: 59·12% C, 5·19% H, 7·93% Cl, 6·27% N, 7·17% S; found: 59·05% C, 5·10% H, 8·16% Cl, 6·82% N, 7·10% S.

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

A mixture of 16·9 g 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2], 70 ml acetonitrile, 2,6 g anhydrous piperazine and 10 g anhydrous potassium carbonate was refluxed under stirring for 16 h. After standing overnight the solid substance was filtered and inorganic salts were removed by digestion with 80—90°C water. Drying yielded 13·5 g solid product which was boiled with 300 ml benzene. After 4 h of standing, the insoluble product was removed by filtration (5·5 g compound melting at 302—303°C which was not identified) and the benzene filtrate was shaken with 80 ml 3M-HCl. After 24 h of standing the precipitated hydrochloride was filtered, suspended in chloroform and decomposed by shaking the suspension with excess aqueous ammonia. Evaporation of the chloroform solution yielded 6·4 g of the base, melting at 201—203°C (toluene). UV spectrum: λ_{max} 253 and 267 nm. IR spectrum: 750 (1,2-disubstituted benzene), 814 (1,2,4-trisubstituted benzene), 1573 and 1613 (Ar) cm^{-1}. For $C_{32}H_{28}Cl_2N_2S_2$ (575·6) calculated: 66·77% C, 4·90% H, 12·32% Cl, 4·86% N, 11·14% S; found: 67·14% C, 4·97% H, 12·30% Cl, 4·80% N, 11·06% S.

Monomethanesulfonate, m.p. 256—257°C. During recrystallization from a mixture of aqueous ethanol and benzene it loses some methanesulfonic acid which accounts for the higher carbon

* More recently the monohydrochloride of base *III* was also prepared; m.p. 258—263°C (ethanol). For $C_{18}H_{20}Cl_2N_2S$ (367·3) calculated: 58·85% C, 5·49% H, 19·31% Cl, 7·63% N, 8·72% S; found: 59·00% C, 5·60% H, 19·23% Cl, 7·61% N, 9·04% S (added in proof).

content found. For $C_{33}H_{32}Cl_2N_2O_3S_3$ (671·7) calculated: 59·00% C, 4·80% H, 10·55% Cl, 4·17% N, 14·32% S; found: 59·80% C, 4·80% H, 10·73% Cl, 4·51% N, 13·97% S.

Dimethanesulfonate, m.p. 272—274°C (ethanol–benzene). For $C_{34}H_{36}Cl_2N_2O_6S_4$ (767·8) calculated: 53·18% C, 4·72% H, 9·23% Cl, 3·65% N, 16·70% S; found: 53·53% C, 4·64% H, 9·30% Cl, 4·02% N, 16·74% S.

8-Chloro-10-(4-allylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*V*) (Method (*D*)

A mixture of 8·3 g amine *III*, 90 ml 1-butanol, 3·70 g allyl bromide and 4·10 g anhydrous potassium carbonate was heated for 12 h at 110—120°C. After cooling, the inorganic salts were filtered and the filtrate was evaporated at reduced pressure. The residue (12 g) was dissolved in 30 ml benzene and chromatographed on a column of 200 g neutral alumina (activity II). Elution with benzene yielded 5·9 g homogeneous base, m.p. 44—47°C (ethanol). UV spectrum: λ_{max} 257 nm (log ε 3·967), 266 nm (3·969). IR spectrum: 758 (1,2-disubstituted benzene), 835 and 900 (1,2,4-trisubstituted benzene), 929 (vinyl) cm^{-1}. Neutralization with maleic acid in ethanol yields the maleate melting at 192—193°C (ethanol). Analysis of the base as well as of the maleate are shown in Table I.

8-Chloro-10-[bis(2-hydroxyethyl)amino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XLVIII*)

A mixture of 30·0 g 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin and 28·5 g diethanolamine was heated for 4 h to 125°C and treated similarly to the preparation of *II*. A total of 23·9 g oily base was obtained, which was neutralized with maleic acid in acetone to 17·0 g hydrogen maleate which was prepared completely pure by crystallization from a mixture of acetone and ethanol; m.p. 123—125°C (the compound is a solvate containing 1 molecule of acetone). For $C_{25}H_{30}$·.$ClNO_7S$ (524·0) calculated: 57·30% C, 5·77% H, 6·77% Cl, 2·67% N, 6·12% S; found: 57·30% C, 5·69% H, 7·01% Cl, 2·56% N, 6·31% S.

Decomposition of the maleate with aqueous ammonia and extraction with benzene yielded the pure base, melting at 95—96°C (cyclohexane–benzene). The UV spectrum: λ_{max} 259 nm (log ε 3·986). IR spectrum: 752 (1,2-disubstituted benzene), 808 (1,2,4-trisubstituted benzene), 1 019, 1 047 and 3 270 (primary alcohol) cm^{-1}. For $C_{18}H_{20}ClNO_2S$ (349·9) calculated: 61·79% C, 5·76% H, 10·13% Cl, 4·00% N, 9·16% S; found: 62·35% C, 5·76% H, 10·25% Cl, 3·95% N, 9·22% S.

8-Chloro-10-[bis(2-chloroethyl)amino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XLIX*)

A solution of 8·5 g base *XLVIII* in 30 ml thionyl chloride was refluxed for 2·5 h and the excess thionyl chloride was evaporated at reduced pressure. The residue was decomposed with 150 ml water and 35 ml concentrated aqueous ammonia and the base was isolated by extraction with benzene; 8·3 g, m.p. 97—98°C (cyclohexane). UV spectrum: λ_{max} 255 nm (log ε 4·052), 265 nm (4·056). IR spectrum: 757 (1,2-disubstituted benzene), 806 (1,2,4-trisubstituted benzene) cm^{-1}. NMR spectrum: δ 6·85—7·75 (mult., 7 H, aromatic protons), 3·70—4·20 (mult., 3 H, —CH_2—CH—), 3·45 (triplet, 4 H, 2 × CH_2Cl), 3·02 (triplet, 4 H, —CH_2NCH_2—). For $C_{18}H_{18}Cl_3NS$ (386·7) calculated: 55·90% C, 4·69% H, 27·50% Cl, 3·62% N, 8·29% S; found: 55·90% C, 4·72% H, 27·55% Cl, 3·53% N, 8·23% S.

Hydrochloride, m.p. 118—123°C (it softens from 108°C up). During recrystallization from ethanol it dissociates and loses hydrogen chloride; for this reason the crude product was analyzed. For $C_{18}H_{19}Cl_4NS$ (423·2) calculated: 51·08% C, 4·53% H, 33·51% Cl, 3·31% N, 7·57% S; found: 51·69% C, 4·58% H, 33·86% Cl, 3·06% N, 7·64% S.

8-Chloro-10-(4-cyclopropylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*VII*) (Method *E*)

A mixture of 8·0 g base *XLIX*, 70 ml 1-butanol and 1·29 g cyclopropylamine was heated in an autoclave for 5 h at 150°C. After cooling, the solvent was evaporated at reduced pressure and a basic fraction was isolated from the residue (2·12 g), *via* the hydrochloride, similarly to the preceding cases. The crude base was chromatographed on a column of alumina (50 g, activity II), using benzene for elution. A total of 0·98 g homogeneous product was eluted. Neutralization with maleic acid in a mixture of ethanol and ether yielded the crystalline maleate, m.p. 175–176°C (ethanol). Analysis of this salt is shown in Table I.

1-(2-Dimethylaminoethyl)piperazine (*LV*)

A mixture of 39·5 g 1-ethoxycarbonylpiperazine[6], 72 g 2-dimethylaminoethyl chloride (hydrochloride), 26·5 g anhydrous sodium carbonate and 500 ml 50% aqueous ethanol was refluxed under stirring for 12 h. After evaporation of the volatile fractions the residue was extracted with chloroform and the extracts treated by distillation. A total of 24·5 g crude carbamate *LIV* boiling at 140–150°C/10 Torr was obtained. The entire amount of the product (24·5 g) was heated with 30 g potassium hydroxide and 18 ml ethanol for 2·5 h under a reflux condenser in a 120°C bath. After cooling, the product was extracted with benzene and the extract distilled: 9·0 g, b.p. 98 to 105°C/15 Torr. *Picrate*, m.p. 244–250°C (aqueous ethanol), apparently identical with tripicrate (m.p. 243–244°C, decomp.), described by Hromatka and Kraup[17] and obtained from a base prepared by a different procedure.

8-Chloro-10-[4-(2-cyanoethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XIII*) (Method *F*)

A supension of 10·0 g amine *III* in 60 ml tert-butanol was mixed with 1 ml 50% solution of triethylbenzylammonium hydroxide in methanol. A solution of 4·8 g acrylonitrile in 15 ml tert-butanol was then added dropwise and the mixture was stirred for 2 h at room temperature and for further 2 h at 40–50°C. After standing overnight, the tertiary butanol was distilled at reduced pressure, the residue was dissolved in 100 ml benzene and the solution was washed with water. The benzene solution was then shaken with 80 ml 3M-HCl, the precipitated hydrochloride was filtered after 2 h of standing and washed with water and benzene. After decomposition with aqueous ammonia the base was isolated by extraction with benzene: 11·5 g, m.p. 111–112°C (ethanol). UV spectrum: λ_{max} 265 nm (log ε 3·950). IR spectrum: 768 (1,2-disubstituted benzene), 816, 830 and 890 (1,2,4-trisubstituted benzene), 2248 (CN) cm^{-1}. Maleate can be obtained by the usual procedure, m.p. 170–171°C (ethanol). The analyses of the base and of the maleate are shown in Table I.

8-Chloro-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIII*) (Method *G*)

A solution of 5·0 g ester *XV* in a mixture of 5 ml tetrahydrofuran and 60 ml ether was reduced with 0·91 g lithium aluminium hydride in further 25 ml ether. The mixture was refluxed for 3·5 h and processed as usual. A total of 3·3 g (71%) crystalline product was obtained; m.p. 114–116°C (aqueous ethanol). The compound is identical with the product obtained by substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin with 1-(3-hydroxypropyl)piperazine (method *B*) and yields a *di(methanesulfonate) monohydrate*, melting at 166–168°C (ethanol-ether) and a *di(hydrogen maleate)* melting at 139–140°C (ethanol). The analyses of the base and of the salts are shown in Table I.

8-Chloro-10-[4-(3-hydroxybutyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XIX*)

A solution of 1·0 g sodium borohydride in 4 ml water with 0·1 ml 10% sodium hydroxide was added to a solution of 3·0 g ketone *XVI* in 80 ml methanol at 50°C. The mixture was refluxed under stirring for 3 h, methanol was then evaporated at reduced pressure, the residue divided by shaking between benzene and water and the benzene solution was evaporated. A total of 3·0 g glassy base was obtained and it was neutralized in 13 ml ethanol with 0·85 g maleic acid. A total of 2·6 g *maleate* was obtained, melting at 155–160°C (it softens from 145°C up) which does not change on crystallization from ethanol. For $C_{26}H_{31}ClN_2O_5S$ (519·0) calculated: 60·16% C, 6·02% H, 6·83% Cl, 5·40% N, 6·17% S; found: 59·73% C, 5·93% H, 6·70% Cl, 5·66% N, 6·24% S.

Decomposition of 1·6 g maleate with aqueous ammonia and extraction with benzene yielded an oily base (1·34 g) which partly crystallized on dissolving in 10 ml light petroleum and on cooling the solution. In this way, a total of 0·90 g *base A* melting at 92–97°C was obtained. UV spectrum: λ_{max} 268 nm (log ε 4·003). IR spectrum: 750 (1,2-disubstituted benzene), 810, 830 and 880 (1,2,4-trisubstituted benzene), 1005, 1117, 1152 and 3220 (OH) cm^{-1}. For $C_{22}H_{27}ClN_2OS$ (403·0) calculated: 8·80% Cl, 6·95% N, 7·95% S; found: 8·54% Cl, 6·52% N, 7·86% S.

Evaporation of the mother liquor and crystallization of the residue from cyclopentane yielded a small amount of *base B* melting at 76–78°C. Its spectra are identical with those of the base A. For $C_{22}H_{27}ClN_2OS$ (403·0) calculated: 8·80% Cl, 6·95% N, 7·95% S; found: 8·81% Cl, 6·84% N, 7·66% S,

8-Chloro-10-[4-(3-carboxypropionyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XX*)

A mixture of 8·3 g amine *III*, 2·5 g succinic anhydride and 250 ml chloroform was refluxed for 8 h and the clear solution obtained was evaporated *in vacuo*. An oily product (10·5 g) was obtained in a theoretical yield, part of which (5·0 g) was dissolved in 100 ml 2·5% sodium hydroxide whereafter a solution of 11·0 g maleic acid was added. A total of 6·0 g *hydrogen maleate* precipitated, m.p. 161–162°C (aqueous ethanol). For $C_{26}H_{27}ClN_2O_7S$ (547·0) calculated: 57·09% C, 4·97% H, 6·48% Cl, 5·12% N, 5·86% S; found: 57·26% C, 4·86% H, 6·43% Cl, 5·15% N, 6·00% S.

8-Chloro-10-[4-(4-hydroxybutyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXI*)

A solution of 6·0 g crude amino acid *XX* in 110 ml tetrahydrofuran was reduced with the aid of 3·0 g lithium aluminium hydride. The mixture was stirred for 1 h at room temperature, refluxed for 4 h, after cooling decomposed by successive additions of 3 ml water, 3 ml 15% solution of sodium hydroxide and 9 ml water, the precipitate was filtered and the filtrate evaporated at reduced pressure. The remaining oil was dissolved in 100 ml benzene, the solution washed with 15% sodium hydroxide and evaporated again. A crude base (4·3 g) was obtained which was converted by the conventional procedure to the *di(hydrogen maleate)*, m.p. 136–138°C (ethanol–acetone). For $C_{30}H_{35}ClN_2O_9S$ (635·1) calculated: 56·73% C, 5·55% H, 5·58% Cl, 4·41% N, 5·05% S; found: 57·00% C, 5·59% H, 5·48% Cl, 4·01% N, 5·24% S.

Decomposition of the maleate with aqueous ammonia and benzene extraction yielded a *base*, m.p. 116–117°C (aqueous ethanol). UV spectrum: λ_{max} 265 nm (log ε 3·974). IR spectrum: 751 (1,2-disubstituted benzene), 813, 879 (1,2,4-trisubstituted benzene), 1010, 3210 (OH), 1552, 1571, 1574 (Ar) cm^{-1}. For $C_{22}H_{27}ClN_2OS$ (403·0) calculated: 65·57% C, 6·75% H, 8·80 Cl, 6·95% N, 7·95% S; found: 66·12% C, 7·14% H, 8·87% Cl, 7·11% N, 8·05% S.

8-Chloro-10-[4-(2-acetoxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXII*) (Method *H*)

4·0 ml acetyl chloride was added to a solution of 3·5 g alcohol *XVII* in a mixture of 15 ml benzene and 5 ml chloroform. The mixture which heated spontaneously to 50°C was left overnight at room temperature whereafter a solid precipitated. The mixture was diluted with 50 ml benzene, 50 ml water was added, made alkaline with aqueous ammonia and shaken. The benzene layer was dried and evaporated: 3·8 g oily base. Conventional procedure yielded the *di(hydrogen maleate)*, m.p. 160—161°C (aqueous acetone). Its analysis is shown in Table I.

8-Chloro-10-[4-(2-carboxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVI*)

A solution of 5·0 g nitrile *XIII* and 30 g potassium hydroxide in 130 ml ethanol and 1 ml water was refluxed under stirring for 15 h and then evaporated to dryness at reduced pressure. The residue was dissolved in 300 ml warm water and the warm solution was neutralized with acetic acid. The product precipitated first in an oily form but crystallized on cooling; 5·6 g, m.p. 175—178°C (aqueous ethanol). The product was a *monohydrate of the amino acid* XXVI. For $C_{21}H_{25}ClN_2O_3S$ (420·9) calculated: 59·92% C, 5·99% H, 8·42% Cl, 6·65% N, 7·62% S; found: 60·46% C, 5·65% H, 8·33% Cl, 6·50% N, 7·56% S.

Maleate, m.p. 184—185°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: 57·92% C, 5·26% H, 7·05% Cl, 4·98% N, 6·42% S.

8-Chloro-10-[4-(3-aminopropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVII*)

A solution of 5·0 g nitrile *XIII* in 80 ml ether and 10 ml tetrahydrofuran was added dropwise and under stirring to a suspension of 1·49 g lithium aluminium hydride in 30 ml ether. The mixture was stirred for 2 h at room temperature, left overnight without stirring, decomposed by successive additions of 1·5 ml water, 1·5 ml 15% sodium hydroxide and 4·5 ml water. After filtration, the filtrate was dried and evaporated. 4·0 g of an oily base was obtained which was converted to the *dimaleate* (solvate with 1 molecule of ethanol), m.p. 161—163°C (ethanol). For $C_{31}H_{40}ClN_3O_9S$ (666·2) calculated: 55·89% C, 6·05% H, 5·32% Cl, 6·31% N, 4·81% S; found: 55·82% C, 6·01% H, 5·30% Cl, 6·26% N, 5·16% S.

8-Chloro-10-[4-(3-amino-3-oximinipropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVIII*)

A solution of 1·65 g hydroxylamine[20] in 45 ml 1-butanol was added to a warm solution of 9·55 g nitrile *XIII* in 40 ml 1-butanol, the mixture was left for 48 h at room temperature, then it was heated for 16 h to 80—90°C and, after standing overnight, the precipitated product was filtered: 6·2 g, m.p. 202—204°C (1-butanol). For $C_{21}H_{25}ClN_4OS$ (417·0) calculated: 60·49% C, 6·04% H, 8·50% Cl, 13·44% N, 7·69% S; found: 60·37% C, 6·25% H, 8·62% Cl, 13·34% N, 7·65% S.

Maleate, m.p. 134—136°C (ethanol). For $C_{25}H_{29}ClN_4O_5S$ (533·0) calculated: 56·33% C, 5·48% H, 6·65% Cl, 10·51% N, 6·02% S; found: 56·55% C, 5·60% H, 6·76% Cl, 10·51% N, 6·25% S.

8-Chloro-10-[4-(3-oximinobutyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXIX*)

It crystallizes in the form of *monohydrochloride* upon mixing warm solutions of 2·65 g ketone *XVI* in 15 ml ethanol and 0·75 g hydroxylamine hydrochloride in 5 ml 90% ethanol: 2·60 g, m.p. 214—217°C. For $C_{22}H_{27}Cl_2N_3OS$ (452·4) calculated: 58·40% C, 6·01% H, 15·67% Cl, 9·29% N, 7·09% S; found: 58·59% C, 6·24% H, 15·73% Cl, 9·51% N, 7·04% S.

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

A mixture of 5·0 g amine *III*, 2·1 g S-methylisothiuronium sulfate, 5 ml ethanol and 5 ml water was refluxed for 8 h and left to stand overnight in a cold room. A total of 4·6 g nonhomogeneous solid precipitated which was separated from the more soluble component by boiling in 50 ml aqueous (1 : 1) ethanol. A total of 2·4 g (38%) *hemisulfate* resulted, m.p. 302–304°C (decomp.). For $C_{19}H_{21}ClN_4S.\frac{1}{2}H_2SO_4$ (421·9) calculated: 54·08% C, 5·25% H, 8·40% Cl, 13·28% N, 11·40% S; found: 53·97% C, 5·30% H, 8·52% Cl, 13·27% N, 11·72% S.

10-(4-Guanidinopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XLVII*)

A mixture of 5·0 g 10-(4-aminopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[4], 2·35 g S-methylisothiuronium sulfate, 5 ml ethanol and 6 ml water was refluxed for 10 h. After cooling, 3·64 g crude *hemisulfate* was filtered and freed of the more soluble contaminants by boiling with 50 ml 70% ethanol; m.p. 215°C (it softens from 208°C). For $C_{19}H_{23}N_5S.\frac{1}{2}H_2SO_4$ (402·5) calculated: 17·40% N, 11·95% S; found: 17·41% N, 11·73% S.

8-Chloro-10-[4-(3-guanidinopropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*XXXI*)

Similarly to the preceding cases, a reaction of 5·0 g base *XXVII* with 1·79 g S-methylisothiuronium sulfate in 10 ml aqueous ethanol (1 : 1) yielded 6·3 g *hemisulfate* which was purified first by boiling with 70% aqueous ethanol and then by recrystallization from a larger volume of 50% ethanol; m.p. 145–149°C (monohydrate). For $C_{22}H_{30}ClN_5OS.\frac{1}{2}H_2SO_4$ (497·1) calculated: 53·16% C, 6·29% H, 7·13% Cl, 14·09% N, 9·68% S; found: 52·98% C, 6·22% H, 7·13% Cl, 14·39% N, 9·77% S.

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

A solution of 3·0 g potassium cyanate in 15 ml water was added to a solution of 5·0 g amine *III* in 40 ml 90% acetic acid, the mixture was heated for 3 h to 60°C, then it was evaporated under reduced pressure and the *base* was released from the residue with dilute aqueous ammonia: 3·0 g (55%), m.p. 203–207°C (ethanol). For $C_{19}H_{20}ClN_3OS$ (373·9) calculated: 61·03% C, 5·39% H, 9·48% Cl, 11·24% N, 8·57% S; found: 61·12% C, 5·57% H, 9·60% Cl, 10·99% N, 8·85% S.

Methanesulfonate (solvate with 1 molecule of ethanol), m.p. 177–179°C under decomposition (aqueous ethanol). For $C_{22}H_{30}ClN_3O_5S_2$ (516·1) calculated: 51·20% C, 5·86% H, 6·87% Cl, 8·14% N, 12·42% S; found: 51·43% C, 6·00% H, 6·99% Cl, 8·23% N, 12·64% S.

8-Chloro-10-(4-methanesulfonylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XXXIV*) (Method *J*)

Methanesulfonyl chloride (3·5 ml) was added dropwise to a solution of 10·0 g amine *III* in 20 ml pyridine and the mixture was heated for 1 h to 90°C. After cooling, it was diluted with 100 ml water, 20 ml concentrated aqueous ammonia was added and the mixture was extracted with benzene; 12·0 g, m.p. 190–192°C (ethanol–benzene). *Methanesulfonate*, m.p. 217–218°C (aqueous ethanol). Analyses of base and salt are shown in Table I.

4-Methyl-2-piperazinone (*LVI*)

Methyl iodide (57 g) was added in parts to a mixture of 15·0 g 2-piperazinone[26] (m.p. 133–135°C) and 45 ml ethanol. The mixture was refluxed for 4 h and after cooling, 36·2 g (99%) crude hydro-

iodide of the product was filtered. This was recrystallized for analysis from aqueous ethanol; m.p. 198–204°C. For $C_5H_{11}IN_2O$ (242·1) calculated: 24·81% C, 4·58% H, 52·43% I, 11·57% N; found: 24·87% C, 4·81% H, 52·47% I, 11·48% N.

Decomposition of the hydroiodide with a solution of sodium methoxide released the *base* which was isolated by the usual procedure: m.p. 84–87°C (acetone–light petroleum). For $C_5H_{10}N_2O$ (114·2) calculated: 52·61% C, 8·83% H, 24·54% N; found: 52·28% C, 8·86% H, 24·26% N.

Hydrochloride, m.p. 250–253°C (aqueous ethanol–acetone). For $C_5H_{11}ClN_2O$ (150·6) calculated: 39·87% C, 7·36% H, 23·54% Cl, 18·60% N; found: 39·82% C, 7·51% H, 23·27% Cl, 18·50% N.

In a different experiment where a substantially lower amount of methyl iodide was used a significant by-product was 2-*piperazinone hydroiodide*; m.p. 255–258°C (aqueous ethanol–acetone). For $C_4H_9IN_2O$ (228·1) calculated: 21·07% C, 3·98% H, 55·65% I, 12·29% N; found: 21·27% C, 4·15% H, 55·66% I, 12·65% N.

O-(2-Dimethylaminoethyl)-10-oximino-11*H*-dibenzo[*b*,*f*]thiepin (*LVII*)

A solution of sodium ethoxide (0·53 g sodium in 30 ml ethanol) was added to a solution of 5·30 g 10-oximino-11*H*-dibenzo[*b*,*f*]thiepin[29] in 70 ml absolute ethanol. This was followed by 2·5 g 2-dimethylaminoethyl chloride. The mixture was left for 3 days at room temperature, then it was refluxed for 4 h. After cooling, the precipitated sodium chloride was filtered and the filtrate evaporated. The remaining oil (6·9 g) was converted in an ether solution to the maleate (a mixture of oil and crystals) which was decomposed by aqueous ammonia and extracted with benzene to obtain the crude base (4·0 g, 59%). The base was freed of the more polar contaminant by chromatography on a column of 120 g neutral alumina (activity II). Elution with benzene and with benzene containing 3% ethanol yielded a homogeneous base, 3·80 g. UV spectrum: λ_{max} 247 nm (log ε 4·242), 310 nm (3·634). IR spectrum: 757 (1,2-disubstituted benzene), 1040 (—O—), 1600 (C=N) cm^{-1}.

Hydrogen maleate, m.p. 107–108°C (ethanol–ether). For $C_{22}H_{24}N_2O_5S$ (428·5) calculated: 61·67% C, 5·64% H, 6·54% N, 7·48% S; found: 61·63% C, 5·90% H, 6·57% N, 7·72% S.

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