NONCATALEPTIC POTENTIAL NEUROLEPTICS; 2-HALOGENO-10-PIPERAZINODIBENZO[*b*,*f*]THIEPINS*

J.O.JÍLEK, K.ŠINDELÁŘ, M.RAJŠNER, A.DLABAČ, J.METYŠOVÁ, Z.VOTAVA, J.POMYKÁČEK and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

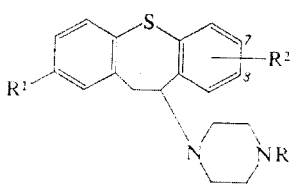
Received November 8th, 1974

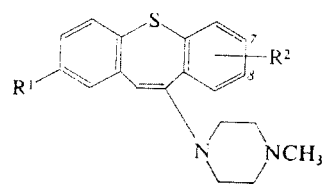
10-Piperazinodibenzo[*b*,*f*]thiepin derivatives *I*—*VIII* substituted in position 2 with an atom of fluorine (*a*), chlorine (*b*), bromine (*c*) and iodine (*d*) were synthesized *via* intermediates *IX*—*XVI*, the 2-chloro substitution being combined with the presence of fluorine in position 7 (*e*) or 8 (*f*). By their high degree of central depressant activity with practically no cataleptic effect, most of the compounds prepared resemble "clozapine"; outstanding in this respect are *Ib*, *Ic*, *Id* and *IIb*. The 2-chloro-7-fluoro derivatives *Ie*, *IIe*, *IIIe* and *VIIIe* display an extraordinarily low toxicity. Cataleptic activity was preserved only by substances containing fluorine in position 2 (*Ia*) or 8 (*If*) as well as by all the enamines prepared (*VIIIb*, *VIIIe*, *VIIIf*). For detailed investigation, 2-chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*, *f*]thiepin (*IIb*) was selected as a noncataleptic potential neuroleptic.

Until recently, our systematic pharmacochemical studies in the series of 10-piperazinodibenzo[*b*,*f*]thiepin derivatives were focussed on finding neuroleptics with the highest possible central depressant and cataleptic activity. It was then found that the requirements are best met by 8-substitution derivatives, among them especially the 8-halogeno derivatives[1-6]. In the case of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (octoclothepin)[1-3,7], neuroleptic and antipsychotic efficacy were confirmed even clinically[8] and the preparation has been used therapeutically. In the present communication we concentrate on the 2-halogeno derivatives of 10-piperazino dibenzo[*b*,*f*]thiepins where, in contrast with the preceding group, a very low cataleptic activity is to be expected together with preserved central depressant activity and where clinically they might resemble the properties of dibenzo[*b*,*e*]-1,4-diazepine derivative clozapine[9,10], *i.e.* an antipsychotic activity free of the extrapyramidal side effects. The paper is a sequel to two recent communications of this series[11,12] where analogous 2-methoxy, 2-methylthio, 2-(dimethylsulfamoyl), 2-trifluoromethyl, 2-acetamido, 2-amino and 2-acetyl derivatives were taken up; in the previous parts of the series the new general approach has been explained and it is thus not presented here.

* Part LXXXVIII in the series Neurotropic and Psychotropic Agents; Part LXXXVII: This Journal *40*, 2667 (1975).

The primary objective was the synthesis of methylpiperazine derivatives *I*, their substituent R^1 in position 2 being fluorine (series *a*), chlorine (series *b*), bromine (series *c*), and iodine (series *d*). The work has been further extended to 2-chloro-7-fluoro derivatives (series *e*) and 2-chloro-8-fluoro derivatives (series *f*). The synthesis of these compounds proceeded mostly according to the frequently used pattern[2,5], *i.e. via* the intermediates *IX*–*XVI*. By the reaction of 2-iodo-5-halogenobenzoic acids with the corresponding thiophenols in boiling aqueous potassium hydroxide in the presence of copper (method *A*), acids *IX* were obtained to be reduced to alcohols *X* with lithium aluminium hydride in ether (method *B*) or sodium dihydridobis(2-methoxyethoxy)aluminate in benzene[13,14]. Conversion of alcohols *X* to chlorides *XI* was carried out with the aid of thionyl chloride in boiling benzene (method *C*), or without a medium in the presence of pyridine. Chlorides *XI* were converted to nitriles *XII* in a reaction with sodium cyanide in aqueous ethanol or in dimethylformamide. Hydrolysis of the nitriles to acids *XIII* was done with potassium hydroxide in aqueous ethanol (method *D*). A general method of preparing ketones *XIV* was the cyclization of acids *XIII* with polyphosphoric acid at 120–150°C (method *E*); the method was not used for the synthesis of ketone *XIVc* and *XIVd* as will be shown below. Ketones *XIV* were reduced to alcohols *XV* always with sodium borohydride (method *F*) either in aqueous ethanol, in absolute ethanol or in aqueous dioxane. Transformation to chlorides *XVI* was done by means of hydrogen chloride (method *G*) in benzene or in chloroform. Chlorides *XVI* were converted to the piperazine derivatives *I*–*III* and *V* by substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-(3-hydroxypropyl)piperazine[15] and 1-(ethoxycarbonyl)piperazine[16] (method *H*); small amounts of dibenzo[*b*,*f*]thiepins *XVII* were isolated as the products of elimination proceeding in parallel. In two cases, the amino alcohols *II* were esterified by treatment with decanoyl chloride[17] in chloroform (method *J*) to the corresponding decanoates (see[18]). In three cases,





VIII

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 = $COOC_2H_5$
VI, R = H
VII, R = CH_2CH_2CN

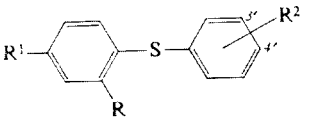
Formulas in series: *a*, R^1 = F, R^2 = H; *b*, R^1 = Cl, R^2 = H; *c*, R^1 = Br, R^2 = H; *d*, R^1 = I, R^2 = H; *e*, R^1 = Cl, R^2 = 7(3′)-F; *f*, R^1 = Cl, R^2 = 8(4′)-F.

reactions of ketones *XIV* with 1-methylpiperazine in boiling benzene in the presence of titanium tetrachloride (method *K*) led to the corresponding enamines *VIII* (see[5]).

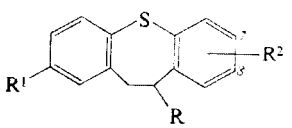
In series *a*, work proceeded from 5-fluoro-2-iodobenzoic acid, the preparation of which has been recently described[19]. The entire synthesis was based on conventional methods and led to the desired methylpiperazino derivative *Ia*; the elimination product was 2-fluorodibenzo[*b*,*f*]thiepin (*XVIIa*), also described here before[2]. In series *b* some work has been done earlier[20] so that the immediate starting products here were ketone *XIVb* and chloride *XVIb*. Preparation of the methylpiperazino derivative *Ib* (ref.[20]) was improved by using method *H* and its methanesulfonate was prepared here. Using conventional methods, amino alcohol *IIb*, decanoate *IVb* and enamine *VIIIb* were prepared in this series (see also[21]).

In series *c*, the conventional procedure was not used; ketone *XIVc* was prepared from 2-aminodibenzo[*b*,*f*]thiepin-10(11*H*)-one[12] by Sandmeyers's reaction. Further procedure led to the intermediates *XVc* and *XVIc*, the final product of preparation being the methylpiperazino derivative *Ic*; the 2-bromodibenzo[*b*,*f*]thiepin (*XVIIc*) isolated as a by-product was found to be identical with the product prepared before[2]. Likewise, in series *d*, the starting compound was the above mentioned amino ketone[12] which was diazotized and converted to the iodo ketone *XIVd* by treatment with potassium iodide in the presence of iodine (for analogy see[4]). Like in the preceding case, the final product prepared was the methylpiperazino derivative *Id*; the 2-iodo-dibenzo[*b*,*f*]thiepin (*XVIId*) formed simultaneously was described in an earlier paper[4].

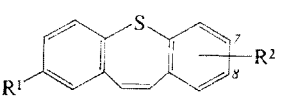
Most extensive work was done in series *e*, which was due to the pharmacological attractiveness of the isomeric 8-chloro-3-fluoro derivatives with a similar juxtaposed



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



XIV, R = =O
XV, R = OH
XVI, R = Cl



XVII

position of the two halogen atoms[19]. The parent compound here was 5-chloro--2-iodobenzoic acid[20] which was first combined with 3-fluorothiophenol[22]. The synthesis proceeded by using conventional methods up to the methylpiperazino derivative *Ie*; in the last stage, elimination gave rise to a small amount of 2-chloro--7-fluorodibenzo[*b*,*f*]thiepin (*XVIIe*), recently prepared here in a different context[19]. In series *e*, method *H* was further applied to the preparation of amino alcohols *IIe* and *IIIe*, and of carbamate *Ve*. Compound *IIe* was converted to the decanoate *IVe* and carbamate *Ve* was hydrolyzed to the secondary amine *VIe* which added acrylonitrile to yield *VIIe* (for analogy see[6]). Enamine *VIIIe* was prepared by using method *K*.

Finally in series *f*, the starting compound was 5-chloro-2-(4-fluorophenylthio)-benzoic acid (*IXf*), the preparation of which was recently described[19]. The synthesis proceeded by conventional methods described before. Nitrile *XIIf* has not been isolated in the pure state and was directly hydrolyzed to acid *XIIIf*. The final product was the methylpiperazino derivative *If*, a "quasi"-symmetrical position isomer of the recently prepared 2-fluoro derivative of octoclothepin[19]; the elimination product in the last stage was 2-chloro-8-fluorodibenzo[*b*,*f*]thiepin[19] (*XVIIf*). Also prepared in this series was the enamine *VIIIf*.

All the compounds prepared are collected together with the usual experimental data in Table I. After termination of the present work, a patent application appeared[23] where some of our intermediates of series *a*, *c* and *d* are described but without data on yields, analyses and with only scant characteristics; the appropriate references are shown in the experimental section or in the notes to Table I.

In the form of salts the compounds prepared were subjected to pharmacological tests when they were applied first of all *per os*. The acute toxicity for mice was estimated and is expressed as the mean lethal dose LD_{50}. The incoordinating effect was examined in the rotating-rod test in mice and is expressed as the mean effective dose ED_{50} bringing about ataxia; this is taken as the indicator of central depressant activity. Finally, as a criterion of neuroleptic efficacy, the cataleptic effect on rats was estimated (for pharmacological methods see[24]), this being expressed as the mean effective dose ED_{50}. The numerical data on toxicity and efficacy (in mg/kg) are collected in Table II and refer to the corresponding bases. The table also includes clozapine[9] and octoclothepin[7] for reference.

The table permits to draw several conclusions on the relationship between structure and pharmacodynamic properties.

1) The toxicity of 2-fluoro and 2-chloro derivatives (*Ia Ib, IIb*) is practically the same, being identical with that of octoclothepin; as the size of the halogen is increased toxicity decreases so that the 2-bromo derivative (*Ic*) and especially the 2-iodo derivative (*Id*) are substantially less toxic; the very low toxicity of all the 2-chloro-7-fluoro derivatives (*Ie, IIe, IIIe, VIIIe*) is quite typical; somewhat surprising is the relatively

low toxicity of the enamines (*VIIIb*, *VIIIe*, *VIIIf*) which is at variance with our earlier observations on this type of compounds[5].

2) All the substances display a high degree of central depressant activity where the 2-chloro derivatives *Ib*, *IIb* and *VIIIb*, the 2-bromo derivative *Ic* and the 2-chloro--8-fluoro derivatives *If* and *VIIIf* exceed clozapine as well as octoclothepin; a number of the compounds exhibit a more favourable ratio of toxicity to depressant activity than clozapine (expecially *IIb* and *IIe*).

3) Clear cataleptic efficacy is retained only by the 2-fluoro derivative *Ia*, the 2-chloro-8-fluoro derivative *If* and by all the three enamines (*VIIIb*, *VIIIe*, *VIIIf*). All the other compounds when applied at the high dose of 50 mg/kg are either ineffective or do not yet attain ED_{50}. Some of the compounds at this high dose bring about a deep depression; if there are signs of catalepsy it is not a true cataleptic effect ("pseudocatalepsy"). By the absence of the cataleptic effect and by their high depressant efficacy some of the compounds resemble clozapine (*Ib*, *Ic*, *Id*, *IIb*) so that they may be considered as potential noncataleptic neuroleptics.

2-Chloro-10-[4-(2 hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIb*, succinate VÚFB-10032) was selected for detailed tests, being the most potent depressant of the whole series, with a more favourable relationship between toxicity and depressant activity than with clozapine and with only slight signs of a cataleptic effect at the high *p.o.* dose of 50 mg/kg. The compound potentiates the narcotic effect of thiopental in mice significantly from 0·75 mg/kg *p.o.* on. In the test according to Ther[25] it depresses motor activity in mice (males) at doses of 1–10 mg/kg *p.o.* In male rats at a dose of 100 mg/kg *p.o.* (the compound was administered 60 min before apomorphine) it does not depress chewing brought about by apomorphine; on the other hand, agitation is depressed by this dose with statistical significance (the effect disappears after 2 h). It potentiates the antiapomorphine effect of perphenazine in rats at a dose of 25 mg/kg *p.o.* It has further a procataleptogenic effect in rats when administered together with perphenazine or 30 min before perphenazine. The effect is clear from the dose of 25 mg/kg *p.o.* on. With monkeys a dose of 10 mg/kg does not depress chewing and oral stereotypy after apomorphine but brings about a slight behavioural inhibition.

Using rabbits with implanted electrodes, the effects of *IIb* and clozapine were compared in the EEG record and reactions caused by sonic stimulation and by excitation of reticular formation after a single intravenous application of 0·05–1·0 mg/kg. The effect of the two compounds was similar and a dose of 0·2 mg/kg caused a depression of the response to excitation of reticular formation. In a similar arrangement, the effect of *IIb*, clozapine and octoclothepin was compared, using the EEG arousal reaction, brought about by apomorphine which stimulates the dopaminergic receptors (0·1 mg/kg apomorphine *i.v.*; compounds administered intravenously at a dose of 1 mg/kg; apomorphine was applied 10 min after the tested compound). In this

TABLE I

2-Halogeno-10-piperazinodibenzo[*b*, *f*]thiepins (*I*—*VIII*), Intermediates (*IX*—*XVI*) and Elimination Products (*XVII*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found				
				% C	% H	% N	% S	% Hal
IXa	*A* (87)	175—177[b] (aqueous ethanol)	$C_{13}H_9FO_2S$ (248·3)	62·89 63·11	3·65 3·59	— —	12·92 12·99	— —
IXe	A[c] (89)	173—174 (aqueous ethanol)	$C_{13}H_8ClFO_2S$ (282·7)	55·22 55·20	2·85 2·89	6·72[d] 6·74	11·34 11·05	12·54[e] 12·33
Xa	*B* (90)	132/0·1[f]	$C_{13}H_{11}FOS$ (234·3)	66·64 66·72	4·73 4·40	— —	13·69 13·69	— —
Xe	*c*	56—57 (cyclohexane)	$C_{13}H_{10}ClFOS$ (268·7)	58·10 58·57	3·75 3·78	— —	11·93 11·34	7·07[d] 7·04
Xf	*B*[c] (86)	148/0·01	$C_{13}H_{10}ClFOS$ (268·7)	58·10 57·87	3·75 3·86	— —	11·93 11·79	13·19[e] 13·34
XIa	*C* (80)	122/0·2[g]	$C_{13}H_{10}ClFS$ (252·7)	61·77 62·33	3·99 4·05	— —	12·69 12·22	14·03[e] 14·11
XIe	*c*	47—48 (light petroleum)	$C_{13}H_9Cl_2FS$ (287·2)	54·37 54·67	3·16 3·19	6·61[d] 6·57	11·17 11·29	24·69[e] 24·50
XIf	*C*[c] (60)	135/0·03	$C_{13}H_9Cl_2FS$ (287·2)	54·37 54·52	3·16 3·16	— —	11·17 11·19	24·69[e] 24·23
XIIa	*c*	134/0·05	$C_{14}H_{10}FNS$ (243·3)	69·11 69·29	4·14 4·25	— —	13·18 13·25	— —
XIIe	*c*	142—143/0·1	$C_{14}H_9ClFNS$ (277·7)	— —	— —	5·04 5·03	— —	— —
XIIIa	*D* (75)	100—102[h] (benzene–light petroleum	$C_{14}H_{11}FO_2S$ (262·3)	64·10 64·52	4·23 4·34	— —	12·23 12·12	— —
XIIIe	*D* (90)	127—128[i] (aqueous ethanol)	$C_{14}H_{10}ClFO_2S$ (296·7)	56·66 56·58	3·40 3·39	6·40[d] 6·50	10·81 10·86	11·95[e] 11·97
XIIIf	*D*[c] (86)	95—97 (benzene–light petroleum)	$C_{14}H_{10}ClFO_2S$ (296·8)	56·66 56·75	3·40 3·55	— —	10·81 10·30	11·95[e] 11·67
XIVa	*E*[j] (92)	115—117[k] (benzene–light petroleum)	$C_{14}H_9FOS$ (244·3)	68·83 68·79	3·71 3·64	— —	13·13 13·01	— —
XIVc	*c*	144—145 (chloroform–ethanol)	$C_{14}H_9BrOS$ (305·2)	55·09 54·76	2·97 2·98	— —	10·51 10·25	26·19 26·01
XIVd	*c*	131—133 (ethanol)	$C_{14}H_9IOS$ (352·2)	47·74 48·19	2·58 2·31	— —	9·11 8·96	36·03 35·46

TABLE I (*continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found				
				% C	% H	% N	% S	% Hal
XIVe	*E*[c]	119	$C_{14}H_8ClFOS$	60·33	2·89	6·82[d]	11·50	12·72[e]
	(94)	(ethanol)	(278·7)	60·39	2·83	6·97	11·71	12·94
XIVf	*E*[m]	132—134[n]	$C_{14}H_8ClFOS$	60·33	2·89	—	11·50	12·72[e]
	(94)	(ethanol)	(278·7)	60·53	3·03	—	11·39	12·78
XVa	*F*[o]	119—120[p]	$C_{14}H_{11}FOS$	68·27	4·50	—	13·02	—
	(96)	(benzene–light petroleum)	(246·3)	68·08	4·70	—	12·96	—
XVc	*F*[q]	110—112[r]	$C_{14}H_{11}BrOS$	54·73	3·61	—	10·44	26·01
	(96)	(ethanol)	(307·2)	54·39	3·62	—	10·46	25·86
XVd	*F*[q]	130—131[s]	$C_{14}H_{11}IOS$	47·47	3·13	—	9·05	35·83
	(96)	(ethanol)	(354·2)	47·76	3·20	—	8·57	35·92
XVe	*F*[c]	99—100	$C_{14}H_{10}ClFOS$	59·90	3·59	—	11·42	—
	(96)	(cyclohexane)	(280·7)	59·50	3·48	—	11·54	—
XVf	*F*[o]	87—89[t]	$C_{14}H_{10}ClFOS$	59·90	3·59	—	11·42	12·63[e]
	(90)	(benzene–light petroleum)	(280·8)	59·89	3·68	—	11·40	12·92
XVIa	*G*	105—107[u]	$C_{14}H_{10}ClFS$	63·51	3·81	—	12·11	13·39
	(94)	(cyclohexane)	(264·7)	63·85	3·77	—	12·10	13·14
XVIc	*G*[v]	126—127[w]	$C_{14}H_{10}BrClS$	51·63	3·10	24·54[x]	9·85	10·88[e]
	(85)	(benzene–light petroleum)	(325·7)	51·79	3·24	24·34	9·73	10·81
XVId	*G*	89—90[y]	$C_{14}H_{10}ClIS$	45·12	2·71	34·05[z]	8·60	9·52[e]
	(80)	(cyclohexane–light petroleum)	(372·7)	45·13	2·77	33·43	8·43	9·55
XVIe	*G*[c]	118—119	$C_{14}H_9Cl_2FS$	56·20	3·03	6·35[d]	10·72	23·70[e]
	(100)	(cyclohexane)	(299·2)	57·00	3·22	6·31	10·72	23·82
XVIf	*G*	77—79	$C_{14}H_9Cl_2FS$[aa]	56·20	3·03	—	—	—
	(95)	(light petroleum)	(299·2)	57·14	3·50	—	—	—
Ia	*H*	132—133[bb]	$C_{19}H_{21}FN_2S$	69·48	6·44	—	9·76	—
	(75)	(cyclohexane)	(328·5)	69·98	6·36	—	9·97	—
Ia-M	—	175—176	$C_{23}H_{25}FN_2O_4S$	62·15	5·67	—	7·21	—
		(ethanol)	(444·5)	62·06	5·58	—	7·62	—
XVIIa	*H*	80—82[cc]	—	—	—	—	—	—
		(ethanol)		—	—	—	—	—
Ib	*H*	111—112[dd]	$C_{19}H_{21}ClN_2S$	66·16	6·14	8·12	9·29	10·28
	(73)	(cyclohexane)	(344·9)	66·12	6·52	8·14	9·37	10·35
Ib-MS[ee]	—	138—141	$C_{22}H_{31}ClN_2O_4S_2$	54·25	6·42	5·75	13·16	7·28
		(aqueous ethanol)	(487·1)	54·14	6·80	5·58	13·02	7·30

TABLE I (*continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found				
				% C	% H	% N	% S	% Hal
Ic	*H* (77)	92–94[ff] (aqueous methanol)	$C_{19}H_{21}BrN_2S$ (389·4)	— —	— —	7·19 7·26	8·23 8·49	20·53 20·22
Ic-2MS	—	194–195 (ethanol–ether)	$C_{21}H_{29}BrN_2O_2S_3$ (581·6)	43·37 43·29	5·03 5·21	4·82 4·92	16·54 16·29	13·74 13·85
XVIIc	*H*	92–95[gg] (ethanol)	—	— —	— —	— —	— —	— —
Id	*H* (80)	137–139[hh] (ethanol)	$C_{19}H_{21}IN_2S$ (436·4)	— —	— —	6·42 6·05	7·35 7·51	— —
Id-2MS[ii]	—	187–189 (ethanol–ether)	$C_{21}H_{30}IN_2O_{6.5}S_3$ (637·7)	39·56 39·96	4·74 4·82	4·39 4·28	15·09 14·65	19·90 19·44
XVIId	*H*	115–117[jj] (ethanol)	—	— —	— —	— —	— —	— —
Ie	*H*[c] (69)	111 (light petroleum)	$C_{19}H_{20}ClFN_2S$ (362·9)	62·89 62·97	5·55 5·92	7·72 8·05	8·83 9·14	— —
Ie-MS	—	189–190 (ethanol–ether)	$C_{20}H_{24}ClFN_2O_3S_2$ (459·0)[kk]	52·34 52·59	5·27 5·52	6·10 6·00	13·97 13·82	7·72[e] 7·91
XVIIe	*H*[c]	98 (cyclohexane)	$C_{14}H_8ClFS$ (262·7)	64·00 63·71	3·07 3·16	7·23[d] 7·25	12·20 12·09	13·50 13·67
If	*H* (45)	123–124[mm] (cyclohexane)	$C_{19}H_{20}ClFN_2S$ (362·9)	62·88 63·45	5·56 5·93	7·72 7·53	8·84 8·81	9·77[e] 9·63
If-M	—	179–180 (ethanol)	$C_{23}H_{24}ClFN_2O_4S$ (479·0)	57·67 57·94	5·05 5·24	5·85 5·74	6·70 6·81	7·40[e] 7·66
XVIIf	*H*	122–124[nn] (cyclohexane)	—	— —	— —	— —	— —	— —
IIb	*H* (65)	102–103 (acetone)	$C_{20}H_{23}ClN_2OS$ (374·9)	64·07 64·12	6·18 6·43	7·47 7·37	8·55 8·72	9·45 9·32
IIb-M	—	122–124 (acetone–ether)	$C_{24}H_{27}ClN_2O_5S$ (491·0)	58·70 58·74	5·54 5·62	5·70 5·60	6·53 6·73	7·22 7·39
IIb-S	—	167–168 (ethanol)	$C_{24}H_{29}ClN_2O_5S$ (493·0)	58·47 58·56	5·93 6·04	5·68 5·51	6·50 6·70	7·19 7·29
IIb-MS	—	150–151 (ethanol)	$C_{21}H_{27}ClN_2O_4S_2$ (471·0)	53·55 53·45	5·78 5·89	5·94 5·79	13·61 13·43	7·53 7·67
IIe	*H* (75)	80–84[oo] (benzene–light petroleum)	$C_{20}H_{22}ClFN_2OS$ (392·9)	61·13 60·85	5·64 5·92	7·13 7·29	— —	— —
IIe-2M	—	143–145 (ethanol)	$C_{28}H_{30}ClFN_2O_9S$ (625·1)[pp]	53·80 53·64	4·84 4·89	4·48 4·54	5·13 5·33	5·67[e] 5·64

TABLE I (*continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (solvent)	Calculated/Found				
				% C	% H	% N	% S	% Hal
IIIe-M	*H* (75)	86–88 (ethanol)	$C_{25}H_{28}ClFN_2O_5S$ (523·0)[qq]	57·41 57·18	5·39 5·64	5·36 5·17	6·13 6·03	6·78[e] 6·99
IVb-2M	*J*[c] (42)	109–112 (acetone)	$C_{38}H_{49}ClN_2O_{10}S$ (761·3)	59·95 59·33	6·48 6·46	3·68 3·56	4·21 4·59	4·66 5·01
IVe-2M	*J* (45)	110–113 (acetone–ether)	$C_{38}H_{48}ClFN_2O_{10}S$ (779·3)[rr]	58·56 58·48	6·21 6·36	3·59 3·45	4·11 4·26	4·55[e] 4·65
Ve	*H*[ss] (78)	120[tt] (ethanol)	$C_{21}H_{22}ClFN_2O_2S$ (420·9)	59·92 60·12	5·27 5·59	6·66 6·54	7·62 7·71	— —
VIe	*c*	155–157 (ethanol)	$C_{18}H_{18}ClFN_2S$ (348·8)	61·97 62·01	5·20 5·48	8·03 7·82	9·19 9·24	10·17 10·22
VIIe-M	*c*	168–169 (ethanol)	$C_{25}H_{25}ClFN_3O_4S$ (518·0)[uu]	57·97 58·04	4·86 5·05	8·11 7·73	6·19 6·05	6·84[e] 6·65
VIIIb	*K* (70)	147–148[vv] (ethanol)	$C_{19}H_{19}ClN_2S$ (342·9)	66·55 66·38	5·59 5·77	8·17 8·07	9·35 9·44	10·34 10·33
VIIIb-MS	—	259–261 (ethanol)	$C_{20}H_{23}ClN_2O_3S_2$ (439·0)	54·72 54·69	5·28 5·45	6·38 6·12	14·61 14·67	8·08 7·90
VIIIe	*K*[c] (83)	135–136 (ethanol)	$C_{19}H_{18}ClFN_2S$ (360·8)	63·24 63·36	5·03 5·32	7·76 7·91	8·88 8·85	9·83 9·96
VIIIe-MS	—	265–266 (ethanol)	$C_{20}H_{22}ClFN_2O_3S_2$ (457·0)	52·57 52·00	4·85 5·04	6·13 6·09	14·04 13·78	4·15[d] 4·19
VIIIf	*K* (50)	150–152[ww] (ethanol)	$C_{19}H_{18}ClFN_2S$ (360·9)	63·23 62·63	5·03 5·42	7·76 7·37	8·89 8·74	9·83[e] 9·80
VIIIf-M	—	243–244 (decomp.) (aqueous ethanol)	$C_{23}H_{22}ClFN_2O_4S$ (477·0)	57·92 58·06	4·65 4·41	5·88 5·81	6·72 6·53	7·43[e] 7·54

[a] M maleate, MS methanesulfonate, S succinate. [b] IR spectrum: 700, 763, 820, 896 (5 and 2 adjacent and solitary Ar—H), 1256 (COOH), 1473, 1572, 1607 (Ar), 1690 cm^{-1} (ArCOOH); NMR spectrum (CD_3SOCD_3): δ 6·80–8·00 (m, 3 H, aromatic protons of benzoic acid), 7·70 (s, 5 H, C_6H_5); patent application[23] reports for a similarly synthesized product a m.p. of 146 to 148°C. [c] See Experimental. [d] Fluorine content. [e] Chlorine content. [f] IR spectrum ($CHCl_3$): 826, 883 (Ar—H), 1031 (CH_2OH), 1476, 1585, 1605 (Ar), 3610 cm^{-1} (OH); patent application[23] describes the preparation of the compound by reduction of acid *IXa* with sodium dihydridobis-(2-methoxyethoxy)aluminate. [g] Patent application[23] describes the preparation of the substance by a similar method. [h] For a similarly prepared compound, patent application[23] reports a m.p. of 80–83°C. [i] IR spectrum: 680, 732, 824, 871, 881 (3 and 2 adjacent and solitary Ar—H), 938, 1237 (COOH), 1474, 1579, 1597 (Ar), 1714, 2555, 2635, 2735 cm^{-1} (COOH). [j] Cyclization

Explanation to Table I

carried out at 110—120°C using a reaction period of 1·5 h. [k] IR spectrum: 763, 827, 880 (4 and 2 adjacent and solitary Ar—H), 1246 (Ar—F), 1590, 1603 (Ar), 1665 cm^{-1} (ArCO); for a similarly prepared compound patent application[23] reports a m.p. of 98—100°C. [m] Reaction period of 2 h. [n] UV spectrum: λ_{max} 230 nm (log ε 4·39), infl. 260 nm (4·00), 338 nm (3·59); IR spectrum: 818, 828, 870, 887, 899 (2 adjacent and solitary Ar—H), 1091 (Ar—F), 1565, 1594 (Ar), 1672 cm^{-1} (ArCO); NMR spectrum δ 7·84 (dd, J = 9·0; 3·0 Hz, 1 H, 9-H), 6·85—7·65 (m, 5 H, remaining aromatic protons), 4·25 (s, 2 H, $ArCH_2CO$). [o] Reduction was done in ethanol in the absence of water. [p] IR spectrum: 763, 817, 835 (Ar—H), 1005 (CHOH), 1245 (Ar—F), 1587, 1603 (Ar), 3320 cm^{-1} (OH); for an analogously prepared compound patent application[23] reports a m.p. 110—113°C. [q] Reduction was done in aqueous dioxane. [r] IR spectrum (Nujol): 750, 821, 869 (4 and 2 adjacent and solitary Ar—H), 1030, 1060 (CHOH in a ring), 3310, 3370 cm^{-1} (OH); for an analogously prepared compound patent application[23] reports a m.p. of 108—110°C. [s] IR spectrum (Nujol): 750, 763, 819, 869 (4 and 2 adjacent and solitary Ar—H), 1059 (CHOH in a ring), 1520 (Ar), 3300 cm^{-1} (OH); NMR spectrum: δ 7·00—7·70 (m, 7 H, aromatic protons), 5·30 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·21 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·03 (s, disappears after D_2O, 1 H, OH); for a similarly prepared product patent application[23] reports a m.p. of 131—133°C. [t] IR spectrum: 815, 880 (2 adjacent and solitary Ar—H), 1005, 1052 (CHOH in a ring), 1580, 1600 (Ar), 3320 cm^{-1} (OH). [u] NMR spectrum: δ 6·70—7·50 (m, 7 H, aromatic protons), 5·79 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·02 and 3·56 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$); for a similarly prepared compound, patent application[23] reports a m.p. of 90—92°C. [v] Reaction was carried out in chloroform. [w] NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 5·76 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·94 and 3·54 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$); for a preparation synthesized analogously, patent application[23] reports a m.p. of 122·5—124°C. [x] Content of bromine. [y] NMR spectrum: δ 7·00—7·75 (m, 7 H, aromatic protons), 5·77 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·93 and 3·55 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$); patent application[23] describes the preparation by a reaction of *XVd* with $SOCl_2$ in chloroform in the presence of pyridine. [z] Content of iodine. [aa] Analysis indicates that the compound is not pure but it was used for further work as such. [bb] NMR spectrum: δ 6·60—7·80 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·55 and 2·40 (2 m, 8 H, 4 CH_2 of piperazine), 2·20 (s, 3 H, NCH_3). [cc] UV spectrum: λ_{max} 221 nm (log ε 4·42), 261 nm (4·38), 293 nm (3·75); IR spectrum; 751, 830, 885 (4 and 2 adjacent and solitary Ar—H), 797 (CH=CH *cis*), 1245 (Ar—F), 1474, 1572, 1600 cm^{-1} (Ar); for this compound a m.p. of 82—83°C was reported earlier[2]. [dd] NMR spectrum: δ 6·90—7·80 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 and 2·38 (2 t, 8 H, 4 CH_2 of piperazine), 2·21 (s, 3 H, NCH_3); the compound was prepared before[20] in a 55% yield but only the maleate was then characterized in a crystalline form. [ee] Solvate with a molecule of ethanol. [ff] NMR spectrum: δ 6·90—7·70 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·56 and 2·45 (2 m, 8 H, 4 CH_2 of piperazine), 2·25 (s, 3 H, NCH_3). [gg] In an earlier paper[2] a m.p. of 93—95°C was reported for this compound. [hh] NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 2·90—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 and 2·48 (2 m, 8 H, 4 CH_2 of piperazine), 2·30 (s, 3 H, NCH_3). [ii] Hemihydrate. [jj] A m.p. of 117—118°C was reported[4] for this compound. [kk] Calculated: 4·14% F; found: 4·18% F. [mm] IR spectrum: 830, 892 (2 adjacent and solitary Ar—H), 1100 (Ar—F), 1587, 1605 (Ar), 2700, 2760 cm^{-1} (NCH_2); NMR spectrum: δ 6·50—7·50 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 and 2·35 (2 t, 8 H, 4 CH_2 of piperazine), 2·15 (s, 3 H, NCH_3). [nn] In ref.[19] the same m.p. was reported. [oo] IR spectrum (Nujol): 825, 840, 871, 893 (2 adjacent and solitary Ar—H), 1009, 1059 (CH_2OH), 1220 (C—F), 1480, 1600 cm^{-1} (Ar); NMR spectrum:

Explanation to Table I

δ 6·70—7·85 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·61 (t, J = 6·0 Hz, 2 H, CH_2O), 2·66 (bs, disappears after D_2O, 1 H, OH), c. 2·60 (m, 10 H, 5 NCH_2). [pp] Calculated: 3·04% F; found: 3·17% F. [qq] Calculated: 3·63% F; found: 3·60% F. [rr] Calculated: 2·44% F; found: 2·27% F. [ss] Substitution reaction carried out without chloroform at 105—110°C (4 h). [tt] IR spectrum (Nujol): 818, 840, 862, 878 (2 adjacent and solitary Ar—H), 1247 (CO—O—C), 1581, 1598 (Ar), 1690 cm^{-1} (NCOOR); NMR spectrum: δ 6·70—7·80 (m, 6 H, aromatic protons), 4·13 (q, J = 7·0 Hz, 2 H, $NCOOCH_2$), 2·90—3·95 (m, 3 H, $ArCH_2CHAr$), 3·44 and 2·55 (2 t, J = 5·0 and 5·0 Hz, 8 H, 4 CH_2 of piperazine), 1·24 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). [uu] Calculated: 3·67% F; found: 3·74% F. [vv] UV spectrum: λ_{max} 238 nm (log ε 4·24), 271·5 nm (4·02), 306 nm (3·95); NMR spectrum: δ 7·05—7·95 (m, 7 H, aromatic protons), 6·32 (s, 1 H, ArCH=), 3·02 (t, J = 5·0 Hz, 4 H, $CH_2N^1CH_2$ of piperazine), 2·56 (t, J = 5·0 Hz, 4 H, $CH_2N^4CH_2$ of piperazine), 2·35 (s, 3 H, NCH_3); maleate of this compound is mentioned in patent application[21]. [ww] UV spectrum: λ_{max} 240 nm infl. (log ε 4·26), 265 nm (4·06), 304 nm (3·95); IR spectrum: 825, 886 (2 adjacent and solitary Ar—H), 1475, 1550, 1575 (Ar); 1615 (ArC=C), 2720, 2765, 2790 cm^{-1} (N—CH_2); NMR spectrum: δ 6·75—7·60 (m, 6 H, aromatic protons), 6·19 (s, 1 H, ArCH=), 2·95 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3).

TABLE II

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

Compound	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy[a] ED_{50}
Ia	78	3·5	38
Ib	70	1·2	>50 (1/10)
Ic	128	1·35	>50 (0/10)[b]
Id	190	2·2	>50 (0/10)[b,c]
Ie	221	2·4	>50 (4/10)
If	71	1·0	14
IIb	84	0·8	>50 (2/10)
IIe	560	3·6	>50 (3/10)
IIIe	430	5·4	>50 (4/10)
VIIIb	155	1·5	40
VIIIe	270	2·0	20
VIIIf	127	1·1	19
Clozapine	210	3·8	>50 (0/10)
Octoclothepin	78	2·2	4·3

[a] The ratio in parentheses indicates the number of rats where the dose shown brought about a state of catalepsy, over the total number of animals in the group. [b] The dose shown brings about heavy depression but the animals are not cataleptic. [c] The compound was applied also in a dose of 100 mg/kg *p.o.*, this bringing about pseudocatalepsy in 10% of the animals.

test the new compound *IIb* lies between octoclothepine (which blocks the apomorphine reaction completely) and clozapine (which has a slight effect only). On the other hand, the arousal action of cholinomimetics (nicotine, arecoline and physostigmine at a dose of 0·025 mg/kg *i.v.*) was not antagonized by *IIb* and octoclothepin but was highly inhibited by clozapine.

Compound *IIIe* was subjected to general pharmacological screening in the form of maleate after intravenous administration (Dr M. Bartošová, at the affiliated unit of this Institute at Rosice n/L). Acute toxicity LD_{50} = 87·5 mg/kg. The compound potentiates thiopental sleep in mice (dose which doubles the duration of sleep lies between 1·0 and 2·5 mg/kg *i.v.*), it depresses the rectal temperature of rats (2·5 mg/kg *i.v.* brings about a temperature drop of 1·0°C), it has an incoordinating effect in the rotating-rod test in mice (ED_{50} = 2·5 mg/kg *i.v.*), it depresses motility of mice in known as well as unknown surroundings (ED = 1 mg/kg *s.c.*), it depresses the ability of mice to adjust their position on a horizontal wire (ED_{50} = 2·5 mg/kg *s.c.*), it antagonizes the lethal action of amphetamine (ED_{50} = 0·25 mg/kg *i.v.*), at a higher dose it brings about catalepsy in rats (ED_{50} = 10 mg/kg *i.p.*). Further, *IIIe* has a pronounced antihistamine effect in the test of histamine detoxication in guinea-pigs (ED_{50} = 1 mg/kg *p.o.*), it antagonizes the pressor effect of adrenaline in rats (ED_{50} between 0·05 and 0·1 mg/kg *i.v.*), it has a negative inotropic effect on the isolated

TABLE III

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

Compound[a]	Microorganism[b]										
	1	2	3	4	5	6	7	8	9	10	11
Ia-M	50	—	50	12·5	—	—	—	—	—	—	—
Ib-MS	25	—	25	12·5	—	—	—	125	125	—	—
Ic-2MS	20	20	25	6·2	100	100	100	25	25	100	100
Id-2MS	10	20	12·5	12·5	100	100	100	100	25	100	100
Ie-MS	25	25	25	25	—	—	—	6·2	12·5	50	50
IIb-S	25	—	25	12·5	—	—	—	—	—	—	—
IIe-2M	50	50	50	50	—	—	—	25	25	—	—
IIIe-M	25	25	25	25	—	—	—	25	25	—	—
VIIIb-MS	25	—	25	12·5	—	—	—	62·5	62·5	125	125
VIIIe-MS	6·2	6·2	6·2	6·2	—	—	—	3·1	6·2	50	50

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

rabbit auricle (at a concentration of 25–50 μg/ml it decreases inotropy by 25%) and prolongs the survival of mouse myocard during asphyxia (ED between 5 and 10 mg/kg *i.p.*). Thus the compound has the general character of a neuroleptic with a lower cataleptic efficacy, as suggested by the values in Table II.

The compounds prepared were tested for antimicrobial activity *in vitro* (Dr J. Turinová, Dr A. Čapek); Table III shows the minimum inhibitory concentrations against several typical microorganisms. Mention should be made of the wide spectrum of antimicrobial activity of *Ic* and *Id*, of the relatively high antitubercular activity of *Ic* and *VIIIe*, as well as of the high efficacy of *VIIIe* toward cocci and yeasts.

EXPERIMENTAL

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

5-Chloro-2-(3-fluorophenylthio)benzoic Acid (*IXe*) (Method *A*)

A solution of 19 g KOH in 200 ml water was consecutively combined at 50°C with 12·8 g 3-fluorothiophenol[22] (b.p. 160–162°C), 28·2 g 5-chloro-2-iodobenzoic acid[20] and 1·0 g Cu paste, and the mixture was refluxed under stirring for 7 h. It was filtered while hot and the warm filtrate was acidified with hydrochloric acid. After standing overnight, it was filtered, yielding 24·9 g (89%) product, m.p. 160–170°C. Analytical product, m.p. 173–174°C (aqueous ethanol). IR spectrum: 691, 784, 827, 869, 883 (3 and 2 adjacent and solitary Ar—H), 925 (COOH), 1246 (ArCOOH), 1544, 1581 (Ar), 1687 (ArCOOH), 2545, 2605, 2655 and 2710 cm^{-1} (COOH).

5-Chloro-2-(3-fluorophenylthio)benzyl Alcohol (*Xe*)

A 50% benzene solution (49 g) of sodium dihydridobis(2-methoxyethoxy)aluminate was added dropwise under stirring to a suspension of 17·2 g *IXe* in 170 ml benzene, the temperature being kept below 40°C. The mixture was stirred for 2·5 h at room temperature and 90 ml 10% solution of NaOH was added dropwise under cooling. After 1 h of stirring it was separated, the benzene layer was dried with K_2CO_3 and evaporated. Distillation yielded 13·1 g (80%) product boiling at 142–144°C/0·1 Torr, which crystallizes from cyclohexane, m.p. 56–57°C. IR spectrum: 677, 787, 875, 884 (Ar—H), 1037 (CH_2OH), 1582 (Ar), 3200, 3280 cm^{-1} (OH).

5-Chloro-2-(4-fluorophenylthio)benzyl Alcohol (*Xf*) (Method *B*)

5-Chloro-2-(4-fluorophenylthio)benzoic acid[19] (*IXf*; 8·8 g) was added in parts and under stirring to a solution of 1·6 g $LiAlH_4$ in 175 ml ether so as to keep the mixture refluxing. The refluxing was continued for 4 h; after cooling, it was decomposed by adding dropwise 3 ml water and 65 ml dilute hydrochloric acid (1 : 4). Processing of the ether layer yielded 7·2 g (86%) product boiling

at 148°C/0·01 Torr. IR spectrum ($CHCl_3$): 832 and 877 (2 adjacent and solitary Ar—H), 1020, 1040 (CH_2OH), 1108 (Ar—F), 1493, 1595 (Ar), 3610 cm^{-1} (OH).

5-Chloro-2-(3-fluorophenylthio)benzyl Chloride (*XIe*)

$SOCl_2$ (5·3 g) was added dropwise and with cooling in an ice bath to a mixture of 9·80 g *Xe* and 3·7 g pyridine. The mixture was stirred for 2 h at room temperature, on the following day heated for 2 h at 40—50°C and, after cooling, decomposed by adding dropwise 120 ml water. The product was isolated by extraction with benzene; after recrystallization from light petroleum, the yield was 7·4 g (71%), m.p. 47—48°C.

5-Chloro-2-(4-fluorophenylthio)benzyl Chloride (*XIf*) (Method *C*)

$SOCl_2$ (4·1 g) was slowly added dropwise under stirring and refluxing to a solution of 6·3 g *Xf* in 15 ml benzene. The mixture was refluxed for 1 h and distilled; 4·0 g (60%), b.p. 135°C/0·03 Torr. The low yield was due to partial decomposition during distillation. With larger batches, the crude product (residue after evaporation) was used for further work.

5-Fluoro-2-(phenylthio)phenylacetonitrile (*XIIa*)

A mixture of 18·4 g crude *XIa* (residue), 25 ml dimethylformamide, 4·7 g NaCN and 1·2 ml water was stirred for 2 h at room temperature, diluted with water and the product was isolated by extraction with benzene; 12·8 g (72%), b.p. 134°C/0·05 Torr. According to thin-layer chromatography on silica gel, the product is contaminated with a small amount of alcohol *Xa*. For analysis and spectrometry, the contaminant was removed by chromatography on alumina (activity II). NMR spectrum: δ 6·80—7·70 (m, 8 H, aromatic protons), 3·80 (s, 2 H, $ArCH_2CN$). Patent application[23] describes a similar preparation of this compound using dimethyl sulfoxide as the medium.

5-Chloro-2-(3-fluorophenylthio)phenylacetonitrile (*XIIe*)

A solution of 174·5 g crude *XIe* in 250 ml ethanol was added to a solution of 4·3 g NaCN in 75 ml water and the mixture was refluxed for 7 h. After evaporation of the volatile fractions, the residue was mixed with water and the product was isolated by extraction with benzene; a total of 163 g oily residue was obtained and this was used for further work. A 10·0 g sample was distilled, yielding 8·36 g product boiling at 150—160°C/0·9 Torr. The preparation yield was thus 81%. A sample for analyiss was redistilled; b.p. 142—143°C/0·1 Torr.

5-Chloro-2-(4-fluorophenylthio)phenylacetic Acid (*XIIIf*) (Method *D*)

Reaction of 20·2 g crude *XIf* and 5·2 g NaCN in 27 ml dimethylformamide yielded, similarly to the preparation of *XIIa*, 19·2 g crude nitrile *XIIf* (residue). Solution of 17·0 g of this product in 70 ml ethanol was mixed with a solution of 17 g KOH in 35 ml water and the mixture was refluxed for 6 h. After evaporation of ethanol the residue was diluted with water, the solution washed with ether, acidified with hydrochloric acid and the product was isolated by extraction with chloroform; 15·7 g (86%) oil which crystallizes on standing, m.p. 95—97°C (benzene–light petroleum). IR spectrum: 820, 847, 880 (2 adjacent and solitary Ar—H), 945, 1230 (COOH), 1497, 1600 (Ar), 1715, 2660 cm^{-1} (COOH).

2-Bromodibenzo[*b*,*f*]thiepin-10(11H)-one (*XIVc*)

A solution of 3·1 g $NaNO_2$ in 10 ml water was added dropwise at 0°C to a suspension of 10·1 g 2-aminodibenzo[*b*,*f*]thiepin-10(11*H*)-one[12] in a mixture of 40 ml concentrated hydrobromic acid and 160 ml water. The mixture was stirred for 2 h at °C and poured into a solution of 14·4 g CuBr in hydrobromic acid. The mixture formed was stirred for 1 h at room temperature and for 2 h at 50—60°C. After standing overnight, the precipitate was filtered, dissolved in benzene and the solution was washed with water. The crude product obtained by evaporation was purified by filtration through a column of 150 g Al_2O_3 (activity II); elution with a mixture of benzene and light petroleum yielded 7·31 g (57%) product melting at 142—144°C. An analytical sample was obtained by crystallization from a mixture of chloroform and ethanol, m.p. 144—145°C. UV spectrum: λ_{max} 231·5 nm (log ε 4·48), infl. 265 nm (4·09), 328 nm (3·64). IR spectrum (Nujol): 749, 813, 870, 888 (4 and 2 adjacent and solitary Ar—H), 1 520, 1 556, 1 571, 1 587 (Ar), 1 669 cm^{-1} (ArCO). NMR spectrum: δ 8·20 (m, 1 H, 9-H), 7·15—7·65 (m, 6 H, remaining aromatic protons), 4·30 (s, 2 H, $ArCH_2CO$). Patent application[23] describes the preparation of the compound by cyclization of 5-bromo-2-(phenylthio)phenylacetic acid and reports a m.p. of 143—145°C.

2-Iododibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIVd*)

A solution of 2·5 g $NaNO_2$ in 5 ml water was added dropwise at 0°C to a suspension of 8·0 g 2-aminodibenzo[*b*,*f*]thiepin-10(11*H*)-one[12] in a mixture of 30 ml hydrochloric acid and 120 ml water. The mixture was stirred for 2 h at 0°C; it was combined with a cooled solution of 10 gKI and 1 g iodine in 15 ml water, stirred for 3 h at 20°C, 100 ml benzene was then added and the mixture stirred for another hour and then filtered. The benzene layer of the filtrate was separated, washed with 5% NaOH, with a solution of sodium hydrosulfite, dried with $MgSO_4$ and evaporated. The semicrystalline residue (9·7 g) was purified partly by crystallization from a mixture of benzene and ethanol, partly by chromatography on alumina (activity II), eluting with a mixture of benzene and light petroleum. A total of 6·7 g (57%) pure product was obtained, m.p. 131 to 133°C (ethanol). UV spectrum: λ_{max} 235·4 nm (log ε 4·50), infl. 263 nm (4·07), 328 nm (3·57). IR spectrum (Nujol): 748, 759, 766, 810 (Ar—H), 1 550, 1 563, 1 583 (Ar), 1 677 cm^{-1} (ArCO). NMR spectrum: δ 8·20 (m, 1 H, 9-H), 7·81 (d, J = 2·5 Hz, 1 H, 1-H), 7·20—7·70 (m, 5 H, remaining aromatic protons), 4·28 (s, 2 H, $ArCH_2CO$). Patent application[23] describes the preparation of the compound by a similar method and reports a m.p. of 129—131°C.

2-Chloro-7-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIVe*) (Method *E*)

A mixture of 50 g polyphosphoric acid and 5·1 g *XIIIe* was stirred for 8 h at 140—150°C. After cooling, it was decomposed with ice and water and the product was isolated by extraction with benzene. The extract was washed with a 5% solution of NaOH (acidification of the alkaline solution recovered 0·9 g *XIIIe*) and with water and then evaporated; 3·7 g (94% per conversion), m.p. 119°C (ethanol). UV spectrum: λ_{max} 226 nm (log ε 4·33), 242 nm (4·26), 265 nm (4·06), 306 nm (3·57). IR spectrum (Nujol): 815, 840, 862, 870, 898 (2 adjacent and solitary Ar—H), 1 560, 1 594 (Ar), 1 670 cm^{-1} (ArCO). NMR spectrum: δ 8·25 (dd, J = 9·0; 6·0 Hz, 1 H, 9-H), 7·56 (d, J = 9·0 Hz, 1 H, 4-H), 7·39 (d, J = 2·5 Hz, 1 H, 1-H), 7·30 (q, J = 9·0; 2·5 Hz, 1 H, 3-H), 6·80—7·20 (m, 2 H, 6,8-H_2), 4·27 (s, 2 H, $ArCH_2CO$).

2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XVe*) (Method *F*)

A solution of 1·0 g $NaBH_4$ in 10 ml water with 0·5 ml 5% NaOH was added dropwise under stirring over a 15-min period to a 70°C solution of 3·0 g *XIVe* in 60 ml ethanol. The mixture was

refluxed for 3·5 h and then evaporated. The residue was mixed with water and extracted with benzene. Processing of the extract yielded 2·90 g (96%) crude product melting at 95—97°C. The analytical product was obtained by crystallization from cyclohexane, m.p. 99—100°C. IR spectum: 817, 834, 864, 870, 877 (2 adjacent and solitary Ar—H), 1043, 1054 (CHOH in a ring), 1488, 1565, 1583, 1602 (Ar), 3290, 3340 cm^{-1} (OH).

2,10-Dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIe*) (Method *G*)

Powdered anhydrous calcium chloride (2 g) was added to a solution of 2·3 g *XVe* in 60 ml benzene and the suspension was saturated for 40 min under stirring with anhydrous hydrogen chloride. After standing overnight it was filtered and the filtrate was evaporated at reduced pressure; 2·45 g (theoretical yield) of crude crystalline product melting at 110—113°C. For analysis, it was recrystallized from cyclohexane, m.p. 118—119°C.

2-Chloro-7-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ie*) (Method *H*)

A mixture of 10·0 g *XVIe*, 10 g 1-methylpiperazine and 12 ml chloroform was refluxed for 8 h. Chloroform was then evaporated and the residue was divided between water and benzene. The benzene layer was washed with water and shaken with 80 ml 3M-HCl. Processing of the benzene layer containing the nonbasic product yielded 2·26 g 2-chloro-7-fluorodibenzo[*b*,*f*]thiepin (*XVIIe*) as an elimination product, m.p. 98°C (cyclohexane). For the same compound prepared recently[19] in another connection, a m.p. of 100—101°C was found.

The acid aqueous solution containing the separated oily hydrochloride was made alkaline with NH_4OH and the liberated base *Ie* was isolated by extraction with benzene; 8·3 g (69%). Crystallization from light petroleum yielded the analytical product, m.p. 111°C. NMR spectrum: δ 6·65—7·80 (m, 6 H, aromatic protons), 2·95—4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 and 2·38 (2 t, 8 H, 4 CH_2 of piperazine), 2·25 (s, 3 H, NCH_3). Neutralization of the base solution in trichloroethylene with ethanolic solution of methanesulfonic acid and addition of ether resulted in methanesulfonate, m.p. 189—190°C (ethanol–ether).

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

Decanoyl chloride[17] (7·6 g) was added to a solution of 7·5 g *IIb* in 60 ml chloroform and the mixture was left overnight at room temperature. 70 ml water and 70 ml chloroform were then added and the mixture was stirred for 2 h. After filtration, the chloroform layer was separated from the filtrate, quickly washed with cold 5% NaOH and water and evaporated. The oily residue (11·0 g) was dissolved in acetone and neutralized with a solution of 4·80 g maleic acid in acetone. On standing and cooling, 6·40 g (42%) bis(hydrogen maleate) precipitated, m.p. 109—112°C (acetone).

2-Chloro-7-fluoro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIe*)

A mixture of 11·0 g *Ve*, 5·5 g KOH and 11 ml ethanol was refluxed under stirring for 3·5 h in a 120—130°C bath. After diluting with water, it was extracted with benzene and the extract was shaken with 90 ml 3M-HCl. The precipitated hydrochloride of the product was filtered after 1 h of standing and suspended in water; treatment with NH_4OH liberated the base which was isolated by extraction with benzene; 8·5 g (94%), m.p. 155—157°C (ethanol). NMR spectrum: δ 6·60 to 7·80 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·75 and 3·52 (2 t, 8 H, 4 CH_2 of piperazine), 1·68 (bs, disappears after D_2O, 1 H, NH).

2-Chloro-10-[4-(2-cyanoethyl)piperazino]-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIe*)

A suspension of 6·65 g *VIe* in 45 ml tertiary butyl alcohol was combined with 1 ml 50% methanol solution of triethylbenzylammonium hydroxide. Under stirring a solution of 3·02 g acrylonitrile in further 10 ml tertiary butyl alcohol was added dropwise. The mixture was stirred for 2 h at room temperature and for 3 h at 40—50°C. After standing overnight, the solvent was evaporated at reduced pressure, the residue was dissolved in benzene, the solution was washed with water, filtered and shaken with 70 ml 3M-HCl. The precipitated hydrochloride was left to stand overnight, filtered, washed with benzene, suspended in water, made alkaline with NH_4OH and the liberated base was isolated by extraction with benzene; 6·4 g (84%) oily product. Neutralization with maleic acid in ethanol and addition of ether resulted in the precipitation of a maleate m.p. 168—169°C (ethanol).

2-Chloro-7-fluoro-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*VIIIe*) (Method *K*)

1-Methylpiperazine (25 g) was added to a solution of 13·9 g *XIVe* in 100 ml benzene and a solution of 4·75 g $TiCl_4$ in 25 ml benzene was added dropwise over 5 min under stirring. The mixture was refluxed for 24 h, cooled, decomposed by adding dropwise 140 ml water, the precipitate was filtered after 40 min of stirring and washed with benzene. The benzene phase of the filtrate was washed with water, dried and evaporated. The residue crystallized after combining with light petroleum; 15·0 g (83%), m.p. 125—130°C. Analytical sample, m.p. 135—136°C (ethanol). UV spectrum: λ_{max} 240 nm infl. (log ε 4·25), 273 nm (4·11), 308 nm (3·98). IR spectrum (Nujol): 813, 837, 850, 865, 878, 898 (2 adjacent and solitary Ar—H), 1487, 1590, 1605 cm^{-1} (Ar). NMR spectrum: δ 6·80—7·80 (m, 6 H, aromatic protons), 6·18 (s, 1 H, ArCH=C), 2·96 (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). *Methanesulfonate*, m.p. 265—266°C (ethanol).

The authors are indebted to Dr B. Kakáč, Dr J. Holubek, and Dr E. Svátek (physico-chemical department of this Institute) for measuring and interpretation of the spectra, to Mr F. Mikšík for technical assistance with the synthesis of some compounds and to Mr M. Čech, Mrs J. Komancová, Mr K. Havel, Mrs V. Šmídová, Mrs A. Slavíková, Mrs J. Hrdá and Mrs Z. Volková (analytical department of this institute) for chemical analyses.

REFERENCES

1. Protiva M., Jílek J. O., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I. Pelz K., Pomykáček J.: Farmaco (Pavia) Ed. Sci. *20*, 721 (1965).
2. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
3. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
4. Šindelář K., Metyšová J., Protiva M.: This Journal *38*, 2484 (1973).
5. Jílek J. O., Šindelář K., Metyšová J., Metyš J., Pomykáček J., Protiva M.: This Journal *35*, 3721 (1970).
6. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
7. Metyš J., Metyšová J., Votava Z., Benešová O., Dlabač A., Kazdová E., Franc Z., Queisnerová M., Kraus P., Vaněček M., Hradil F., Jílek J. O., Protiva M.: Farmakoterap. Zprávy *17*, 131 (1971).
8. Náhunek K., Švestka J., Rodová A.: Farmakoterap. Zprávy *17*, 211 (1971).
9. Stille G., Lauener H., Eichenberger E.: Farmaco (Pavia) Ed. Prat. *26*, 603 (1971).

10. Bürki H. R., Ruch W., Asper H., Baggiolini M., Stille G.: Schweiz. Med. Wochschr. *103*, 1716 (1973).
11. Šindelář K., Dlabač A., Metyšová J., Kakáč B., Holubek J., Svátek E., Šedivý Z., Protiva M.: This Journal *40*, 1940 (1975).
12. Šindelář K., Dlabač A., Kakáč B., Svátek E., Holubek J., Šedivý Z., Princová E., Protiva M.: This Journal *40*, 2649 (1975).
13. Černý M., Málek J., Čapka M., Chvalovský V.: This Journal *34*, 1025 (1969).
14. Šindelář K., Metyšová J., Protiva M.: This Journal *34*, 3801 (1969).
15. Zawisza T., Machoń Z., Kuczyński L.: Acta Pol. Pharm. *22*, 477 (1965).
16. Moore T. S., Boyle M., Thorn V. M.: J. Chem. Soc. *1929*, 39.
17. Fierz - David H. E., Kuster W.: Helv. Chim. Acta *22*, 82 (1939).
18. Jílek J. O., Šindelář K., Dlabač A., Kazdová E., Pomykáček J., Šedivý Z., Protiva M.: This Journal *38*, 1190 (1973).
19. Rajšner M., Metyšová J., Svátek E., Mikšík F., Protiva M.: This Journal *40*, 719 (1975).
20. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
21. Umio S., Ueda I., Sato Y., Maeno S. (Fujisawa Pharmaceutical Co., Ltd.): Ger. Offen. 1 801 523 (Appl. 5. X. 1968); Chem. Abstr. *71*, 112 976 (1969).
22. Rajšner M., Protiva M.: This Journal *32*, 2021 (1967).
23. Gerecke M., Kaplan J. - P., Kyburz E. (F. Hoffmann - La Roche & Co. AG.): Ger. Offen. 2 336 130 (31. I. 1974); Chem. Abstr. *80*, 108 576 (1974).
24. Šindelář K., Metyšová J., Protiva M.: This Journal *38*, 2137 (1973).
25. Ther L.: Deut. Apoth. - Ztg. *93*, 292 (1953).

Translated by A. Kotyk.