2-AND 3-FLUORO DERIVATIVES OF CLOROTEPIN AND RELATED COMPOUNDS; 6- AND 7-FLUORO DERIVATIVE OF CHLORPROTHIXENE*

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Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

Starting from 5-fluoro-2-iodobenzoic acid (*X*) and from 4-fluoro-2-iodobenzoic acid (*XI*) or from the corresponding bromofluorobenzoic acids, 8-chloro-2-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXa*) and the 3-fluoro isomer (*XXb*) were synthesized in six steps. These were converted in three further steps to the 2- and 3-fluoro derivatives of clorotepin (*Ia*, *Ib*) and the corresponding amino alcohols, *IIa* and *IIb*. The ketones *XXa* and *XXb* reacted with 1-methylpiperazine in the presence of titanium tetrachloride to enamines *IIIa* and *IIIb*. Acids *XIVa*, *XIX* and *XIVb* were cyclized to the thioxanthones *Va* and *Vb* which were converted in two steps to the 7- and 6-fluoro derivatives of chlorprothixene *IVa* and *IVb*. Compounds *Iab*—*IIIab* are effective neuroleptics, the 3-fluoro derivatives *Ib*—*IIIb* being more potent and exhibiting signs of protracted effect upon oral application. Of the fluoro derivatives of chlorprothixene, a high degree of neuroleptic activity was retained only by the 6-fluoro derivative *IVb*.

A typical group of highly effective neuroleptics are the 4-piperidino-*p*-fluorobutyrophenones and 4,4-bis(*p*-fluorophenyl)-butylpiperidines[1,2]; the fluorine atoms in *para* positions of the benzene rings are important for achieving a high degree of activity and duration of effect which may be explained by their blocking the sites of the usual metabolic hydroxylation, thus inhibiting the biotransformation process, often associated with detoxication and inactivation. In connection with a recently published study[3] on the 2- and 3-hydroxy derivatives of the neuroleptic clorotepin[4] (octoclothepin), *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*, R = H)[5,6] which were synthesized as potential metabolites of the above preparation and at least partly identified as such[7], the present paper is devoted to the fluoro analogues *Ia* and *Ib* of these compounds, further the corresponding amino alcohols *IIa* and *IIb* and finally the enamines *IIIa* and *IIIb*. A similar approach to deriving other active agents has not been applied so far to the classical neuroleptic chlorpromazine, *i.e.* 2-chloro-10-(3-dimethylaminopropyl)phenothiazine, although it is known to be metabolized to the 7- and 8-hydroxy derivatives (a review in ref.[3]). Likewise, the cor-

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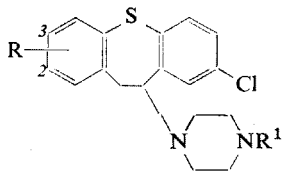
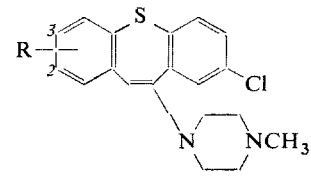
responding fluoro derivatives are not known with another neuroleptic, chlorprothixene[8,9], which is *cis*-2-chloro-9-(3-dimethylaminopropylidene)thioxanthene (*IV*, R = = H). The gap is being filled in the present paper where the synthesis of the 7- and 6-fluoro derivatives of chlorprothixene *IVa* and *IVb* is described.

For synthesizing *I*–*IV*, similar procedures were employed as in the synthesis of analogous compounds (*e.g.*[3,5,10]). The starting compounds used were 5-fluoro-2-iodobenzoic acid (*X*) and 4-fluoro-2-iodobenzoic acid (*XI*). The first of these was obtained from 5-fluoro-2-nitrotoluene[11] which was hydrogenated on Raney nickel under normal pressure to 2-amino-5-fluorotoluene (its preparation by reduction of the nitro compound with tin and hydrochloric acid is described in ref.[11]). The 2-acetamido--5-fluorotoluene (*VII*) obtained with the aid of acetic anhydride was oxidized by potassium permanganate to 2-acetamido-5-fluorobenzoic acid (*VIII*) which was then hydrolyzed to 5-fluoroanthranilic acid (*IX*), the preparation of which by a different procedure had been known from the literature[12]. Transformation to acid *X* led *via* a diazonium salt.

In preparing acid *XI* we proceeded from 2-nitro-4-fluorotoluene[13] which was reduced according to ref.[13] with iron and hydrochloric acid in methanol (method[14]) as well as with hydrogen in the presence of Raney nickel in ethanol. When the analogous hydrogenation was carried out in methanol, a crystalline compound precipitated after a part of the hydrogen was consumed – this led to a stop in further hydrogen consumption. The precipitated compound was identified as 2,2'-dimethyl--5,5'-difluorazoxybenzene (*XIII*). Further hydrogenation on fresh Raney nickel in warm methanol led to the desired 2-amino-4-fluorotoluene. Further procedure

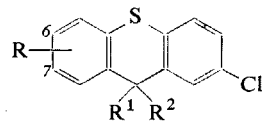


I, $R^1 = CH_3$
II, $R^1 = (CH_2)_3OH$



III

[*a*, R = 2-F; *b*, R = 3-F]

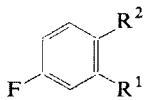


IV, $R^1R^2 = =CH(CH_2)_2N(CH_3)_2$
V, $R^1R^2 = O$
VI, $R^1 = OH$, $R^2 = (CH_2)_3N(CH_3)_2$

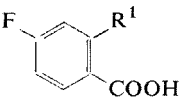
[*a*, R = 7-F; *b*, R = 6-F]

according to ref.[13] led to 4-fluoroanthranilic acid which was diazotized and the diazonium salt reacted with potassium iodide to acid *XI*.

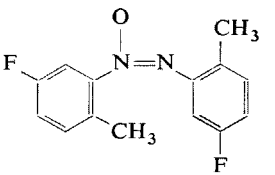
Acids *X* and *XI* were condensed with 4-chlorothiophenol in a boiling solution of potassium hydroxide in the presence of copper to acids *XIVa* and *XIVb*. The acid *XIVa* was obtained through the reaction of the described[15] 2-bromo-5-fluorobenzoic acid with 4-chlorothiophenol in dimethylformamide in the presence of anhydrous potassium carbonate and copper. In a similar way, the acid *XIVb* was prepared from 2-bromo-4-fluorobenzoic acid obtained by oxidation of 2-bromo-4-fluorotoluene[16] with potassium permanganate (for a preparation by a different oxidation method see ref.[16]). In the case that acid *XI* was added to the potassium hydroxide solution before adding 4-chlorothiophenol, the reactive iodine atom was rapidly replaced with hydroxyl, resulting in 4-fluorosalicylic acid (*XII*), the formation of which by a different procedure had been known[17]. Reduction of acids *XIVa* and *XIVb* with lithium aluminium hydride in ether led to alcohols *XVa* and *XVb* which were treated with thionyl chloride in benzene to convert them to chlorides *XVIa* and *XVIb*. The transformation of chloride *XVIa* to nitrile *XVIIa* with the aid of sodium cyanide was



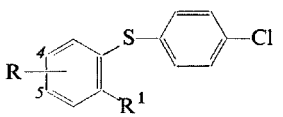
VII, $R^1 = CH_3$, $R^2 = NHCOCH_3$
VIII, $R^1 = COOH$, $R^2 = NHCOCH_3$
IX, $R^1 = COOH$, $R^2 = NH_2$
X, $R^1 = COOH$, $R^2 = I$



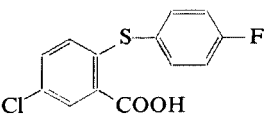
XI, $R^1 = I$
XII, $R^1 = OH$



XIII



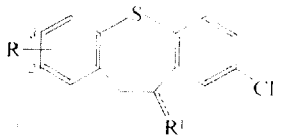
XIV, R = COOH
XV, R = CH_2OH
XVI, R = CH_2Cl
XVII, R = CH_2CN
XVIII, R = CH_2COOH



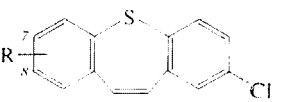
XIX

[*a*, R = 5-F; *b*, R = 4-F]

carried out both in dimethylformamide and in aqueous ethanol. Since the first yielded a rather inhomogeneous product, chloride *XVIb* was converted to nitrile *XVIIb* by the second procedure. Both nitriles were hydrolyzed with aqueous-ethanolic potassium hydroxide to acids *XVIIIa* and *XVIIIb*.



XX, $R^1 = =O$
XXI, $R^1 = OH$
XXII, $R^1 = Cl$



XXIII, R = 8-F
XXIV, R = 7-F

[*a*, R = 2-F; *b*, R = 3-F]

Acids *XVIIIa* and *XVIIIb* were cyclized by heating to 140–150°C with polyphosphoric acid, producing a high yield of ketones *XXa* and *XXb* which were reduced with sodium borohydride in ethanol to alcohols *XXIa* and *XXIb*. Action of anhydrous hydrogen chloride in benzene yielded the chlorides *XXIIa* and *XXIIb*. Their substitution reaction with 1-methylpiperazine and 1-(3-hydroxypropyl)piperazine[18] in boiling chloroform yielded as main products the bases *Ia*, *Ib*, *IIa* and *IIb*. Elimination was observed in a minor extent, its products having been isolated and characterized as 2-chloro-8-fluorodibenzo[*b*,*f*]thiepin (*XXIII*) and 2-chloro-7-fluorodibenzo[*b*,*f*]-thiepin (*XXIV*). Reactions of ketones *XXa* and *XXb* with 1-methyl piperazine and titanium tetrachloride in boiling benzene produced enamines *IIIa* and *IIIb* (see ref.[19]).

Heating of acids *XIVa* and *XIVb* with sulfuric acid resulted in cyclization to the chlorofluorothioxanthones *Va* and *Vb*. The first of these (*Va*) was obtained by a similar cyclization of isomeric 2-(4-fluorophenylthio)-5-chlorobenzoic acid (*XIX*) prepared in a reaction of 5-chloro-2-iodobenzoic acid[20] with 4-fluorothiophenol[21,22]. This thiophenol was obtained by reduction of 4-fluorobenzenesulfonyl chloride[21] with iodine and phosphorus in boiling acetic acid[23]. Reactions of ketones *Va* and *Vb* with 3-dimethylaminopropylmagnesium chloride[24] produced amino alcohols *VIa* and *VIb* which were dehydrated by heating with dilute sulfuric acid. The bases obtained were isolated in the form of hydrochlorides. Whereas with *IVa* the symmetrical position of the two halogen atoms prevents the application of the IR spectrum[10,25,26] to distinguish the geometrical isomers so that the possibility exists that the present product is a mixture of both isomers, in case of *IVb* a hydrochloride was obtained which appears homogeneous and where the IR spectrum indicates its belonging to the series of active *cis*-chlorprothixene (mutual position of the side chain and the chlorine atom). This conclusion is supported also by the pharmacodynamic properties of the compound.

The fluorinated derivatives of clorotepin, chlorprothixene and their analogues (*Ia*—*IVb*) were subjected to a pharmacological evaluation. They were applied in the form of the corresponding salts in doses referring to the base. The common administration was per os in the form of solutions or suspensions in water, prepared by addition of 25% gum acacia. Only *Ib* (maleate) and, for comparison, clorotepin (*I*, R = H) (methanesulfonate) were administered also parenterally, dissolved in 5% glucose. With mice, the acute toxicity of the compounds and further the incoordinating effect in the rotating-rod test (as indicator of central depressant activity) were estimated. Using rats, the cataleptic effect as indicator of neuroleptic activity was examined. With several compounds, the antagonistic effect toward apomorphine chewing of rats was studied (as indicator of neuroleptic activity). At the same time, effect on agitation was investigated. The results are shown in Table I which includes as standards the corresponding nonfluorinated compounds, *i.e.* clorotepin[4,6] (*I*, R = H), oxyclothepin[27,28] (*II*, R = H), dehydroclothepin[19] (*III*, R = H), chlorprothixene[29] (*IV*, R = H), and penfluridol[30,31], *i.e.* 1-[4,4-bis(4-fluorophenyl)butyl]-4-hydroxy-4-(3-trifluoromethyl-4-chlorophenyl)piperidine.

The acute toxicity of the compounds was determined in female mice, in groups of ten, after an oral application within 7 days, after an intravenous one within 2 days. The motor coordination in mice (groups of ten females) was examined in the rotating-rod test[32]. The intervals between oral application of the compound and testing the coordination were 15, 30, 45, 60, 90 and 120 min, with intravenous application 5, 10, 15, 30, 45 and 60 min, and further 24 and 48 h. Catalepsy was tested in female rats according to Boissier and Simon[33]. The individual doses were administered to groups of ten animals and catalepsy was evaluated with oral administration after 1 h and further in 30-min intervals for 5 h; with parenteral administration in 30-min intervals for 4 h and further after 24 or 48 h to complete cessation of effect. The values were used to calculate the mean effective doses (ED_{50}). The antiapomorphine effect was examined in male rats using the test of Janssen and coworkers[34,35], following an intravenous application of apomorphine in a dose of 1·25 mg/kg. The individual doses were administered orally to groups of ten animals 4 h before apomorphine. The intensity of chewing and agitation was evaluated in four grades (0—3) in five-minute intervals for 15 min following injection of apomorphine. The doses decreasing the average control value by 50% (D_{50}) were calculated. Table I shows the acute effects, Table II the effects after 24 or 48 h.

The fluorinated derivatives of the clorotepin series are generally more toxic than clorotepin, the 3-fluoro derivatives being more toxic than the 2-fluoro ones. On the other hand, the fluoro derivatives of chlorprothixene are similarly toxic as chlorprothixene itself. Toxic symptoms are depression, paresis of limbs, ptosis and, in higher doses, clonic spasms; the animals died usually one day after application, in smaller numbers also on subsequent days.

As to the incoordinating effect, the 2-fluoro derivatives of the clorotepin series (*Ia*—*IIIa*) match clorotepin or are better. The 3-fluoro derivatives are 2—3 times more potent, the relationships being maintained even on parenteral application (*cf.* the pair of *Ib* and clorotepin). The 3-fluoro derivatives show an incoordinating effect in a significant part of the animals even on the following day, compound *Ib* even on the third day after oral administration (Table II); after intravenous application, the effect wanes on the second day already, simiarly to the case with clorotepin. While the 7-fluoro derivative of chlorprothixene (*IVa*) is little effective (which may be due to the fact that it contains a good part of the *trans* isomer), the 6-fluoro derivative

IVb is more potent than chlorprothixene; its effect is still apparent on the second day after application.

The cataleptic activity of fluorinated derivatives of clorotepin and oxyclothepin (ref.[27] reports an erroneously high ED_{50} in the catalepsy test after oral administration) exhibits no substantial differences between the individual compounds and is comparable to the activity of nonfluorinated compounds. The activity of the enamines *IIIa* and *IIIb* is higher, resembling the effective doses of dehydroclothepin[19]. Whereas the 7-fluoro derivative of chlorprothixene (*IVa*) is cataleptically practically ineffective,

TABLE I

Pharmacological Effects of Fluorinated Derivatives of Clorotepin, Chlorprothixene and Analogues (mg/kg)

Compound	Administration	Mice			Rats	
		acute toxicity LD_{50}	rotating rod ED_{50}[a]	catalepsy ED_{50}[b]	antiapomorphine effects[c] chewing D_{50}	antiapomorphine effects[c] agitation D_{50}
Ia	*p.o.*	56	2·3	3·4	7·5	7·9
Ib	*p.o.*	28·5	0·8	3·8	3·4	3·1
Ib	*i.v.*	22·5	0·03	0·19[d]	—	—
IIa	*p.o.*	115·0	1·5	5·3	—	—
IIb	*p.o.*	36·0	0·7	4·2	—	
IIIa	*p.o.*	[e]	1·2	<1·0[f]	—	—
IIIb	*p.o.*	39·0	0·9	<2·5[g]	0·8	0·8
IVa	*p.o.*	235	36·0	>100[h]	—	—
IVb	*p.o.*	140	2·1	10·0	—	—
I, R = H[j]	*p.o.*	78·0	2·2	4·3	2·2	2·5
I, R = H[j]	*i.v.*	46·3	0·06	2·4[d]	—	—
II, R = H[k]	*p.o.*	145	3·4	4·5	—	—
III, R = H[m]	*p.o.*	44	0·43	1·4	—	—
IV, R = H[n]	*p.o.*	245	5·2	23·0	—	—
Penfluridol	*p.o.*	330	[o]	>30·0[p]	10—30	10—30

[a] Mean effective dose at the time of maximum effect of tested substance. [b] Dose bringing about catalepsy in 50% animals. [c] Dose decreasing the mean control value by 50%. [d] Intraperitoneally. [e] Toxicity has not been determined. [f] A dose of 1 mg/kg brings about catalepsy in 60% rats, 2·5 mg/kg in 90% rats, 5 mg/kg in 100% rats (groups of ten). [g] Doses of 2·5 and 5·0 mg/kg bring about catalepsy in 90% animals. [h] Dose of 100 mg/kg brings about catalepsy in one rat out of ten. [i] After a dose of 100 mg/kg three mice out of ten died. [j] Clorotepin[4,6]. [k] Oxyclothepin[27,28]. [m] Dehydroclothepin[19]. [n] Chlorprothixene[29]. [o] A dose of 40 mg/kg *p.o.* caused motor incoordination of at most 20% mice in the course of a two-hour observation period. [p] A dose of 30 mg/kg *p.o.* brings about catalepsy in 40% rats.

the 6-fluoro derivative *IVb* is about twice as effective as chlorprothixene. This may be used as an argument for its classification in the *cis*-chloroprothixene series. With the exception of *IIa* and *IVa*, the cataleptic effect of the fluorinated derivatives of the clorotepin and chlorprothixene series was demonstrable on the second day, in the case of 3-fluorooxyclothepin (*IIb*) even on the third day after administration (the effect of clorotepin vanishes on the second day). The 3-fluoro derivative of clorotepin (*Ib*) displays an enormous cataleptic activity after intraperitoneal application, exceeding clorotepin by more then ten-fold. However, its effect is less protracted than after oral administration, being apparent only in one rat out of ten 24 h after an *i.p.* administration.

The compounds tested inhibit apomorphine chewing and agitation in the same doses. The highest activity was shown by enamine *IIIb* which exceeds clorotepin significantly. To follow the duration of effect, the compounds tested were applied in a dose which in a 4 h interval inhibited maximally the apomorphine effect. These

TABLE II

Duration of Effect of Fluorinated Derivatives of Clorotepin, Chlorprothixene and Analogues after Oral Administration to Rats and Mice

Compound	Catalepsy[a]		Antiapomorphine effect		Motor coordination[a]	
	24 h	48 h	chewing 24 h	agitation 24 h	24 h	48 h
Ia	0—3	1	0[b]	0	0	0
Ib	0—2[c]	1	0[d]	0	0—9[e]	0—4
IIa	0	0	—	—	0—4	0
IIb	3—4	0—3	—	—	0—9	0
IIIa	0—4	0	—	—	0	0
IIIb	—	—	[f]	0	0—3	0
IVa	0	0	—	—	0	0
IVb	0—4	0	—	—	0—1	0
I, R = H[g]	0	0	0[h]	0	0	0
Penfluridol	1—2	1—4	[i]	[i]	0	0

[a] Data for minimum and maximum number of animals from groups of ten displaying the effect after 24 or 48 h, following doses allowing to calculate the ED_{50} on the day of administration. [b] The compound was administered in a dose of 20 mg/kg. [c] After doses of 10 and 25 mg/kg one rat died before the second day. [d] Administered in a dose of 15 mg/kg. [e] After the highest dose given (5 mg/kg), one mouse died before the second day. [f] At a dose of 10 mg/kg, the compound inhibited with statistical significance ($p = 0{\cdot}05$, using the *t*-test against the control group) the apomorphine chewing to 70% of the control group. [g] Clorotepin. [h] Administered in a dose of 5 mg/kg. [i] Administered in a dose of 30 mg/kg, the compound shows a significant antiapomorphine effect.

doses were 20 mg/kg for *Ia*, 15 mg/kg for *Ib*, 10 mg/kg for *IIIb* and 5 mg/kg for clorotepin. At 24 h after oral application of these doses, a statistically significant inhibition of apomorphine chewing was observed only with enamine *IIIb*; apomorphine agitation was not affected at this time interval by any of the compounds used.

In conclusion, it may be said that introduction of the fluorine atom into position 2 and especially into position 3 of the clorotepin neuroleptics produced novel central depressants and neuroleptics of higher activity, exceeding, in some cases significantly, the nonfluorinated analogues (particularly as far as the 3-fluoro derivatives are concerned) and displaying a certain prolongation of effects after oral administration. However, toxicity rises in parallel with activity. Fluorination of chlorprothixene in position 6 also favourably affects the activity.

A special mention should be devoted to penfluridol[30,31]. This appears to be a neuroleptic of a completely different type, tests in mice and rats being unsuitable for it. In acute tests it is almost inactive and in tests where prolongation of effect was examined it does not appear to be more advantageous than the compounds tested here.

Some of the compounds prepared were tested for antimicrobial activity *in vitro*; Table III shows the minimum inhibitory concentrations toward several typical microorganisms (Dr J. Turinová and Dr A. Čapek). The 6-fluoro derivative of chlorprothixene (*IVb*) prolongs with statistical significance the survival of C 57 mice bearing LAH leukemia when administered from the first day after transplantation until death. The compound has a more pronounced effect than chlorprothixene[36–38] even if it does not differ from it significantly. When injected in a single dose on the third day after transplantation in amounts of 6, 12, 18 or 21 mg/kg, it does not prolong survival. Negative results were obtained when testing the antileukemic activity of *Ia*, *IIa*, *IIb* and *IIIb* (Dr V. Pujman).

TABLE III

Antimicrobial Activity of Several Agents *in vitro* (the minimum inhibitory concentrations in μg/ml are shown)

Microorganism	Compound[a]			
	Ia	*Ib*	*IIa*	*IVa*
Streptococcus β-haemolyticus	—	12·5	25	50
Staphylococcus pyogenes aureus	—	25	25	50
Mycobacterium tuberculosis H37Rv	25	—	12·5	12·5
Saccharomyces pasterianus	125	125	125	—
Trichophyton mentagrophytes	125	125	125	125
Aspergillus niger	—	125	—	—

[a] The first three compounds were tested in the form of maleates, the fourth as hydrochloride.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 0·5 Torr over P_2O_5 at a suitable temperature (100°C at most). UV spectra (in methanol unless stated otherwise) were registered in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200 G spectrophotometer or in a Hilger and Watts Infrascan, 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.

2-Acetamido-5-fluorotoluene (*VII*)

A solution of 50·0 g 5-fluoro-2-nitrotoluene[11] (b.p. 98—100°C/10 Torr) in 300 ml ethanol was hydrogenated in the presence of 50 g Raney nickel at atmospheric pressure and 50°C. After cessation of hydrogen uptake the catalyst was filtered and the filtrate was distilled. A total of 36·7 g (91%) 2-amino-5-fluorotoluene was obtained; b.p. 100—102°C/25 Torr. For a product obtained by reduction of the same nitro-compound with tin and hydrochloric acid, ref.[11] reports a b.p. of 97°C/20 Torr.

A mixture of 69 g amine and 100 g acetic anhydride was left without cooling overnight, decomposed by adding 1 liter water, the precipitated product was filtered, washed with water and dried; 84·4 g (92%), m.p. 113—114°C (benzene). For $C_9H_{10}FNO$ (167·2) calculated: 64·66% C, 6·03% H, 8·38% N; found: 65·34% C, 5·92% H, 8·49% N.

2-Acetamido-5-fluorobenzoic Acid (*VIII*)

VII (51 g) was added to a solution of 140 g $KMnO_4$ and 58 g $MgSO_4$ in 4300 ml water and the mixture was heated under stirring for 2·5 h to 80°C. After partial cooling, it was filtered, the filtrate was purified with charcoal and after its removal acidified with hydrochloric acid. A total of 41·2 g (69%) acid precipitated which, after recrystallization from aqueous ethanol, melts at 180—181°C. For $C_9H_8FNO_3$ (197·2) calculated: 54·82% C, 4·09% H; found: 54·77% C, 3·97% H.

5-Fluoroanthranilic Acid (*IX*)

A mixture of 14·7 g *VIII*, 150 ml ethanol and 22 ml hydrochloric acid was refluxed for 40 min. After partial cooling, the ethanol was evaporated at reduced pressure, the residue was dissolved in a slight excess of 5M-NaOH and the solution was filtered and then acidified with acetic acid to pH 6. After partial evaporation *in vacuo* and cooling, 10·3 g (89%) crude product crystallized; this was recrystallized for analysis from water; m.p. 182—183°C under decomposition. Ref.[12] reports a m.p. of 180°C for a product obtained in a different way.

5,5'-Difluoro-2,2'-dimethylazoxybenzene (*XIII*)

A solution of 100 g 4-fluoro-2-nitrotoluene[13] (b.p. 107°C/21 Torr) in 800 ml methanol was hydrogenated in the presence of 100 g Raney nickel and under moderate heating. When about one-half of the theoretical amount of hydrogen was taken up, hydrogenation stopped and a crystalline compound precipitated. A sample was recrystallized from methanol, m.p. 112—113°C. UV spectrum: λ_{max} 230 nm (log ε 3·90), 307 nm (3·92). IR spectrum: 810, 815, 850, 865 (2 adjacent and solitary Ar—H), 1250, 1263, 1317 (N=N—O), 1571, 1610 cm^{-1} (Ar, N=N). For $C_{14}H_{12}F_2N_2O$ (263·3) calculated: 64·11% C, 4·61% H, 10·69% N; found: 63·85% C, 4·62% H, 10·90% N.

2-Amino-4-fluorotoluene

A) Reduction of 4-fluoro-2-nitrotoluene[13] according to ref.[13] by means of iron powder and hydrochloric acid in boiling methanol (method[14]) proceeds slowly and even after 5 h and when using iron of different quality, the product obtained (b.p. 105—108°C/25 Torr) contains mostly the starting compound. This is demonstrated also by the fact that 27·7 g of the substance obtained is acetylated with acetic anhydride[13] only to 9·0 g 2-acetamido-4-fluorotoluene, m.p. 133—135°C (ref.[13] reports a m.p. of 133·5—134°C).

B) A solution of 15·5 g 4-fluoro-2-nitrotoluene[13] in 100 ml methanol was hydrogenated in the presence of 15 g Raney nickel under occasional cooling with ice water. Usual processing yielded 10·2 g (82%) amine boiling at 95°C/15 Torr. Ref.[13] reports a b.p. of 100—101°C/16 Torr. The product thus obtained forms the desired acetyl derivative (m.p. 133—135°C) in a 88% yield.

C) Compound *XIII*, obtained by hydrogenation of 100 g 4-fluoro-2-nitrotoluene was dissolved in 800 ml boiling methanol, the catalyst was removed by filtration, the filtrate was diluted with 800 ml methanol and, after adding further 100 g Raney nickel, hydrogenation concluded. A total of 55·8 g (69%) amine was obtained (b.p. 95°C/15 Torr) which yielded the acetyl derivative in a high yield.

5-Fluoro-2-iodobenzoic Acid (*X*)

A solution of 31·5 g *IX* in 33 ml concentrated hydrochloric acid and 200 ml water was diazotized under stirring at 0°C with a solution of 14·5 g $NaNO_2$ in 32 ml water. The solution of diazonium salt obtained was combined under stirring with a solution of 51·5 g KI in dilute sulfuric acid (12 ml H_2SO_4 in 85 ml water). The mixture was heated to 100°C and stirred for 2 h at this temperature. The precipitated iodine was removed by steam-distillation and the remaining liquid was cooled whereupon 49·5 g (92%) product precipitated; m.p. 149—150°C (benzene). IR spectrum: 828 and 890 (2 adjacent and solitary Ar—H), 929, 1215, 1260, 1295 (COOH), 1575, 1590 (Ar), 1660, 1700 (Ar—COOH), 2640 cm^{-1} (COOH). For $C_7H_4FIO_2$ (266·0) calculated: 31·60% C, 1·52% H, 47·71% I; found: 31·77% C, 1·55% H, 47·78% I.

4-Fluoro-2-iodobenzoic Acid (*XI*)

Similarly to the preceding case, 19·8 g 4-fluoroanthranilic acid[13] (m.p. 195—197°C) was used to prepared 30·7 g (90%) product which was recrystallized from benzene for analysis; m.p. 147 to 149°C. UV spectrum: infl. 227 nm ($\log \varepsilon$ 3·98). IR spectrum: 1695 cm^{-1} (Ar—COOH). For $C_7H_4FIO_2$ (266·0) calculated: 31·60% C, 1·52% H, 7·14% F, 47·71% I; found: 31·63% C, 1·54% H, 7·31% F, 47·78% I.

2-Bromo-4-fluorobenzoic Acid

2-Bromo-4-fluorotoluene[16] (43·8 g, b.p. 171—174°C/760 Torr) was boiled for 5 h with a solution of 106 g $KMnO_4$ and 52 g $MgSO_4$ in 3000 ml water. The nonreacted starting compound was steam-distilled (a recovery of 9·1 g), the remaining liquid was filtered while hot, the filtrate was decolourized by adding $Na_2S_2O_5$ and made acid with hydrochloric acid. After cooling, 21·4 g (55% per conversion) compound was filtered; m.p. 173—175°C. Ref.[16] reports for a product obtained by a different oxidation method a m.p. of 171—172·5°C.

2-(4-Chlorophenylthio)-5-fluorobenzoic Acid (*XIVa*)

A) 4-Chlorothiophenol (16·2 g) was dissolved in a solution of 20·2 g KOH in 210 ml water under stirring and then combined with 28·0 g *X* and 1·2 g Cu. The mixture was refluxed under stirring for 2 h, filtered while hot and the filtrate acidified with hydrochloric acid. After cooling, filtration yielded 27·0 g (91%) product, a sample of which was crystallized from ethanol; m.p. 184—186°C. For $C_{13}H_8ClFO_2S$ (282·7) calculated: 55·22% C, 2·85% H, 12·54% Cl, 11·34% S; found: 55·20% C, 2·75% H, 12·48% Cl, 11·27% S.

B) A mixture of 1·5 g 2-bromo-5-fluorobenzoic acid[15] (m.p. 155—157°C), 3·0 ml dimethylformamide, 1·2 g 4-chlorothiophenol 1·15 g K_2CO_3 and 0·1 g Cu was refluxed under stirring for 2 h in a 150—160°C bath. It was then diluted with 20 ml water, filtered while hot and the filtrate acidified with hydrochloric acid. After cooling, 1·9 g (90%) acid melting at 178—182°C was obtained. It was identical with the product prepared according to (*A*).

4-Fluoro-2-(4-chlorophenylthio)benzoic Acid (*XIVb*)

A) Acid *XI* (40 g) was processed as in the preceding case under (*A*). The product obtained was boiled with 200 ml ethanol; after cooling, 40·4 g product (95%) was filtered and a sample was recrystallized from ethanol, m.p. 255—257°C. UV spectrum: λ_{max} 224 nm (log ε 4·23), 257 nm (3·81), 282 nm (3·57). IR spectrum: 770, 782 (C—Cl), 820, 870 (2 adjacent and solitary Ar—H), 905, 1250, 1265 (COOH), 1562, 1585 (Ar), 1673 (Ar—COOH), 2565, 2645, 2680 cm^{-1} (COOH). For $C_{13}H_8ClFO_2S$ (282·7) calculated: 55·22% C, 2·85% H, 12·54% Cl, 6·72% F, 11·34% S; found: 55·47% C, 2·99% H, 12·54% Cl, 6·83% F, 11·20% S.

B) 2-Bromo-4-fluorobenzoic acid (1·5 g) was processed as in the preceding case according to (*B*). A total of 1·8 g (90%) product was obtained; m.p. 246—251°C, the product being identical with the crude product prepared under (*A*).

4-Fluorosalicylic Acid (*XII*)

Acid *XI* (6·0 g) and 0·2 g copper were added to a solution of 4·3 g KOH in 45 ml water. The mixture was boiled for 5 min, 3·4 g 4-chlorothiophenol was added and processed similarly to the two preceding cases as under (*A*). A total of 3·6 g acid *XII* was obtained; m.p. 190—193°C (aqueous ethanol). IR spectrum: 855, 890 (2 adjacent and solitary Ar—H), 980 (Ar—OH), 1135, 1210 (C—F), 1250, 1260 (COOH), 1595, 1620 (Ar), 1670 (Ar—COOH), 2535 (COOH), 3250 cm^{-1} (OH). For $C_7H_5FO_3$ (156·1) calculated: 53·85% C, 3·23% H, 12·17% F; found: 54·12% C, 3·21% H, 12·30% F. Ref.[17] reports a m.p. of 186°C for the same compound obtained in a different way.

2-(4-Chlorophenylthio)-5-fluorobenzyl Alcohol (*XVa*)

Acid *XIVa* (38·0 g) was added to a stirred suspension of 6·8 g $LiAlH_4$ in 750 ml ether and the mixture was refluxed for 4 h. After cooling, 15 ml water was added dropwise and this was followed with 300 ml diluted hydrochloric acid (1 : 4). After separation, the ether layer was washed with water and 5% NaOH, dried with K_2CO_3 and evaporated. An almost theoretical yield (35·8 g) of a crystalline residue was obtained; a sample was recrystallized from cyclohexane; m.p. 63—65°C. IR spectrum: 812, 820, 870 and 882 (2 adjacent and solitary Ar—H), 1031 (CH_2OH), 1095 (Ar—F), 1582, 1600 (Ar), 3240 cm^{-1} (OH). For $C_{13}H_{10}ClFOS$ (268·7) calculated: 58·10% C, 3·75% H, 13·19% Cl, 11·93% S; found: 58·68% C, 3·76% H, 13·09% Cl, 12·02% S.

2-(4-Chlorophenylthio)-4-fluorobenzyl Alcohol (*XVb*)

Acid *XIVb* (5·6 g) was reduced with 1·0 g $LiAlH_4$ like in the preceding case. A total of 5·1 g (95%) product was obtained; m.p. 82—84°C (cyclohexane). IR spectrum: 819, 850, 897 (2 adjacent and solitary Ar—H), 1010 (CH_2OH), 1568, 1572, 1599 (Ar), 3200 and 3310 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: 58·48% C, 3·77% H, 12·88% Cl, 7·30% F, 12·06% S.

2-(4-Chlorophenylthio)-5-fluorobenzyl Chloride (*XVIa*)

$SOCl_2$ (15 ml) was added dropwise to a boiling solution of 35·8 g crude *XVa* in 100 ml benzene. The mixture was refluxed for 30 min and evaporated at reduced pressure. A theoretical amount (38·9 g) of an oily crude product was obtained. A sample for analysis was redistilled; b.p. 135°C/ /0·1 Torr. For $C_{13}H_9Cl_2FS$ (287·2) calculated: 54·37% C, 3·16% H, 24·69% Cl, 11·17% S; found: 55·00% C, 3·03% H, 24·32% Cl, 11·26% S.

2-(4-Chlorophenylthio)-4-fluorobenzyl Chloride (*XVIb*)

As in the preceding case, 30·6 g crude *XVb* reacted with 12 ml $SOCl_2$ in 75 ml benzene. A total of 32·5 g oily residue was obtained and this was used for further work. A sample for analysis was recrystallized from ethanol; m.p. 71—72°C. For $C_{13}H_9Cl_2FS$ (287·2) calculated: 54·37% C, 3·16% H, 24·69% Cl, 6·61% F, 11·17% S; found: 54·22% C, 3·27% H, 24·18% Cl, 6·90% F, 11·22% S.

2-(4-Chlorophenylthio)-5-fluorophenylacetonitrile (*XVIIa*)

A) A mixture of 2·6 g *XVIa*, 0·7 g NaCN and 5 ml dimethylformamide was refluxed for 2 h. After cooling, it was diluted with water and the product was extracted with chloroform. Distillation yielded 1·35 g chromatographically nonhomogeneous liquid boiling at 142—160°C/0·2 Torr which was chromatographed on a column of 30 g alumina (*II*). Elution with benzene yielded 1·0 g product, melting at 87—89°C (cyclohexane). NMR spectrum: δ 7·40—7·80 (m, 3 H, aromatic protons of phenylacetonitrile), 7·38 and 7·11 (2 d, $J = 9·0$ Hz, 4 H, aromatic protons of 4-chlorophenylthio group), 3·84 (s, 2 H, $ArCH_2CN$). For $C_{14}H_9ClFNS$ (277·8) calculated: 60·54% C, 3·27% H, 12·77% Cl, 11·54% S; found: 60·73% C, 3·07% H, 12·68% Cl, 11·63% S.

B) A mixture of solutions of 38·9 g crude *XVIa* in 40 ml ethanol and 8·7 g NaCN in 15 ml water was refluxed for 6 h. Ethanol was evaporated at reduced pressure and the residue diluted with water and extracted with benzene. Processing of the extract produced 36·4 g (97%) crude product which crystallized after seeding and which is a practically homogeneous nitrile *XVIIa*.

2-(4-Chlorophenylthio)-4-fluorophenylacetonitrile (*XVIIb*)

Reaction of 22 g crude *XVIb* with 4·9 g NaCN in 20 ml ethanol and 10 ml water as in the preceding case according to (*B*) yielded 20·5 g product which crystallized. A sample was recrystallized from ethanol; m.p. 63—64°C. IR spectrum: 815, 828, 855, 891 (2 adjacent and solitary Ar—H), 1568, 1598 (Ar), 2248 cm^{-1} (R—CN). For $C_{14}H_9ClFNS$ (277·8) calculated: 60·54% C, 3·27% H, 12·77% Cl, 6·84% F, 11·54% S; found: 60·58% C, 3·19% H, 12·72% Cl, 6·95% F, 11·53% S.

2-(4-Chlorophenylthio)-5-fluorophenylacetic Acid (*XVIIIa*)

A mixture of 36·4 g crude *XVIIa*, 125 ml ethanol and 33 g KOH in 65 ml water was refluxed for 3 h. Ethanol was evaporated at reduced pressure, the residue was diluted with water and the solution was washed with chloroform. After filtration with charcoal, the filtrate was acidified with hydrochloric acid. A total of 20·9 g (54%) acid (m.p. 136—141°C) was obtained. Recrystallization from a mixture of benzene and light petroleum raised the m.p. to 140—142°C. IR spectrum (KBr): 821, 834, 878 (2 adjacent and solitary Ar—H), 915, 1236, 1250 (COOH), 1483, 1585, 1610 (Ar), 1712 cm^{-1} (R—COOH). NMR spectrum: δ 10·70 (bs, disappears after D_2O, 1 H, COOH), 7·20—7·80 (m, 3 H, aromatic protons of phenylacetic acid), 7·35 and 7·10 (2 d, J = = 9·0 Hz, 4 H, aromatic protons of the 4-chlorophenylthio group), 3·88 (s, 2 H, $ArCH_2COO$). For $C_{14}H_{10}ClFO_2S$ (296·7) calculated: 11·95% Cl, 10·81% S; found 11·59% Cl, 11·18% S.

2-(4-Chlorophenylthio)-4-fluorophenylacetic Acid (*XVIIIb*)

Hydrolysis of 19·0 g crude *XVIIb* with the aid of 18 g KOH in 35 ml water and 65 ml ethanol yielded like in the preceding case 14·7 g (73%) acid melting at 122—125°C; after recrystallization from a mixture of benzene and light petroleum it melted at 124—125°C. IR spectrum (KBr): 807, 825, 840, 861, 869 (two adjacent and solitary Ar—H), 900, 925, 1232 (COOH), 1572, 1600 (Ar), 1700 cm^{-1} (R—COOH). For $C_{14}H_{10}ClFO_2S$ (296·7) calculated: 56·66% C, 3·40% H, 11·95% Cl, 6·40% F, 10·81% S; found: 56·97% C, 3·56% H, 11·89% Cl, 6·07% F, 10·76% S.

8-Chloro-2-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXa*)

A mixture of 112 g P_2O_5 and 75 ml 85% H_3PO_4 was heated to 140—150°C. After adding 14·9 g *XVIIIa* it was heated under stirring for 2 h at the same temperature, then it was partly cooled and decomposed with 400 ml water and extracted with chloroform. The extract was washed with 5% NaOH and water, dried and evaporated. A total of 13·2 g (94%) product was obtained; recrystallization from benzene yielded a ketone melting at 189—191°C. UV spectrum: λ_{max} 243 nm (log ε 4·27), 342 nm (3·71), infl. 265 nm. IR spectrum: 736 (C—Cl), 820, 888 (2 adjacent and solitary Ar—H), 1105 (C—F), 1580, 1600 (Ar), 1670 cm^{-1} (Ar—CO). For $C_{14}H_8ClFOS$ (278·7) calculated: 60·32% C, 2·89% H, 12·72% Cl, 11·51% S; found: 60·45% C, 2·92% H, 12·98% Cl, 11·36% S.

8-Chloro-3-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXb*)

Similarly to the preceding case, 20·0 g *XVIIIb* was cyclized to 17·0 g (90%) product melting at 115—118°C; after recrystallization from a mixture of benzene and light petroleum it melted at 120—122°C. UV spectrum: λ_{max} 229 nm (log ε 4·25), 240 nm (4·24), 259 nm infl. (4·03), 333 nm (3·61). IR spectrum (KBr): 810, 827, 849, 880 (2 adjacent and solitary Ar—H), 1103 (C—F), 1577, 1599 (Ar), 1672 cm^{-1} (Ar—CO). NMR spectrum: δ 8·19 (d, J = 3·0 Hz, 1 H, 9-H), 6·90—7·60 (m, 5 H, remaining aromatic protons), 4·34 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8ClFOS$ (278·7) calculated: 60·32% C, 2·89% H, 12·72% Cl, 6·82% F, 11·51% S; found: 60·10% C, 2·90% H, 12·69% Cl, 6·68% F, 11·48% S.

8-Chloro-2-fluoro-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIa*)

A solution of 11·0 g crude *XXa* in 220 ml ethanol was brought to boil and after partial cooling under stirring, 2·2 g $NaBH_4$ was gradually added. The mixture was refluxed for 30 min, ethanol was evaporated at reduced pressure, the residue was diluted with water and the product isolated

by extraction with chloroform; 11·0 g (almost the theoretical amount) product which was recrystallized from a mixture of benzene and light petroleum, m.p. 95—97°C. IR spectrum (KBr): 825, 835, 863 (2 adjacent and solitary Ar—H), 1025, 1060, 1088 (CHOH in a ring), 1212 (Ar—F), 1578, 1600 (Ar), 3350 cm^{-1} (OH). NMR spectrum: δ 6·60—7·70 (m, 6 H, aromatic protons), 4·30 (m, after D_2O dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—O), 3·70 and 3·25 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·22 (bs, disappears after D_2O, 1 H, OH). For $C_{14}H_{10}ClFOS$ (280·7) calculated: 59·89% C, 3·59% H, 12·63% Cl, 11·42% S; found: 60·00% C, 3·63% H, 12·38%Cl, 11·45% S.

8-Chloro-3-fluoro-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIb*)

This was obtained by reduction of *XXb* similarly to the preceding case; m.p. 131—133°C (benzene–light petroleum). IR spectrum: 814, 830, 865, 881 (2 adjacent and solitary Ar—H), 995, 1055, 1110 (CHOH in a ring), 1230 (C—F), 1489, 1579 (Ar), 3300 and 3365 cm^{-1} (OH). NMR spectrum (CD_3COCD_3): δ 7·65 (d, J = 2·0 Hz, 1 H, 9-H), 6·75—7·55 (m, 5 H, remaining aromatic protons), 5·46 (m, after D_2O dd, J = 10·0; 5·0 Hz, 1 H, Ar—CH—O), 4·85 (d, J = 5·0 Hz, disappears after D_2O, 1 H, OH), 3·55 and 3·10 (2 dd, J = 16·0; 5·0 and 16·0; 10·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_{10}ClFOS$ (280·7) calculated: 59·89% C, 3·59% H, 12·63% Cl, 6·77% F, 11·42% S; found: 60·00% C, 3·17% H, 12·53% Cl, 6·62% F, 11·44% S.

8,10-Dichloro-2-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIIa*)

Dry hydrogen chloride was passed for 6 h into a solution of 11·1 g crude *XXIa* in 110 ml benzene with 5 g $CaCl_2$. The crude product obtained by evaporation (11·8 g) contains according to the chromatographic check some 10% starting *XXIa*. The sample was crystallized from cyclohexane; m.p. 90—92°C. NMR spectrum: δ 6·70—7·60 (m. 6 H, aromatic protons), 5·68 (dd, J = 9·0; 5·0 Hz, 1 H, Ar—CH—Cl), 3·96 and 3·66 (2 dd, J = 15·0; 5·0 and 15·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_9Cl_2FS$ (299·2) calculated: 23·70% Cl, 10·72% S; found: 23·18% Cl, 11·00% S.

8,10-Dichloro-3-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIIb*)

Similarly to the preceding case, a solution of 10·4 g *XXIb* in 200 ml benzene was saturated for 8 h with hydrogen chloride; a total of 9·7 g (87%) product was obtained; m.p. 120—124°C. The analytical sample was obtained by crystallization from cyclohexane, m.p. 125—126°C. NMR spectrum: δ 7·53 (d, J = 3·5 Hz, 1 H, 9-H), 6·85—7·50 (m, 5 H, remaining aromatic protons), 5·69 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·55 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_9Cl_2FS$ (299·2) calculated: 56·20% C, 3·03% H, 23·70% Cl, 6·35% F, 10·72% S; found: 56·23% C, 3·13% H, 23·76% Cl, 6·28% F, 10·65% S.

8-Chloro-2-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*)

A mixture of 6·0 g crude *XXIIa*, 10 g 1-methylpiperazine and 15 ml chloroform was refluxed for 4 h, diluted with chloroform and washed with water. The base was extracted from the chloroform solution by a larger volume of dilute sulfuric acid, from the acid solution it was liberated with NH_4OH and extracted with chloroform; 4·8 g (66%), m.p. 107—109°C (cyclohexane). NMR spectrum: δ 7·65 (d, J = 3·0 Hz, 1 H, 9-H), 6·60—7·60 (m, 5 H, remaining aromatic protons), c. 3·84 (m, 2 H, $ArCH_2$), 3·15 (m, 1 H, Ar—CH—N), 2·68 (t, 4 H, $CH_2N^1CH_2$), 2·45 (t, 4 H, $CH_2N^4CH_2$), 2·25 (s, 3 H, N-CH_3). For $C_{19}H_{20}ClFN_2S$ (362·9) calculated: 62·88% C, 5·56% H, 9·77% Cl, 7·72% N, 8·84% S; found: 63·40% C, 5·59% H, 9·96% Cl, 7·35% N, 9·01% S.

Maleate, m.p. 201—202°C under decomposition (ethanol). For $C_{23}H_{24}ClFN_2O_4S$ (479·0) calculated: 57·67% C, 5·05% H, 7·40% Cl, 5·85% N, 6·70% S; found: 58·00% C, 5·20% H, 7·24% Cl, 5·65% N, 6·85% S.

The chloroform solution after removal of basic fractions was washed with water, dried with K_2CO_3, filtered with charcoal and evaporated. A total of 1·5 g 2-chloro-8-fluorodibenzo[*b,f*]thiepin (*XXIII*) was obtained; m.p. 122—124°C (cyclohexane). NMR spectrum: δ 6·80—7·60 (m, 6 H, aromatic protons), 7·00 (s, 2 H, olefinic CH=CH). For $C_{14}H_8ClFS$ (262·7) calculated: 64·00% C, 3·07% H, 13·50% Cl, 12·20% S; found: 64·25% C, 3·18% H, 13·31% Cl, 11·90% S.

8-Chloro-3-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

Similarly to the preceding case, 3·1 g *XXIIb* reacted with 4·6 g 1-methylpiperazine; a total of 2·3 g (62%) base was obtained; m.p. 112—114°C (cyclohexane). NMR spectrum: δ 7·62 (d, J = 2·5 Hz, 1 H, 9-H), 6·80—7·50 (m, 5 H, remaining aromatic protons), 3·00—4·00 (m, 3 H, Ar—CH_2CH—Ar), 2·58 (m, 4 H, $CH_2N^1CH_2$), 2·40 (m, 4 H, $CH_2N^4CH_2$), 2·25 (s, 3 H, N—CH_3). For $C_{19}H_{20}ClFN_2S$ (362·9) calculated: 62·88% C, 5·56% H, 9·77% Cl, 5·23% F, 8·84% S; found: 63·03% C, 5·78% H, 9·92% Cl, 5·31% F, 9·10% S.

Maleate, m.p. 144—145°C (ethanol–ether). For $C_{23}H_{24}ClFN_2O_4S$ (479·0) calculated: 57·67% C, 5·05% H, 7·40% Cl, 3·97% F, 6·70% S; found: 57·67% C, 5·20% H, 7·18% Cl, 3·86% F, 6·69% S.

Like in the preceding case, the elimination product was isolated: 2-chloro-7-fluorodibenzo[*b,f*]thiepin (*XXIV*); 0·9 g (33%), m.p. 100—101°C (cyclohexane). UV spectrum: λ_{max} 221 nm (log ε 4·46), 264·5 nm (4·39), 296 nm (3·56). IR spectrum: 688, 698 (Ar—Cl), 778 (*cis*-CH=CH), 818, 822, 838, 878, 885 (2 adjacent and solitary Ar—H), 1150 (Ar—F), 1570 and 1595 cm^{-1} (Ar). NMR spectrum: δ 7·10—7·50 (m, 6 H, aromatic protons), 7·10 and 6·80 (ABq, J = 12·0; 12·0 Hz, 2 H, olefinic CH=CH). For $C_{14}H_8ClFS$ (262·7) calculated: 64·00% C, 3·07% H, 13·50% Cl, 7·23% F, 12·20% S; found: 63·66% C, 3·01% H, 13·37% Cl, 7·24% F, 12·52% S.

8-Chloro-2-fluoro-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIa*)

Like in the preceding cases, 5·6 g *XXIIa* reacted with 6·0 g 1-(3-hydroxypropyl)piperazine[18] in boiling chloroform, yielding 4·7 g (62%) base, m.p.142—143°C (ethanol). IR spectrum ($CHCl_3$): 1145 (CH_2OH), 1580, 1595 (Ar), 3250 cm^{-1} (OH). NMR spectrum: δ 7·74 (d, J = 3·0 Hz, 1 H, 9-H), 7·39 (d, J = 9·0 Hz, 1 H, 6-H), 6·70—7·60 (m, 4 H, remaining aromatic protons), 5·20 (bs, disappears after D_2O, 1 H, OH), 3·80 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 10 H, 5 NCH_2), 1·75 (m, 2 H, CH_2 in the middle of propyl). For $C_{21}H_{24}ClFN_2OS$ (406·9) calculated: 61·98% C, 5·94% H, 8·71% Cl, 6·89% N, 7·88% S; found: 62·23% C, 6·13% H, 8·93% Cl, 6·90% N, 8·05% S.

Maleate, m.p. 151—152°C (ethanol–ether). For $C_{25}H_{28}ClFN_2O_5S$ (523·0) calculated: 57·41% C, 5·40% H, 6·78% Cl, 5·36% N, 6·13% S; found: 57·34% C, 5·59% H, 6·93% Cl, 5·37% N, 6·37% S.

8-Chloro-3-fluoro-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIb*)

Like in the preceding case, 3·5 g *XXIIb* yielded 4·1 g (86%) base, m.p. 92—94°C (benzene–light petroleum or cyclohexane). NMR spectrum: δ 7·64 (d, J = 2·5 Hz, 1 H, 9-H), 6·80—7·50 (m, 5 H, remaining aromatic protons), 4·75 (bs, disappears after D_2O, 1 H, OH), 2·80—3·80 (m, 5 H, CH_2O and $ArCH_2CHAr$), 2·54 (bs, 10 H, 5 NCH_2), 1·70 (m, 2 H, CH_2 in the middle of

propyl). For $C_{21}H_{24}ClFN_2OS$ (406·9) calculated: 61·98% C, 5·94% H, 8·71% Cl, 4·67% F, 7·88% S; found: 62·09% C, 6·05% H, 8·64% Cl, 4·69% F, 8·08% S.

Maleate, m.p. 157–159°C (ethanol). For $C_{25}H_{28}ClFN_2O_5S$ (523·0) calculated: 57·41% C, 5·40% H, 6·78% Cl, 6·13% S; found: 57·70% C, 5·56% H, 6·50% Cl, 6·16% S.

8-Chloro-2-fluoro-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IIIa*)

A solution of 0·5 g $TiCl_4$ in 3 ml benzene was added dropwise under stirring to a solution of 1·4 g *XXa* and 2·5 g 1-methylpiperazine in 10 ml benzene and the mixture was refluxed for 16 h. After cooling, it was decomposed by adding dropwise 30 ml water, the precipitate was filtered and washed with benzene, the benzene layer was removed from the filtrate, dried with K_2CO_3 and, after filtration with charcoal, evaporated at reduced pressure. The residue was recrystallized from 7 ml ethanol; 0·9 g (50%) base, m.p. 150–151°C (ethanol). UV spectrum (C_2H_5OH): λ_{max} 215 nm (log ε 4·40), infl. 243 nm (4·05), 272 nm (3·72), 313 nm (3·51). NMR spectrum: δ 7·65 (d, J = 3·0 Hz, 1 H, 9-H), 7·52 (d, J = 9·0 Hz, 1 H, 6-H), 7·25 (q, J = 9·0; 3·0 Hz, 1 H, 7-H), 6·70–7·30 (m, 3 H, remaining aromatic protons), 6·27 (s, 1 H, ArCH=), 2·98 (t, 4 H, $CH_2N^1CH_2$), 2·55 (t, 4 H, $CH_2N^4CH_2$), 2·31 (s, 3 H, N—CH_3). For $C_{19}H_{18}ClFN_2S$ (360·9) calculated: 63·23% C, 5·03% H, 9·83% Cl, 8·89% S; found: 62·71% C, 4·94% H, 9·75% Cl, 8·64% S.

Maleate, m.p. 242°C under decomposition (aqueous ethanol). For $C_{23}H_{22}ClFN_2O_4S$ (477·0) calculated: 57·92% C, 4·65% H, 7·43% Cl, 5·88% N, 6·72% S; found: 57·43% C, 4·81% H, 7·52% Cl, 5·70% N, 6·99% S.

8-Chloro-3-fluoro-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IIIb*)

Similarly to the preceding case, 2·8 g *XXb* yielded 2·2 g (61%) base; m.p. 164–165°C (ethanol). UV spectrum: λ_{max} 216 nm (log ε 4·55), infl. 237 nm (4·17), 266 nm (4·07), 312 nm (3·80), IR spectrum: 808, 840, 890 (2 adjacent and solitary Ar—H), 1550, 1588 (Ar), 1610 (ArC=C), 2765 cm^{-1} (N—CH_3). NMR spectrum: δ 7·60 (d, J = 2·5 Hz, 1 H, 9-H), 6·70–7·50 (m, 5 H, remaining aromatic protons), 6·25 (s, 1 H, ArCH=), 2·80 (m, 4 H, $CH_2N^1CH_2$), 2·50 (m, 4 H, $CH_2N^4CH_2$), 2·29 (s, 3 H, N—CH_3). For $C_{19}H_{18}ClFN_2S$ (360·9) calculated: 63·23% C, 5·03% H, 9·83% Cl, 5·26% F, 8·89% S; found: 63·27% C, 5·03% H, 9·64% Cl, 5·23% F, 9·00% S.

Maleate, m.p. 177–179°C (ethanol). For $C_{23}H_{22}ClFN_2O_4S$ (477·0) calculated: 57·82% C, 4·65% H, 7·43% Cl, 6·72% S; found: 58·03% C, 4·66% H, 7·35% Cl, 6·89% S.

4-Fluorothiophenol

4-Fluorobenzenesulfonyl chloride[21] (103 g) (b.p. 112°C/14 Torr) was boiled for 6 h with a mixture of 27 g P, 22 g I and 150 ml acetic acid[23]; 39·2 g (58%) product, b.p. 95°C/60 Torr. Ref.[21,22] report for a compound obtained by reduction with zinc and sulfuric acid, a b.p. of 167–168°C/760 Torr, 64–65°C/12 Torr or 60°C/15 Torr.

5-Chloro-2-(4-fluorophenylthio)benzoic Acid (*XIX*)

4-Fluorothiophenol (13·0 g) was dissolved in a warm solution of 1·5 g KOH in 120 ml water and the solution combined with 27·0 g 5-chloro-2-iodobenzoic acid[20] and 1 g Cu and the mixture was processed like with the preparation of *XIVa* according to (*A*). A total of 22·1 g (82%) product was obtained, m.p. 178–181°C (aqueous ethanol). IR spectrum (KBr): 767 (C—Cl), 835, 867 (2 adjacent and solitary Ar—H), 908, 1237 (COOH), 1550, 1593 (Ar), 1695 cm^{-1} (Ar—COOH).

NMR spectrum: δ 10·40 (bs, disappears after D_2O, 1 H, COOH), 8·25 (d, J = 2·5 Hz, 1 H, 6-H of benzoic acid), 7·38 (q, J = 9·0; 2·5 Hz, 1 H, 4-H of benzoic acid), 7·00–7·90 (m, 4 H, aromatic protons of the 4-fluorophenylthio group), 6·80 (d, J = 9·0 Hz, 1 H, 3-H of benzoic acid). For $C_{13}H_8ClFO_2S$ (282·7) calculated: 55·22% C, 2·85% H, 12·54% Cl, 11·34% S; found: 55·18% C, 2·99% H, 12·64% Cl, 11·46% S.

2-Chloro-7-fluorothioxanthone (*Va*)

A) A mixture of 15 ml H_2SO_4 and 3·2 g *XIVa* was heated for 1 h to 100°C. After cooling, it was poured into 150 ml ice water, the precipitate was filtered, dissolved in 150 ml chloroform, the solution was washed with 5% NaOH and water, dried, filtered with charcoal and evaporated. The residue melted at 232–234°C (acetic acid). UV spectrum: λ_{max} 214 nm (log ε 4·14), 219 nm (4·16), 251 nm (4·50), 262·5 (4·52), infl. 275 nm (4·30), 295 nm (3·47), 307·5 nm (3·37), 380 nm (3·67), 394 nm (3·76). IR spectrum (KBr): 813, 823, 887 (2 adjacent and solitary Ar—H), 1112, 1275 (CO), 1258 (Ar—F), 1455, 1577, 1590, 1610 (Ar), 1640 cm^{-1} (Ar_2CO). For $C_{13}H_6ClFOS$ (264·7) calculated: 58·98% C, 2·28% H, 13·39% Cl, 12·12% S; found: 58·80% C, 2·30% H, 13·68% Cl, 12·20% S.

B) A mixture of 50 ml H_2SO_4 and 10·0 g *XIX* was heated for 1·5 h to 100°C. After cooling and pouring into 500 ml mixture of ice and water, the crude product was filtered, washed with water, dispersed in 10% NaOH, filtered again, washed and dried; 9·2 g (98%), m.p. 230–232°C.

2-Chloro-6-fluorothioxanthone (*Vb*)

Acid *XIVb* (10·0 g) was cyclized with the aid of 50 ml H_2SO_4 like in the preceding case according to (*B*). A total of 8·7 g (93%) product was obtained; m.p. 229–231°C (acetic acid). UV spectrum: λ_{max} 220 nm (log ε 4·17), 258 nm (4·62), 287 nm (3·76), 297 nm (3·54), 377 nm (3·75). IR spectrum (KBr): 812, 880, 902 (2 adjacent and solitary Ar—H), 1459, 1581, 1603 (Ar), 1631 cm^{-1} (Ar_2CO). For $C_{13}H_6ClFOS$ (264·7) calculated: 58·98% C, 2·28% H, 13·39% Cl, 12·12% S; found: 59·27% C, 2·45% H, 13·04% Cl, 11·65% S.

2-Chloro-9-(3-dimethylaminopropyl)-7-fluorothioxanthen-9-ol (*VIa*)

Reaction of 1·6 g Mg with 8·2 g 3-dimethylaminopropyl chloride in 20 ml tetrahydrofuran (initiated with a grain of iodine and a drop of 1,2-dibromoethane) yielded the Grignard reagent[24] which was cooled under stirring and combined dropwise with a suspension of 8·9 g *Va* in 80 ml tetrahydrofuran. The mixture was stirred for 1 h at room temperature, left to stand overnight, decomposed under cooling with 40 ml 20% NH_4Cl and extracted with chloroform. The usual processing of the extract and crystallization of the residue from a mixture of benzene and light petroleum yielded 9·1 g (77%) product; m.p. 153–155°C (cyclohexane). IR spectrum ($CHCl_3$): 817, 895 (2 adjacent and solitary Ar—H), 1113 (R_3C—OH), 1580, 1600 (Ar), 2780 (NCH_3), 2600–3000 cm^{-1} (OH ··· N). NMR spectrum: δ 8·00 (d, J = 3·0 Hz, 1 H, 1-H), 6·80–7·90 (m, 5 H, remaining aromatic protons), 2·40 (s, 6 H, CH_3NCH_3), 1·80–2·50 (m, 4 H, CH_2—C—CH_2 of propyl), 1·24 (m, 2 H, CH_2 in the middle of propyl). For $C_{18}H_{19}ClFNOS$ (351·9) calculated: 61·44% C, 5·44% H, 10·08% Cl, 3·98% N, 9·11% S; found: 61·65% C, 5·67% H, 10·12% Cl, 4·02% N, 9·24% S.

2-Chloro-6-fluoro-9-(3-dimethylaminopropyl)thioxanthen-9-ol (*VIb*)

Like in the preceding case, reaction of 9·3 g *Vb* with a reagent prepared from 8·5 g 3-dimethylaminopropyl chloride, yielded 11·1 g (90%) product; m.p. 159–161°C (benzene). IR spectrum

(KBr): 813, 825, 900 (2 adjacent and solitary Ar—H), 1100 (R_3C—OH), 1227 (Ar—F), 1455, 1601 cm^{-1} (Ar). NMR spectrum: δ 6·90—8·30 (m, 6 H, aromatic protons), 2·39 (s, 6 H, CH_3NCH_3), 1·80—2·40 (CH_2—C—CH_2 of propyl), 1·20 (m, 2 H, CH_2 in the middle of propyl). For $C_{18}H_{19}ClFNOS$ (351·9) calculated: 61·44% C, 5·44% H, 10·08% Cl, 3·98% N, 9·11% S; found: 61·97% C, 5·59% H, 9·99% Cl, 3·90% N, 9·18% S.

2-Chloro-9-(3-dimethylaminopropylidene)-7-fluorothioxanthene (*IVa*)

A mixture of 9·1 g *VIa* and dilute sulfuric acid (6·7 ml H_2SO_4 in 57 ml water) was refluxed for 1·5 h. After cooling, it was diluted with 100 ml water and made alkaline with NH_4OH. The precipitated base was isolated by extraction with ether. Processing of the extract yielded a residue which was dissolved in ethanol, the solution was neutralized with an ether solution of hydrogen chloride and, on adding further ether, a hydrochloride precipitated; 5·6 g (58%), m.p. 200—202°C. After repeated crystallization from a mixture of ethanol and ether it melted at 202—204°C. UV spectrum (C_2H_5OH): λ_{max} 229 nm (log ε 4·68), 271 nm (4·31), 325 nm (3·74). IR spectrum: 810, 852, 866, 883 (2 adjacent and solitary Ar—H), 1570, 1597, 1698 cm^{-1} (Ar). For $C_{18}H_{18} \cdot Cl_2FNS$ (370·3) calculated: 58·38% C, 4·90% H, 19·15% Cl, 3·78% N, 8·66% S; found: 58·38% C, 4·98% H, 18·97% Cl, 4·12% N, 9·06% S.

2-Chloro-9-(3-dimethylaminopropylidene)-6-fluorothioxanthene (*IVb*)

Dehydration of 6·0 g *VIb* with dilute sulfuric acid was carried out like in the preceding case. The base obtained (5·3 g) was converted to the hydrochloride (4·0 g), which softens in the crude state above 194°C and melts diffusely at 204—210°C. After two crystallizations from ethanol the m.p. settled at 229—231°C. UV spectrum: λ_{max} 230 nm (log ε 4·51), 271 nm (4·17), 3·20 nm (3·57). IR spectrum: 810, 855, 890, 900 (2 adjacent and solitary Ar—H), 1100 (Ar—F), 1550, 1595 (Ar), 2440 cm^{-1} (NH^+). The band at 900 cm^{-1} suggests the classification of the compound with the *cis*-series (with respect to the position of the side chain and the chlorine atom; *cf.* ref.[10,25,26]). For $C_{18}H_{18}Cl_2FNS$ (370·3) calculated: 58·38% C, 4·90% H, 19·15% Cl, 3·78% N, 8·66% S; found: 58·83% C, 5·04% H, 18·97% Cl, 3·76% N, 8·95% S.

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