POTENT NEUROLEPTICS WITH PROLONGED ACTIVITY AND DIMINISHED TOXICITY: 7,8-DIHALOGENO--10-PIPERAZINODIBENZO[*b*,*f*]THIEPINS*

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7,8-Dihalogenodibenzo[*b*,*f*]thiepin-10(11*H*)-ones (*XVa*—*XVd*) were synthesized from 3,4--dichloro- (*XIXa*), 4-chloro-3-fluoro- (*XIXb*), 3-chloro-4-fluoro- (*XIXc*) and 3,4-difluorothiophenol (*XIXd*), *via* intermediates *X*—*XIV*. The products were converted *via XVI* and *XVII* to the 7,8-dihalogeno derivatives of perathiepin *Ia*—*Id*, or directly to enamines *VIIIa*—*VIIId*. In addition some further piperazino derivatives of types *II*—*VII*, *IX* and *XXII* were prepared. All the 7,8-dihalogeno derivatives have low toxicity on oral administration. Enamines *VIIIb*—*VIIId* are highly cataleptic, *VIIIb* and *VIIId* with a prolonged effect. Enamines *VIIIb*—*VIIId* are most active as central depressants but a significant prolongation of effect is displayed by 10,11-dihydro derivatives *Ic* and *Id*. The 7-fluoro derivative of octoclothepin (*Ib*) is somewhat more effective in the antiapomorphine test on rats than octoclothepin, in other tests it is somewhat weaker but it is 10 times less toxic.

The following dihalogeno derivatives of perathiepin (10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin)[1–4] which is the prototype of the systematically studied series of neuroleptics, have been prepared so far: 2,8-dichloro[5], 3,8-dichloro[6], 6,8-dichloro[7], 6,9-dichloro[7], 2-chloro-7-fluoro[8,9], 2-chloro-8-fluoro[8,9], 3-chloro-7-fluoro[9], 3-chloro-8-fluoro[6,9], 8-chloro--2-fluoro[10] and 8-chloro-3-fluoro[10]. The first three and the last two are simultaneously derivatives of octoclothepin (8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin)[11,12] which is a typical representative of cataleptic neuroleptics of the present series. Only the third and the fourth compound (6,8- and 6,9-dichloro) have both halogen atoms at the same aromatic ring. As long as data are available on the central depressant and/or cataleptic activity of the dihalogeno derivatives the 8-chloro derivatives (derivatives of octoclothepin) usually retain a cataleptic activity[7,10], even with a markedly decreased central depressant activity[7] while the 2-chloro derivatives rather retain a depressant activity and are weaker as cataleptics[8]. The most interesting compound of the series is the 3-fluoro derivative of octoclothepin which is more toxic than octoclothepin but, at the same time, it is more powerful as a sedative and cataleptic and its effects on *p.o.* application are more protracted than those of octoclothepin[10]. The fluorine atom blocks a position in this compound where apparently the octoclothepin is metabolically hydroxylated[13]. The position was deduced on the basis of analogy with the known course of metabolic hydroxylation of chloropromazine which proceeds mainly into position 7 (ref.[14,15]), somewhat less into

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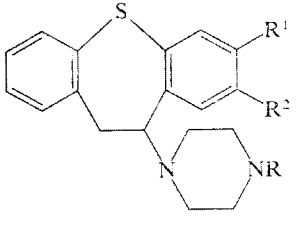
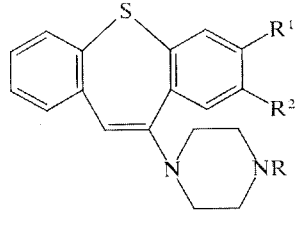
positions 3 and 8 (ref.[16-18]) or into their combinations (7,8 and 3,7) (ref.[19-22]). Positions 3, 7 and 8 in the chlorpromazine molecule correspond to positions 7, 3 and 2 in the molecule of octoclothepin. Further halogenation in these positions (in particular fluorination) is interesting from the point of view of a possible effect on the neuroleptic activity by blocking the possibility of metabolic hydroxylation.

As mentioned before, 2- and 3-chloro derivatives and fluoro derivatives of octoclothepin have been prepared, as well as compounds with interchanged atoms of chlorine and fluorine[5,6,8-10]. There is no information at present on the effect of further halogenation in position 7 of the octoclothepin molecule on efficacy. Filling of this gap motivated the present work which deals with the synthesis of 7-chloro (*Ia*) and 7-fluoro derivatives of octoclothepin (*Ib*), further with the compound with interchanged atoms of chlorine and fluorine, *i.e.* 7-chloro-8-fluoro (*Ic*) and finally with the 7,8-difluoro derivative (*Id*); besides, other analogues of type *II*–*IX* were prepared.



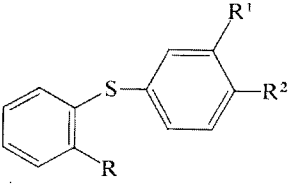


I, R = CH_3
II, R = CH_2CH_2OH
III, R = $CH_2CH_2CH_2OH$
IV, R = $(CH_2)_2OCO(CH_2)_8CH_3$
V, R = $(CH_2)_3OCO(CH_2)_6CH_3$
VI, R = $COOC_2H_5$
VII, R = H

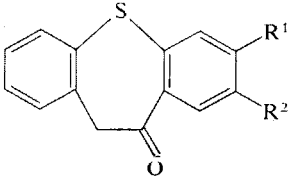
VIII, R = CH_3
IX, R = CH_2CH_2OH
Formulae in series:
a, $R^1 = R^2 = Cl$
b, $R^1 = F$, $R^2 = Cl$
c, $R^1 = Cl$, $R^2 = F$
d, $R^1 = R^2 = F$

In the synthesis of *Ia*–*Id* methods analogous to those in preparation of octoclothepin were used[11,23]. The syntheses proceeded from the corresponding thiophenols *XIX* and *via* intermediates *X*–*XVII*. The following general reactions were used: synthesis of acids *X* by a reaction of 2-iodobenzoic acid[24] with thiophenols *XIX* in boiling aqueous solution of potassium hydroxide in the presence of copper (method *A*), transformation of alcohols *XI* by treatment with thionyl chloride in the presence of pyridine to chlorides *XII* (method *B*), conversion of chlorides *XII* to nitriles *XIII* by the reaction with sodium cyanide in boiling aqueous ethanol (method *C*), hydrolysis of nitriles *XIII* to acids *XIV* by a boiling aqueous–ethanolic solution of potassium hydroxide (method *D*), direct conversion of thiophenols *XIX* to acids *XIV* by a reaction with 2-iodophenylacetic acid[25] in the presence of copper in a solution

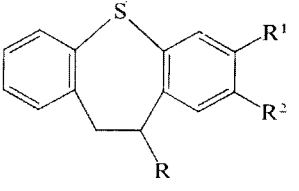
of potassium hydroxide (method *E*), cyclization of acids *XIV* to ketones *XV* by the action of polyphosphoric acid at 115–140°C (method *F*), reduction of ketones *XV* to alcohols *XVI* with sodium borohydride in a mixture of aqueous ethanol and benzene (method *G*), conversion of alcohols *XVI* to chlorides *XVII* by treatment with anhydrous hydrogen chloride in benzene solution (Method *H*), substitution reactions of chlorides *XVII* with 1-methylpiperazine in boiling chloroform yielding both the desired bases *I* and elimination products *XVIII* (method *J*).



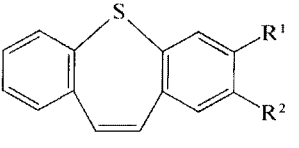
X, R = COOH
XI, R = CH_2OH
XII, R = CH_2Cl
XIII, R = CH_2CN
XIV, R = CH_2COOH



XV

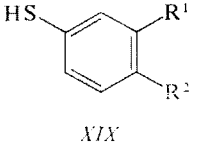


XVI, R = OH
XVII, R = Cl

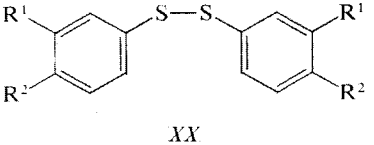


XVIII

In series *a*, the starting compound was 3,4-dichlorobenzenesulfonyl chloride[26], the reduction of which to 3,4-dichlorothiophenol (*XIXa*) was described, using zinc and dilute sulfuric acid[27] (ref.[28] also describes the preparation of the compound from 3,4-dichloroaniline *via* the corresponding diazonium xanthate). Best results were obtained with reduction of the crude sulfonyl chloride with phosphorus and iodine in boiling acetic acid (method[29]). By working in an atmosphere of nitrogen one can achieve 75% yields; in the presence of air, disulfide *XXa* is formed as a by-product; it is crystalline and stable and can be used for characterization of thiol *XIXa*. This



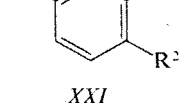
XIX



XX

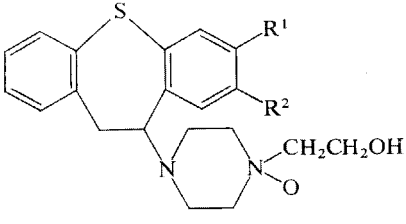
thiol was converted to acid *Xa* using method *A*; to reduce acid *Xa* to alcohol *XIa*, sodium dihydridobis(2-methoxyethoxy)aluminate in benzene was used (method[30,31]). In further steps, up to *Ia*, conventional general methods were employed. When using 1-(3-hydroxypropyl)piperazine[32] and 1-(ethoxycarbonyl)piperazine[33] in the sense of method *J* the amino alcohol *IIIa* and the carbamate *VIa* were formed; in all three cases, a small amount of the elimination product 2,3-dichlorodibenzo[*b*,*f*]thiepin (*XVIIIa*) is formed in parallel. Aminoalcohol *IIIa* was esterified by action of octanoyl chloride[34] to ester *Va* which was purified by crystallization of the dimaleate (method *K*; ref.[35]). Carbamate *VIa* was converted by alkaline hydrolysis to the secondary amine *VIIa*. Starting from ketone *XVa*, treatment with 1-methylpiperazine and titanium tetrachloride in boiling benzene resulted in enamine *VIIIa* (method *L*; ref.[36]).

The starting 4-chloro-3-fluorothiophenol (*XIXb*) required in series *b* was prepared from 2-chloronitrobenzene which was reduced with iron and hydrochloric acid in aqueous ethanol (method[37]) to 2-chloroaniline[38]. According to ref.[39], bromination led to 5-bromo-2-chloroaniline which was converted by Schiemann's reaction to 5-bromo-2-chlorofluorobenzene (*XXIb*). The Grignard reagent formed from this compound reacted with sulfur and underwent hydrolysis to thiol *XIXb*. The starting 5-bromo-2-chloroaniline was prepared more suitably by reduction of 5-bromo-2-chloronitrobenzene[40] with iron and hydrochloric acid (method[37]; reduction with zinc and acetic acid was also described[41]). Another attempt at synthesis of thiol *XIXb* *via* 4-chloro-3-fluoroaniline[42] was halted by the unsuccessful reproduction of the described[42] Friedel–Crafts acylation of 2-chlorofluorobenzene[43,44] (it was obtained by Schiemann's reaction[45–47] from 2-chloroaniline) with benzoyl chloride. Likewise, the preparation proceeding from 2-chloro-5-nitroaniline[48] did not reach its final stage because the compound could not be converted in a satisfactory yield by Schiemann's reaction to 4-chloro-3-fluoronitrobenzene (its preparation by a different procedure was described[44]). Starting from thiol *XIXb*, method *A* was applied to obtain acid *Xb* which was reduced to alcohol *XIb* with diborane (method[25]). The further steps up to *Ib* used conventional methods. 1-(2-Hydroxyethyl)piperazine was used for the substitution reaction (method *J*) with chloride *XVIIb*, resulting in amino alcohol *IIb*; a by-product of the substitution reactions was 2-chloro-3-fluorodibenzo[*b*,*f*]thiepin (*XVIIIb*). Amino alcohol *IIb* was esterified with decanoyl chloride[34] according to method *K* to ester *IVb*, and oxidized with hydrogen peroxide in boiling ethanol (method *M*; analogy[49]) to N-oxide *XXIIb*. Starting from ketone *XVb* and 1-methylpiperazine, method *L* was used to prepare enamine *VIIIb*.

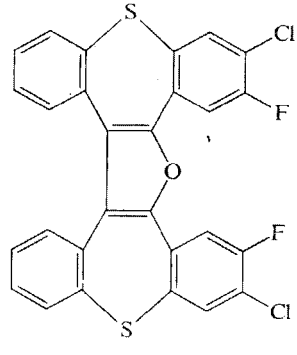


XXI

The 3-chloro-4-fluorothiophenol (*XIXc*) required as the starting compound in series *c*, was obtained from 4-bromo-2-chloroaniline[50,51] which was converted by Schiemann's reaction to 4-bromo-2-chlorofluorobenzene (*XXIc*). Its transformation to thiol *XIXc* was done in analogy to series *b*. Thiol *XIXc* was converted directly to acid *XIVc* by method *E*. The synthesis proceeded then up to *Ic* using conventional method. When attempting to cyclize *XIVc* with polyphosphoric acid under more stringent conditions the main product was a neutral substance different from ketone *XVc*. On the basis of mass spectrum and of analogies[31,52], it is asigned the structure of *XXIII*. For a substitution reaction with chloride *XVIIc*, 1-methylpiperazine as well as 1-(2-hydroxyethyl)piperazine were used, which resulted in amino alcohol *IIc*. The by-product of the substitution reactions was identified as 3-chloro-2-fluorodibenzo[*b*,*f*]thiepin (*XVIIIc*). Using method *L*, enamines *VIIIc* and *IXc* were prepared from ketone *XVc* and from 1-methylpiperazine or 1-(2-hydroxyethyl)piperazine.



XXII



XXIII

In series *d* we proceeded from 1,2-difluorobenzene[53] which was brominated to the known 4-bromo-1,2-difluorobenzene[54] (*XXId*). Starting from this compound, we prepared a Grignard reagent which was converted by exposure to sulfur and by subsequent hydrolysis to 3,4-difluorothiophenol (*XIXd*), characterized in the form of disulfide *XXd*. Thiol *XIXd* was converted by method *E* to acid *XIVd* from which the synthesis progressed up to *Id*, using conventional methods. For the substitution reaction of chloride *XVIId*, 1-(2-hydroxyethyl)piperazine was used again, yielding amino alcohol *IId*. (The elimination product characterized here was 2,3-difluorodibenzo[*b*,*f*]thiepin *XVIIId*). Amino alcohol *IId* was oxidized by method *M* to the N-oxide *XXIId*. Enamine *VIIId* was prepared from ketone *XVd* and 1-methylpiperazine by method *L*.

In series *d*, the dibenzo[*b*,*f*]thiepin derivatives contain in their IR spectra a band at 804 (*XVd*) or 810 cm^{-1} (*XVId*, *Id*, *XXIId*) in the region of extraplanar vibrations

TABLE I

Piperazine Derivatives *I*—*IX* and *XXII*, Intermediates of Their Preparation *X*—*XVII* and Elimination Products *XVIII*

Compound[a]	Method (yield%)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found					
				% C	% H	% N	% Cl	% F	% S
Xa	*A*[b]	239—240	$C_{13}H_8Cl_2O_2S$	52·19	2·69	—	23·70	—	10·72
	(76)	(ethanol)	(299·2)	52·30	2·76	—	23·23	—	10·61
Xb	*A*	231—232[c]	$C_{13}H_8ClFO_2S$	55·22	2·85	—	12·54	—	11·34
	(85)	(ethanol)	(282·7)	55·46	2·79	—	12·33	—	11·40
XIa	[b]	200—202/2·5	$C_{13}H_{10}Cl_2OS$	54·75	3·53	—	24·86	—	11·25
			(285·2)	54·79	3·53	—	24·70	—	10·94
XIb	[b]	175—178/0·5	$C_{13}H_{10}ClFOS$	58·10	3·75	—	13·19	—	11·93
			(268·7)	57·91	3·64	—	13·47	—	11·98
XIIa	*B*	155—157/0·5	$C_{13}H_9Cl_3S$	—	—	—	—	—	10·56
	(91)		(303·6)	—	—	—	—	—	10·53
XIIb	*B*[b]	159—160/1	$C_{13}H_9Cl_2FS$	—	—	—	—	—	11·17
	(86)		(287·2)	—	—	—	—	—	10·90
XIIIa	*C*[b]	48—49	$C_{14}H_9Cl_2NS$	57·15	3·08	4·76	24·10	—	10·90
	(80)	(ethanol)	(294·2)	57·34	3·12	4·62	24·25	—	10·81
XIIIb	*C*	80—81[d]	$C_{14}H_9ClFNS$	60·54	3·26	5·04	12·77	—	11·55
	(81)	(ethanol)	(277·8)	60·35	3·27	4·81	13·17	—	12·10
XIVa	*D*	105—107[c]	$C_{14}H_{10}Cl_2O_2S$	53·69	3·22	—	22·64	—	10·24
	(80)	(benzene–light petroleum)	(313·2)	53·78	3·30	—	22·45	—	10·22
XIVb	*D*[b]	118—119	$C_{14}H_{10}ClFO_2S$	56·66	3·40	—	11·95	6·40	10·81
	(90)	(benzene–light petroleum)	(296·8)	56·46	3·37	—	11·95	6·30	10·86

XIVc	*E*[b]	85—87	$C_{14}H_{10}ClFO_2S$	56·66	3·40	—	—	—	10·81
	(72)	(cyclohexane–hexane)	(296·7)	57·11	3·49	—	—	—	10·38
XIVd	*E*	56—58[f]	$C_{14}H_{10}F_2O_2S$	59·99	3·59	—	—	13·56	11·44
	(83)	(hexane)	(280·3)	59·96	3·75	—	—	13·59	11·47
XVa	*F*	133—135[g]	$C_{14}H_8Cl_2OS$	56·96	2·73	—	24·02	—	10·87
	(76)	(ethanol–benzene)	(295·2)	57·08	2·79	—	24·18	—	10·93
XVb	*F*	126—128[h]	$C_{14}H_8ClFOS$	60·32	2·89	—	12·72	6·82	11·51
	(84)	(ethanol)	(278·7)	60·33	3·15	—	12·66	6·71	11·53
XVc	*F*[b]	124—126	$C_{14}H_8ClFOS$	60·32	2·89	—	12·72	6·82	11·51
	(90)	(ethanol)	(278·7)	60·82	3·15	—	12·35	6·55	11·23
XVd	*F*	110—112[i]	$C_{14}H_8F_2OS$	64·11	3·07	—	—	14·49	12·23
	(82)	(ethanol)	(262·3)	64·04	3·17	—	—	14·49	12·35
XVIa	*G*	124—126[j]	$C_{14}H_{10}Cl_2OS$	56·57	3·39	—	23·86	—	—
	(88)	(ethanol)	(297·2)	56·74	3·52	—	23·64	—	—
XVIb	*G*	69—71[k]	$C_{14}H_{10}ClFOS$	59·89	3·59	—	12·63	6·77	11·42
	(89)	(hexane)	(280·7)	60·00	3·60	—	12·23	6·76	11·35
XVIc	*G*	86—88[m]	$C_{14}H_{10}ClFOS$	59·89	3·59	—	—	—	11·42
	(94)	(hexane)	(280·8)	59·84	3·55	—	—	—	11·08
XVId	*G*[b]	98—100	$C_{14}H_{10}F_2OS$	63·62	3·81	—	—	14·38	12·13
	(89)	(cyclohexane)	(264·3)	63·78	3·88	—	—	14·61	12·39
XVIIa	*H*	130—131[n]	$C_{14}H_9Cl_3S$	53·27	2·87	—	33·70	—	10·16
	(88)	(benzene)	(315·6)	53·98	2·95	—	33·12	—	10·46
XVIIb	*H*[b]	94—96	$C_{14}H_9Cl_2FS$	56·20	3·03	—	23·70	6·35	10·72
	(83)	(acetone)	(299·2)	56·25	3·01	—	23·70	6·33	10·95
XVIIc	*H*	108—110[o]	$C_{14}H_9Cl_2FS$	56·20	3·03	—	23·70	—	10·72
	(81)	(cyclohexane)	(299·2)	56·36	3·08	—	23·52	—	10·75

TABLE I
(*Continued*)

Compound[a]	Method (yield%)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found					
				% C	% H	% N	% Cl	% F	% S
XVIId	*H* (86)	70—72 (ethanol)	$C_{14}H_9ClF_2S$ (282·7)	59·47 59·61	3·21 3·19	— —	12·54 12·49	13·44 13·90	11·34 11·32
Ia	*J* (59)	131—132[p] (ethanol)	$C_{19}H_{20}Cl_2N_2S$ (379·4)	60·15 60·27	5·31 5·47	7·39 7·26	18·69 18·42	— —	8·45 8·55
Ia-M	—	163—166 (ethanol)	$C_{23}H_{24}Cl_2N_2O_4S$ (495·4)	55·76 55·71	4·88 5·03	5·66 5·59	14·31 14·54	— —	6·47 6·77
Ib	*J* (74)	105—107 (acetone)	$C_{19}H_{20}ClFN_2S$ (362·9)	62·88 63·24	5·56 5·57	7·72 7·52	— —	— —	— —
Ib-M	—	168—169 (ethanol)	$C_{23}H_{24}ClFN_2O_4S$ (479·0)	57·67 57·71	5·05 5·10	5·85 6·11	— —	— —	6·70 6·57
Ic	*J* (72)	137—139[q] (ethanol)	$C_{19}H_{20}ClFN_2S$ (362·9)	62·88 62·89	5·56 5·46	7·72 7·66	9·77 9·48	— —	8·83 8·88
Ic-M	—	171—173 (ethanol)	$C_{23}H_{24}ClFN_2O_4S$ (479·0)	57·67 57·81	5·05 5·27	5·85 5·79	7·40 7·34	3·97 3·84	6·70 6·53
Id	*J* (75)	106—108[r] (acetone)	$C_{19}H_{20}F_2N_2S$ (346·4)	65·87 65·94	5·82 5·78	8·09 8·06	— —	10·97 10·70	9·25 9·30
Id-M-HH	—	161—163 (ethanol)	$C_{23}H_{25}F_2N_2O_{4.5}S$ (471·5)	58·58 58·48	5·34 5·48	5·94 6·05	— —	8·06 7·96	6·80 6·82
Id-MS	—	244—247 (ethanol–acetone)	$C_{20}H_{24}F_2N_2O_3S_2$ (442·6)	54·28 54·58	5·46 5·41	6·33 6·16	— —	— —	14·50 14·66
IIb	*J* (81)	150—152[s] (acetone)	$C_{20}H_{22}ClFN_2OS$ (392·9)	61·13 61·59	5·65 5·79	7·13 7·00	— —	4·84 4·76	8·16 8·12

IIc[t]	*J*	87—91[u]	$C_{23}H_{28}ClFN_2OS$	63·50	6·49	6·44	8·15	—	7·37
	(84)	(cyclohexane)	(435·0)	63·58	6·29	6·42	8·43	—	7·72
IIc-M	—	167—170	$C_{24}H_{26}ClFN_2O_5S$	56·63	5·15	5·50	—	—	6·30
		(ethanol)	(509·0)	56·62	5·46	5·43	—	—	6·35
IId-HH	*J*	98—102[v]	$C_{20}H_{23}F_2N_2O_{1\cdot5}S$	62·31	6·01	7·27	—	9·86	8·32
	(83)	(acetone)	(385·5)	62·38	6·22	7·37	—	9·98	8·37
IIIa	*J*	126—128[w]	$C_{21}H_{24}Cl_2N_2OS$	59·57	5·71	6·62	16·75	—	7·57
	(65)	(ethanol)	(423·4)	59·29	6·10	6·24	16·49	—	7·69
IIIa-2MS-MH	—	196—199	$C_{23}H_{34}Cl_2N_2O_8S_3$	43·60	5·41	4·42	11·19	—	15·18
		(ethanol)	(633·6)	43·55	5·34	4·30	11·31	—	15·06
XVIIIa	*J*	114—115[x]	$C_{14}H_8Cl_2S$	60·23	2·89	—	25·40	—	11·48
		(ethanol)	(279·2)	60·29	2·76	—	25·37	—	11·61
XVIIIb	*J*[b]	110—112	$C_{14}H_8ClFS$	—	—	—	13·50	7·24	12·21
		(ethanol)	(262·7)	—	—	—	13·24	7·39	11·87
XVIIIc	*J*	87—89[y]	$C_{14}H_8ClFS$	64·00	3·05	—	13·50	7·24	12·21
		(ethanol)	(262·7)	64·27	3·14	—	13·26	7·12	11·99
XVIIId	*J*	76—78[z]	$C_{14}H_8F_2S$	68·28	3·27	—	—	15·43	13·02
		(ethanol)	(246·3)	68·31	3·53	—	—	15·37	13·04
IVb-2M	*K*[b]	125—127	$C_{38}H_{48}ClFN_2O_{10}S$	58·55	6·21	3·60	4·55	2·44	4·11
	(85)	(acetone)	(779·3)	58·53	6·62	3·50	4·84	2·45	4·25
Va-2M	*K*	144—148	$C_{37}H_{46}Cl_2N_2O_{10}S$	56·84	5·93	3·58	9·07	—	4·10
	(80)	(acetone)	(781·7)	57·31	6·09	3·43	9·37	—	4·25
VIa-M	*J*	184—186	$C_{25}H_{26}Cl_2N_2O_6S$	54·25	4·74	5·06	12·81	—	5·79
	(82)	(ethanol)	(553·3)	54·39	4·76	5·01	12·97	—	6·00
VIIa	[b]	133—135·5	$C_{18}H_{18}Cl_2N_2S$	59·18	4·96	7·67	—	—	8·78
		(acetone)	(365·3)	59·95	5·14	7·43	—	—	8·78
VIIIa	*L*	157—158[aa]	$C_{19}H_{18}Cl_2N_2S$	60·48	4·81	7·42	18·79	—	8·50
	(58)	(ethanol)	(377·3)	60·57	4·87	7·22	18·50	—	8·47
VIIIa-M	—	229—232	$C_{23}H_{22}Cl_2N_2O_4S$	55·98	4·49	5·68	14·37	—	6·50
		(ethanol)	(493·4)	56·27	4·70	5·63	14·51	—	6·72

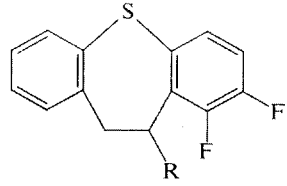
TABLE I
(*Continued*)

Compound[a]	Method (yield%)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found					
				% C	% H	% N	% Cl	% F	% S
VIIIb	*L* (75)	107—108·5[bb] (ethanol)	$C_{19}H_{18}ClFN_2S$ (360·9)	63·24 63·44	5·03 5·05	7·76 7·63	— —	— —	— —
VIIIb-M	—	215—219 (ethanol)	$C_{23}H_{22}ClFN_2O_4S$ (476·9)	57·92 58·03	4·65 5·04	5·87 5·78	7·43 7·53	3·98 3·86	6·72 6·70
VIIIc	*L* (75)	158—160[cc] (ethanol)	$C_{19}H_{18}ClFN_2S$ (360·9)	63·23 63·52	5·03 5·03	7·76 7·70	— —	— —	— —
VIIIc-M		228—230 (aqueous ethanol)	$C_{23}H_{22}ClFN_2O_4S$ (476·9)	57·91 58·32	4·65 4·68	5·89 5·64	— —	3·98 3·63	6·72 6·98
VIIId	*L*[b] (74)	119—121 (acetone)	$C_{19}H_{18}F_2N_2S$ (344·4)	66·25 66·50	5·27 5·32	8·14 8·45	— —	11·03 11·10	9·31 9·40
VIIId-MS		300—303 (95% ethanol)	$C_{20}H_{22}F_2N_2O_3S_2$ (440·5)	54·52 54·75	5·03 5·28	6·36 6·27	—	8·63 8·56	14·56 14·61
IXc	*L* (45)	144—147[dd] (acetone)	$C_{20}H_{20}ClFN_2OS$ (390·9)	61·45 61·79	5·16 5·17	7·17 7·24	— —	— —	8·20 8·15
IXc-M[ee]		187—192 (ethanol)	$C_{25}H_{27}ClFN_2O_{5,5}S$ (530·0)	56·65 56·72	5·14 5·30	5·29 5·28	6·69 6·91	3·58 3·32	6·05 6·00
XXIIb-MH	*M*[b]	186—189 (acetone)	$C_{20}H_{24}ClFN_2O_3S$ (426·9)	56·26 56·28	5·67 5·69	6·56 6·44	8·31 8·19	— —	7·51 7·96
XXIIb-2 HCl-HH		167—169 (aqueous ethanol)	$C_{20}H_{25}Cl_3FN_2O_{2,5}S$ (490·9)	48·94 49·15	5·13 5·47	5·71 5·81	21·67 21·03	— —	— —
XXIId-2 HCl	*M*	152—155[ff] (aqueous ethanol)	$C_{20}H_{24}Cl_2F_2N_2O_2S$ (465·4)	51·61 51·40	5·20 5·57	6·02 5·88	15·24 14·90	8·16 8·23	6·89 6·85

Explanation to Table I

[a] M maleate, MS methanesulfonate, HH hemihydrate, MH monohydrate. [b] See experimental. [c] NMR spectrum (CD_3SOCD_3): δ 7·90 (m, 1 H, 6-H of benzoic acid), 7·00–7·75 (m, 5 H, remaining aromatic protons except the following), 6·84 (mcd, J = 9·0 Hz, 1 H, 6-H of arylthio group). [d] IR spectrum: 753, 816, 885 (4 and 2 adjacent and solitary Ar—H), 1223 (Ar—F), 1561 (Ar), 2240 cm^{-1} (R—CN). [e] IR spectrum (Nujol): 670 (Ar—Cl), 750, 818, 866 (4 and 2 adjacent and solitary Ar—H), 900 (COOH), 1230 (C—O), 1550, 1570 (Ar), 1700 cm^{-1} (R—COOH). [f] IR spectrum: 773, 820, 870, (4 and 2 adjacent and solitary Ar—H), 945, 1250, 1286 (COOH), 1510 (Ar), 1715 (R—COOH), 3000 cm^{-1} (COOH). [g] UV spectrum: λ_{max} 251 nm (log ε 4·39), 345 nm (3·65); IR spectrum (Nujol): 688 (C—Cl), 747, 860 (4 adjacent and solitary Ar—H), 1240 (C—O), 1565 (Ar), 1675 cm^{-1} (Ar—CO). [h] UV spectrum: λ_{max} 242·5 nm (log ε 4·27), infl. 266·5 nm (4·03), infl. 273 nm (4·02), 329 nm (3·50); IR spectrum: 749, 856 (4 adjacent and solitary Ar—H), 1229, 1252 (CO), 1577 (Ar), 1670 cm^{-1} (Ar—CO); ^{1}H-NMR spectrum: δ 8·15 (d, J = 8·0 Hz, 1 H, 9-H), 7·00–7·70 (m, 5 H, remaining aromatic protons), 4·24 (s, 2 H, $ArCH_2CO$). [i] UV spectrum: λ_{max} 225 nm (log ε 4·20), 240 nm (4·17), 328 nm (3·50); IR spectrum (Nujol): 749, (804!), 873 (Ar—H), 1273 (C—F), 1492, 1578, 1604 (Ar), 1669 cm^{-1} (Ar—CO); ^{1}H-NMR spectrum: δ 8·02 (dd, J = 12·0$_{(o-F)}$; 8·0 $Hz_{(m-F)}$, 1 H, 9-H), 7·00–7·75 (m, 5 H, remaining aromatic protons), 4·30 (s, 2 H, $ArCH_2CO$). [j] UV spectrum: λ_{max} 272 nm (log ε 3·99); IR spectrum (Nujol): 750, 889 (4 adjacent and solitary Ar—H), 1036, 1049, 1063, 1079 (CHOH), 1570 (Ar), 3310, 3375 cm^{-1} (OH). [k] IR spectrum: 747, 758, 772, 888 (4 adjacent and solitary Ar—H), 1038 (CHOH), 1475, 1575, 1592 (Ar), 3295 cm^{-1} (OH). [m] IR spectrum (Nujol): 721, 749, 887 (4 adjacent and solitary Ar—H), 1089 (CHOH), 3390 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 7·00–7·60 (m, 6 H, aromatic protons), 5·30 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·68 and 3·20 (2dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·30 (s, disappears after D_2O, 1 H, OH). [n] NMR spectrum: δ 7·45–7·80 (m, 3 H, aromatic 4,6,9-H_3), 7·10–7·45 (m, 3 H, remaining aromatic protons), 5·75 (dd, J = 5·0 and 8·0 Hz, 1 H, Ar—CH—Cl), 3·50–4·10 (m, 2 H, $ArCH_2$). [o] ^{1}H-NMR spectrum: δ 7·00–7·50 (m, 6 H, aromatic protons), 5·72 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·96 and 3·64 (2dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). [p] NMR spectrum δ 7·85 (s, 1 H, 6-H), 7·05–7·60 (m, 5 H, remaining aromatic protons), 3·60 to 4·00 (m, 2 H, $ArCH_2$), 2·95–3·30 (t, J = 5·0 Hz, 1 H, Ar—CH—N), 2·30–2·90 (m, 8 H, 4 CH_2 of piperazine), 2·26 (s, 3 H, NCH_3). [q] ^{1}H-NMR spectrum: δ 6·90–7·67 (m, 6 H, aromatic protons), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·26 (s, 3 H, NCH_3). [r] IR spectrum: 760, 810 (!) 870, 900 (Ar—H), 1505, 1600 (Ar), 2810, 2835 cm^{-1} (C—CH_3); ^{1}H-NMR spectrum: δ 6·90–7·80 (m, 6 H, aromatic protons), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·46 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·28 (s, 3 H, NCH_3). [s] IR spectrum: 756, 767, 831(!), 861, 902 (Ar—H), 1057 (CH_2OH), 1474, 1566, 1590 (Ar), 3160 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 7·70 (d, J = 8·0 Hz, 1 H, 9-H), 7·12 (d, J = 12·0 Hz, 1 H, 6-H), 7·00–7·50 (m, 4 H, remaining aromatic protons), 2·95–4·00 (m, 3 H, $ArCH_2CHAr$), 3·55 (t, J = 6·0 Hz, 2 H, CH_2O), 2·84 (s, disappears after D_2O 1 H, OH), 2·30–2·80 (m, 10 H, 5 NCH_2). [t] Solvate with one-half cyclohexane molecule. [u] ^{1}H-NMR-spectrum (T-80): δ 7·00–7·70 (m, 6 H, aromatic protons), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·65 (t, J = 6·0 Hz, 2 H, CH_2O), 2·82 (bs, disappears after D_2O, 1 H, OH), 2·40–2·90 (m, 10 H, 5 NCH_2), 1·44 (s, CH_2 of cyclohexane). [v] ^{1}H-NMR spectrum: δ 6·90–7·80 (m, 6 H, aromatic protons), 2·95–3·90 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 6·0 Hz, 2 H, CH_2O), 2·75 (bs, disappears after D_2O, 2 H, OH and 0·5 H_2O), c. 2·60 (m, 10 H, 5 NCH_2). [w] IR spectrum: 760, 900 (4 adjacent and solitary Ar—H), 1010 (CH_2OH), 3195, 3430 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 7·86 (s, 1 H, 6-H), 7·00–7·70 (m, 5 H, remaining, aromatic protons), 3·50–3·95 (m, 4 H, $ArCH_2$ and CH_2O), 2·90–3·30 (t, J = 5·0 Hz, 1 H,

which can be interpreted with probability as to belong to two adjacent aromatic C—H bonds. This indicates that the cyclization of acid *XIVd* does not proceed unambiguously to 7,8-difluoro ketone *XVd* but that some 8,9-difluoro derivative *XXIV* (R = 0) is also formed. Compounds with the general formula *XXIV* occur



XXIV

as contaminants in other dibenzo[*b*,*f*]thiepin derivatives of series *d*. The phenomenon is apparently made possible by low steric requirements of the fluorine atom. In principle, a similar possibility exists in series *b* but there, with the exception

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Explanation to Table I (continued)

Ar—CH—N), 2·35—2·90 (m, 10 H, 5 NCH_2), 1·50—2·00 (m, 2 H, CH_2 in the middle of the propane residue. [x] UV spectrum: λ_{max} 220 nm (log ε 4·48), 266 nm (4·33), 297 nm (3·78); IR spectrum (Nujol): 745, 890 (4 adjacent and solitary Ar—H), 788 (CH=CH), 1570 cm^{-1} (Ar); ^{1}H-NMR spectrum: δ 7·55 (s, 1 H, 4-H), 7·15—7·50 (m, 4 H, 6,7,8,9-H_4), 7·25 (s, 1 H, 1-H), 7·10 and 6·80 (ABq, J = 12·0; 12·0 Hz, 2 H, ArCH=CHAr). [y] UV spectrum: λ_{max} 223 nm (log ε 4·42), 263 nm (4·32), 295 nm (3·80); IR spectrum: 711, 727, 740, 787, 870, 886 (Ar—H), 1547, 1585 cm^{-1} (Ar); ^{1}H-NMR spectrum (T-80): δ 7·51 (d, $J_{(H-F)}$ = 7·5 Hz, 1 H, 4-H), 7·10—7·45 (m, 4 H, 6,7,8,9-H_4), 6·95 (d, $J_{(H-F)}$ = 10·0 Hz, 1 H, 1-H), 7·08 and 6·82 (2d, J = 13·0 Hz, 2 H, ArCH=CHAr). [z] UV spectrum: λ_{max} 259 nm (log ε 4·36), 290 nm (3·67); ^{1}H-NMR spectrum: δ 6·70—7·50 (m, aromatic and olefinic protons). [aa] UV spectrum: λ_{max} 219 nm (log ε 4·58), 240 nm infl. (4·29), infl. 270 nm (4·12), 315 nm (3·86); IR spectrum: 751, 840, 880, 900 (4 adjacent and solitary Ar—H), 1559, 1570, 1609 (Ar), 2755, 2770 cm^{-1} (N—CH_2). [bb] ^{1}H-NMR spectrum: δ 7·58 (d, J = 8·0 Hz, 1 H, 9-H), 7·22 (d, J = 12·0 Hz, 1 H, 6-H), 7·00—7·40 (m, 4 H, remaining aromatic protons), 6·23 (s, 1 H, ArCH=C), 2·93 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). [cc] UV spectrum: λ_{max} 235 nm (log ε 4·35), infl. 264 nm (4·13), 310 nm (3·88); ^{1}H-NMR spectrum (T-80): δ 7·60 (d, J = 7·0 Hz, 1 H, 6-H), 7·44 (d, J = 10·0 Hz, 1 H, 9-H), c. 7·45 (m, 1 H, 4-H), 7·24 (m, 3 H, 1,2,3-H_3), 6·36 (s, 1 H, ArCH=C), 3·00 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·56 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·37 (s, 3 H, NCH_3). [dd] UV spectrum: λ_{max} 236 nm (log ε 4·34), infl. 264 nm (4·13), 310 nm (3·90); ^{1}H-NMR spectrum (T-80): δ 7·60 (d, J = 7·0 Hz, 1 H, 6-H), 7·44 (d, J = 10·0 Hz, 1 H, 9-H), c. 7·45 (m, 1 H, 4-H), 7·24 (m, 3 H, 1,2,3-H_3), 6·36 (s, 1 H, ArCH=C), 3·68 (t, J = 5·5 Hz, 2 H, CH_2O), 3·00 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 3·00 (s, disappears after D_2O, 1 H, OH), 2·64 (m, 6 H, remaining 3 NCH_2). [ee] Solvate with one-half ethanol molecule. [ff] It is reduced polarographically at $E_{1/2}$ −0·39 V (against a saturated calomel electrode) which corresponds to the behaviour of the N—O group. IR spectrum: 775, 810(!), 905 (Ar—H), 1055 (CH_2OH), 1510, 1600 (Ar), 2600, 2680 (NH^+), 3390 cm^{-1} (OH).

of a weak band at 831 cm^{-1} with *IIb*, it has not been encountered there. The selectivity of cyclization of 2-(3-substituted phenylthio)phenylacetic acids was taken up in some previous papers of this series[5,7,55–58].

Table I contains the experimental data on all the final products *I–IX* and *XXII*, intermediates *X–XVII* and elimination products *XVIII*. The experimental section shows only examples of preparation by the general methods *A-M*, and descriptions of preparations where these general methods were not used.

The pharmacological testing of most of the prepared piperazine derivatives was done after their oral application with a view to the expected central depressant and neuroleptic activity, their effect being examined also with emphasis on prolongation of action. A summary of the acute effects is presented in Table II which includes octoclothepin[12] (*I*, R^1 = H, R^2 = Cl) and fluothepin (*I*, R^1 = H, R^2 = F)[11] as standards. The first column shows the acute toxicity for mice expressed by the mean lethal dose (LD_{50}). In the experiments, female mice in groups of ten were used; survival was followed up to 7 days after *p.o.* administration. The toxicity of the new compounds is lower than that of octoclothepin and fluothepin. The least toxic is the 7-fluoro derivative of octoclothepin (*Ib*) which, even at a dose of 1 000 mg/kg, caused no death of animals. The toxic effects observed included depression, limb paresis, at higher doses clonic spasms. The animals died usually on the day of application, only rarely on subsequent days.

In the rotating-rod test in mice, the effect of the compounds on motor coordination was examined, this being taken as one of the indicators of central depressant action[59]. The ability of female mice to maintain balance for 1 min on a horizontally rotating rod was evaluated in groups of ten. The intervals between oral application of the compound and examination of coordination were 15, 30, 45, 60, 90 and 120 min and 24, 48, or 72 h. The mean effective doses (ED_{50}) were evaluated at the time of optimal effect of all the compounds tested (values in min in parentheses). Enamines *VIIIa–VIIId* were found in this respect to be 2–7 times more active than 10,11-dihydro derivatives *Ia–Id*. From the point of view of 7,8-substitution, higher effects were displayed by the 7,8-difluoro derivatives (series *d*), medium ones by both types of chlorofluoro derivatives (series *b* and *c*) and weaker ones by the 7,8-dichloro derivatives (series *a*). The lowest activity was found in the amino alcohols and their N-oxides (*IIc*, *IIIa*, *XXIIbd*). A clear prolongation of the effect in this test was exhibited by only two compounds. The 7-chloro-8-fluoro derivative *Ic* was applied in doses of 5·0–30·0 mg/kg; within 24 h after application, motor disturbance was still apparent in 6 animals and after 48 h in 2 animals out of 10. Likewise, the 7,8-difluoro derivative *Id* was applied in doses of 2·5–20·0 mg/kg; after 24 h, the effect was apparent still in 6 animals, after 48 h in 6 animals and after 72 h in 3 animals out of 10. The effects of octoclothepin (applied in doses of 1·0–6·0 mg/kg) and fluothepin (2·5–10·0 mg/kg) disappeared within 24 h.

The effect on locomotor activity of mice was studied by the photo-cell method[60] with *Ia–Id* and with both standards, using male mice placed in groups of three in glass cylinders for 15 min. For every dose 5 groups of animals were employed. The compounds were administered orally in the form of solutions in a volume of 0·4 ml/20 g. Insoluble compounds were administered as suspensions. The control group was given only distilled water in the same corresponding volume. The effect on locomotor activity was examined after 1 h and repeatedly every 24 h up to disappearance of effect. Dose D_{50} which reduces the mean control value of locomotor activity by 50% was processed statistically. On prolonged examination of the effects the drop of activity was evaluated in percent, the activity of the control being taken for 100. The results indicate that the effects in this test do not proceed in parallel with the incoordinating effects in spite of the fact that this test is also considered as the criterion of central depressant action. Least active in this test

was the 7-chloro-8-fluoro derivative of perathiepin (*Ic*) while the others (*Ia*, *Ib* and *Id*) resemble octoclothepin in their effect. The most potent compound was fluothepin. 24 h after administration there were apparent effects of *Ia* (dose and % activity of control: 2·5 mg/kg, 77%; 10·0 mg/kg, 46%), octoclothepin (2·0 mg/kg, 55%; 4·0 mg/kg, 39%) and fluothepin (1·0 mg/kg, 65%; 2·5 mg/kg, 59%).

The cataleptic effect was investigated in female rats weighing 105—155 g[61]. Catalepsy was inferred if the animal remained for 5 s in a position with crossed paws. The individual doses were applied per os to groups of ten animals and catalepsy was assessed after 1 h and then in 30 min intervals for 5 h. From the optimal values, obtained during the experiment, the mean effective doses (ED_{50}) shown in Table II were computed. The cataleptic effect was followed every 24 h up to its disappearance. Cataleptically most active are the fluorine-containing enamines *VIIIb*—*VIIId*. As to the character of 7,8-substitution, the most potent are the 8-chloro-7-fluoro

TABLE II

Pharmacological Properties of the Compounds Prepared on Oral Application (mg/kg)

Compound[a]	Acute toxicity	Rotating rod[b]	Locomotor activity	Cataleptic effect	Antiapomorphine effect D_{50}	
	LD_{50}	ED_{50}	D_{50}	ED_{50}	chewing	agitation
Ia	[c]	10·6 (90)	2·7	10·2	8·4	7·6
Ib	< 1 000[d]	7·0 (60)	2·0	5·5	3·7	3·4
Ic	[c]	7·6 (45)	4·1	6·4	17·5	20·5
Id	320	4·0 (60)	2·6	19·0	37·6	33·4
IIc	650	15·0 (60)	—	16·0	—	—
IIIa	540	25·0 (45—90)	—	32·0	—	—
VIIIa	210	4·8 (90—120)	—	12·5	—	—
VIIIb	370	1·4 (60—90)	—	0·8	—	—
VIIIc	270	0·8 (90)	—	1·2	—	—
VIIId	235	0·6 (120)	—	0·5	—	—
XXIIb	440	24·5 (90)	—	30·0	—	—
XXIId	430	10·0 (90)	—	32·0	—	—
OCTO[e]	78	2·2 (120)	1·9	2·5	4·1	4·5
FLUO[f]	102	3·3 (60)	0·63	20·0	[g]	[g]

[a] The compounds were administered in the form of salts as shown in Table I; the values reported refer to the bases. [b] In parentheses, the time in min is shown that elapsed between the moment of administration and the attainment of maximum effect. [c] Toxicity was not determined. [d] The dose of 1000 mg/kg *p.o.* caused no death of mice. [e] Octoclothepin[12] (*I*, R^1 = H, R^2 = Cl). [f] Fluothepin[11] (*I*, R^1 = H, R^2 = F). [g] Doses of 20, 40, and 80 mg/kg *p.o.* had only a slight antiapomorphine effect.

derivatives (series *b*), followed by the 7-chloro-8-fluoro derivatives (series *c*), 7,8-dichloro derivatives (series *a*) and finally the 7,8-difluoro derivatives (series *d*); an exception in the last group is formed by enamine *VIIId* which was found to be cataleptically most effective of the whole series of compounds tested. Amino alcohols *IIc* and *IIIa* and their N-oxides *XXIIb* and *XXIId* were again relatively little active. Likewise, the cataleptic activity of fluothepin is low. A prolongation of the cataleptic effect was exhibited first of all by 8-chloro-7-fluoro derivatives *VIIIb* (doses 0·5—5·0 mg/kg, after 24 h 4 and after 48 h 3 rats out of a group of 10 remain cataleptic) and *Ib* (doses 2·5—25·0 mg/kg, after 24 h still two cataleptic rats out of 10, after 48 h the effect disappears) and further the 7-chloro-8-fluoro derivative *VIIIc* (0·5—5·0 mg/kg; 24 h 3/10, 48 h 2/10). The effects of octoclothepin and fluothepin vanish completely after 24 h.

The antiapomorphine effect on rats[62,63] was examined with *Ia—d* and with both standards using female rats weighing 150—260 g. The individual doses were applied *p.o.* to groups of ten animals in a volume of 0·5 ml for 100 g. The control group received the same volume of distilled water. Four h after application of the substances and again after 24 h, apomorphine was injected *i.v.* at a dose of 1·25 mg/kg and then the chewing and agitation of rats placed in plastic cages was examined. Statistical evaluation was used for the dose decreasing the mean control value of the two parameters by 50% (D_{50}); during prolonged tests the inhibition of apomorphine chewing and agitation was expressed in percent, setting the control equal to 100%. An efficacy comparable with that of octoclothepin was exhibited in this test only by the 7-fluoro derivative of octoclothepin (*Ib*); the dichloro derivative *Ia* was about twice weaker and the other two compounds were substantially less effective. The almost complete inactivity of fluothepin in this test is of interest. A prolongation of the effect on apomorphine chewing was found only with the dichloro derivative *Ia*; at dose of 20 mg/kg the apomorphine chewing is significantly depressed after 24 h to 76% of the control value.

The effects observed permit to draw the following conclusions. *1*) A higher cataleptic activity is found with substances containing different halogen atoms in positions 7, 8. *2*) Compounds substituted with chlorine in position 8 are more effective in the apomorphine test while the 8-fluoro derivatives are more active as depressants. *3*) In this group of compounds, too, the enamines *VIII* are more active as depressants and cataleptics than the 10,11-dihydro derivatives *I*. *4*) The 7-fluoro derivative of octoclothepin *Ib* is more than 10 times less toxic than octoclothepin, in the rotating-rod test it is about 3 times weaker, it affects locomotor activity in the same degree, in the catalepsy test it is twice weaker and in the antiapomorphine test it is somewhat more effective. Its positive properties confirm to a certain degree the correctness of the working hypothesis on the rationality of the blockade of the sites of assumed metabolic hydroxylation with a fluorine atom. 5) The detoxicating effect of the fluorine atom in position 7 of the skeleton was again confirmed[8].

The enamine of the 7,8-dichloro series (*VIIIa*) was evaluated by methods of general pharmacological screening at the affiliated unit of this institute at Rosice n/L under the direction of Dr J. Němec. Besides the above-mentioned effects, the following have been established (administered *p.o.* throughout): an analgetic effect on mice in Haffner's test at doses of 25—50 mg/kg (this is apparently associated with the general depressant activity of the compound); at a dose of 50 to 100 mg/kg it increases the blood pressure of normotensive rats by 10%; at a dose of 1·0—2·5 mg it depresses the body temperature of rats by 1°C (measured *in recto*); at a dose of 10 mg/kg it has an antihistamine effect in the test of histamine detoxication in guinea-pigs (the dose shown

protects 50% animals from the lethal effect of an intrajugular dose of 5 mg histamine per kg); at a dose of 1·0—2·5 mg/kg it doubles the duration of thiopental sleep; it has an antiamphetamine effect on mice — a dose of 1 mg/kg protects 50% animals from the lethal effect of a dose of 30 mg/kg amphetamine administered *i.p.* The effects further characterize *VIIIa* as a neuroleptic.

Ester *Va* is first of all a potential depot neuroleptic intended for intramuscular application in the form of oil solutions of the base. In the form of dimaleate it was subjected, like the preceding preparation, to a general pharmacological screening on oral application. A tentative value of LD_{50} for mice was found to be 2 g/kg; in the rotating-rod test ED_{50} = 100 mg/kg; an analgetic effect on mice at doses of 100—300 mg/kg; at a dose of 50 mg/kg it depresses the blood pressure of rats by 10%; at a dose of 25—50 mg/kg it depresses the body temperature of rats by 1°C; the ED_{50} in the histamine detoxication test in guinea-pigs was 25—50 mg/kg; a dose of 2·5—5·0 mg/kg extends thiopental sleep to twice the control value; a dose of 10 mg/kg protects 50% mice from the lethal effect of 30 mg amphetamine/kg, *i.p.*; the ED_{50} in the catalepsy test in rats was 50 to 100 mg/kg. It may be seen that the substance is a clear neuroleptic at higher doses.

Most of the piperazine derivatives prepared were tested for antimicrobial activity in tests carried out *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this

TABLE III

Antimicrobial Activity of the Prepared Compounds *in vitro* (minimum inhibitory concentration in μg/ml)

Compound[a]	Microorganism[b]											
	1	2	3	4	5	6	7	8	9	10	11	12
Ia-M	25	—	25	—	—	—	—	12·5	31·2	62·3	125	62·3
Ib-M	12·5	—	12·5	—	—	—	—	12·5	—	—	—	—
Ic-M	6·25	6·25	12·5	—	100	100	100	100	50	25	50	50
Id-MS	6·25	12·5	25	—	100	100	100	50	25	50	100	100
IIc-M	25	25	25	—	—	—	—	100	25	25	100	50
IIIa-2 MS-MH	—	—	—	—	—	—	—	—	62·3	62·3	125	125
VIIIa-M	12·5	—	12·5	100	—	—	—	12·5	15·6	31·3	62·3	31·2
VIIIb-M	12·5	—	12·5	—	—	—	—	12·5	62·5	125	125	62·5
VIIIc-M	25	25	—	—	—	—	—	—	6·2	12·5	25	25
VIIId-MS	25	25	25	—	—	—	—	25	50	50	100	100
XXIIb-2 HCl-HH	50	50	50	—	—	—	—	50	—	—	—	—
XXIId-2 HCl	6·25	50	50	—	100	100	100	100	100	50	100	100

[a] M maleate, MS methanesulfonate, MH monohydrate, HH hemihydrate. [b] 1 *Streptococcus β-haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Klebsiella pneumoniae*, 5 *Pseudomonas aeruginosa*, 6 *Escherichia coli*, 7 *Proteus vulgaris*, 8 *Mycobacterium tuberculosis* H37Rv, 9 *Saccharomyces pasterianus*, 10 *Trichophyton mentagrophytes*, 11 *Candida albicans*, 12 *Aspergillus niger*.

institute) toward a standard set of typical microorganisms. The effects are shown in Table III in the form of the values of minimum inhibitory concentrations (μg/ml). It may be seen that some of the compounds possess a broad spectrum of antimicrobial activity (*Ic*, *Id*, *XXIId*), some of them display a high degree of efficacy of specific type (thus *e.g. Ic* and *Id* toward cocci, *Ia*, *Ib*, *VIIIa* and *VIIIb* toward mycobacteria and *VIIIc* toward yeasts).

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 77°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 in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra, unless stated otherwise, in $CDCl_3$ using a Zeiss ZKR 60 spectrometer (where T-80 is mentioned the use of a Tesla BC 487 80 MHz spectrometer is indicated) and the mass spectrum in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of alumina. The analyses of all the compounds *I*—*XVIII* and *XXII* and of their salts are shown in Table I.

2-Chloroaniline

Hydrochloric acid (9 ml) in 180 ml 75% ethanol was added dropwise over a period of 30 min under stirring to a refluxing mixture of 300 ml 75% aqueous ethanol, 100 g Fe powder and 95g 2-chloronitrobenzene. The mixture was refluxed under stirring for 2 h, 90 ml hydrochloric acid was added, ethanol was distilled off, the residue was made alkaline with 90 ml 15% NaOH and steam-distilled. The product was isolated from the distillate by extraction with ether; 56·9 g (75%), b.p. 96—97°C/15 Torr, or 101—103°C/20 Torr. Ref.[64] reports a b.p. of 82—83°C/5 Torr.

5-Bromo-2-chloroaniline

Like in the preceding case, 262 g 5-bromo-2-chloronitrobenzene[40] (m.p. 69—72°C) was reduced with 186 g Fe and 22 ml hydrochloric acid in 1 litre boiling 75% ethanol. After steam distillation, the product separated from the distillate, was filtered and dried in air; 182 g (80%), m.p. 48 to 50°C. Ref.[41] reports a m.p. of 44·5°C for a product obtained by reduction with zinc in acetic acid. Bromination of 2-chloroaniline yielded the desired product in the maximum amount of 61%, m.p. 45—48°C while ref.[39] reports a yield of 73% and a m.p. of 48·5—49·5°C.

2-Chlorofluorobenzene

A mixture of 260 ml hydrochloric acid and 51 g 2-chloroaniline was heated under stirring on a boiling-water bath, cooled to 0°C and the suspension formed was diazotized at that temperature with a solution of 30 g $NaNO_2$ in 60 ml water added dropwise over a period of 1 h. After further 15 min of stirring, 220 ml of a solution of fluoroboric acid (prepared from 222 ml 40% H_2F_2 and 79 g H_3BO_3) was added under continual external cooling. After 15 min of stirring and 30 min of standing at room temperature, the precipitate salt was filtered, washed with a solution of HBF_4, with ethanol and ether. After drying in air and *in vacuo* at 40°C, a total of 75·6 g (84%) diazonium fluoroborate was obtained which was divided into two parts and thermally decomposed in a distillation apparatus using direct-flame heating. The crude product was dissolved in ether,

the solution was washed with 3% NaOH and water, dried with Na_2SO_4 and, after evaporation of the ether, the residue was redistilled; 32·0 g (73% referred to fluoroborate), b.p. 135—138°C. For the compound obtained in a different way, ref.[43] reports a b.p. of 138·5°C/774 Torr or 138—140°C/758 Torr[44]. The nearest analogy to the present procedure was the preparation of 3-chlorofluorobenzene described in ref.[47]. Japanese authors[65] prepared 2-chlorofluorobenzene by a somewhat different procedure.

5-Bromo-2-chlorofluorobenzene (*XXIb*)

A solution of 182 g 5-bromo-2-chloroaniline in 140 ml ethanol was added to 530 ml hydrochloric acid, the mixture was heated almost to boiling and cooled to 0°C. Like in the preceding case, it was diazotized with a solution of 65 g $NaNO_2$ in 250 ml water over a period of 1 h, the solution of diazonium chloride was combined under cooling with 500 ml solution of HBF_4 (concentration like in the previous case) and after 45 min of stirring at room temperature, the separated diazonium fluoroborate was filtered, washed and dried; 260 g (96%). It was decomposed as before, the yield being 131 g (74% referred to fluoroborate) product boiling at 84°C/15 Torr. A sample for analysis was obtained by redistillation; b.p. 73°C/9 Torr. IR spectrum (film): 815, 865, 883 (2 adjacent and solitary Ar—H), 1480, 1583 cm^{-1} (Ar). For C_6H_3BrClF (209·5) calculated: 34·40% C, 1·44% H; found: 33·94% C, 1·35% H.

4-Bromo-2-chlorofluorobenzene (*XXIc*)

In analogy to the preceding case, diazotization of 81·5 g 4-bromo-2-chloroaniline[50,51] (m.p. 70—72°C) and subsequent reaction with HBF_4 yielded 86·7 g (72%) diazonium fluoroborate (m.p. 160—162°C, decomposed at 185°C); its thermal decomposition yielded 42·5 g (72% referred to fluoroborate) product boiling at 84—86°C/18 Torr or 93—95°C/30 Torr. The analytical sample was redistilled (b.p. 92°C/35 Torr). For C_6H_3BrClF (209·5) calculated: 34·40% C, 1·44% H, 9·07% F; found: 33·91% C, 1·49% H, 8·98% F.

3,4-Dichlorothiophenol (*XIXa*)

1,2-Dichlorobenzene (73·5 g; according to gas chromatography it contains 85% of the substance) was added dropwise over a 10 min period under stirring to 120 ml chlorosulfonic acid at 145 to 150°C and the mixture was stirred for 20 min at this temperature and then for 2 h at room temperature. After standing overnight, the mixture was decomposed by pouring onto 600 g ice and the precipitated crude 3,4-dichlorobenzenesulfonyl chloride[26] was isolated by extraction with ether (97 g, 79%). The total quantity was dissolved in 70 ml acetic acid and the solution was added dropwise under stirring over a period of 30 min to a prewarmed mixture of 110 ml acetic acid, 25 g red phosphorus and 1·4 g iodine. The mixture was then refluxed for 3 h, cooled, combined with 30 ml water and refluxed for further 2·5 h. Then it was cooled, diluted with 350 ml water and the product was isolated by extraction with chloroform. Distillation yielded 53·9 g (60% referred to dichlorobenzene) of the desired product boiling at 120—124°C/14 Torr. Ref.[28] reports for a product obtained by a different procedure a b.p. of 115°C/8 Torr. If the hydrolysis of the primary reaction mixture was carried out under nitrogen, a 75% yield was attained. The residue after distillation can be purified by recrystallization from a mixture of ethanol and acetone; m.p. 87—89°C. It is bis(3,4-dichlorophenyl) disulfide (*XXa*). ^{1}H-NMR spectrum: δ 7·20—7·75 (m, aromatic protons). For $C_{12}H_6Cl_4S_2$ (365·1) calculated: 40·47% C, 1·69% H, 39·82% Cl, 18·01% S; found: 40·58% C, 1·72% H, 39·54% Cl, 17·90% S.

4-Chloro-3-fluorothiophenol (*XIXb*)

Reaction of 131 g *XXIb* with 15·2 g Mg in 300 ml tetrahydrofuran yielded a Grignard reagent. During refluxing in a nitrogen atmosphere, powder sulfur (18·5 g) was added in parts over a period of 1·5 h. The mixture was refluxed for 1·5 h, cooled and poured into a mixture of 600 g ice and 140 ml hydrochloric acid. The product was isolated by extraction with ether, the extract was shaken with 400 ml 10% NaOH, the aqueous layer was separated, made acid with hydrochloric acid and the product was isolated by extraction with ether; 72·8 g (72%), b.p. 88°C/14 Torr. For C_6H_4ClFS (162·6) calculated: 44·31% C, 2·48% H, 21·80% Cl, 19·72% S; found: 44·01% C, 2·22% H, 21·60% Cl, 19·33% S.

3-Chloro-4-fluorothiophenol (*XIXc*)

Like in the preceding case, a Grignard reagent was prepared in the reaction of 8·38 g *XXIc* with 10·7 g Mg in 240 ml ether. Sulfur (10·0 g) was added under stirring at 23—25°C over a period of 45 min, 80 ml ether were added and the mixture was stirred for 1 h at 23°C. After 48 h of standing, the mixture was processed and the product obtained in the final extraction with benzene in a yield of 34·5 g (53%) boiled at 87—88°C/15 Torr. The analytical sample was redistilled; b.p. 91—92°C/20 Torr. For C_6H_4ClFS (162·6) calculated: 44·31% C, 2·48% H, 21·80% Cl, 19·72% S; found: 44·29% C, 2·62% H, 21·72% Cl, 19·37% S.

3,4-Difluorothiophenol (*XIXd*)

Like in the preceding case, the reaction of 57·9 g *XXId* (ref.[54]) (b.p. 150—152°C) with 8·0 g Mg in 150 ml ether yielded a Grignard reagent. Reaction with 7·2 g sulfur and subsequent processing yielded 20·1 g (46%) product boiling at 70°C/13 Torr. This is a crude product which can be processed further but even a redistillation does not lead to an analytically pure compound. A sample of the substance was oxidized in a solution of 10% NaOH with 25% hydrogen peroxide. Bis(3,4-difluorophenyl) disulfide (*XXd*) was isolated by extraction with benzene and by distillation; b.p. 135—140°C/18 Torr. IR spectrum ($CHCl_3$): 815, 868, 902 (2 adjacent and solitary Ar—H), 1273 (C—F), 1500, 1598 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·85—7·60 (m, aromatic protons). For $C_{12}H_6F_4S_2$ (290·3) calculated: 49·64% C, 2·08% H, 26·18% F, 22·09% S; found: 49·36% C, 2·05% H, 26·25% F, 22·74% S.

2-(3,4-Dichlorophenylthio)benzoic Acid (*Xa*) (Method *A*)

XIXa (53·8 g) was added under stirring at 50°C to a solution of 57 g KOH in 600 ml water, followed after 10 min with 2·0 g Cu and 74·4 g 2-iodobenzoic acid[24]. The mixture was refluxed under stirring for 7 h, filtered while hot and the filtrate was cooled and acidified with hydrochloric acid. The precipitated product was filtered after 12 h of standing, washed with water and recrystallized from 600 ml ethanol; 68·5 g (76%), m.p. 232—237°C. The analytical product melted at 239—240°C (ethanol). IR spectrum (Nujol): 680, 702 (C—Cl), 750, 812, 885 (4 and 2 adjacent and solitary Ar—H), 920 (COOH), 1260 (C—O), 1560, 1586 (Ar), 1675 cm^{-1} (Ar—COOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·80—8·10 (m, aromatic protons and COOH).

2-(3,4-Dichlorophenylthio)benzyl Alcohol (*XIa*)

A 70% benzene solution (240 g) of sodium dihydridobis(2-methoxyethoxy)aluminate was added dropwise under stirring and cooling to a mixture of 125 g acid *Xa* and 800 ml benzene over

a period of 1 h. The mixture was stirred for 3 h at room temperature. The solution formed was decomposed by adding 600 ml 10% NaOH, the benzene layer was separated, washed with water, dried with K_2CO_3 and processed by distillation; 93·8 g (81%), b.p. 188—191°C/0·4 Torr. The analytical product was redistilled, b.p. 200—202°C/2·5 Torr. ^{1}H-NMR spectrum: δ 7·20—7·70 (m, 5 H, aromatic protons of benzyl alcohol and 2-H in the arylthio group), 7·36 (d, J = 9·0 Hz, 1 H, 6-H in the arylthio group), 6·98 (mcd, J = 9·0; 2·0 Hz, 1 H, 5-H of arylthio group), 4·78 (bs, 2 H, $ArCH_2O$), 2·25 (bs, 1 H, OH).

2-(4-Chloro-3-fluorophenylthio)benzyl Alcohol (*XIb*)

90% $NaBH_4$ (4·0 g) was added under cooling in a nitrogen atmosphere to a mixture of 26·8 g acid *Xb* and 75 ml tetrahydrofuran and this was followed over a period of 20 min at room temperature by a dropwise addition of 15 ml BF_3 etherate in 15 ml tetrahydrofuran. The mixture was stirred for 3 h at room temperature, left to stand for 12 h, decomposed with dilute hydrochloric acid, diluted with water and extracted with benzene. The organic phase was washed with 5% NaOH and water, dried with Na_2SO_4 and evaporated. Distillation yielded 21·5 g (84%) product boiling at 175—178°C/0·5 Torr. IR spectrum (film): 762, 815, 862 (4 and 2 adjacent and solitary Ar—H), 1036, 1067 (CH_2OH), 1233 (C—F), 1572, 1591 (Ar), 3360 cm^{-1} (OH).

2-(4-Chloro-3-fluorophenylthio)benzyl Chloride (*XIIb*) (Method *B*)

$SOCl_2$ (4·4 ml) was added dropwise over a period of 30 min under stirring at 10°C to a mixture of 12·9 g *XIb* and 4·9 ml pyridine and the mixture was stirred for 2 h at room temperature and for 1 h at 40°C. It was cooled, combined with 20 ml water, stirred for 45 min, diluted with benzene and the organic layer was separated. After washing with 1M-HCl, 5% NaOH and water, the solution was dried with $CaCl_2$ and evaporated. A total of 11·8 g (86%) crude product was obtained which was processed further in this form. A sample was redistilled for analysis (b.p. 159—160°C/1 Torr).

2-(3,4-Dichlorophenylthio)phenylacetonitrile (*XIIIa*) (Method *C*)

A solution of 30·4 g crude *XIIa* in 30 ml ethanol was added to a solution of 7·35 g NaCN in 12 ml water and the mixture was refluxed under stirring for 15 h. After evaporation of ethanol the residue was diluted with 50 ml water and extracted with benzene. The extract was washed with water, dried and distilled; 23·9 g (80%), b.p. 185—205°C/0·8 Torr. The distillate crystallized on standing; m.p. 48—49°C (ethanol). ^{1}H-NMR spectrum: δ 7·50—7·80 (m, 4 H, aromatic protons of phenylacetonitrile), 7·44 (d, J = 9·0 Hz, 1 H, 5-H of the arylthio group), 7·29 (mcs, J = 2·0 Hz, 1 H, 2-H of the arythio group), 7·00 (mcd, J = 9·0; 2·0 Hz, 1 H, 6-H of the arylthio group), 3·87 (s, 2 H, $ArCH_2CN$).

2-(4-Chloro-3-fluorophenylthio)phenylacetic Acid (*XIVb*) (Method *D*)

A mixture of 44·5 g *XIIIb*, 40 g KOH, 150 ml ethanol and 100 ml water was refluxed for 4 h. After evaporation of ethanol at reduced pressure, the residue was diluted with 500 ml water, the solution was washed with ether and made acid with hydrochloric acid. On the next day the product was filtered, dried and rectrystallized from a mixture of 50 ml benzene and 50 ml light petroleum; 42·6 g (90%), m.p. 115—117°C. A sample for analysis melted at 118—119°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 9·95 (bs, disappears after D_2O, 1 H, COOH), 6·50 to 7·50 (m, 7 H, aromatic protons), 3·73 (s, 2 H, $ArCH_2CO$).

2-(3-Chloro-4-fluorophenylthio)phenylacetic Acid (*XIVc*) (Method *E*)

A solution of 40 g KOH in 425 ml water was combined at 50°C with 34·5 g *XIXc* and, after 10 min of stirring, with 2 g Cu and 55·0 g 2-iodophenylacetic acid[25]. The mixture was refluxed for 24 h, the solution was filtered while hot, the filtrate was acidified with hydrochloric acid and extracted with benzene. The benzene solution was shaken with 300 ml 10% NaOH. The alkaline solution was filtered with charcoal and the filtrate was left for 24 at 0°C. The precipitated salt was filtered, washed with ice cold water, suspended in water and acidified with hydrochloric acid to liberate the desired acid. This was filtered and recrystallized from 100 ml ethanol to which water was added until slight turbidity appeared; 45·1 g (72%), m.p. 84–86°C. Analytical sample melted at 85–87°C (cyclohexane–hexane). IR spectrum: 745, 835, 870 (4 and 2 adjacent and solitary Ar—H), 930, 1245, 1265 (COOH), 1485, 1590 (Ar), 1700 (R—COOH), 2550, 2650 cm^{-1} (COOH).

7-Chloro-8-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVc*) (Method *F*)

A mixture of 60 g polyphosphoric acid (prepared by heating a mixture of 100 ml 85% H_3PO_4 with 200 g P_2O_5 for 8 h at 140°C) and 6·0 g *XIVc* was heated under stirring for 4 h to 130–140°C. It was cooled, mixed with 200 g ice and water and extracted with benzene. The extract was washed with 5% NaOH and water, dried and evaporated: 4·96 g (90%), m.p. 118–124°C. The analytical product melts at 124–126°C (ethanol). IR spectrum: 735, 758, 880 (4 adjacent and solitary Ar—H), 1595 (Ar), 1682 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 7·92 (d, $J_{(H-F)}$ = = 10·0 Hz, 1 H, 9-H), 7·64 (d, J = 7·0 Hz, 1 H, 6-H), c. 7·60 (m, 1 H, 4-H), 7·10–7·50 (m, 3 H, remaining aromatic protons), 4·31 (s, 2 H, $ArCH_2CO$). For the preparation of other ketones *XV* the reaction temperature was 115–125°C.

Furo[3,2-*m*; 4,5-*m'*]bis(3-chloro-2-fluorodibenzo[*b*,*f*]thiepin) (*XXIII*)

Polyphosphoric acid (15 g) (prepared some time before by heating 335 ml 83% H_3PO_4 with 525 g P_2O_5 for 8 h at 130°C) was combined with 3·0 g P_2O_5 and heated under stirring for 2 h at 140°C. Acid *XIVc* (1·83 g) was then added and the mixture was heated for 8 h to 140–150°C with stirring. After cooling, it was decomposed with water and ice and extracted with benzene. The extract was washed with a 10% solution of NaOH and water and evaporated. A total of 1·34 g compound melting at 312–325°C was obtained which was recrystallized from a mixture of benzene and light petroleum and melted at 330–333°C. The mass spectrum displays a molecular ion at *m/e* 536, corresponding to $C_{28}H_{12}Cl_2F_2OS_2$ which agrees with the analysis. For $C_{28}H_{12}$ . . $Cl_2F_2OS_2$ (537·4) calculated: 62·57% C, 2·25% H, 7·07% F; found: 62·83% C, 2·44% H, 6·80% F.

7,8-Difluoro-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVId*) (Method *G*)

A solution of 1·35 g $NaBH_4$ in 10 ml water with 0·1 ml 15% NaOH was added dropwise to a solution of 22·8 g *XVd* in a mixture of 200 ml ethanol and 50 ml benzene. The mixture was refluxed for 3 h, ethanol was evaporated *in vacuo*, the residue was decomposed with water and the product was isolated by extraction with benzene. The crude product obtained in a practically theoretical amount is analytically pure after two crystallizations from cyclohexane; 20·4 g (89%), m.p. 98–100°C. IR spectrum: 760, 810, 890 (Ar—H), 1030 (CHOH), 1510, 1595 (Ar), 3520 cm^{-1} (OH).

8,10-Dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIIb*) (Method *H*)

Powdery $CaCl_2$ (20 g) was added to a solution of 31·0 g *XVIb* in 200 ml benzene and the suspension was saturated for 3 h with anhydrous hydrogen chloride. After 12 h of standing at room temperature it was filtered, the filtrate was evaporated *in vacuo* and the residue was recrystallized from 40 ml acetone; 27·6 g (83%), m.p. 92–94°C; analytical product, m.p. 94–96°C (acetone). NMR spectrum: δ 7·45 (d, J = 8·0 Hz, 1 H, 9-H), 7·15 (d, J = 12 Hz, 1 H, 6-H), 7·00–7·40 (m, 4 H, 1,2,3,4-H_4), 5·54 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·85 and 3·50 (2dd, J = = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$).

8-Chloro-7-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ib*) (Method *J*)

A mixture of 7·48 g *XVIIb*, 5·2 ml 1-methylpiperazine and 7 ml chloroform was refluxed for 7 h in a 115°C bath. After evaporation of chloroform at reduced pressure, the residue was mixed with 50 ml water and extracted with benzene. The extract was washed with water and shaken with 200 ml 3M-HCl. The precipitated hydrochloride of the product was filtered, added to the aqueous layer of the filtrate and the suspension was made alkaline with NH_4OH. The released base was isolated by extraction with benzene; 6·66 (74%). Crystallization from acetone yielded the analytical product melting at 105–107°C. ^{1}H-NMR spectrum: δ 7·66 (d, J = 8·0 Hz, 1 H, 9-H), 7·15 (d, J = 13·0 Hz, 1 H, 6-H), 7·05–7·50 (m, 4 H, 1,2,3,4-H_4), 2·90–4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·21 (s, 3 H, NCH_3). Maleate, m.p. 168–169°C (ethanol).

The benzene layer of the filtrate after filtration of the crude hydrochloride *Ib* was washed with further 3M-HCl, dried and evaporated. The residue was purified by crystallization from ethanol, m.p. 110–112°C. It is 2-chloro-3-fluorodibenzo[*b*,*f*]thiepin (*XVIIIb*). UV spectrum: λ_{max} 263 nm (log ε 4·42), 292 nm (3·71). IR spectrum (Nujol): 760, 860, 885 (4 adjacent and solitary Ar—H), 800 (CH=CH *cis*), 1485, 1585 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·15–7·60 (m, 6 H, aromatic protons), 7·09 and 6·83 (ABq, J = 14·0 Hz, 2 H, ArCH=CHAr).

8-Chloro-10-[4-(2-decanoyloxyethyl)piperazino]-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVb*) (Method *K*)

Decanoyl chloride[34] (4·59 g) was added to a solution of 3·93 g *IIb* in 30 ml chloroform and the mixture was left overnight at room temperature. It was diluted with 30 ml chloroform, 30 ml water, 60 ml ice-cold 10% NaOH, shaken and separated. After washing with water, the chloroform solution was dried with K_2CO_3 and evaporated. The residue was dissolved in benzene and the solution was chromatographed on a column of 150 g Al_2O_3 (activity II). The product was eluted with benzene as the least polar fraction; 4·67 g (85%) oil. Neutralization of this base with maleic acid in acetone yielded the crystalline dimaleate, m.p. 125–127°C (acetone).

7,8-Dichloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIa*)

A mixture of 3·5 g base *VIa*, 1·75 g KOH and 3·5 ml ethanol was refluxed for 3 h under stirring in a bath at 125°C. 50 ml water was then added and the mixture was extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue crystallized from acetone to 1·87 g (64%) compound melting at 131–135°C; analytical product, m.p. 133 to 135·5°C (acetone).

7,8-Difluoro-10-(4-methylpiperazino)dibenzo[*b*, *f*]thiepin (*VIIId*) (Method *L*)

1-Methylpiperazine (15 g) was added to a solution of 7·87 g ketone *XVd* in 75 ml benzene and this was followed by a dropwise addition of 1·8 ml $TiCl_4$ in 25 ml benzene. The mixture was refluxed under stirring for 25 h. After cooling, it was decomposed by adding 120 ml water, the precipitated solid was filtered and washed with benzene. The benzene phase was separated from the filtrate, washed with water and after drying (Na_2SO_4) evaporated *in vacuo*. The residue was crystallized from hexane and from acetone to yield 7·60 g (74%) base melting at 117—120°C: analytical product, m.p. 119—121°C. ^{1}H-NMR spectrum: δ 7·00—7·70 (m, 6 H, aromatic protons), 6·34 (s, 1 H, ArCH=C), 2·96 (t, J = 4·0 Hz, 4 H, $CH_2N^1CH_2$ of piperazine), 2·49 (t, J = 4·0 Hz, 4 H, $CH_2N^4CH_2$ of piperazine), 2·32 (s, 3 H, NCH_3). Neutralization with methanesulfonic acid in a mixture of ethanol and acetone yielded the methanesulfonate melting at 300 to 303°C (95% ethanol).

8-Chloro-7-fluoro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*, *f*]thiepin N^4-Oxide (*XXIIb*) (Method *M*)

26·7% H_2O_2 (3·6 ml) was added to a solution of 7·86 g base *IIb* in 40 ml ethanol. The mixture was refluxed for 3 h, boiled for 1 h with a platinum foil, diluted with water, filtered and evaporated *in vacuo*. The base monohydrate was obtained in a practically theoretical yield (8·5 g). This was crystallized from acetone; m.p. 186—189°C. It is polarographically reduced in 0·5M-HCl at $E_{1/2}$ −0·4 V (against a saturated calomel electrode) which corresponds to the bahaviour of the N-oxide. Colorimetric test for the presence of S-oxide was negative. IR spectrum: 775, 786, 868 (4 adjacent and solitary Ar—H), 982 (N—O), 1069 (CH_2OH), 1485, 1575, 1600 (Ar), 3470 cm^{-1} (OH, H_2O). Neutralization with hydrogen chloride in ethanol yields the dihydrochloride which crystallizes from aqueous ethanol as hemihydrate, m.p. 167—169°C.

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