NEW POTENTIAL NEUROLEPTICS OF THE PERATHIEPIN AND OCTOCLOTHEPIN SERIES: 8-CHLORO-7-METHOXY, 8-CHLORO-7-TRIFLUOROMETHYL- AND 7-FLUORO-8-METHYL--10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN*

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4-Chloro-3-methoxythiophenol (*XIIIa*), 4-chloro-3-trifluoromethylthiophenol (*XIIIb*) and 3--fluoro-4-methylthiophenol (*XIIIc*) were converted to intermediates *III*—*VII* to synthesize the corresponding 7,8-disubstituted dibenzo[*b,f*]thiepin-10(11*H*)-ones *VIIIa*—*c*. *Via* alcohols *IX* and chlorides *X* the title compounds *Ia*—*c* were then prepared while enamines *IIa* and *IIb* were synthesized directly from ketones *VIII*. During cyclization of acid *VIIb* with polyphosphoric acid ketone *VIIIb* was accompanied by keto acid *XVI* and enol-lactone *XVII*. The 7-fluoro-6-methyl derivative of perathiepin *Ic* shows a clear central depressant and cataleptic activity but there is no protraction of the effect.

In an earlier communication[1] we described the synthesis and the neuroleptic properties of 7,8-dihalogeno derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin. Interesting in this connection was the 7-fluoro derivative of octoclothepin which, while being very little toxic, was highly effective, its action persisting longer than that of octoclothepin. We wish to describe now the synthesis of further three 7,8-disubstituted derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin *Ia*—*Ic* and of two enamines *IIa* and *IIb*. Compounds *Ia* and *Ib* are 7-substitution derivatives of octoclothepin and the objective in preparing them was to establish the effect of introducing other substituents besides halogen on their activity. In the case of *Ia*, another objective was involved: the 7-methoxy derivative of octoclothepin *Ia* is a potential synthetic precursor of the unknown 7-hydroxy derivative of octoclothepin which might be a metabolite of this neuroleptic (in analogy to the 3-hydroxy derivative of chloropromazine[2-5]). The present paper thus describes an attempt to prepare this potential metabolite of octo-

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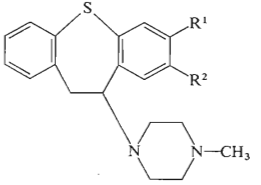
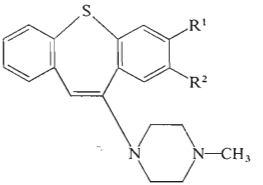
clothepin by demethylation of *Ia*. Finally, the aim of preparing *Ic* was to establish whether the 8-chloro-7-fluoro substitution is specific for the given set of favourable properties[1] (low toxicity, high and protracted neuroleptic activity) or whether the chlorine atom can be replaced by another "neuroleptic" substituent; in our case we selected for this purpose the methyl group (8-methyl analogue of octoclothepin see in ref.[6]).



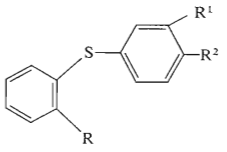
I



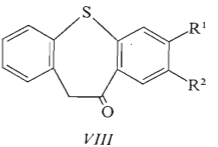
II

a, $R^1 = OCH_3$, $R^2 = Cl$
b, $R^1 = CF_3$, $R^2 = Cl$
c, $R^1 = F$, $R^2 = CH_3$

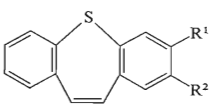
During the synthesis of *I* and *II* we used a procedure analogous to that in earlier work[1,6] and proceeded *via* intermediates *III*–*X*. The following methods were used: *A*) Reaction of thiophenols *XIII* with 2-iodobenzoic acid[7] in boiling aqueous



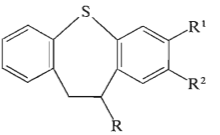
III, R = COOH
IV, R = CH_2OH
V, R = CH_2Cl
VI, R = CH_2CN
VII, R = CH_2COOH



VIII



XI

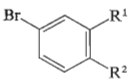


IX, R = OH
X, R = Cl

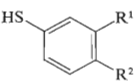
solution of potassium hydroxide in the presence of copper. *B*) Reduction of the acids *III* obtained with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene to alcohols *IV*. *C*) Transformation of alcohols *IV* to benzyl chlorides *V* in a reaction with thionyl chloride in the presence of pyridine. *D*) Conversion of chlorides *V* to phenylacetonitriles *VI* in a reaction with sodium cyanide in aqueous ethanol. *E*) Hydrolysis of nitriles *VI* to acids *VII* with aqueous–alcoholic potassium hydroxide. *F*) Cyclization of acids *VII* to ketones *VIII* with polyphosphoric acid in various experimental arrangements. *G*) Reduction of ketones *VIII* to alcohols *IX* with sodium borohydride in aqueous ethanol. *H*) Conversion of alcohols *IX* to chlorides *X* by treatment with anhydrous hydrogen chloride in benzene. *J*) Substitution reaction of chlorides *X* with 1-methylpiperazine in boiling chloroform which gives rise to the desired bases *I* as main products and to dibenzo[*b*,*f*]thiepins *XI* as elimination by-products. *K*) Reaction of ketones *VIII* with 1-methylpiperazine and titanium tetrachloride in boiling benzene which yields enamines *II*.

In series *a* the starting compound was the new 4-chloro-3-methoxythiophenol (*XIIIa*). It was prepared in a reaction of 4-chloro-3-methoxyphenylmagnesium bromide with sulfur (for analogy see ref.[1]). The required 5-bromo-2-chloroanisol (*XIIa*) was obtained by Sandmeyer's reaction from 2-amino-5-bromoanisol[8]; ref.[9] reports an analogous preparation from 5-amino-2-chloroanisol. (In one of the batches 3,5-dibromo-2-chloroanisol[10] (*XIV*) was also detected, its source being apparently 2-amino-3,5-dibromoanisol[11–13] contaminating the starting 2-amino-5-bromoanisol). From thiol *XIIIa* synthesis proceeded using the above general methods. Cyclization of *VIIa* to 8-chloro-7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIIa*) with polyphosphoric acid (method *F*) proceeded best in the presence of boiling toluene (analogy *e.g.*[6]). The subsequent reduction to alcohol *IXa* (method *G*) was modified by the addition of benzene because of the poor solubility of the starting compound in ethanol alone. Chloride *Xa* obtained in the following step (method *H*) is rather unstable; it eliminates hydrogen chloride on drying *in vacuo* at 60°C. In an attempt to prepare this chloride by a reaction of alcohol *IXa* with thionyl chloride in benzene at 60°C, hydrogen chloride was also eliminated and the only product obtained was 2-chloro-3-methoxydibenzo[*b*,*f*]thiepin (*XIa*). Substitution reaction of chloride *Xa* with 1-methylpiperazine in chloroform (method *J*) proceeded in a normal fashion and the crude base *Ia* was obtained in a 87% yield; the neutral product obtained was again *XIa*. Application of method *K* yielded enamine *IIa*; an attempt to reduce it to the dihydro derivative *Ia* with diborane, generated in a reaction of sodium borohydride with acetic acid in tetrahydrofuran (method[14]) did not yield the desired result. To demethylate base *Ia* to the 7-hydroxy derivative of octoclothepin we used boron tribromide in dichloromethane, a method applied recently to prepare analogous 2-, 3-, 6-, 8-hydroxy, and 2,3-dihydroxy derivatives[15–20]. In the present case the only characterized product obtained was 2-chloro-3-hydroxydibenzo[*b*,*f*]-thiepin (*XV*). Thus again it was not possible to prepare a compound

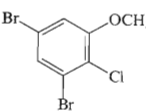
in this series that would have a free hydroxyl group in position 7 (for similar cases see ref.[19,20]).



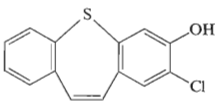
XII



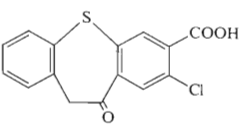
XIII



XIV



XV

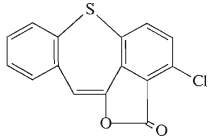


XVI

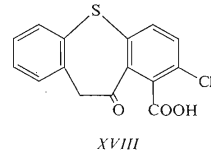
In series *b* the starting compound was 5-bromo-2-chlorobenzotrifluoride[21,22] (*XIIb*) which was converted to 4-chloro-3-trifluoromethylthiophenol[23] (*XIIIb*). Transformation to acid *IIIb* was done by method *A*. Method *B* was not found to be usitable for subsequent reduction to alcohol *IVb* and hence it was done with diborane (see ref.[1]). Acid *VIIb* was prepared according to the conventional methods shown.

The chemically more interesting step was the cyclization. It could be expected that the trifluoromethyl group in the *para*-position toward the point of attack of the acylium cation will complicate the reaction and that its lability in polyphosphoric acid at higher temperatures will become an important factor. Both assumptions were found to be justified. On heating *VIIb* with polyphosphoric acid to 150°C no cyclization took place and the starting acid is practically completely recovered. At 180–190°C the main product obtained was a nonhomogeneous acid fraction and, as a by-product, a red neutral compound with a high melting point, not corresponding by its character to ketones of the dibenzo[*b*,*f*]thiepin series. Useful results were obtained only by cyclization with polyphosphoric acid in boiling *o*-dichlorobenzene, *i.e.* at 180°C. In this arrangement, a neutral fraction was obtained in an about 50% yield; this served for separating the above red compound $C_{15}H_7.ClO_2S$, melting at 221–222°C. The composition was confirmed by the mass spectrum (*m*/*e* 286) which excluded the possibility of a dimer. The intense band in the IR spectrum at 1792 cm^{-1} suggested the compound to be an unsaturated lactone with the probable structure shown by *XVII*. Another neutral compound obtained from the mother liquor was then identified as the desired 8-chloro-7-trifluoromethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIIb*). Acid $C_{15}H_9ClO_3S$ was isolated from the

acid fraction after cyclization. The IR spectrum (in dioxane) contains two bands in the carbonyl region (1 700 and 1 748 cm^{-1}) ascribed to the vibrations of CO groups in the aromatic ketone and aromatic acid; IR spectrum in KBr contains a band at 875 cm^{-1} in the region of extraplanar vibrations which suggests the presence of a solitary aromatic hydrogen. All the facts support the structure shown by *XVI*, formed by cyclization and hydrolysis of the trifluoromethyl group.



XVII



XVIII

The keto acid formed by alkaline hydrolysis of lactone *XVII* is isomeric with *XVI* but clearly distinct from it. The IR spectrum shows two bands at 1 684 and 1 710 cm^{-1} corresponding to vibrations of carbonyl groups in an aromatic ketone and an aromatic acid; further it contains a band at 826 cm^{-1} indicating the presence of two adjacent aromatic hydrogens. All these facts are compatible with the structure shown by *XVIII* which supports the structure of the enol-lactone *XVII*. The formation of a relatively large amount of this lactone (some 10%) is remarkable in view of earlier findings on the course of cyclization of 2-(*m*-substituted phenylthio)phenylacetic acids which indicated that the only[24-27] or practically only[1,28] products here are the sterically more favorable 7-substituted dibenzo[*b*,*f*]thiepin-10(11*H*)-ones. The sterically unfavorable 9-substituted dibenzo[*b*,*f*]thiepin-10(11*H*)-ones were prepared only in the case that cyclization could not proceed differently[29] or when using a method completely different from a Friedel–Crafts acylation[25,30,31]. An explanation for the observed formation of *XVII* is possible on the assumption of simultaneous role of two factors. The first of these is the reversibility of Friedel-Crafts cyclizations of this type when certain equilibrium states must exist in the presence of polyphosphoric acid between the acylium cations and the resulting ketones (see also[32] and other papers quoted there). The other factor is the possibility that the enol-lactone *XVII* is the only stable compound in the whole reaction mixture and that it does not undergo further transformations. A precursor for lactone *XVII* could thus be acid *XVI* (or its mixed anhydride with polyphosphoric acid) which, in polyphosphoric acid, is in equilibrium with the corresponding opened acylium cation. To a small extent, this undergoes cyclization to acid *XVIII* which is immediately cyclized to the stable enol-lactone *XVII* and thus disappears from the system. With the long reaction time used, the ketone *VIIIb* can be slowly transformed to acid *XVI* and this

can be converted to enol-lactone *XVII* as indicated. Another precursor of enol-lactone *XVII* might be the internal ansa-cyclic anhydride of dicarboxylic acid derived by hydrolysis of trifluoromethyl in acid *VIIb*; this di-acid has not been isolated but its presence in the acid fraction of the reaction product is highly probable.

Method *G* modified by using a mixture of ethanol and dioxane as medium was used for reducing ketone *VIIIb*. Alcohol *IXb* thus obtained could not be converted to chloride *Xb* by method *H*; the reaction required thionyl chloride. Preparation of the final bases *Ib* and *IIb* was done by using general methods (*J*, *K*); in the first case the by-product resulting from the mixture was 2-chloro-3-trifluoromethyldibenzo[*b*,*f*]thiepin (*XIb*).

In series *c*, the starting material was 4-amino-2-fluorotoluene[33] which was converted to 3-fluoro-4-methylthiophenol (*XIIIc*) by the xanthogenate method (analogy[34]). General methods were used up to the stage of chloride *Vc* where synthesis was interrupted for low yields. The desired acid *VIIc* was prepared in a reaction of (2-iodophenyl)acetic acid[35] with thiophenol *XIIIc* (analogy[35]). Cyclization of acid *VIIc* to ketone *VIIIc* proceeded by heating with polyphosphoric acid to 120 to 125°C. Further steps up to base *Ic* were done by conventional methods; in the last step, 3-fluoro-2-methyldibenzo[*b*,*f*]thiepin (*XIc*) was the by-product.

Table I gives the experimental data for the final products *I* and *II*, as well as for the intermediates *III*–*X* and elimination products *XI*. The experimental section only shows examples of preparations by general methods *A*–*K* and further describes preparations where the general method were not used or were modified.

TABLE I

Piperazine Derivatives *I* and *II*, Intermediates *III*–*X* and Elimination Products *XI*

Compound[a]	Method (yield, %)	M.p., °C (solvent) or b.p., °C/Torr	Formula (m.w.)	Calculated/Found					
				% C	% H	% Cl	% F	% N	% S
IIIa	*A*	245–247[b]	$C_{14}H_{11}ClO_3S$	57·05	3·76	12·03	—	—	10·88
	(77)	(ethanol)	(294·7)	57·26	3·86	12·00	—	—	10·80
IIIb	*A*[c]	187–189	$C_{14}H_8ClF_3O_2S$	50·53	2·42	10·66	—	—	9·64
	(73)	(ethanol)	(332·7)	50·55	2·13	11·20	—	—	10·18
IIIc	*A*	190–191[d]	$C_{14}H_{11}FO_2S$	64·10	4·23	—	7·24	—	12·23
	(58)	(ethanol)	(262·3)	63·97	4·29	—	7·20	—	12·28
IVa	*B*[c]	78–80	$C_{14}H_{13}ClO_2S$	59·89	4·66	—	—	—	—
	(91)	(benzene–light petroleum)	(280·8)	60·30	4·79	—	—	—	—

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	M.p., °C (solvent) or b.p., °C/Torr	Formula (m.w.)	Calculated/Found					
				% C	% H	% Cl	% F	% N	% S
IVb	[c]	180—182/4·3	$C_{14}H_{10}ClF_3OS$	52·75	3·16	11·12	—	—	—
			(318·8)	52·88	3·15	10·94	—	—	—
IVc	*B*	182/0·9	$C_{14}H_{13}FOS$	67·72	5·28	—	7·65	—	12·91
	(68)		(248·3)	67·60	5·17	—	7·99	—	12·71
Va	*C*	57—59	$C_{14}H_{12}Cl_2OS$	56·19	4·04	—	—	—	—
	(85)	(hexane)	(299·2)	56·58	4·05	—	—	—	—
Vb	*C*	165—167/0·8	$C_{14}H_9Cl_2F_3S$	—	—	—	—	—	9·51
	(90)		(337·2)	—	—	—	—	—	9·90
Vc	*C*[c]	172/1·2	$C_{14}H_{12}ClFS$	63·03	4·54	13·29	7·12	—	12·02
	(87)	—	(266·7)	63·60	4·68	13·35	7·12	—	11·98
VIa	*D*[c]	78—80	$C_{15}H_{12}ClNOS$	62·17	4·17	—	—	4·83	—
	(90)	(ethanol)	(289·8)	62·37	4·21	—	—	5·11	—
VIb	*D*	69—70[e]	$C_{15}H_9ClF_3NS$	54·96	2·77	10·82	17·89	4·27	9·79
	(63)	(ethanol)	(327·8)	54·82	2·84	10·86	17·64	4·29	9·51
VIIa	*E*[c]	103—105	$C_{15}H_{13}ClO_3S$	58·34	4·24	—	—	—	—
	(90)	(benzene–light petroleum)	(308·8)	58·81	4·22	—	—	—	—
VIIb	*E*	128—130[f]	$C_{15}H_{10}ClF_3O_2S$	51·95	2·91	10·22	16·44	—	9·25
	(89)	(benzene)	(346·8)	52·27	2·90	10·25	16·55	—	9·67
VIIc	[c]	123—124	$C_{15}H_{13}FO_2S$	65·19	4·74	—	6·88	—	11·60
		(ethanol)	(276·3)	64·74	4·79	—	7·04	—	11·76
VIIIa	*F*[c]	172—173	$C_{15}H_{11}ClO_2S$	61·96	3·81	—	—	—	—
	(78)	(benzene)	(290·8)	62·33	3·85	—	—	—	—
VIIIb	*F*[c]	137—139	$C_{15}H_8ClF_3OS$	54·80	2·45	10·79	17·34	—	9·75
	(40)	(cyclohexane)	(328·7)	55·02	2·44	10·98	17·33	—	9·90
VIIIc	*F*[c]	88—89	$C_{15}H_{11}FOS$	69·75	4·29	—	7·36	—	12·41
	(79)	(ethanol)	(258·3)	69·90	4·37	—	7·36	—	12·72
IXa	*G*[g]	130—132[h]	$C_{15}H_{13}ClO_2S$	61·53	4·47	12·11	—	—	10·95
	(83)	(ethanol)	(292·8)	62·03	4·72	11·97	—	—	10·51
IXb	*G*[i]	123—124[j]	$C_{15}H_{10}ClF_3OS$	54·47	3·05	10·72	17·23	—	9·69
	(88)	(cyclohexane)	(330·8)	54·70	3·28	11·14	17·27	—	10·14
IXc	*G*[c]	61—64	$C_{15}H_{13}FOS$	69·20	5·03	—	7·30	—	12·32
	(82)	(hexane)	(260·3)	69·20	5·06	—	7·42	—	12·22

TABLE I
(*Continued*)

Compound[a]	Method (yield %)	M.p., °C (solvent) or b.p. °C/Torr	Formula (m.w.)	Calculated/Found					
				% C	% H	% Cl	% F	% N	% S
Xa	*H*[k]	130–132	$C_{15}H_{12}Cl_2OS$	57·88	3·89	22·78	—	—	10·30
	(72)	(cyclohexane)	(311·2)	57·95	3·92	22·71	—	—	10·14
Xb	[c]	100–102	$C_{15}H_9Cl_2F_3S$	51·59	2·60	20·31	16·32	—	9·18
		(acetone)	(349·2)	51·60	2·70	20·42	16·42	—	9·58
Xc	*H*[c]	110–112	$C_{15}H_{12}ClFS$	64·62	4·34	12·72	6·81	—	11·50
	(81)	(acetone)	(278·8)	64·57	4·50	12·62	6·73	—	11·74
Ia	*J*	121–124[l]	$C_{20}H_{23}ClN_2OS$	64·07	6·18	9·45	—	7·47	8·55
	(85)	(acetone)	(374·9)	63·88	6·32	9·83	—	7·26	8·95
Ia-2HM	—	169–172	$C_{28}H_{31}ClN_2O_9S$	55·40	5·15	5·84	—	4·61	5·28
		(methanol)	(607·1)	55·27	5·43	5·81	—	4·64	5·33
XIa	*J*	114–117	$C_{15}H_{11}ClOS$	65·56	4·04	12·90	—	—	11·67
	(see[c])	(acetone)	(274·8)	65·87	4·16	12·84	—	—	11·50
Ib-M	*J*	197–200[m]	$C_{24}H_{24}ClF_3N_2O_4S$	54·49	4·57	6·70	10·78	5·30	6·06
	(56)	(ethanol)	(529·0)	54·62	4·74	6·91	10·82	5·38	6·29
XIb	*J*	79–81[n]	$C_{15}H_8ClF_3S$	57·60	2·58	11·34	18·23	—	10·25
		(ethanol)	(312·7)	57·51	2·50	11·11	18·05	—	10·38
Ic	*J*[c]	109–111	$C_{20}H_{23}FN_2S$	70·14	6·77	—	5·55	8·18	9·36
	(82)	(ethanol)	(342·5)	70·31	6·87	—	5·50	8·01	9·84
Ic-2MS[o]	—	170–172	$C_{22}H_{32}FN_2O_{6.5}S_3$	48·60	5·93	—	3·49	5·15	17·70
		(ethanol–ether)	(543·7)	48·70	5·89	—	3·84	5·04	17·70
XIc	*J*[c]	95–97	$C_{15}H_{11}FS$	74·35	4·58	—	7·84	—	13·23
		(ethanol)	(242·3)	74·54	4·72	—	7·82	—	13·02
IIa	*K*[c]	144–146	$C_{20}H_{21}ClN_2OS$	64·41	5·68	9·51	—	7·51	8·60
	(67)	(ethanol)	(372·9)	64·80	5·90	9·50	—	7·27	8·57
IIa-M	—	210–213	$C_{24}H_{25}ClN_2O_5S$	58·95	5·15	7·25	—	5·73	6·56
		(ethanol)	(489·0)	58·78	5·06	7·26	—	5·74	6·60
IIb-MS[p]	*K*	267–270[q]	$C_{21}H_{24}ClF_3N_2O_4S_2$	48·04	4·60	—	10·86	5·33	12·22
	(50)	(acetone)	(525·0)	48·04	4·39	—	11·14	5·28	12·64

[a] HM hydrogen maleate, M maleate, MS methanesulfonate. [b] IR spectrum: 745, 806, 852 (4 and 2 adjacent and solitary Ar—H), 920 (COOH), 1024, 1039, 1055 ($ArOCH_3$), 1250 (COOH), 1574 (Ar), 1661 (Ar—COOH), 2400–3200 cm^{-1} (COOH). [c] See Experimental. [d] IR spectrum (Nujol): 745, 813, 833, 870 (4 and 2 adjacent and solitary Ar—H), 1259, 1319 (COOH), 1490, 1588, 1608 (Ar), 1680 (Ar—COOH), 2565, 2660 cm^{-1} (COOH). [e] IR spectrum: 764, 845, 900 (4 and 2 adjacent and solitary

Maleates of bases *Ia* and *Ib* and methanesulfonates of bases *Ic* and *IIb* were evaluated pharmacologically from the point of view of expected central depressant and neuroleptic activities. The results are shown in Table II (acute toxicity for mice, rotating-rod test as a criterion of central depressant activity and catalepsy test on rats as a criterion of neuroleptic activity). For comparison, the table includes octoclothepin[36] (*I*, R^1 = H, R^2 = Cl) and further the 7-fluoro derivative of octoclothepin[1] (*I*, R^1 = F, R^2 = Cl). It follows from the values in the table that substitution of the hydrogen atom in position 7 of the octoclothepin molecule with a methoxy or a trifluoromethyl group has an unfavourable effect on activity; toxicity is substantially reduced but depressant activity is by at least an order of magnitude weaker than with octoclothepin and, the same holds for cataleptic activity. Enamine *IIb* with a trifluoromethyl in position 7 is rather uninteresting. The most interesting compound is the 7-fluoro-8-methyl derivative *Ic* which is comparable in its efficacy with the 7-fluoro derivative of octoclothepin but it is more toxic and its effects disappear within 24 h of administration (no indication of protracted effect).

TABLE I

(*Continued*)

Ar—H), 1133, 1184, 1315 (Ar—CF_3), 1475, 1570, 1582 (Ar), 2280 cm^{-1} (R—CN). [f] ^{1}H-NMR spectrum (ZKR-60): δ 8·60 (bs, disappears after D_2O, 1 H, COOH), 6·80—7·50 (m, 7 H, Ar—H), 3·74 (s, 2 H, $ArCH_2CO$). [g] The method was modified by dissolving the starting *VIIIa* in a mixture of ethanol and benzene (4 : 3). [h] IR spectrum (Nujol): 763, 897 (4 adjacent and solitary Ar—H), 1040 (CHOH in a cycle), 1246, 1289 ($ArOCH_3$), 1488, 1499, 1587 (Ar), 3300, 3370 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 7·40 (s, 1 H, 9-H), 7·40 (mcd, 1 H, 4-H), 7·00—7·30 (m, 3 H, 1,2,3-H_3), 6·89 (s, 1 H, 6-H), 5·03 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·80 (s, 3 H, OCH_3), 3·62 and 3·26 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). 2·10 (s, 1 H, OH). [i] The method was modified by dissolving the starting *VIIIb* in a 3 : 1 mixture of ethanol and dioxane. [j] IR spectrum (Nujol): 752, 762, 908 (4 adjacent and solitary Ar—H), 1069, 1076 (CHOH in a ring), 1129, 1143, 1318, 1354 (Ar—CF_3), 3495 cm^{-1} (OH); ^{1}H-NMR spectrum (ZKR-60): δ 7·00—7·90 (m, 6 H, Ar—H), 5·35 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·70 and 3·30 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·14 (bs, disappears after D_2O, 1 H, OH). [k] The compound was dried in vacuo at room temperature. [l] IR spectrum: 749, 880 (4 adjacent and solitary Ar—H), 1240, 1290 ($ArOCH_3$), 1493, 1590 (Ar), 2790, 2835 cm^{-1} (N—CH_3); ^{1}H-NMR spectrum: δ 7·63 (s, 1 H, 9-H), 7·47 (mcd, 1 H, 4-H), 7·00—7·30 (m, 3 H, 1,2,3-H_3), 6·88 (s, 1 H, 6-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·82 (s, 3 H, OCH_3), 2·66 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·22 (s, 3 H, NCH_3). [m] IR spectrum (Nujol): 763, 888 (4 adjacent and solitary Ar—H), 1139, 1158, 1366 (Ar—CF_3), 1490, 1576 (Ar), 1620 (COO^-), 1711 cm^{-1} (COOH); ^{1}H-NMR spectrum (ZKR-60, CD_3SOCD_3): δ 7·00—8·00 (m, 6 H, Ar—H), 6·08 (s, 2 H, CH=CH of maleic acid), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·15 and 2·80 (2 m, 8 H, 4 NCH_2 of piperazine), 2·76 (s, 3 H, NCH_3). [n] UV spectrum: λ_{max} 236 nm infl. (log ε 4·31), 265 nm (4·34), 300 nm (3·88); IR spectrum: 761 (4 adjacent Ar—H), 805 (*cis*-CH=CH), 915 (solitary Ar—H), 1138, 1162, 1295 (Ar—CF_3), 1600 cm^{-1} (Ar). [o] Hemihydrate. [p] Monohydrate. [q] UV spectrum: λ_{max} 270 nm (log ε 4·34), 319 nm (4·10); IR spectrum (Nujol): 752, 880 (4 adjacent and solitary Ar—H), 1145, 1184, 1230 (Ar—CF_3), 1537, 1586, 1613 (Ar), 3300 cm^{-1} (H_2O).

TABLE II

Pharmacological Properties of the Piperazine Derivatives Prepared (in mg/kg on oral administration)

Compound[a]	Code No VÚFB-	Acute toxicity LD_{50}[b]	Rotating rod ED_{50}[c]	Catalepsy ED_{50}[d]
Ia-2HM	10·703	375	52	>50[e]
Ib-M	10·511	>500[f]	22	30
Ic-2MS[g]	12·327	270	3·8[h]	8·2
IIb-MS[i]	10·528	[j]	50	<50[k]
I, R^1 = H, R^2 = Cl[l]		78	2·2	4·3
I, R^1 = F, R^2 = Cl[m]		>1 000	7·0	5·5

[a] HM hydrogen maleate, M maleate, MS methanesulfonate; the substances were administered in the form of salts but the doses given were calculated for bases. [b] Mean lethal doses in mice. [c] Mean effective doses bringing about disturbance of coordination (ataxia) in mice. [d] Mean effective doses bringing about catalepsy in rats. [e] The dose given was cataleptic only in 20% of animals. [f] The dose given was lethal for 20% of animals. [g] Hemihydrate. [h] In the test of influencing the locomotor activity in mice by the photo-cell method, the dose D_{50} decreasing the activity to 50% of the control value was 3·1 mg/kg (in the interval of 1 h after administration). [i] Monohydrate. [j] The toxicity not estimated. [k] The dose given was cataleptic for 60% of animals. [l] Octoclothepin.[36] [m] 7-Fluoro derivative of octoclothepin[1].

Compounds *Ia*, *Ic*, *IIb* were tested for antimicrobial activity in tests *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this institute). The results are shown in the form of minimum inhibitory concentrations (μg/ml) unless they were higher than 100 μg/ml: *Streptococcus β-haemolyticus*, *Ic* 25; *Streptococcus faecalis*, *Ia* 100, *Ic* 50; *Staphylococcus pyogenes aureus*, *Ic* 25; *Mycobacterium tuberculosis* H37Rv, *Ia* 50, *Ic* 6·25; *Saccharomyces pasterianus*, *Ia* 100, *Ic* 50, *IIb* 1·5; *Trichophyton mentagrophytes*, *Ia* 50, *Ic* 50, *IIb* 6·2; *Candida albicans*, *Ia* 100, *IIb* 50; *Aspergillus niger*, *IIb* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at 0·5 Torr over P_2O_5 at room temperature or at 62°C. The UV spectra (in methanol) were registered in a Unicam SP 8000 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) for the most part in a Tesla BS 487C (80 MHz) spectrometer, occasionally in a Zeiss ZKR 60 (60 MHz) spectrometer. ^{19}F-NMR spectra (in $CHCl_3$, δ $CFCl_3$ = 0) were registered in the Tesla BS 487C apparatus and mass spectra in a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of alumina. Analyses of all the compounds *I*—*XI* are shown in Table I.

5-Bromo-2-chloroanisol (*XIIa*)

A solution of 20·2 g 2-amino-5-bromoanisol[8] (m.p. 58—61°C) in a mixture of 50 ml concentrated hydrochloric acid and 50 ml water was diazotized for 30 min at 0—4°C with a solution of 7·5 g $NaNO_2$ in 20 ml water. After further 15 min of stirring the solution of diazonium salt was combined with a solution of 13·5 g CuCl in 40 ml hydrochloric acid, the mixture was stirred for 10 min at room temperature and for 15 min in a boiling-water bath. The product was steam-distilled (1 litre of distillate) and the distillate was extracted with benzene. The extract was washed with 5% NaOH, 1M-HCl and water, dried with Na_2SO_4 and distilled; 16·6 g (75%), b.p. 114—116°C/ /9 Torr. The analytical product boiled at 114°C/9 Torr and melted at 27—28°C. For C_7H_6BrClO (221·5) calculated; 37·96% C, 2·73% H, 36·08% Br, 16·01% Cl; found: 37·67% C, 2·50% H, 36·00% Br, 15·99% Cl. Ref.[9] reports a b.p. of 128—130°C/12 Torr.

In one larger batch, crude 2-amino-5-bromoanisol[8] (172 g) was used and it did not crystallize. Processing produced 116 g (64%) *XIIa* boiling at 137—142°C/25 Torr and a distillation residue which was recrystallized from a mixture of benzene and light petroleum; 12·5 g, m.p. 99—100°C. The compound was identified as 3,5-dibromo-2-chloroanisol (*XIV*) for which ref.[10] reports a m.p. of 102·5°C.

4-Chloro-3-methoxythiophenol (*XIIIa*)

A solution of 88·6 g *XIIa* in 160 ml tetrahydrofuran was added dropwise over a period of 90 min to 10·7 g Mg stirred in 80 ml tetrahydrofuran. The mixture was refluxed for 1·5 h and then, at 22—25°C over a period of 60 min, 10·5 g powdered sulfur was added. The mixture was stirred for 30 min and left to stand overnight. On the following day it was refluxed for 60 min and poured on 600 g ice with water and 120 ml hydrochloric acid and then extracted with benzene. The extract was shaken with excess 10% NaOH, the alkaline extract was separated, acidified with hydrochloric acid and re-extracted with benzene. After drying, benzene was evaporated an the residue distilled under reduced pressure; 40·5 g (58%), b.p. 149—153°C/27 Torr. For C_7H_7ClOS (174·7) calculated: 48·14% C, 4·04% H, 20·30% Cl, 18·36% S; found: 48·53% C, 4·16% H, 20·47% Cl, 18·04% S.

4-Chloro-3-trifluoromethylthiophenol (*XIIIb*)

A Grignard reagent was prepared in a reaction of 25·6 g Mg with 248·3 g 5-bromo-2-chlorobenzotrifluoride[22] (b.p. 81—83°C/13 Torr) in 500 ml ether. The mixture was refluxed for 1·5 h, cooled to 24°C, and 23·9 g powdered sulfur was added over 1 h under stirring. On the following day, 400 ml dilute (1 : 1) hydrochloric acid was added dropwise, the product was extracted from the separated ether phase with excess 10% NaOH whence it was released with hydrochloric acid and extracted with benzene. Processing of the extract yielded 130 g (64%) product boiling at 99—102°C/ /20 Torr. For analysis we used a redistilled product boiling at 98—99°C/18 Torr. IR spectrum: 825, 880 (2 adjacent and solitary Ar—H), 1115, 1180, 1320 (Ar—CF_3), 1475, 1570, 1590 (Ar), 2600 (SH), 3100 cm^{-1} (Ar). ^{1}H-NMR spectrum (ZKR 60): δ 7·48 (bs, 1 H, 2-H), 7·23 (m, 2 H, 5,6-H_2), 3·46 (s, disappears after D_2O, 1 H, SH). For $C_7H_4ClF_3S$ (212·6) calculated: 39·54% C, 1·89% H, 16·67% Cl, 15·08% S; found: 38·86% C, 1·61% H, 16·80% Cl, 15·38% S. Literature[23] described another method of preparation of *XIIIb*; b.p. 83·5°C/8 Torr was given.

3-Fluoro-4-methyl-thiophenol (*XIIIc*)

Dilute (1 : 1) hydrochloric acid (160 ml) was combined under stirring with 50 g 4-amino-2-fluorotoluene[33] (b.p. 96—98°C/15 Torr), the suspension thus formed was cooled to 0—3°C and at that

temperature it was diazotized under stirring over 60 min with a solution of 28 g $NaNO_2$ in 65 ml water. Under cooling it was stirred for further 30 min and then, over a period of 2 h, a cold solution of diazonium salt was added dropwise to a solution of 76 g potassium ethyl xanthate in 100 ml water, the temperature being maintained at 40—45°C. The mixture was stirred, left overnight at room temperature and then extracted with ether. The extract was washed with water and ether was evaporated. The residue was dissolved in 240 ml ethanol, the solution was heated to boiling temperature and then gradually 96 g KOH was added to as to maintain spontaneous boiling. Refluxing was continued for 10 h. Ethanol was evaporated, the residue was dissolved in 300 ml water and the solution was washed with ether. The aqueous solution was then combined with 8·0 g zinc powder and the mixture was acidified under cooling and stirring with 160 ml hydrochloric acid. The liberated thiol was isolated by extraction with ether and the extract was dried with Na_2SO_4 and distilled; 29·5 g (65%), b.p. 88—90°C/26 Torr. For analysis it was redistilled; b.p. 80—81°C/18 Torr, m.p. about 30°C. For C_7H_7FS (142·2) calculated: 59·13% C, 4·97% H, 13·36% F, 22·54% S; found: 59·09% C, 5·05% H, 13·66% F, 22·28% S.

2-(4-Chloro-3-trifluoromethylphenylthio)benzoic Acid (*IIIb*) (Method *A*)

A solution of 117 g KOH in 1 200 ml water was combined at 50°C with 130 g *XIIIb* and, after 10 min of stirring, with 4·0 g "molecular" copper and 152 g 2-iodobenzoic acid[7]. The mixture was refluxed for 7·5 h, filtered while warm and the filtrate was acidified with hydrochloric acid. On standing overnight in a refrigerator a product was precipitated which was then filtered and recrystallized from ethanol; 149 g (73%), m.p. 184—187°C. The analytical product was obtained by repeated crystallization from ethanol, m.p. 187—189°C. ^{1}H-NMR spectrum (ZKR-60, CD_3SOCD_3): δ 6·84 (mcd, 1 H, 6-H in a phenylthio group), 7·00—8·10 (m, 6 H, remaining Ar—H).

2-(4-Chloro-3-methoxyphenylthio)benzyl Alcohol (*IVa*) (Method *B*)

A suspension of 54·3 g *IIIa* in 375 ml benzene was combined under stirring at 10—15°C over 60 min with 140 ml 55% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate. The mixture was stirred for 3 h at room temperature, combined with 220 ml 10% NaOH (external cooling, temperature below 15°C) added dropwise and stirred for 1 h. The benzene layer was separated and the aqueous one extracted with benzene. The combined benzene extracts were dried with Na_2SO_4 and evaporated. The residue was recrystallized from a mixture of 100 ml benzene and 100 ml light petroleum; 47·2g (91%), m.p. 78—79°C. Analytical sample, m.p. 78—80°C. IR spectrum (Nujol): 770, 804, 874 (4 and 2 adjacent and solitary Ar—H), 1 030 (CH_2OH), 1 270 ($ArOCH_3$), 1 487, 1 578 (Ar), 3 568 cm^{-1} (OH).

2-(4-Chloro-3-trifluoromethylphenylthio)benzyl Alcohol (*IVb*)

Sodium borohydride (10·3 g) was added under stirring in nitrogen atmosphere to a suspension of 81 g *IIIb* in 125 ml tetrahydrofuran; over a period of 30 min at 20°C, 32 ml boron trifluoride etherate in 20 ml tetrahydrofuran was added dropwise. The mixture was stirred for 3 h at 22 to 24°C. After standing overnight it was decomposed by adding dropwise 50 ml 1·5M-HCl; 50 ml water plus 70 ml benzene was added and the mixture was filtered. The benzene layer was separated from the filtrate, the aqueous one was extracted with benzene. The combined benzene solutions were washed with 10% NaOH and water, dried with Na_2SO_4 and distilled; 66·1 g (85%); b.p. 160—163°C/0·2 Torr. The analytical product was redistilled; b.p. 180—182°C/4·3 Torr.

^{1}H-NMR spectrum (ZKR-60): δ 6·85—7·60 (m, 7 H, Ar—H), 4·54 (s, 2 H, $ArCH_2O$), 2·62 (bs, disappears after D_2O, 1 H, OH).

2-(3-Fluoro-4-methylphenylthio)benzyl Chloride (*Vc*) (Method *C*)

Thionyl chloride (4·7 g) was added dropwise at 10°C to a mixture of 8·4 g *IVc* and 3·2 g pyridine. After standing overnight, it was stirred for 1 h at 40°C, cooled and decomposed by adding dropwise 13 ml water; the whole was stirred for 30 min. The product was isolated by extraction with benzene. The extract was washed with 1M-HCl, 5% NaOH and water, dried with $CaCl_2$ and distilled; 7·94 g (87%), b.p. 172°C/1·2 Tor.

2-(4-Chloro-3-methoxyphenylthio)phenylacetonitrile (*VIa*) (Method *D*)

A mixture of solution of 10·2 g *Va* in 11 ml ethanol and of solution of 2·45 g NaCN in 5 ml water was refluxed for 8 h. Ethanol was then evaporated at reduced pressure, the residue was diluted with water and extracted with benzene. The extract was washed with water, dried with $CaCl_2$ and evaporated. The residue was recrystallized from 15 ml ethanol; 8·83 g (90%), m.p. 76—77·5°C. The analytical sample melted at 78—80°C (ethanol). IR spectrum (Nujol): 749, 809, 878 (4 and 2 adjacent and solitary Ar—H), 1254, 1270 ($ArOCH_3$), 1486, 1580 (Ar), 2255 cm^{-1} (R—CN).

2-(4-Chloro-3-methoxyphenylthio)phenylacetic Acid (*VIIa*) (Method *E*)

A solution of 8·8 g *VIa* in 30 ml ethanol was combined with a solution of 8·25 g KOH in 20 ml water and refluxed for 4 h. Ethanol was then evaporated and acidified with hydrochloric acid. The precipitated crude acid was filtered and recrystallized from a mixture of 10 ml benzene and 25 ml light petroleum; 8·50 g (90%), m.p. 101—104°C. Analytical product, m.p. 103—105°C. IR spectrum: 740, 755, 808, 855, 875 (4 and 2 adjacent and solitary Ar—H), 925, 1237 (COOH), 1476, 1571 (Ar), 1701, 2400—3200 cm^{-1} (COOH).

2-(3-Fluoro-4-methylphenylthio)phenylacetic Acid (*VIIc*)

A solution of 39·3 g KOH in 400 ml water was combined one by one with 29·5 g *XIIIc*, 1·5 g Cu and 54·4 g (2-iodophenyl)acetic acid[35]; the mixture was refluxed under stirring for 10 h, filtered while hot and the filtrate was cooled and acidified with hydrochloric acid. After standing overnight, the precipitated substance was filtered and recrystallized from aqueous ethanol; 44·8 g (78%), m.p. 119—122°C. Analytical product, m.p. 123—124°C (ethanol). IR spectrum (Nujol): 770, 812, 866, 894 (4 and 2 adjacent and solitary Ar—H), 942 (COOH), 1499, 1572 (Ar), 1705, 2565, 2640, 2740 cm^{-1} (COOH). ^{1}H-NMR spectrum: δ 11·20 (bs, 1 H, COOH), 6·60 to 7·50 (m, 7 H, Ar—H), 3·80 (s, 2 H, $ArCH_2CO$), 2·15 (mcs, J = 1·5 Hz, 3 H, Ar—CH_3). ^{19}F-NMR spectrum: δ —116·4 (m).

8-Chloro-7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*VIIIa*)

A solution of 5·50 g *VIIa* in 20 ml toluene was added at 100°C to 45 g polyphosporic acid. The mixture was refluxed under stirring for 3 h, left to cool and decomposed with 80 ml ice-cold water and extracted with benzene. The organic layer was washed with 5% NaOH and water and evaporated after drying. The residue was recrystallized from 35 ml benzene; 4·05 g (78%), m.p. 171—172°C. Analytical product, m.p. 172—173°C. UV spectrum: λ_{max} 227 nm (log ε 4·26), 262 nm (4·41), 324 nm (3·58). IR spectrum: 731, 748, 766, 855 (4 adjacent and solitary Ar—H),

1020, 1240, 1253, 1261 ($ArOCH_3$), 1570 (Ar), 1652 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 8·20 (s, 1 H, 9-H), 7·60 (m, 1 H, 4-H), 7·10—7·50 (m, 3 H, 1,2,3-H_3), 7·05 (s, 1 H, 6-H), 4·34 (s, 2 H, $ArCH_2CO$), 3·96 (s, 3 H, OCH_3).

8-Chloro-7-trifluoromethyldibenzo[*b,f*]thiepin-10(11*H*)-one (*VIIIb*)

Polyphosphoric acid (prepared from 60 g P_2O_5 and 30 ml 85% H_3PO_4) was combined with 150 ml *o*-dichlorobenzene and 8·7 g *VIIb*. The mixture was refluxed under stirring for 16 h (a 200°C bath), cooled and decomposed with ice-cold water; the organic phase was separated, washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated *in vacuo*. The residue (4·7 g) crystallized from benzene to 0·68 g (9·5%) red substance melting at 221—222°C which was identified as the enol-lactone of 8-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one-9-carboxylic acid (*XVII*). UV spectrum: λ_{max} 262·5 nm (log ε 4·35), infl. 280 nm (4·21), infl. 291 nm (4·15), 325:5 nm (4·04), 403 nm (3·45). IR spectrum: 747, 762, 837, 851, 881 (Ar—H), 1470, 1586 (Ar), 1792 cm^{-1} (=C—OCO—Ar, lactone). Mass spectrum (*m/e* 286·8) proves the empirical formula of $C_{15}H_7 . ClO_2S$. For $C_{15}H_7ClO_2S$ (286·8) calculated: 62·83% C, 2·46% H, 12·36% Cl, 11·18% S; found: 62·84% C, 2·42% H, 12·36% Cl, 10·68% S.

Evaporation of the mother liquor after the preceding substance and crystallization of the residue from cyclohexane yielded 3·44 g (40%) ketone *VIIIb*, m.p. 137—139°C. UV spectrum: λ_{max} 225 nm (log ε 3·83), 270 nm (3·61), 347 nm (3·27). IR spectrum: 756, 903 (4 adjacent and solitary Ar—H), 1124, 1152, 1167, 1364 (CF_3), 1474 (Ar), 1683 cm^{-1} (ArCO). ^{1}H-NMR spectrum (ZKR 60): δ 8·20 (s, 1 H, 9-H), 7·85 (s, 1 H, 6-H), 7·00—7·60 (m, 4 H, 1,2,3,4-H_4), 4·30 (s, 2 H, $ArCH_2$).

Acidification of the alkaline aqueous phase (obtained from washing the dichlorobenzene solution) with hydrochloric acid yielded 2·57 g crude acid fraction which was crystallized from aqueous ethanol or from a mixture of benzene and light petroleum and yielded pure 8-chlorodibenzo[*b,f*]-thiepin-10(11*H*)-one-7-carboxylic acid (*XVI*), m.p. 264—268°C. UV spectrum: λ_{max} 222 nm (log ε 4·28), 247 nm (4·34), 349 nm (3·57). IR spectrum: 757, 875 (4 adjacent and solitary Ar—H), 918, 1231, 1344 (COOH), 1461, 1525 (Ar), 1682, 1710, 1736 (ArCO, ArCOOH and ArCO...HO), 3000 cm^{-1} (COOH). IR spectrum (dioxane): 1700 and 1748 cm^{-1} (COAr and COOH). The mass spectrum indicates by *m/e* of 304 the empirical formula of $C_{15}H_9ClO_3S$. For $C_{15}H_9ClO_3S$ (304·8) calculated: 59·11% C, 2·98% H, 11·63% Cl, 10·54% S; found: 59·00% C, 3·01% H, 11·45% Cl, 10·68% S. Mother liquor after acid *XVI* was evaporated and crystallized from a mixture of benzene and light petroleum to a small amount of acid *VIIIb*, m.p. 128—130°C.

8-Chlorodibenzo[*b,f*]thiepin-10(11*H*)-one-9-carboxylic Acid (*XVIII*)

A mixture of 0·27 g *XVII*, 20 ml 10% NaOH and 10 ml ethanol was refluxed for 15 min. After evaporation of ethanol it was diluted with some water and acidified with hydrochloric acid. Filtration, washing with water and drying yielded 0·25 g crude acid which was recrystallized from benzene to melt at 200—202°C. UV spectrum: λ_{max} 224 nm infl. (log ε 4·23), 244 nm (4·14), 270 nm (infl.) (3·95), infl. 295 nm (3·63), 341 nm (3·57). IR spectrum: 750, 826 (4 and 2 adjacent Ar—H), 946, 1186, 1331 (COOH), 1473, 1560 (Ar), 1684 (COAr), 1710 (ArCOOH), 3070 cm^{-1} (COOH). ^{1}H-NMR spectrum (ZKR-60, C_5D_5N): δ 13·20 (bs, 1 H, COOH), 6·90—7·55 (m, 6 H, Ar—H), 4·08 (s, 2 H, $ArCH_2CO$). The mass spectrum (*m/e* 304) indicates an empirical formula of $C_{15}H_9ClO_3S$ but it is not identical with the spectrum of acid *XVI*. For $C_{15}H_9ClO_3S$ (304·8) calculated: 59·11% C, 2·98% H, 11·63% Cl, 10·54% S; found: 59·38% C, 3·05% H, 11·71% Cl, 10·79% S.

7-Fluoro-8-methyldibenzo[*b,f*]thiepin-10(11*H*)-one (*VIIIc*) (Method *F*)

A mixture of 250 g polyphosphoric acid and 44·8 g *VIIc* was heated under stirring for 4 h to 120—125°C. It was cooled and decomposed with 400 g of a mixture of ice and water and the product was extracted with benzene. The extract was washed with 5% NaOH and water, dried and evaporated. The residue was recrystallized from 250 ml ethanol; 33·1 g (79%), m.p. 87—89°C; analytical sample, m.p. 88—89°C. UV spectrum: λ_{max} 241 nm (log ε 4·30), infl. 261 nm, 323 nm (3·55). IR spectrum: 753, 770, 880 (4 adjacent and solitary Ar—H), 1560, 1614 (Ar), 1674 cm^{-1} (COAr). ^{1}H-NMR spectrum: δ 8·00 (d, $J_{(H-F)}$ = 8·0 Hz, 1 H, 9-H), 7·58 (mcd, 1 H 4-H), 7·00—7·40 (m, 4 H, 1,2,3,6-H_4), 4·30 (s, 2 H, $ArCH_2CO$), 2·18 (mcs, J = 1·0 Hz, 3 H, Ar—CH_3).

7-Fluoro-8-methyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IXc*) (Method *G*)

A solution of 1·33 g $NaBH_4$ in 12 ml water containing 0·2 ml 10% NaOH was added dropwise at 70°C under stirring to a solution of 25·8 g *VIIIc* in 475 ml ethanol. The mixture was then refluxed for 4 h, some ethanol was evaporated and, after cooling, it was decomposed with 150 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated; 21·4 g (82%), m.p. 57—60°C (light petroleum). Analytical sample, m.p. 61—64°C (hexane). IR spectrum (Nujol): 760, 865, 893 (4 adjacent and solitary Ar—H), 1019 (CHOH in a ring), 1482, 1561, 1610 (Ar), 3170, 3230 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 6 H, Ar—H), 5·15 (m, 1 H, Ar—CH—O), 3·68 and 3·28 (2 dd, J = 14·0; 4·0 Hz and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·18 (mcs, J = 1·0 Hz, 3 H, Ar—CH_3), 2·10 (d, J = 7·0 Hz, 1 H, OH). ^{19}F-NMR spectrum: δ —119·2 (m).

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

A mixture of 5·88 g *IXb* and 3·1 g $SOCl_2$ was left to stand overnight at room temperature and refluxed on the following day for 1 h on a boiling-water bath. After adding 20 ml chloroform, the volatile fractions were evaporated *in vacuo* at 25°C and the residue was recrystallized from acetone; 5·62 g (91%), m.p. 100—102°C. ^{1}H-NMR spectrum (ZKR 60): δ 7·77 and 7·66 (2 s, 2 H, 6,9-H_2), 7·00—7·60 (m, 4 H, 1,2,3,4-H_4), 6·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·58 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$).

10-Chloro-7-fluoro-8-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*Xc*) (Method *H*)

A solution of 16·2 g *IXc* in 100 ml benzene with 4·0 g $CaCl_2$ was saturated at room temperature with anhydrous hydrogen chloride. After standing overnight it was filtered, the filtrate was evaporated *in vacuo* and the residue was recrystallized from acetone; 14·1 g (81%), m.p. 110—111°C. Further crystallization yielded an analytical product melting at 110—112°C. ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 6 H, Ar—H), 5·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·62 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·15 (mcs, J = 1·0 Hz, 3 H, $ArCH_3$). ^{19}F-NMR: δ —117·9 (m).

2-Chloro-3-methoxydibenzo[*b,f*]thiepin (*XIa*)

Thionyl chloride (1·2 ml) was added to a solution of 2·93 g *IXa* in 20 ml benzene, the mixture was stirred for 2 h without heating and for 2 h on a 60°C bath. Then it was evaporated *in vacuo* and the residue was dissolved in water and again evaporated *in vacuo*. The residue was recrystallized from acetone; 0·89 g (32%), m.p. 113—115°C; analytical sample, m.p. 114—117°C. UV

spectrum: λ_{max} 232·5 nm (log ε 4·50), 266 nm (4·49), 293 nm (3·79), infl. 340 nm (3·72). IR spectrum (Nujol): 752, 889 (4 adjacent and solitary Ar—H), 1249 ($ArOCH_3$), 1488, 1586 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·20—7·50 (m, 4 H, 6,7,8,9-H_4), 7·18 (s, 1 H, 1-H), 7·03 (s, 1 H, 4-H), 6·97 and 6·80 (ABq, J = 12·0 Hz, 2 H, CH=CH), 3·80 (s, 3 H, OCH_3).

7-Fluoro-8-methyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo [*b,f*]thiepin (*Ic*) (Method *J*)

A mixture of 3·70 g *Xc*, 4 ml chloroform and 4·2 ml 1-methylpiperazine was refluxed for 7 h in a 115°C bath. Chloroform was then evaporated *in vacuo*, the residue was divided by shaking between 100 ml benzene and 20 ml water and the organic phase was then washed with water and shaken with excess 3M-HCl. The acid aqueous phase was made alkaline with NH_4OH and extracted with benzene. After drying with K_2CO_3 the extract was evaporated to dryness; 3·66 g (82%) crude base which was purified by crystallization from ethanol, m.p. 109—111°C. ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 (def. t., 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (def. t., 4 H, $CH_2N^4CH_2$ of piperazine), 2·22 (s, 3 H, NCH_3), 2·12 (mcs, J = 1·0 Hz, 3 H, $ArCH_3$). Neutralization of the base with methanesulfonic acid in ethanol with an addition of ether gave dimethanesulfonate which crystallizes from a mixture of 95% ethanol and ether as hemihydrate and which melts at 170—172°C.

The benzene solution was washed with water, dried and evaporated. The residue was repeatedly crystallized from ethanol to yield 3-fluoro-2-methyldibenzo[*b,f*]thiepin (*XIc*) melting at 95—97°C. UV spectrum: λ_{max} 261 nm (log ε 4·43), 293 nm (3·62), infl. 322·5 nm (3·02). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 6 H, Ar—H), 6·87 (s, 2 H, CH=CH), 2·12 (mcs, J = 2·0 Hz, 3 H, $ArCH_3$). ^{19}F-NMR: δ —118·2 (m).

8-Chloro-7-methoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*IIa*) (Method *K*)

A solution of 1·76 g $TiCl_4$ in 15 ml benzene was added dropwise over 5 min under stirring to a mixture of 5·06 g *VIIIa*, 45 ml benzene and 8·2 g 1-methylpiperazine. The mixture was refluxed for 25 h, cooled, decomposed with 70 ml water, the precipitated substance was filtered and washed with benzene. The benzene phase was separated from the filtrate, washed with water, dried with Na_2SO_4 and filtered with charcoal. Benzene was distilled at reduced pressure and the nonhomogeneous residue was repeatedly crystallized from ethanol; 4·33 g (67%), m.p. 143—147°C; analytical product, m.p. 144—146°C. UV spectrum: λ_{max} 250·5 nm (log ε 4·35), 272 nm (4·20), infl. 315 nm (3·86). IR spectrum (Nujol): 764, 897 (4 adjacent and solitary Ar—H), 1225, 1253 ($ArOCH_3$), 1494, 1590, 1612 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·59 (s, 1 H, 9-H), 7·40 (m, 1 H, 4-H), 7·18 (m, 3 H, 1,2,3-H_3), 7·05 (s, 1 H, 6-H), 6·25 (s, 1 H, Ar—CH=), 3·85 (s, 3H, OCH_3), 2·94 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·52 (def. t., 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). Neutralization of the base with maleic acid in ethanol yielded a maleate melting at 210—213°C (ethanol).

2-Chloro-3-hydroxydibenzo[*b,f*]thiepin (*XV*)

A solution of 2·5 g BBr_3 in 5 ml dichloromethane was added dropwise over 5 min under stirring and cooling to a solution of 1·12 g *Ia* in 8 ml dichloromethane and the mixture was stirred for 5 h at room temperature. After standing overnight, 5 ml ethanol was added and the suspension was stirred for 8 h. After addition of 20 ml ether the precipitated compound was filtered (1·28 g) and dissolved in boiling ethanol with some water added. The solution was evaporated *in vacuo*, the residue was decomposed with 5% $NaHCO_3$ and extracted with ether. Evaporation of the extract yielded only 0·30 g product melting at 84—86°C (cyclohexane) which was identified as *XV*. UV

spectrum: λ_{max} 231 nm (log ε 4·40), 267 nm (4·43), infl. 297 nm (3·79), infl. 335·5 nm (3·33). IR spectrum: 755 (4 adjacent Ar—H), 790 (*cis*-CH=CH), 893 (solitary Ar—H), 1 200, 1 279 (Ar—OH), 1 484, 1 552, 1 591, 3 065, 3 110 (Ar), 3 470 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00—7·50 (m, 6 H, Ar—H), 6·94 and 6·75 (ABq, J = 12·0 Hz, 2 H, CH=CH), c. 5·55 (bs, 1 H, OH). For $C_{14}H_9ClOS$ (260·7) calculated: 64·50% C, 3·48% H, 13·60% Cl, 12·30% S; found: 63·92% C, 3·70% H, 13·79% Cl, 12·13% S.

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