FLUORINATED NEUROLEPTICS OF THE 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN SERIES; 6-FLUORO DERIVATIVES OF PERATHIEPIN, OCTOCLOTHEPIN, DOCLOTHEPIN AND SOME RELATED COMPOUNDS*

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The synthesis of a series of 6-fluoro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins *Ic—IIIc*, *Vc* and *VIc* is described; these compounds are derivatives of the neuroleptic agents perathiepin (*Ia*), octoclothepin (*IIIa*), doclothepin (*Va*) and their hydroxyethyl analogues *IIa* and *VIa* in which the metabolic hydroxylation to position 6 was made impossible by blockade. The synthesis used common procedures *via* the intermediates *VII—XVIII*. Fluorination in position 6 does not influence much the pharmacological profile of the compounds indicating that hydroxylation in position 6 is only a minor metabolic pathway. The most interesting substance is the 6-fluoro derivative of octoclothepin (*IIIc*) which is a potent central depressant and neuroleptic agent with some protraction of the sedative effects.

A recent report[1] on the identification of the 6-hydroxy derivative of noroctoclothepin (*IVb*) as a metabolite of the neuroleptic agent octoclothepin (*IIIa*), preceded by the synthesis of the 6-hydroxy derivatives of perathiepin and octoclothepin (*Ib*, *IIIb*), as well as of the compound *IVb* (ref.[2,3]), attracted our attention to such derivatives of the neuroleptically and sedatively active substances *Ia—IIIa*, *Va* and *VIa* (ref.[4–8]), in the molecules of which the position 6 would be blocked by fluorination which should make the metabolic hydroxylation into this position impossible. After investigations of the analogous compounds fluorinated in positions 2, 3, 7 and 8 (ref.[8–10]), we are dealing in the present communication with the synthesis of the 6-fluoro derivatives *Ic—IIIc*, *Vc* and *VIc*. The purpose of the study was to determine the influence of fluorination in the said position on the intensity and duration of the central depressant and neuroleptic action.

The synthesis of the mentioned 6-fluoro derivatives made use of the same methods as in our preceding communications[2–10]. In the first line, the corresponding acids *VII—IX* were cyclized with polyphosphoric acid (method *A*) to ketones *X—XII*. The following reduction with sodium borohydride (method *B*) afforded the alcohols

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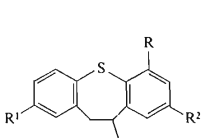
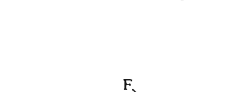
XIII–*XV* which were transformed by treatment with hydrogen chloride (method *C*) to the chloro compounds *XVI*–*XVIII*. Substitution reactions with 1-methylpiperazine or 1-(2-hydroxyethyl)piperazine (method *D*) resulted in the required bases *Ic*–*IIIc*, *Vc* and *VIc*.



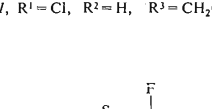
a, R = H
b, R = OH
c, R = F

I, $R^1 = R^2 = H$, $R^3 = CH_3$
II, $R^1 = R^2 = H$, $R^3 = CH_2CH_2OH$
III, $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$

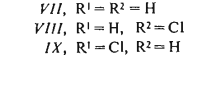
IV, $R^1 = H$, $R^2 = Cl$, $R^3 = H$
V, $R^1 = Cl$, $R^2 = H$, $R^3 = CH_3$
VI, $R^1 = Cl$, $R^2 = H$, $R^3 = CH_2CH_2OH$



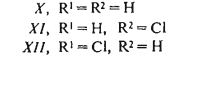
VII, $R^1 = R^2 = H$
VIII, $R^1 = H$, $R^2 = Cl$
IX, $R^1 = Cl$, $R^2 = H$



X, $R^1 = R^2 = H$
XI, $R^1 = H$, $R^2 = Cl$
XII, $R^1 = Cl$, $R^2 = H$



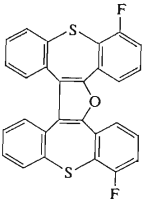
XIII, $R^1 = R^2 = H$
XIV, $R^1 = H$, $R^2 = Cl$
XV, $R^1 = Cl$, $R^2 = H$



XVI, $R^1 = R^2 = H$
XVII, $R^1 = H$, $R^2 = Cl$
XVIII, $R^1 = Cl$, $R^2 = H$

In the perathiepin series, *i.e.* in the synthesis of compounds *Ic* and *IIc*, the situation was rather easy due to the fact that both of the starting substances, necessary for the synthesis of [2-(2-fluorophenylthio)phenyl]acetic acid (*VII*), *i.e.* (2-iodophenyl)acetic acid[11,12] and 2-fluorothiophenol[13,14], are relatively easily accessible. Reaction of both of the mentioned compounds in a boiling aqueous potassium hydroxide soluti-

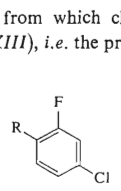
on in the presence of copper resulted in the acid *VII* in a high yield. Its cyclization with polyphosphoric acid proceeds satisfactorily at 140–150°C under the formation of 6-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*X*). This ketone was reduced with sodium borohydride. The alcohol *XIII* obtained was treated with hydrogen chloride in benzene and gave the chloride *XVI*. Substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine were carried out in boiling chloroform; bases *Ic* and *IIc* were obtained in yields of 70–80% and for pharmacological tests converted to salts (methanesulfonate, maleate). As the by-product of the substitution reactions, a neutral inhomogeneous fraction was obtained, a part of which crystallized. It was a rather insolublesubstance with a high melting point (339–341°C), the analysis of which indicated the presence of oxygen. We are thus not dealing here with the expected elimination product, *i.e.* 4-fluorodibenzo[*b*,*f*]-thiepin, but with a compound with a doubled molecule, to which on the basis of analysis, spectra and analogy the structure of the heptacyclic compound *XIX* was assigned. This very unreactive compound must have been formed already in the stage of cyclization of the acid *VII* and evidently formed an impurity of the crude intermediates *X*, *XIII* and *XVI*. We met earlier with similar by-products of cyclizations of (2-arylthiophenyl)acetic acids, we tried to explain their formation and found some analogous cases in the literature[12,15].



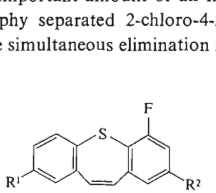
XIX

In the synthesis of compound *IIIc*, *i.e.* the 6-fluoro derivative of octoclothepin, it was first necessary to find a suitable procedure for the preparation of the starting 4-chloro-2-fluorothiophenol (*XXII*). An attempt at its preparation from 2-bromo--5-chlorofluorobenzene[16] by transformation to the Grignard reagent and by the following treatment with sulfur was unsuccessful; even the use of the modification of Dawson and Burger[17] was not of help. Our starting compound is a chloro derivative of 2-bromofluorobenzene, the anomalous behaviour in attempts at its transformation to the Grignard reagent is known[18]; our negative result can thus be explained in a similar way[19]. We used then 4-chloro-2-fluorobenzoic acid[20] as the

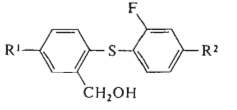
starting material. Its degradation by the Schmidt reaction[21] gave the new 4-chloro--2-fluoroaniline (*XX*), transformed for characterization to the N-acetyl derivative *XXI*. Conversion of the aniline derivative *XX* to the thiophenol *XXII* was then carried out by application of the known sequence, *i.e. via* the corresponding diazonium ethyl xanthate and by the final alkaline hydrolysis of the corresponding S-aryl xanthate[22,23] (in analogy with the procedure for the preparation of 2,4-difluorothiophenol[24]). Reaction of the thiophenol *XXII* with (2-iodophenyl)acetic acid[11,12] was carried out similarly like in the preceding case and resulted in the acid *VIII*. Also the preparation of the intermediates *XI*, *XIV* and *XVII* was carried out using identical methods like in the preceding case. A substitution reaction of the chloride *XVII* with 1-methylpiperazine in boiling chloroform afforded only 50% of the required base *IIIc*. There was formed a rather important amount of an inhomogeneous neutral product from which chromatography separated 2-chloro-4-fluorodibenzo-[*b*,*f*]thiepin (*XXIII*), *i.e.* the product of the simultaneous elimination reaction.



XX, R = NH_2
XXI, R = $NHCOCH_3$
XXII, R = SH



XXIII, R^1 = H, R^2 = Cl
XXIV, R^1 = Cl, R^2 = H



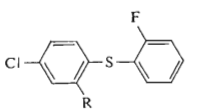
XXV, R^1 = H, R^2 = NO_2
XXVI, R^1 = H, R^2 = NH_2
XXVII, R^1 = H, R^2 = Cl

XXVIII, R^1 = NO_2, R^2 = H
XXIX, R^1 = NH_2, R^2 = H
XXX, R^1 = Cl, R^2 = H

There was still an additional synthetic attempt directed to the acid *VIII* which was abandoned because of preparative difficulties. Heating of a mixture of 4-chloro--3-fluoronitrobenzene[25], 2-(hydroxymethyl)thiophenol[26], potassium carbonate and copper to 170°C gave 2-(2-fluoro-4-nitrophenylthio)benzyl alcohol (*XXV*) which was transformed by reduction with iron and hydrochloric acid in boiling ethanol to the aminoalcohol *XXVI*. Sandmeyer reaction effected the conversion to the chloro alcohol *XXVII*, the further processing of which by treatment with thionyl chloride,

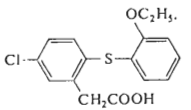
followed by a reaction with sodium cyanide in dimethylformamide, led only to inhomogeneous oily products from which we were not able to isolate the wanted intermediates.

In the doclothepin series, leading to compounds *Vc* and *VIc*, the acid *IX* was obtained using a different approach, consisting in the application of the Willgerodt reaction[27]. The easily accessible 2,5-dichloroacetophenone[28] was heated with 2-fluorothiophenol, potassium carbonate and copper to 150°C resulting in 5-chloro-2-(2-fluorophenylthio)acetophenone (*XXXI*) in a satisfactory yield. Reaction with morpholine and sulfur gave an inhomogeneous product, the crystallization of which afforded about 50% of the required thiomorpholide *XXXII*. The crude product contained probably the corresponding oxothiomorpholide[7,29] which, however, could not be isolated in pure state. An attempt at the common hydrolysis of the thiomorpholide *XXXII* with potassium hydroxide in boiling ethanol led to a fluorine-free product, identified as the ethoxy acid *XXXIII*; rather surprisingly, a nucleophilic substitution of the non-activated fluorine atom took place. The required [5-chloro-2-(2-fluorophenylthio)phenyl]acetic acid (*IX*) was then obtained by carrying out the hydrolysis with a mixture of sulphuric and acetic acid. Its processing to the chloride *XVIII via* the ketone *XII* and the alcohol *XV* was carried out similarly like in the synthesis of the 6-fluoro derivative of perathiepin (*Ic*). Similar procedures were used for the substitution reactions of the chloride *XVIII* with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine; bases *Vc* and *VIc* were obtained in yields of 60–70%. The neutral product of the simultaneous elimination reaction was isolated and identified as 2-chloro-6-fluorodibenzo[*b*,*f*]thiepin (*XXIV*).



XXXI, R = $COCH_3$

XXXII, R = CH_2CSN O

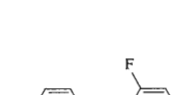


XXXIII

The just described synthesis of the acid *IX* was preceded by an alternative attempt which was not successful. A reaction of 2-iodo-5-nitrobenzoic acid[30] with 2-fluorothiophenol in a boiling aqueous potassium hydroxide solution in the presence of copper gave 2-(2-fluorophenylthio)-5-nitrobenzoic acid (*XXXIV*) which was reduced with diborane, generated from sodium borohydride and boron trifluoride etherate in tetrahydrofuran[11], to the nitro alcohol *XXVIII*. Reduction with stannous chloride

in ether afforded the amino alcohol *XXIX* which was transformed by Sandmeyer reaction to the chloro alcohol *XXX*. Treatment with thionyl chloride in benzene in the presence of pyridine gave the crude substituted benzyl chloride *XXXV* which was processed without purification by reaction with potassium cyanide in dimethylformamide. The oily nitrile *XXXVI* was obtained which was hydrolyzed with potassium hydroxide in boiling ethanol to an oily mixture of acids. Even in this case, the nucleophilic substitution of the fluorine atom with the ethoxy group took apparently partly place and the resulting mixture of acids *IX* and *XXXIII* was not separated.

XXXIV



XXXV, R = Cl
XXXVI, R = CN

Compounds prepared by using the general methods *A* – *D* are summarized with the usual experimental data in Table I. The Experimental contains only examples of these preparations and describes the synthesis of substances prepared by different methods.

The new 6-fluoro compounds were subjected to an orientation pharmacological evaluation; in addition to the acute toxicity in mice (LD_{50}), the incoordinating activity (ED_{50}) in the rotating rod test in mice (ataxia) and the cataleptic activity (ED_{50}) in rats were determined. The basic data found are summarized in Table II. Most of the parent non-fluorinated substances are included for comparison. The compounds tested were administered orally in the form of salts described in Table I; the doses given were calculated for bases.

It is apparent that the 6-fluoro compounds do not differ much from their non-fluorinated prototypes. Compound *Ic* has similar toxicity and incoordinating activity with perathiepin (*Ia*) which is slightly more active cataleptically. After higher doses than the ED_{50}, ataxia was observed in 20% of the animals even after 24 hours. The hydroxyethyl compound *IIc* is very similar to the methyl compound *Ic*. Compound *IIIc*, the 6-fluoro derivative of octoclothepin, is the most interesting substance from the whole series. It is significantly less toxic than octoclothepin, has a comparable central depressant activity (in higher doses than ED_{50}, ataxia is observed in 40% animals after 24 hours after the administration which is a clear indication of the protraction of this effect). Cataleptically, it is three times more active than octoclothepin; the action disappears within 24 hours similarly as with octoclothe-

pin itself. An oral dose of 5 mg/kg of compound *IIIc* inhibits the apomorphine stereotypies in rats (evaluated after 4 hours) to 13·5% of the control value; the action disappears within 24 hours. The 6-fluorinated analogues *Vc* and *VIc* of the non-cataleptic neuroleptics doclothepin and docloxythepin are less toxic and less sedatively active than the parent compounds. On the other hand, they are sligthly more cataleptic. In conclusion, the 6-fluorination in our series is not connected with any dramatic increase of activity and its duration. The 6-hydroxylation hardly represents an important metabolic pathway and its blockade by fluorination is thus not able to bring about important and practically useful changes in the pharmacodynamic profile.

The compounds prepared were also tested for antimicrobial activity *in vitro* towards a standard set of microorganisms (Dr L. Langšádl, bacteriological department of this Institute); microorganisms, numbers of the compounds and minimum inhibitory concentrations in μg/ml (unless they surpass 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *IIIc* 12·5, *Vc* 12·5, *VIc* 25; *Streptococcus faecalis*, *IIc* 100, *IIIc* 50, *Vc* 25, *VIc* 50; *Staphylococcus pyogenes aureus*, *Ic* 100, *IIIc* 12·5, *Vc* 12·5, *VIc* 25; *Escherichia coli*, *Ic* 50, *IIc* 50, *IIIc* 25, *Vc* 25, *VIc* 25; *Mycobacterium tuberculosis* H37Rv, *Ic* 6·25, *IIc* 25, *IIIc* 6·25, *Vc* 3·12, *VIc* 12·5; *Saccharomyces pasterianus*, *IIIc* 50, *Vc* 12·5, *VIc* 50; *Trichophyton mentagrophytes*, *Ic* 25, *IIIc* 50, *Vc* 25, *VIc* 50; *Candida albicans*, *Vc* 50; *Aspergillus niger*, *Vc* 50. In concentrations of 50—100 μg/ml, all compounds were inactive towards *Pseudomonas aeruginosa* and *Proteus vulgaris*. The high antimycobacterial activity is worth mentioning.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 70 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra ($CDCl_3$) were produced with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument; the mass spectrum was recorded with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of alumina or silica gel. Analyses of all of the dibenzo[*b*,*f*]thiepin derivatives prepared are summarized in Table I.

4-Chloro-2-fluoroaniline (*XX*)

A suspension of 55·4 g 4-chloro-2-fluorobenzoic acid[20] in 240 ml H_2SO_4 was stirred and slowly treated at 46—49°C with 24 g NaN_3. The mixture was stirred for 12 h at this temperature, poured into ice and water, made alkaline with NH_4OH and the product was isolated by extraction with ether. The extract was dried (Na_2SO_4) and distilled; 41·4 g (90%), b.p. 104—107°C/ /3·7 kPa. For analysis, a sample was redistilled, b.p. 92°C/2·0 kPa. ^{1}H-NMR spectrum: δ 6·40 to 7·10 (m, 3 H, Ar—H), 3·60 (bs, 2 H, NH_2). ^{19}F-NMR spectrum: δ —133·3 (m). For C_6H_5ClFN (145·6) calculated: 49·50% C, 3·46% H, 24·36% Cl, 13·05% F, 9·62% N; found: 50·06% C, 3·68% H, 23·96% Cl, 12·54% F, 9·66% N.

TABLE I
Dibenzo[*b*,*f*]thiepin Derivatives

Compound[a]	Method (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found					
				% C	% H	% Cl	% F	% N	% S
X	*A*	125—127[b]	$C_{14}H_9FOS$	68·83	3·71	—	7·78	—	13·13
	(75)	(benzene)	(244·3)	69·10	3·81	—	7·93	—	12·74
XI	*A*[c]	127—129	$C_{14}H_8ClFOS$	60·32	2·89	12·72	6·82	—	11·51
	(75)	(benzene)	(278·7)	60·41	2·97	12·68	7·14	—	11·77
XII	*A*	152—154[d]	$C_{14}H_8ClFOS$	60·32	2·89	12·72	6·82	—	11·51
	(81)	(benzene)	(278·7)	60·23	3·09	12·81	7·06	—	11·76
XIII	*B*	84—86[e]	$C_{14}H_{11}FOS$	68·27	4·50	—	7·71	—	13·02
	(86)	(cyclohexane)	(246·3)	68·62	4·67	—	7·49	—	12·82
XIV	*B*	84—86[f]	$C_{14}H_{10}ClFOS$	59·89	3·59	12·63	6·77	—	11·42
	(86)	(hexane)	(280·8)	59·46	3·60	12·71	6·34	—	11·59
XV	*B*[c]	112—114	$C_{14}H_{10}ClFOS$	59·89	3·59	12·63	6·77	—	11·42
	(89)	(benzene)	(280·8)	59·59	3·41	12·63	6·80	—	11·74
XVI	*C*	85—87[g]	$C_{14}H_{10}ClFS$	63·51	3·81	13·39	7·17	—	12·11
	(88)	(hexane)	(264·8)	63·34	3·71	13·22	7·53	—	12·27
XVII	*C*[c]	69—70	$C_{14}H_9Cl_2FS$	56·20	3·03	23·70	6·35	—	10·72
	(94)	(light petroleum)	(299·2)	56·26	3·01	23·41	6·51	—	10·87
XVIII	*C*	145—148	$C_{14}H_9Cl_2FS$	56·20	3·03	23·70	6·35	—	10·72
	(95)	(acetone)	(299·2)	56·34	3·14	23·45	6·64	—	10·57
Ic	*D*[c]	126·5—128·5	$C_{19}H_{21}FN_2S$	69·47	6·45	—	5·78	8·53	9·76
	(68)	(ethanol)	(328·5)	69·66	6·66	—	5·72	8·38	10·00
Ic-2 MS[h]	—	196—199	$C_{21}H_{29}FN_2O_6S_3$	47·62	5·71	—	3·59	5·29	18·16
		(ethanol–ether)	$+0·5\ H_2O$	47·73	5·13	—	3·55	5·46	17·63
			(529·7)						
IIc	*D*	98—101[i]	$C_{20}H_{23}FN_2OS$	67·01	6·47	—	5·30	7·82	8·94
	(81)	(acetone)	(358·5)	66·44	6·70	—	5·08	7·64	9·16
IIc-M	—	134—136	$C_{24}H_{27}FN_2O_5S$	60·74	5·74	—	4·00	5·90	6·76
		(ethanol–ether)	(474·6)	60·47	6·07	—	3·81	5·64	7·00

IIIc	*D*[c]	103—105	$C_{19}H_{20}ClFN_2S$	62·88	5·56	9·77	5·24	7·72	8·83
	(50)	(acetone)	(362·9)	62·98	5·67	9·82	5·11	7·49	8·96
IIIc-2 MS	—	177—180	$C_{21}H_{28}ClFN_2O_6S_3$	45·43	5·08	6·39	3·42	5·05	17·33
		(ethanol)	(555·1)	44·99	5·18	6·33	3·58	4·94	17·37
Vc	*D*	121—123[j]	$C_{19}H_{20}ClFN_2S$	62·88	5·56	—	—	7·72	—
	(72)	(acetone)	(362·9)	62·95	5·61	—	—	7·78	—
Vc-M	—	184—186	$C_{23}H_{24}ClFN_2O_4S$	57·67	5·05	7·40	3·97	5·85	6·70
		(ethanol)	(479·0)	57·56	4·86	7·55	3·77	5·84	6·63
VIc	*D*	153—156[k]	$C_{20}H_{22}ClFN_2OS$	61·13	5·65	—	—	7·13	—
	(68)	(ethanol)	(392·9)	61·32	5·74	—	—	7·06	—
VIc-2 MS	—	184—187	$C_{22}H_{30}ClFN_2O_7S_3$	45·15	5·17	6·06	3·25	4·79	16·44
		(ethanol)	(585·2)	44·89	5·10	6·11	3·44	4·70	16·36
XXIII	*D*[c]	62—64	$C_{14}H_8ClFS$	64·00	3·07	13·49	7·23	—	12·20
	(27)	(cyclohexane)	(262·7)	63·73	3·26	13·45	7·36	—	11·98
XXIV	*D*	143—145[l]	$C_{14}H_8ClFS$	64·00	3·07	13·49	7·23	—	12·20
	(25)	(benzene)	(262·7)	64·44	3·28	13·42	7·30	—	12·11

[a] MS methanesulfonate, M maleate. [b] UV spectrum: λ_{max} 252 nm (log ε 4·09), 330 nm (3·71); IR spectrum: 726, 760, 771, 802 (4 and 3 adjacent Ar—H), 1250, 1260, 1292 (C—O), 1565, 1598 (Ar), 1680 (ArCOR), 3060 cm^{-1} (Ar); ^{1}H-NMR spectrum: δ 8·00 (m, 1 H, 9-H), 7·70 (mcd, 1 H, 4-H), 7·00—7·50 (m, 5 H, 1,2,3,7,8-H_5), 4·35 (s, 2 H, $ArCH_2CO$); ^{19}F-NMR spectrum: δ —107·6 (m). [c] See Experimental. [d] UV spectrum: λ_{max} 229 nm (log ε 4·35), infl. 257 nm (4·05), 330 nm (3·68); IR spectrum: 809, 825, 886, 900, 909 (3 and 2 adjacent and solitary Ar—H), 1239, 1248 (C—O), 1564, 1580, 1596, 3087 (Ar), 1690 cm^{-1} (ArCOR); ^{1}H-NMR spectrum: δ 7·95 (m, 1 H, 9-H), 7·56 (d, J = 8·0 Hz, 1 H, 4-H), 7·40 (mcs, J = 2·5 Hz, 1 H, 1-H), *c.* 7·25 (m, 2 H, 7,8-H_2), 7·15 (mcd, J = 8·0; 2·5 Hz, 1 H, 3-H), 4·30 (s, 2 H, $ArCH_2CO$); ^{19}F-NMR spectrum: δ —107·4 (m). [e] IR spectrum: 700, 755, 774, 802 (3 and 2 adjacent Ar—H), 1042, 1074 (CHOH in a ring), 1257 (C—O), 1470, 1620, 3025, 3073 (Ar), 3370, 3539 cm^{-1} (OH). [f] IR spectrum (KBr): 750, 863, 888 (4 adjacent and solitary Ar—H), 1119 (CHOH in a ring), 1250, 1395, 1420, 1450 (OH), 1480, 1558, 1596, 3080, 3095 (Ar), 3470 cm^{-1} (OH). [g] ^{1}H-NMR spectrum: δ 6·80—7·70 (m, 7 H, Ar—H), 5·82 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·98 and 3·68 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$); ^{19}F-NMR spectrum: δ —107·9 (pcdd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz; $J_{F(p-H)}$ = 1 Hz). [h] Hemihydrate. [i] ^{1}H-NMR spectrum: δ 6·70 (m, 7 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, 2 H, CH_2O), *c.* 2·60 (m, 11 H, 5 NCH_2 and OH); ^{19}F-NMR spectrum: δ —108·4 (pcdd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = = 6·5 Hz; $J_{F(p-H)}$ = 1·0 Hz). [j] ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 and 2·48 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·23 (s, 3 H, NCH_3); ^{19}F-NMR spectrum: δ —108·4 (pcd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz; $J_{F(p-H)}$ = = 1·0 Hz). [k] IR spectrum: 790, 820, 825, 880, 885 (3 and 2 adjacent and solitary Ar—H), 1072 (CH_2OH), 1565, 1582, 1600, 3070, 3095 (Ar), 3230 cm^{-1} (OH); ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 5·0 Hz, 2 H, CH_2O), 2·90 (bs, 1 H, OH), *c.* 2·50 (m, 10 H, 5 NCH_2); ^{19}F-NMR spectrum: δ —108·3 (pcd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz; $J_{F(p-H)}$ = 1·0 Hz). [l] UV spectrum: λ_{max} 259 nm (log ε 4·37), 299 nm (3·55).

4-Chloro-2-fluoroacetanilide (*XXI*)

A mixture of 1·06 g *XX*, 2 ml acetic anhydride and 2 ml acetic acid was refluxed for 10 min and allowed to stand overnight at room temperature. After diluting with 3 ml water, the product was filtered, washed with water and dried *in vacuo*; 1·29 g (95%). For analysis, it was crystallized from ethanol, m.p. 156—158°C. For C_8H_7ClFNO(187·6) calculated: 51·21% C, 3·76% H, 18·90% Cl, 10·13% F, 7·47% N; found: 51·27% C, 3·77% H, 19·01% Cl, 10·01% F, 7·81% N.

2-Fluorothiophenol

A solution of 50·0 g 2-fluoroaniline[31] in 67·5 ml H_2SO_4 and 410 ml water was diazotized at —3 to +2°C with a solution of 36·3 g 98% $NaNO_2$ in 210 ml water. The mixture was stirred for 2 h at about 0°C and then added dropwise over 30 min to a stirred solution of 132 g potassium ethyl xanthate and 505 g $Na_2B_4O_7.10\,H_2O$ in 2 l water, maintained at 70—75°C. It was stirred for 1 h at this temperature and for another 1 h at room temperature. After standing overnight, the separated intermediate was extracted with ether, the extract was evaporated and the residue hydrolyzed for 5 h by refluxing with a solution of 58·5 g KOH in 460 ml ethanol. The solvent was evaporated *in vacuo*, the residue was dissolved in 900 ml water and the solution washed with ether. It was then acidified with 1 : 1 dilute H_2SO_4 and the released product isolated by extraction with ether. The extract was dried (Na_2SO_4) and distilled; 38·1 g (66%), b.p. 52—54°C/1·9 kPa. For analysis, it was redistilled, b.p. 72—73°C/4·7 kPa. For C_6H_5FS (128·2) calculated: 56·22% C, 3·93% H, 14·82% F, 25·02% S; found: 55·52% C, 4·29% H, 15·40% F, 24·87% S. The literature[13,14] reported a b.p. of 162—164°C/100 kPa.

TABLE II

Pharmacological Effects of the 6-Fluoro Derivatives in Comparison With Those of the Parent Compounds (oral doses in mg/kg)

Compound[a]	Generic name or code number	Acute toxicity LD_{50}	Ataxia ED_{50}	Catalepsy[b] ED_{50}
Ia (ref.[4])	Peratbiepin	63	2·4	45
Ic	VÚFB-12·489	54	3·1	>100 (40)
IIc	VÚFB-12·490	71	3·9	> 50 (20)
IIIa (ref.[5])	Octoclothepin	78	2·2	4·3
IIIc	VÚFB-12·429	170	2·5	1·5
Va(ref.[6])	Doclothepin	70	1·2	> 50 (10)
Vc	VÚFB-12·491	117	2·0	> 50 (40)
VIa (ref.[8])	Docloxythepin	84	0·8	> 50 (20)
VIc	VÚFB-12·492	125	3·9	> 50 (40)

[a] The compounds were tested in the form of salts described in the Experimental or in the indicated papers; the doses were calculated for bases. [b] The values in the parentheses indicate the percentage of the animals which were cataleptic after the dose given.

4-Chloro-2-fluorothiophenol (*XXII*)

A solution of 41·4 g *XX* and 42 ml H_2SO_4 in 480 ml water was diazotized with a solution of 22·5 g $NaNO_2$ in 100 ml water and the diazonium salt solution processed like in the preceding case with a solution of 83 g potassium ethyl xanthate and 318 g $Na_2B_4O_7.10\,H_2O$ in 2·5 l water. Similarly with the preceding case, the crude intermediate was hydrolyzed for 5 h by refluxing with 40 g KOH in 250 ml water. An analogous isolation procedure gave 28·5 g (62%), b.p. 104—106°C/5 kPa. Analytical sample, b.p. 78°C/1·9 kPa. For C_6H_4ClFS (162·6) calculated: 44·31% C, 2·48% H, 21·80% Cl, 11·68% F, 19·72% S; found: 44·33% C, 2·63% H, 21·55% Cl, 11·96% F, 19·85% S.

2-(2-Fluorophenylthio)-5-nitrobenzoic Acid (*XXXIV*)

2-Fluorothiophenol (25·0 g) was stirred for 10 min with a solution of 23 g KOH in 500 ml water, the mixture was then treated with 50 g 2-iodo-5-nitrobenzoic acid[30] and 0·5 g "molecular" copper and refluxed under stirring for 4 h. It was filtered while hot and the filtrate was acidified with hydrochloric acid. After standing overnight, the product was filtered, washed with water and recrystallized from ethanol; 44·4 g (89%), m.p. 235—238°C. Analytical sample, m.p. 237 to 238°C (ethanol). IR spectrum: 740, 760, 805, 823, 840 (4 and 2 adjacent and solitary Ar—H), 910, 1255 (COOH), 1050 (Ar—F), 1345, 1511 (Ar—NO_2), 1553, 1597 (Ar), 1692, 2498, 2565, 2633, 2725 cm^{-1} (COOH). For $C_{13}H_8FNO_4S$ (293·3) calculated: 53·24% C, 2·75% H, 6·48% F, 4·78% N, 10·93% S; found: 53·15% C, 2·76% H, 6·42% F, 4·74% N, 11·36% S.

2-(2-Fluoro-4-nitrophenylthio)benzyl Alcohol (*XXV*)

A mixture of 10·5 g 4-chloro-3-fluoronitrobenzene[25], 8·4 g 2-mercaptobenzyl alcohol[26], 4·5 g K_2CO_3 and 0·9 g Cu was stirred and heated for 3·5 h in a bath to 160—170°C. After partial cooling, it was decomposed with 50 ml water and extracted with benzene. The extract was washed with 10% NaOH and water, dried (Na_2SO_4) and evaporated; 14·7 g (88%) oily product. An uneasy crystallization from ethanol gave the analytical product melting at 76—79°C. IR spectrum: 740, 760, 810, 882 (4 and 2 adjacent and solitary Ar—H), 1055 (CH_2OH), 1345, 1515 (Ar—NO_2), 1470, 1590, 3110 (Ar), 3370 cm^{-1} (OH). For $C_{13}H_{10}FNO_3S$ (279·3) calculated: 55·90% C, 3·61% H, 6·80% F, 5·02% N, 11·48% S; found: 55·91% C, 3·67% H, 6·81% F, 4·88% N, 11·53% S.

2-(2-Fluorophenylthio)-5-nitrobenzyl Alcohol (*XXVIII*)

A suspension of 40·0 g *XXXIV* in 70 ml tetrahydrofuran was stirred and treated at 5°C over 20 min with 5·3 g $NaBH_4$. After 30 min stirring, the mixture was treated dropwise over 1 h with 20 g BF_3 etherate at 10—25°C. The mixture was stirred for 3 h at room temperature, decomposed with water and extracted with benzene. The extract was dried ($MgSO_4$) and evaporated; 38·0 g (100%), m.p. 98—101°C. Analytical sample, m.p. 98—101°C (cyclohexane). IR spectrum: 747, 763, 809, 830, 842, 902 (4 and 2 adjacent and solitary Ar—H), 1042 (CH_2OH), 1350, 1519 (Ar—NO_2), 1580, 1600 (Ar), 3280 cm^{-1} (OH). For $C_{13}H_{10}FNO_3S$ (279·3) calculated: 55·90% C, 3·61% H, 5·02% N; found: 55·51% C, 3·76% H, 4·98% N.

2-(4-Amino-2-fluorophenylthio)benzyl Alcohol (*XXVI*)

Fe powder (4·3 g) was added to a solution of 7·1 g *XXV* in 15 ml 75% ethanol, the refluxing mixture was treated dropwise with a solution of 0·55 ml hydrochloric acid in 15 ml 75% ethanol

and the mixture refluxed for 4·5 h. It was then filtered with charcoal, ethanol was evaporated *in vacuo*, the residue decomposed with 20% NaOH and the product extracted with benzene. Processing of the extract gave 5·14 g (82%) crude product, m.p. 75—78°C. Analytical sample was obtaned by crystallization from 50% ethanol, m.p. 79—81°C. IR spectrum: 749, 815, 838, 849 (4 and 2 adjacent and solitary Ar—H), 1060 (CH_2OH), 1492, 1569, 1588, 1609 (Ar), 1641 (Ar—NH_2), 3230, 3340, 3418 cm^{-1} (OH, NH_2). For $C_{13}H_{12}FNOS$ (249·3) calculated: 62·62% C, 4·95% H, 7·62% F, 5·62% N, 12·86% S; found: 63·22% C, 5·02% H, 7·48% F, 5·55% N, 12·75% S.

5-Amino-2-(2-fluorophenylthio)benzyl Alcohol (*XXIX*)

A solution of 39·5 g *XXVIII* in 600 ml ether was stirred and treated under cooling with small portions of 129 g $SnCl_2.2\,H_2O$. The cooling bath was removed and the stirred mixture was treated over 30 min with 115 ml hydrochloric acid, added dropwise in such a rate that gentle refluxing was maintained. It was then refluxed for 4 h. The mixture was decomposed by a slow addition of 600 ml 20% NaOH, the organic layer was separated, washed with 20% NaOH, dried (K_2CO_3) and evaporated; 32·7 g (93%), m.p. 63—65°C. Analytical sample, m.p. 64—66°C (aqueous ethanol). IR spectrum: 758, 763, 810, 827, 880 (4 and 2 adjacent and solitary Ar—H), 1073 (CH_2OH), 1568, 1599 (Ar), 1632 (Ar—NH_2), 3220, 3300, 3430 cm^{-1} (OH, NH_2). ^{1}H-NMR spectrum: δ 7·24 (d, J = 8·0 Hz, 1 H, 3-H), 6·60—7·20 (m, 5 H, 6-H and Ar-H of the *o*-phenylene), 6·49 (mcs, J = 8·0; 3·0 Hz, 1 H, 4-H), 4·56 (s, 2 H, $ArCH_2O$), 3·55 (s, disappears after D_2O, 3 H, NH_2 and OH). ^{19}F-NMR spectrum: δ —113·0 (m). For $C_{13}H_{12}FNOS$ (249·3) calculated: 62·63% C, 4·85% H, 7·62% F, 5·62% N, 12·86% S; found: 62·86% C, 5·07% H, 7·58% F, 5·44% N, 12·79% S.

2-(4-Chloro-2-fluorophenylthio)benzyl Alcohol (*XXVII*)

A solution of 5·1 g *XXVI* in 8 ml ethanol was treated with 10 ml hydrochloric acid and 10 ml water and the mixture was diazotized with a solution of 1·6 g $NaNO_2$ in 5 ml water in the usual way. The solution obtained was stirred for 30 min at 0°C and then poured into a solution of 2·8 g CuCl in 8 ml hydrochloric acid, heated to 100°C. The mixture was heated for 15 min on a boiling water bath and after partial cooling extracted with benzene. The extract was washed with dilute HCl, 5% NaOH and water, dried (Na_2SO_4), and processed by distillation; 3·41 g (62%), b.p. 176—179°C/0·33 kPa. Analytical sample, b.p. 165—167°C/0·13 kPa. IR spectrum: 761, 817, 862, 902 (4 and 2 adjacent and solitary Ar—H), 1040 (CH_2OH), 1475, 1570, 1591 (Ar), 3380 cm^{-1} (OH). For $C_{13}H_{10}ClFOS$ (268·7) calculated: 13·20% Cl, 7·07% F, 11·93% S; found: 12·70% Cl, 6·86% F, 11·68% S.

5-Chloro-2-(2-fluorophenylthio)benzyl Alcohol (*XXX*)

XXIX (29·8 g) was dissolved under heating in a solution of 35 ml hydrochloric acid in 35 ml water. Cooling gave a suspension of the hydrochloride which was stirred and diazotized at —5 to +3°C with a solution of 8·5 g $NaNO_2$ in 50 ml water, added dropwise. The mixture was cooled and stirred for 40 min to obtain a solution of the diazonium salt. This solution was slowly added to a stirred solution of 16 g CuCl in 65 ml hydrochloric acid at room temperature. Under stirring, the mixture was slowly heated on a water bath and maintained for a short time at 100°C. After partial cooling, the product was extracted with benzene, the extract was washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated; 26·0 g (82%) oily product which crystallized from a mixture of benzene and light petroleum. Analytical sample, m.p. 104—106°C (n-hexane). IR spectrum (KBr): 760, 815, 827, 873 (4 and 2 adjacent and solitary Ar—H), 1038

(CH_2OH), 1478, 1577, 1600 (Ar), 3220, 3300 cm^{-1}(OH). For $C_{13}H_{10}ClFOS$ (268·7) calculated: 58·10% C, 3·75% H, 13·19% Cl, 7·07% F, 11·93% S; found: 58·19% C, 3·81% H, 12·91% Cl, 7·14% F, 11·97% S.

[5-Chloro-2-(2-fluorophenylthio)phenyl]acetonitrile (*XXXVI*)

Crude *XXX* (76·5 g) was dissolved in 500 ml benzene and 40 ml pyridine and the stirred solution was treated dropwise with 42 g thionyl chloride. The mixture was refluxed for 2 h, evaporated *in vacuo*, the residue dissolved in 250 ml ether, the solution washed with water, dried ($MgSO_4$) and evaporated giving 57·7 g (70%) crude 5-chloro-2-(2-fluorophenylthio)benzyl chloride (*XXXV*) which was used for further work without purification.

A solution of 57 g crude *XXXV* and 27 g KCN in 250 ml dimethylformamide was stirred and heated for 1 h to 120°C. After cooling, it was diluted with water and extracted with ether. Processing of the extract gave 55 g (almost 100%) of the crude oily product, a sample of which was distilled for analysis, b.p. 180°C/0·13 kPa. For $C_{14}H_9ClFNS$ (277·8) calculated: 60·55% C, 3·26% H, 5·04% N; found: 60·79% C, 3·40% H, 4·78% N.

5-Chloro-2-(2-fluorophenylthio)acetophenone (*XXXI*)

A mixture of 29·6 g 2,5-dichloroacetophenone[28], 22·6 g 2-fluorothiophenol, 38·2 g K_2CO_3 and 0·7 g Cu was stirred and heated for 2·5 h to 140—160°C. After partial cooling, the mixture was extracted with 500 ml boiling benzene, undissolved material was filtered off and the filtrate evaporated *in vacuo*. The residue was crystallized from 250 ml ethanol (the hot solution filtered with charcoal); 38·0 g (86%), m.p. 101—103°C. Analytical sample, m.p. 102—104°C (ethanol). UV spectrum: λ_{max} 234 nm (log ε 4·06), 268 nm (3·95), 343 nm (3·59). IR spectrum (KBr): 760, 820, 830, 880 (4 and 2 adjacent and solitary Ar—H), 1475, 1550, 1575, 1598 (Ar), 1685 cm^{-1} (ArCOR). ^{1}H-NMR spectrum: δ 7·80 (mcs, J = 2·0 Hz, 1 H, 6-H), 7·00—7·70 (m, 5 H, 4-H and Ar—H of the *o*-phenylene), 6·78 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 2·63 (s, 3 H, $COCH_3$). ^{19}F-NMR spectrum: δ —106·7 (m). For $C_{14}H_{10}ClFOS$ (280·8) calculated: 59·89% C, 3·59% H, 12·63% Cl, 6·77% F, 11·42% S; found: 60·38% C, 3·56% H, 12·70% Cl, 6·76% F, 11·54% S.

[5-Chloro-2-(2-fluorophenylthio)phenyl]acetothiomorpholide (*XXXII*)

A mixture of 12·3 g *XXXI*, 2·8 g sulfur and 10 g morpholine was stirred and heated under reflux for 11 h to 140—150°C. After partial cooling, the mixture was dissolved in 120 ml ethanol, the solution was filtered with charcoal and the filtrate evaporated *in vacuo*. The residue was mixed with 25 ml ether and filtered with suction; 9·2 g (55%), m.p. 99—102°C. Analytical sample, m.p. 102—104°C (ethanol). IR spectrum: 753, 814, 862, 871, 890 (4 and 2 adjacent and solitary Ar—H), 1117 (C—O—C), 1500 (CSN), 1557, 1582, 3033, 3055, 3085 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·50 (bs, 1 H, 6-H), 6·90—7·40 (m, 6 H, remaining Ar—H), 4·40 (s, 2 H, $ArCH_2CS$), 3·50—4·50 (m, 8 H, 2 NCH_2CH_2O of morpholine). ^{19}F-NMR spectrum: δ —109·8 (m). For $C_{18}H_{17}ClFNOS_2$ (381·9) calculated: 56·60% C, 4·49% H, 9·28% Cl, 4·97% F, 3·67% N, 16·79% S; found: 56·59% C, 4·40% H, 9·45% Cl, 4·95% F, 3·66% N, 16·96% S.

[5-Chloro-2-(2-ethoxyphenylthio)phenyl]acetic Acid (*XXXIII*)

XXXII (2·45 g), 1·8 g KOH and 6 ml ethanol were refluxed for 3 h. Ethanol was evaporated *in vacuo*, the residue was dissolved in 20 ml water, the solution washed with benzene and acidified with hydrochloric acid. The separated product was extracted with ether, the extract was dried

(Na_2SO_4) and evaporated. Crystallization of the residue from 12 ml cyclohexane gave 1·31 g (63%) acid *XXXIII*, m.p. 97—107°C. Analytical sample, m.p. 108—110°C (cyclohexane). Mass spectrum, *m/e* (%): 322·0443 (M^+, 100, corresponds to $C_{16}H_{15}ClO_3S$), 247 (53), 231 (36), ^{1}H-NMR spectrum: δ 11·00 (bs, 1 H, COOH), 6·70—7·50 (m, 7 H, Ar—H), 4·06 (q, J = 7·0 Hz, 2 H, OCH_2), 3·90 (s, 2 H, $ArCH_2CO$), 1·38 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{16}H_{15}ClO_3S$ (322·8) calculated: 59·53% C, 4·68% H, 10·98% Cl, 9·93% S; found: 59·48% C, 4·78% H, 11·20% Cl, 10·08% S.

[2-(2-Fluorophenylthio)phenyl]acetic Acid (*VII*)

2-Fluorothiophenol (21·8 g) was added to a solution of 32·5 g KOH in 340 ml water, the mixture stirred for 10 min at 50°C, the solution treated with 44·6 g (2-iodophenyl)acetic acid[11,12] and 1·4 g Cu, and the mixture refluxed for 15 h. It was filtered while hot and the filtrate was acidified with hydrochloric acid. After standing overnight, the product was filtered, washed with water and dried *in vacuo*; 37·2 g (84%), m.p. 91—93°C. Analytical sample, m.p. 93—95°C (ethanol). IR spectrum: 764, 772 (4 adjacent Ar—H), 932, 1246, 1710, 2580, 2650, 2680 (COOH), 1482, 1582, 1600, 3040, 3075 cm^{-1} (Ar). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·10% C, 4·23% H, 7·24% F, 12·23% S; found: 64·73% C, 4·24% H, 7·12% F, 12·51% S.

[2-(4-Chloro-2-fluorophenylthio)phenyl] acetic Acid (*VIII*)

The reaction of 28·5 g *XXII*, 45·9 g (2-iodophenyl)acetic acid[11,12], 33·5 g KOH and 1·9 g Cu in 350 ml water was carried out in the same manner like in the preceding case. Processing of the mixture gave 51 g crude product which was crystallized from 60 ml 80% aqueous ethanol; 45·5 g (87%), m.p. 119—120°C. Analytical sample, m.p. 118·5—121°C (80% ethanol). IR spectrum: 747, 828, 864, 896 (4 and 2 adjacent and solitary Ar—H), 953, 1320, 1707, 2565, 2675 (COOH), 1472, 1569, 1580, 3073, 3092 cm^{-1} (Ar). For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·66% C, 3·39% H, 11·95% Cl, 6·40% F, 10·81% S; found: 56·71% C, 3·35% H, 11·84% Cl, 6·26% F, 10·83% S.

[5-Chloro-2-(2-fluorophenylthio)phenyl]acetic Acid (*IX*)

A mixture of 8·4 g *XXXII*, 26·5 ml acetic acid, 14 ml H_2SO_4 and 14 ml water was refluxed for 16 h. It was then poured into 200 ml water and the precipitated crude product filtered. It was dissolved in 170 ml boiling ethanol, the solution was filtered with charcoal, and the filtrate evaporated *in vacuo*: 5·65 g (87%), m.p. 127—135°C. Analytical sample, m.p. 136—137°C (ethanol). IR spectrum: 760, 830, 871 (4 and 2 adjacent and solitary Ar—H), 939, 1247, 1714, 2568, 2645, 2748 (COOH), 1472, 1566, 1572, 1588, 3025, 3083 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 10·98 (bs, 1 H, COOH), 6·80—7·40 (m, 7 H, Ar—H), 3·85 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —109·9 (m). For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·66% C, 3·40% H, 11·95% Cl, 6·40% F, 10·81% S; found: 56·70% C, 3·44% H, 11·95% Cl, 6·24% F, 11·08% S.

8-Chloro-6-fluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XI*) (Method *A*)

A mixture of 5·93 g *VIII* and 30 g polyphosphoric acid was heated for 5 h to 150°C. After cooling, the mixture was decomposed with 100 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from benzene; 4·15 g (75%), m.p. 125—127°C. Analytical sample, m.p. 127—129°C (benzene). UV spectrum: λ_{max} 240 nm (log ε 4·30), 260 nm (4·09), 340 nm (3·72). IR spectrum: 751, 770, 846, 883 (4 adjacent and solitary Ar—H), 1480, 1554, 1590, 3085 (Ar), 1682 cm^{-1} (Ar—CO).

^{1}H-NMR spectrum: δ 7·95 (m, 1 H, 9-H), 7·62 (mcd, 1 H, 4-H), 7·00—7·50 (m, 4 H, remaining Ar—H), 4·30 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —104·8 (dd, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(p-H)}$ = 1·5 Hz).

2-Chloro-6-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XV*) (Method *B*)

A solution of 4·82 g *XII* in 40 ml ethanol and 20 ml benzene was stirred and treated dropwise with a solution of 0·28 g $NaBH_4$ in 2·5 ml water containing 0·1 ml 5% NaOH. The mixture was refluxed for 3·5 h and ethanol was evaporated *in vacuo*. The residue was decomposed with 60 ml water and extracted with benzene. The extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from 5 ml benzene; 4·28 g (89%), m.p. 110—114°C. Analytical sample, m.p. 112—114°C (benzene). IR spectrum: 736, 790, 814, 880, 909 (3 and 2 adjacent and solitary Ar—H), 1 045, 1 070 (CHOH in a ring), 1 250 (Ar—F), 1 500, 1 560, 1 579, 1 586, 1 603, 3 090 (Ar), 3 180, 3 260 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·46 (d, J = = 8·0 Hz, 1 H, 4-H), 6·80—7·40 (m, 5 H, remaining Ar—H), 5·38 (dt, 1 H, Ar—CH—O),3·66 and 3·26 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·45 (bd, J = 8·0 Hz, 1 H, OH). ^{19}F-NMR spectrum: δ —108·6 (pcd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz; $J_{F(p-H)}$ = 1·0 Hz).

8,10-Dichloro-6-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*XVII*) (Method *C*)

$CaCl_2$ (1·5 g) was added to a solution of 2·30 g *XIV* in 15 ml benzene and the suspension was saturated with hydrogen chloride at room temperature. After standing overnight, it was filtered and the filtrate was evaporated *in vacuo*; 2·25 g (94%) crude product. Crystallization from light petroleum gave the pure substance, m.p. 69—70°C. ^{1}H-NMR spectrum: δ 7·55 (m, 1 H, 4-H), 7·10—7·40 (m, 4 H, 1,2,3,9-H_4), 6·99 (mcd, J_{H-F} = 8·0 Hz, J_{H-H} = 2·0 Hz, 1 H, 7-H), 5·75 (dd, J = 6·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 6·0 Hz, 2 H, $ArCH_2$). ^{19}F-NMR spectrum: δ —105·2 (dd, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(p-H)}$ = 1·5 Hz).

6-Fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ic*) (Method *D*)

A mixture of 6·62 g *XVI*, 5·2 ml 1-methylpiperazine and 7 ml chloroform was refluxed for 10 h. Chloroform was evaporated, the residue was decomposed with 40 ml water and extracted with benzene. The extract was shaken with an excess of 1 : 1 dilute hydrochloric acid. A solid hydrochloride precipitated which was filtered off.

The filtrate, containing neutral by-products, was washed with dilute hydrochloric acid and water, dried (Na_2SO_4) and evaporated. The residue (2·05 g) was crystallized from a mixture of benzene and light petroleum; 0·60 g, m.p. 339—341°C. The structure of 1,9-difluorobisdibenzo[2,3; 6,7]thiepino[4,5-*b*; 4′,5′-*d*]furan (*XIX*) (for the nomenclature, *cf*.[32]) was ascribed to this product. UV spectrum: λ_{max} 253 nm (log ε 4·19), infl. 260 nm (4·18), 320 nm (4·15), infl. 340 nm (4·19). IR spectrum: 701, 761, 798, 802 (4 and 3 adjacent Ar—H), 1 253 (=C—O—C=), 1 491, 1 559, 1 567, 3 060 cm^{-1} (Ar). For $C_{28}H_{14}F_2OS_2$ (468·5) calculated: 71·77% C, 3·01% H, 8·11% F, 13·69% S; found: 71·87% C, 3·13% H, 8·14% F, 13·48% S.

The hydrochloride mentioned was decomposed with NH_4OH and the base *Ic* was extracted with benzene. The extract was dried (Na_2SO_4) and evaporated. There were obtained 5·58 g (68%) of the base *Ic*, m.p. 126·5—128·5°C (ethanol). ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 7 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·69 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). ^{19}F-NMR spectrum: δ —108·5 (pcdd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz; $J_{F(p-H)}$ = 1 Hz).

Neutralization with methanesulfonic acid in 95% ethanol and addition of ether resulted in a bis(methanesulfonate) hemihydrate, m.p. 196—199°C (ethanol–ether).

8-Chloro-6-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIc*)

The reaction of 7·48 g *XVII* with 5·2 ml 1-methylpiperazine in 7 ml chloroform was carried out like in the preceding case. Shaking of the benzene solution of the crude base with 3M-HCl gave a solid hydrochloride which was filtered off. The benzene filtrate was washed with dilute hydrochloric acid and water, dried with Na_2SO_4 and evaporated. The residue was chromatographed on a column of 100 g alumina (activity II). Benzene eluted first 1·8 g (27%) of the least polar component which crystallized from cyclohexane (m.p. 62—64°C) and was identified as 2-chloro-4-fluorodibenzo[*b,f*]thiepin (*XXIII*). ^{1}H-NMR spectrum: δ 6·70—7·70 (m, Ar—H and CH=CH).

Decomposition of the hydrochloride with NH_4OH and extraction with benzene gave 4·52 g (50%) base *IIIc*, m.p. 103—105°C (acetone). ^{1}H-NMR spectrum: δ 6·80—7·70 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·70 and 2·45 (2 t, 8 H, 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). ^{19}F-NMR spectrum: δ —105·8 (dd, $J_{F(o-H)} = 8·5$ Hz; $J_{F(p-H)} = 6·5$ Hz).

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