FLUORINATED TRICYCLIC NEUROLEPTICS: 6,7-DIFLUORO DERIVATIVE OF CHLORPROTHIXENE AND 2-FLUORO-3-HYDROXY DERIVATIVE OF OCTOCLOTHEPIN*

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2-Bromo-4,5-difluoronitrobenzene (*VI*) was converted to nitrile *IX* and acid *X* which react with alkaline 4-chlorothiophenolates in dimethylformamide under substitution of the fluorine atom in position 4, to sulfides *XII*—*XIV*. In the reaction of acid *X* with 4-chlorothiophenol in 3-methylbutanol in the presence of potassium carbonate and copper, the bromide atom undergoes substitution giving rise to acid *XV* which was then converted *via* thioxanthone *XVII* to the 6,7-difluoro derivative of chlorprothixene (*I*). Making use of the preferential substitution of the fluorine atom in position 4, nitrile *IX* was treated with sodium methoxide to convert it to methoxynitrile *XXVIII* which was further transformed in six steps to acid *XXXV*. Cyclization with polyphosphoric acid yielded 8-chloro-2-fluoro-3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXXVI*) which was converted *via* *XXXVII* and *XXXVIII* to the 2-fluoro-3-methoxy derivative of octoclothepin (*III*). Demethylation with boron tribromide yielded the title compound *II*. Whereas compound *I* is uninteresting neuroleptically, *II* is a potent tranqzuilizer with a slight cataleptic activity.

The working hypothesis about the increase and prolongation of effects by blocking the sites of metabolic Ar-hydroxylation through fluorination in the molecules of tricyclic neuroleptics provided positive results in the series of derivatives of phenothiazine, thioxanthene and dibenzo[*b*,*f*]thiepin[1]. Most extensive information is available on the effect of fluorination in the series of 10-piperazinodibenzo[*b*,*f*]thiepin derivatives where compounds are known that are fluorinated in position 2 (ref.[2-4]), 3 (ref.[2,3,5]), 7 (ref.[4-7]), 8 (ref.[4,6,8-10]) or difluorinated in positions 3, 7 (ref.[5]) and 7, 8 (ref.[6]). From the point of view of the effects studied the most interesting compounds are those fluorinated in position 3 because in this position metabolic Ar-hydroxylation is most likely to take place[11-13]. This position 3 corresponds to position 7 in phenothiazine and to position 6 in thioxanthene (position 2 carries in both cases the obligatory "neuroleptic" substituent); in agreement with this, in the series

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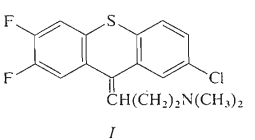
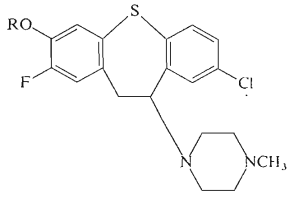
of phenothiazine neuroleptics, the most interesting derivatives (from the point of view of intensity and duration of effects) are the 7-fluoro ones[14]; in the series of thioxanthene neuroleptics the 6-fluoro derivatives[2,15–17]. One of the minor metabolites of chlorpromazine is its 7,8-dihydroxy derivative[18]. At present vicinally difluorinated compounds in positions corresponding to the position of hydroxyls in this metabolite are not known. As it was considered useful to obtain information on the effect of this type of metabolic block by fluorination on the neuroleptic activity, we synthesized the 6,7-difluoro derivative of chlorprothixene (*I*) (positions 6,7 in thioxanthene correspond to positions 7,8 in phenothiazine). An unexpected side reaction then led to intermediates that permitted us to synthesize the 2-fluoro-3-methoxy derivative *III* and the 2-fluoro-3-hydroxy derivative *II* of octoclothepin.

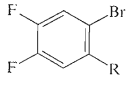


I

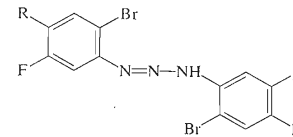


II, R = H
III, R = CH_3

The starting compound of the synthesis was 1,2-difluorobenzene[19] which was brominated in the way described[20] to 4-bromo-1,2-difluorobenzene (*IV*). In this reaction we observed in larger batches the formation of a relatively high amount of a higher-boiling product, a part of which is crystalline and, on the basis of IR spectra and analysis, it can be ascribed the structure of the hitherto unknown 1,2-dibromo-4,5-difluorobenzene (*V*). Nitration of the bromo derivative *IV* according to literature data[20] yielded 2-bromo-4,5-difluoronitrobenzene (*VI*), the characterization of which was completed. Reduction of the nitro compound *VI* with iron in a solution of ammonium chloride (for method see[21]) we obtained the new 2-bromo-4,5-difluoroaniline (*VII*), for the characterization of which we prepared the N-acetyl derivative *VIII*. Diazotization of amine *VII* and subsequent Sandmeyer's reaction resulted in nitrile *IX*. Since the yields of this step were low, different modifications of this procedure were tested. In the attempt to diazotize with butyl nitrite in a mixture of acetic acid and dioxane and in the presence of sulfuric acid (analogies in[22]) and subsequent application of Sandmeyer's reaction gave rise to a mixture from which crystallization produced nitrile *IX* as well as the more readily crystallizing diazoamino derivative *XI*. Hydrolysis of nitrile *IX* with sulfuric acid in acetic acid yielded 2-bromo-4,5-difluorobenzoic acid (*X*).

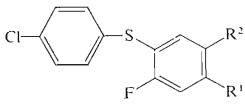


IV, R = H *VII*, R = NH_2
V, R = Br *VIII*, R = $NHCOCH_3$
VI, R = NO_2 *IX*, R = CN
X, R = COOH

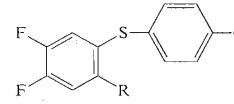


XI, R = F
XXX, R = CH_3O

In an attempt to introduce the 4-chlorophenylthio group in a reaction of nitrile *IX* with sodium 4-chlorothiophenolate in dimethylformamide in the presence of copper there is a preferential exchange of the activated atom of fluorine, with the result of the undesirable 2-bromo-4-(4-chlorophenylthio)-5-fluorobenzonitrile (*XII*). Its alkaline hydrolysis yielded acid *XIII* which is also formed in a reaction of acid *X* with 4-chlorothiophenol in dimethylformamide in the presence of potassium carbonate in the absence of copper. As long as the last reaction was conducted in the presence of copper, the fluorine and bromine atoms were exchanged and a low yield of the bis(4-chlorophenylthio) derivative *XIV* was obtained. Only by using Goldberg's method[23] which was developed for the reaction of 2-halogenobenzoic acids with nucleophilic agents and the selectivity of which was checked for the case of the reaction of 2,4-dichlorobenzoic acid with *p*-toluidine (2-*p*-toluidino-4-chlorobenzoic acid only is formed) was it possible to obtain 2-(4-chlorophenylthio)-4,5-difluorobenzoic acid (*XV*). Its preparation was carried out by the reaction of acid *X* with 4-chlorothiophenol and potassium carbonate in 3-methylbutanol in the presence of copper and cuprous iodide. Compound *XV* is formed in a high yield and the fluorine atom in position 4 is apparently not replaced at all. This result is another confirmation of Goldberg's theory[23], according to which the intermediate of these reaction is the non-ionized six-membered Cu-chelate-complex, in the formation of which only the halogen atom in *ortho*-position toward carboxyl participates. Reduction of acid *XV* with sodium dihydridobis(2-methoxyethoxy)aluminate yielded the primary alcohol *XVI*.

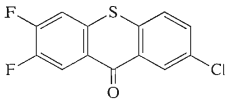


XII, R^1 = CN, R^2 = Br
XIII, R^1 = COOH, R^2 = Br
XIV, R^1 = COOH, R^2 = 4-S−C_6H_4−Cl

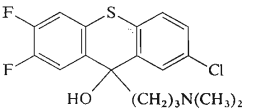


XV, R = COOH
XVI, R = CH_2OH

Acid *XV* is cyclized smothly through the action of sulfuric acid at 60°C, 7-chloro--2,3-difluorothioxanthone (*XVII*) being then formed. Subsequent reaction with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran (method in[24]) resulted in tertiary amino alcohol *XVIII* which was dehydrated with boiling dilute sulfuric acid. The oily base obtained (*I*) which is probably a mixture of the two geometric isomers, is neutralized to a hydrochloride which crystallizes to a homogeneous compound. The IR spectrum does not permit in this case to determine the configuration (the diagnostically important solitary proton occurs here both in position 1 and in position 8; see ref.[25]).

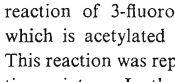


XVII

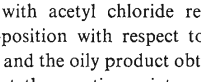


XVIII

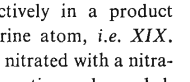
The described synthesis of *I* was preceded by several synthetic attempts which did not produce the desired intermediates but which led to the preparation of several new compounds. The first of these proceeded from the report[26] that a Friedel-Crafts reaction of 3-fluorotoluene with acetyl chloride results selectively in a product which is acetylated in *para*-position with respect to the fluorine atom, *i.e. XIX*. This reaction was reproduced and the oily product obtained was nitrated with a nitration mixture. In the case that the reaction mixture was not continuously cooled, it warmed spontaneously up to 50°C and the only product obtained was a nonhomogeneous carboxylic acid which was purified by recrystallization and identified as acid *XXV*. As long as the nitration was conducted at below 0°C, the acetyl was not oxidized to carboxyl and an inhomogeneous neutral product was formed which apparently



XIX, R = H
XX, R = NO_2
XXI, R = NH_2



XXII, R = H
XXIII, R = NO_2
XXIV, R = NH_2

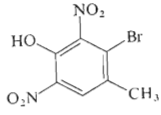


XXV

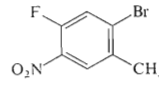
contained the desired nitro derivative *XX*. Reduction of this crude nitro compound with iron and hydrochloric acid in aqueous ethanol yielded a mixture of aminoketones which was separated by chromatography on a column of alumina. The somewhat less polar main product was identified by analysis and spectra as 5-amino-4-

-fluoro-2-methylacetophenone (*XXI*). The more polar minor product is isomeric with the preceding one and was identified by ^{1}H-NMR spectrum as 5-amino-2-fluoro--4-methylacetophenone (*XXIV*). This compound could have arisen only *via* intermediates *XXII* and *XXIII* whence it follows that during the Friedel–Crafts reaction of 3-fluorotoluene the compound *XIX* is formed in mixture with its isomer *XXII*. The literature reference[26] thus does not appear to be correct. After this observation the synthesis was stopped.

In another experiment the starting compound was 2-bromo-4-fluorotoluene[27] which was nitrated under cooling with fuming nitric acid. The inhomogeneous product resulting from the reaction was apparently composed of the mononitro and dinitro derivatives. When washing the chloroform solution with aqueous sodium hydroxide, an orange-red substituted sodium dinitrophenoxide was formed and it could not be decided whether the highly active fluorine atom is replaced with the hydroxyl group during nitration or only during contact with the aqueous solution of sodium hydroxide. The phenol set free by acidification was then identified by analysis and ^{1}H-NMR spectrum as 3-bromo-4-methyl-2,6-dinitrophenol (*XXVI*). The desired 2-bromo-4-fluoro-5-nitrotoluene (*XXVII*) obtained as a minor product was isolated from the chloroform solution. In view of the inhomogeneous course of the nitration reaction this synthetic attempt was then interrupted.



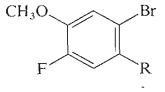
XXVI



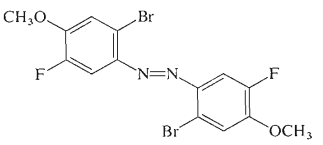
XXVII

The preferential exchange of activated fluorine atom in *IX* during action of nucleophilic agents gave rise to the idea to employ such a reaction for the synthesis of the hitherto unknown 2-fluoro-3-hydroxy derivative of octoclothepin (*II*), *i.e.* a metabolite of octoclothepin with a fluorine-blocked position of further probable metabolic Ar-hydroxylation. Of this type of compounds, the authors have prepared so far the 7-fluoro-3-hydroxy derivative of octoclothepin[5] which retains considerable neuroleptic activity even if lower than that of octoclothepin or its 3-hydroxy metabolite[28]. Reaction of nitrile *IX* with an equivalent of sodium methoxide in boiling methanol produced a high yield of 2-bromo-5-fluoro-4-methoxybenzonitrile (*XXVIII*). A small amount of an orange by-product was identified as the azo-compound *XXX*; the starting crude nitrile *IX* probably contains a contamination of the corresponding dibromotetrafluoroazobenzene, the azo-group of which is sufficient for activating the fluorine atom in *para*-position so that it can be replaced with a methoxy group.

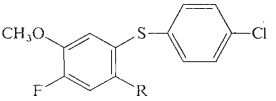
Acid hydrolysis of nitrile *XXVIII* gave rise to acid *XXIX* which was condensed with 4-chlorothiophenol in boiling 3-methylbutanol in the presence of potassium carbonate, copper and cuprous iodide, *i.e.* under the conditions of Goldberg's method[23]. A fine yield of the sulfide-acid *XXXI* was obtained. Similar experiments where dimethylformamide was used as the reaction medium were not successful. Reduction of acid *XXXI* with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene produced alcohol *XXXII* which was converted, *via* uncharacterized intermediates *XXXIII* and *XXXIV* (using the method described[29] for the transformation of 4-methoxybenzyl alcohol to 4-methoxyphenylacetonitrile), to 2-(4-chlorophenylthio)-5-fluoro-4-methoxyphenylacetic acid (*XXXV*).



XXVIII, R = CN
XXIX, R = COOH

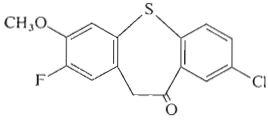


XXX

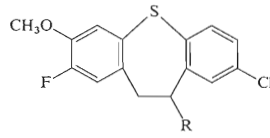


XXXI, R = COOH
XXXII, R = CH_2OH
XXXIII, R = CH_2Cl
XXXIV, R = CH_2CN
XXXV, R = CH_2COOH

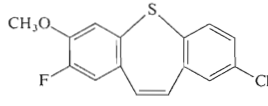
Acid *XXXV* was cyclized with polyphosphoric acid at 140–150°C, the reaction producing a fine yield of 8-chloro-2-fluoro-3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXXVI*). Reduction with sodium borohydride in a mixture of ethanol and benzene accomplished the transformation to alcohol *XXXVII* which was treated with anhydrous hydrogen chloride in benzene to yield chloride *XXXVIII*. A substitution reaction with excess 1-methylpiperazine in boiling chloroform produced as the main basic product the 2-fluoro-3-methoxy derivative of octoclothepin (*III*); 8-chloro-2-fluoro-3-methoxydibenzo[*b*,*f*]thiepin (*XXXIX*) was isolated as a minor product. Demethylation of *III* was done with boron tribromide in dichloromethane and by subsequent hydrolysis with aqueous–ethanolic solution of sodium hydroxide (for analogy see[5,9,28]). Phenolic base *II* was obtained in relatively poor yield as a solvate with benzene and this was converted to di(hydrogen maleate).



XXXVI



XXXVII, R = OH
XXXVIII, R = Cl



XXXIX

Compounds *I* and *II* were evaluated pharmacologically from the point of view of the expected neuroleptic activity. The chlorprothixene derivative *I* possessed an acute toxicity after oral application corresponding to LD_{50} = 80 mg/kg. Its incoordinating effect in the rotating-rod test in mice following oral application is very weak since the dose of 25 mg/kg brought about ataxia in only 30% animals; there was no latency or prolongation of effect since 24 h after application no animal of a group of 10 displayed ataxia. In the catalepsy test in rats the compound is inactive even in the high oral dose of 50 mg/kg. These results are surprising and may be explained only by assuming that the product belongs into the inactive *trans*-series (the side chain is turned away from the chlorine atom at the ring). Compound *II* shows about one-half of the incoordinating activity in the rotating-rod test for mice as compared with octoclothepin[8] (ED_{50} 5·0 mg/kg *p.o.*) and almost one order of magnitude lower cataleptic activity in rats (ED_{50} about 30 mg/kg *p.o.*). It can thus be described as a tranquilizer rather than a neuroleptic.

The compound *I* was tested for its antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek at the bacteriological department of this institute). In the following, the name of the microorganism is followed by the minimum inhibitory concentration in μg/ml. *Streptococcus β-haemolyticus*, 25; *Streptococcus faecalis*, 50; *Staphylococcus pyogenes aureus*, 25; *Pseudomonas aeruginosa*, 100; *Escherichia coli*, >100; *Proteus vulgaris*, 100; *Mycobacterium tuberculosis* H37Rv, 6·25; *Saccharomyces pasterianus*, >100; *Trichophyton mentagrophytes*, 50; *Candida albicans*, >100; *Aspergillus niger*, >100. The antituberculosis activity is striking.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at 0·5 Torr over P_2O_5 at room temperature or at 62°C. UV spectra (in methanol) were registered in a Unicam SP 8000 spectrophotometer, IR spectra

(in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer or in a UR 20 (Zeiss--Jena) spectrophotometer. ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced mainly in a Tesla BS 487C (80 MHz) spectrometer, some of them in a ZKR 60 (60 MHz) spectrometer. ^{19}F-NMR spectra were obtained in $CHCl_3$ ($\delta_{CFCl_3} = 0$) using a Tesla BS 487C apparatus, the mass spectra in a MS 902 AEI spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of alumina or silicagel.

1,2-Dibromo-4,5-difluorobenzene (*V*)

Bromination of 77·3 g refluxing 1,2-difluorobenzene[19] with 44 ml bromine in the presence of 4 g powdered iron yielded a crude product[20] which was distilled. A total of 89·1 g (68%) 4-bromo-1,2-difluorobenzene (*IV*) was obtained; b.p. 150—152°C. There was a considerable residue which was distilled to give 14·4 g inhomogeneous fraction boiling at 180—235°C. On standing, this distillate partly crystallized. The liquid fraction was decanted and the crystals were purified by repeated crystallization from ether; 2·0 g, m.p. 32·5—33·5°C. IR spectrum: 875 (solitary Ar—H), 1 490, 1 600 cm^{-1} (Ar). The compound sublimes quickly even at room temperature which probably affected the analytical results. For $C_6H_2Br_2F_2$ (271·9) calculated: 26·50% C, 0·74% H, 58·78% Br, 13·98% F; found: 26·52% C, 0·71% H, 56·30% Br, 14·32% F.

2-Bromo-4,5-difluoronitrobenzene (*VI*)

Nitration of 19·0 g *IV* according to literature data[20] yielded 18·0 g (77%) product boiling at 91 to 94°C/2 Torr. Since our value of the boiling point was repeatedly higher than that in the literature[20] (72—74°C/4 Torr) we characterized the product by hitherto unpublished spectra and the compound was subjected to a complete elementary analysis. IR spectrum (KBr): 887 (solitary Ar—H), 1350, 1537 (Ar—NO_2), 1600 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·86 (dd, J = 10·0; 7·0 Hz, 1 H, 3-H), 7·60 (dd, J = 10·0; 7·0 Hz, 1 H, 6-H). For $C_6H_2BrF_2NO_2$ (238·0) calculated: 30·28% C, 0·85% H, 33·57% Br, 15·96% F, 5·89% N; found: 29·88% C, 0·80% H, 33·25% Br, 15·83% F, 6·03% N.

2-Bromo-4,5-difluoroaniline (*VII*)

A boiling suspension of 33·6 g Fe in 225 ml 0·8M-NH_4Cl was combined over a period of 75 min with 35·7 g *VI* added dropwise. The mixture was refluxed for 4·5 h. After cooling, it was filtered and the solid on the filter was washed with hot water. The filtrate was made alkaline with 20% NaOH and the product was isolated by extraction with ether. After drying the extract with Na_2SO_4 and evaporation of the solvent, the residue crystallized and was recrystallized from hexane; 28·8 g (92%), m.p. 47—49°C. Like *V*, the product sublimes at room temperature which affects the analytical values. IR spectrum: 862 (solitary Ar—H), 1510, 1600 (Ar), 1625, 3420 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·20 (dd, J = 10·0; 8·0 Hz, 1 H, 3-H), 6·56 (dd, J = 11·0; 7·0 Hz, 1 H, 6-H), 3·88 (bs, 2 H, NH_2). For $C_6H_4BrF_2N$ (208·0) calculated: 34·64% C, 1·94% H, 38·42% Br, 6·73% N; found: 32·69% C, 1·71% H, 37·51% Br, 6·12% N.

Hydrochloride was prepared by neutralization of the base with a solution of hydrogen chloride in ether; m.p. 208—210°C in a sealed capillary (ethanol). For $C_6H_5BrClF_2N$ (244·5) calculated: 29·47% C, 2·06% H, 5·73% N; found: 29·36% C, 2·03% H, 5·65% N.

The N-*acetyl derivative* (VIII) was obtained by heating a mixture of 1·0 g *VII*, 2 ml acetic anhydride and 2 ml acetic acid, subsequent dilution with 3 ml water and by crystallization; m.p. 110—111°C (aqueous ethanol). For $C_8H_6BrF_2NO$ (250·1) calculated: 38·42% C, 2·42% H, 31·96% Br, 15·20% F, 5·60% N; found: 37·79% C, 2·23% H, 31·97% Br, 15·01% F, 5·66% N.

2-Bromo-4,5-difluorobenzonitrile (*IX*)

A solution of 28·8 g *VII* in a mixture of 330 ml water and 28 ml H_2SO_4 was cooled below 0°C and, over a period of 15 min, under stirring, a solution of 9·5 g $NaNO_2$ in 30 ml water was added dropwise. The mixture was stirred at 0°C for 75 min and, over a period of 20 min, it was added under stirring at below 10°C to a solution which was prepared by dissolving 86 g $CuSO_4.5H_2O$ and 91 g KCN in 210 ml water and subsequent addition of 140 ml concentrated NH_4OH. The mixture was combined with 150 ml chloroform and the mixture was stirred for 3 h without cooling and then extracted with chloroform. The extract was washed with dilute H_2SO_4, 5% NaOH and with water, dried with $MgSO_4$ and evaporated. The yield was 24·9 g (82%) crude nitrile which was used for hydrolysis in this form. Crystallization from cyclohexane incurs losses; in a single crystallization the yield drops to 12·7 g (42%) and the product then melts at 42—57°C. Only repeated crystallization produced an analytical product, melting at 63—64°C. IR spectrum: 890 (solitary Ar—H), 1 500, 1 590, 1 608, 1 760 (Ar), 2 240 (Ar—CN), 3 000, 3 065, 3 120 cm^{-1} (Ar). For $C_7H_2BrF_2N$ (218·0) calculated: 38·56% C, 0·92% H, 36·66% Br, 17·43% F, 6·42% N; found: 38·42% C, 0·98% H, 36·51% Br, 17·13% F, 6·38% N.

1,3-Bis(2-bromo-4,5-difluorophenyl)triazene (*XI*)

Sulfuric acid (3·4 ml) was added dropwise under stirring at 5°C to a solution of 6·45 g *VII* in a mixture of 42 ml acetic acid and 42 ml dioxane. The formed suspension of sulfate was cooled to —10°C and, at this temperature, a solution of 4·5 ml n-butyl nitrite[30] in 20 ml dioxane was added dropwise. The solution formed was stirred for 30 min at —5 to —10°C, 570 ml ether was then added and this caused the diazonium sulfate to precipitate in a semisolid form. Ether was removed by decanting and the diazonium sulfate was dissolved in 235 ml ice-cold water. The solution formed was added dropwise at 0—5°C to a solution prepared by dissolving 17·7 g $CuSO_4.5H_2O$ and 18·8 g KCN in 140 ml water. The mixture was stirred for 30 min and the precipitate was filtered. The filtrate was extracted with ether in which the solid on the filter was also dissolved. The ether solution was washed with 3M-HCl, 5% NaOH and water, then it was dried and evaporated. The residue (4·63 g) was boiled with 100 ml benzene and the insoluble fraction was filtered. Evaporation of the filtrate yielded 2·35 g (35%) nitrile *IX*, melting at 59—63°C. The insoluble fraction (2·20 g) was purified by crystallization from a mixture of benzene and light petroleum; m.p. 159—160°C. We are dealing here with triazene *XI*. IR spectrum: 867, 871, 879 (solitary Ar—H), 1 490, 1 529, 1 600 (Ar), 3 320, 3 450 cm^{-1} (NH). For $C_{12}H_5Br_2F_4N_3$ (427·0) calculated: 37·43% Br, 17·79% F, 9·84% N; found: 37·78% Br, 18·33% F, 10·40% N.

2-Bromo-4,5-difluorobenzoic Acid (*X*)

A mixture of 10·5 g nitrile *IX*, 55 ml acetic acid, 5·5 ml H_2SO_4 and 5·5 ml water was refluxed for 17 h and then poured into 750 ml water. The precipitated product was filtered (8·40 g, 74%) and recrystallized from a mixture of 10 ml benzene and 10 ml light petroleum; 6·78 g (59%), m.p. 115—118°C. The analytical product melted at 119—120°C. A practically pure product was obtained by precipitation of the crude product dissolved in a solution of Na_2CO_3 and precipitated by acidification with hydrochloric acid. IR spectrum (KBr): 888 (solitary Ar—H), 940, 1 180, 1 260, 1 280, 1 315, 2 565 (COOH), 1 680 and 1 710 (Ar—COOH), 1 502, 1 588, 1 609 cm^{-1} (Ar). For $C_7H_3BrF_2O_2$ (237·0) calculated: 35·47% C, 1·28% H, 33·72% Br, 16·03% F; found: 35·53% C, 1·46% H, 33·99% Br, 16·28% F.

2-Bromo-4-(4-chlorophenylthio)-5-fluorobenzonitrile (*XII*)

A mixture of 5·45 g *IX*, 5·0 g dry sodium 4-chlorothiophenolate, 6 ml dimethylformamide and 0·4 g "molecular" copper was heated under stirring for 5 h in a 150°C bath. After cooling, it was divided by shaking between 50 ml water and 250 ml benzene. The benzene solution was dried with Na_2SO_4. The product obtained by evaporation was recrystallized from a mixture of benzene and light petroleum; 5·0 g (58%), m.p. 135—145°C. Further crystallization yielded the analytical product melting at 150—152°C. IR spectrum: 818, 838, 895 (2 adjacent and solitary Ar—H), 1596 (Ar), 2235 cm^{-1} (Ar—CN). ^{1}H-NMR spectrum: δ 7·45 (s, 4 H, 4 Ar-H of *p*-phenylene), 7·28 (d, J = 9·0 Hz, 1 H, 6-H), 6·99 (d, J = 6·5 Hz, 1 H, 3-H). ^{19}F-NMR spectrum: δ —111·8 (dd). For $C_{13}H_6BrClFNS$ (342·6) calculated: 45·57% C, 1·76% H, 23·32% Br, 5·54% F, 4·09% N, 9·36% S; found: 45·78% C, 1·76% H, 23·69% Br, 5·84% F, 4·11% N, 9·60% S.

2-Bromo-4-(4-chlorophenylthio)-5-fluorobenzoic Acid (*XIII*)

A. A solution of 1·90 g *IX* in 8 ml ethanol was mixed with a solution of 1·5 g KOH in 4 .ml water and the mixture was refluxed for 10 h on a boiling-water bath. Ethanol was evaporated at reduced pressure, the residue was dissolved in 100 ml water and the solution was washed with ether. After filtration with charcoal the filtrate was acidified with hydrochloric acid. Filtration yielded 0·79 g (51%) acid melting at 220—227°C which was crystallized from ethanol; m.p. 228 to 230°C. IR spectrum: 818, 896 (2 adjacent and solitary Ar—H), 918, 1080, 1213, 1266 (COOH), 1549, 1592 (Ar), 1694 (Ar—COOH), 2610 cm^{-1} (COOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·62 (d, J = 10·0 Hz, 1 H, 6-H), 7·42 (s, 4 H, 4 Ar—H of *p*-phenylene), 7·22 (d, J = 6·5 Hz, 1 H, 3-H). For $C_{13}H_7BrClFO_2S$ (361·6) calculated: 43·17% C, 1·95% H, 22·10% Br, 9·80% Cl, 5·25% F, 8·87% S; found: 43·19% C, 2·09% H, 22·43% Br, 9·84% Cl, 5·33% F, 9·14% S.

B. A mixture of 1·19 g *X*, 0·72 g 4-chlorothiophenol, 1·73 g K_2CO_3 and 1 ml dimethylformamide was heated for 2·5 h in a 120—130°C bath. The volatile fractions were evaporated *in vacuo* and the residue was divided by shaking between a 10% solution of NaOH and benzene. The alkaline layer was filtered with charcoal and the filtrate was acidified. A total of 0·70 g (39%) acid was obtained; m.p. 218—224°C. It was recrystallized from ethanol to yield a compound melting at 228—231°C, identical with the product prepared sub *A*.

2,4-Bis(4-chlorophenylthio)-5-fluorobenzoic Acid (*XIV*)

A mixture of 2·80 g *X*, 1·94 g 4-chlorothiophenol, 4·08 g K_2CO_3, 0·2 g Cu and 3 ml dimethylformamide was heated under stirring for 5 h in a 140—150°C bath. Then it was processed like under *B* in the foregoing paragraph. A total of 1·14 g (22%) crude acid melting at 170—180°C was obtained. Recrystallization from a mixture of benzene and light petroleum raised the m.p. only slightly (to 175—185°C) while further crystallization from 90% ethanol raised it sharply. After another crystallization it stabilized at 250—252°C. The mass spectrum (molecular ion at *m/e* 425, principal fragment at *m/e* 297) supports the view that the compound contains two phenylthio moieties. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·62 (d, J = 10·0 Hz, 1 H, 6-H), 7·23 (s, 8 H, Ar—H of two *p*-phenylenes), 5·93 (d, J = 7·0 Hz, 1 H, 3-H). For $C_{19}H_{11}Cl_2FO_2S_2$ (425·3) calculated: 53·65% C, 2·61% H, 16·67% Cl, 4·47% F, 15·08% S; found: 54·03% C, 2·62% H, 16·76% Cl, 5·07% F, 15·22% S.

2-(4-Chlorophenylthio)-4,5-difluorobenzoic Acid (*XV*)

A mixture of 8·77 g *X*, 50 ml 3-methylbutanol, 7·0 g K_2CO_3, 8·03 g 4-chlorothiophenol, 0·3 g Cu and 0·3 g CuI was heated for 6 h in a 130—140°C bath. 3-Methylbutanol was then steamdistilled,

the remaining solution was filtered and acidified with dilute H_2SO_4. Crystallization of the crude acid from ethanol yielded 8·45 g (76%) compound melting at 192—202°C. The analytical product melted at 207—209°C (ethanol). UV spectrum: λ_{max} 222 nm (log ε 4·31), 253 nm (4·05), 283 nm (3·83). IR spectrum (KBr): 824, 900 (2 adjacent and solitary Ar—H), 1178, 1248, 1283 (COOH), 1480, 1500, 1588 (Ar), 1708 (Ar—COOH), 2544 (COOH), 3050 cm^{-1} (Ar). For $C_{13}H_7ClF_2O_2S$ (300·7) calculated: 51·92% C, 2·35% H, 11·79% Cl, 12·64% F, 10·66% S; found: 52·06% C, 2·20% H, 11·86% Cl, 12·74% F, 10·42% S.

2-(4-Chlorophenylthio)-4,5-difluorobenzyl Alcohol (*XVI*)

A 50% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate (14 ml) was added dropwise at 5—10°C over a period of 30 min to a suspension of 7 g *XV* in 70 ml benzene. The mixture was stirred for 3 h at 15°C and left to stand overnight at room temperature. On the following day, 27 ml 10% NaOH was added dropwise under stirring and the product was extracted with benzene. After drying the benzene solution, the solvent was evaporated and the residue recrystallized from 10 ml hexane; 5·12 g (77%), m.p. 50—53°C. The analytical product melted at 51—53°C. IR spectrum (KBr): 826, 874 (2 adjacent and solitary Ar—H), 1046, 3300 (CH_2OH), 1487, 1574, 1600 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 6 H, Ar—H), 4·64 (s,2 H, Ar—CH_2—O), 2·18 (bs, 1 H, OH). ^{19}F-NMR spectrum: δ —124·6, —125·8. For $C_{13}H_9ClF_2OS$ (286·7) calculated: 54·45% C, 3·16% H, 12·37% Cl, 13·25% F, 11·18% S; found: 54·88% C, 3·29% H, 12·37% Cl, 13·45% F, 11·10% S.

7-Chloro-2,3-difluorothioxanthone (*XVII*)

A mixture of 20 ml H_2SO_4 and 3·0 g *XV* was heated for 2 h to 60°C. After partial cooling, it was poured into a mixture of ice and water, the precipitated yellow product was filtered, washed with 10% NaOH and water and, after drying in air, it was recrystallized from 200 ml benzene; 2·29 g (81%), m.p. 246—249°C. The analytical product melted at 248—249°C. UV spectrum: λ_{max} 259 nm (log ε 4·60), 366 nm (3·87). IR spectrum: 770, 782, 820, 907 (2 adjacent and solitary Ar—H), 1509, 1551, 1590, 1617, 3060 (Ar), 1640 cm^{-1} (ArCOAr). For $C_{13}H_5ClF_2OS$ (282·7) calculated: 55·23% C, 1·78% H, 12·54% Cl, 13·44% F, 11·34% S; found: 55·18% C, 1·86% H, 12·97% Cl, 13·94% F, 11·73% S.

7-Chloro-2,3-difluoro-9-(3-dimethylaminopropyl)thioxanthen-9-ol (*XVIII*)

Reaction of 3·94 g 3-dimethylaminopropyl chloride with 0·78 g Mg in 25 ml tetrahydrofuran yielded the corresponding Grignard reagent[24] to which a suspension of 3·06 g *XVII* in 50 ml tetrahydrofuran was added dropwise over a period of 10 min under refluxing. The mixture was then refluxed for 1 h and left to stand at room temperature overnight. Then 50 ml 20% solution of NH_4Cl was added and the solution extracted with chloroform. The extract was dried with Na_2SO_4 and evaporated. Crystallization of the residue from 90 ml ethanol yielded 3·08 g (77%) product melting at 166·5—169°C. On further crystallization the m.p. did not change. IR spectrum (KBr): 798, 805, 843, 893 (2 adjacent and solitary Ar—H), 1027, 1090 (R_3C—OH in a ring), 1285 (C—F), 1390, 1483, 1599 (Ar), 2620 (OH···N), 3040, 3070, 3090 (Ar), 3440 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·88 (mcs, 1 H, 8-H), 7·00—7·80 (m, 4 H, remaining Ar—H), 24·0 (s, 6 H, CH_3NCH_3), 2·25 (m, 2 H, CH_2N), 2·00 (m, 2 H, O—C—CH_2), 1·20 (m, 2 H, C—CH_2—C—N). For $C_{18}H_{18}ClF_2NOS$ (369·9) calculated: 58·45% C, 4·90% H, 9·59% Cl, 10·27% F, 3·79% N, 8·67% S; found: 58·83% C, 4·97% H, 9·75% Cl, 10·15% F, 3·52% N, 8·86% S.

The *hydrochloride* was obtained by shaking the chloroform solution of the base with dilute (1 : 1) hydrochloric acid, subsequent evaporation of the chloroform solution at reduced pressure and crystallization of the residue from a larger amount of benzene; m.p. 200—202°C. The mass spectrum displays a molecular ion of the base at *m/e* 369. For $C_{18}H_{19}Cl_2F_2NOS$ (406·3) calculated: 53·20% C, 4·71% H, 17·45% Cl, 9·35% F, 3·45% N, 7·89% S; found: 53·54% C, 4·70% H, 17·54% Cl, 9·71% F, 3·26% N, 7·75% S.

7-Chloro-2,3-difluoro-9-(3-dimethylaminopropylidene)thioxanthene (*I*)

A solution of 8·6 ml H_2SO_4 in 42 ml water was refluxed with 6·80 g *XVIII* for 2 h in a 150°C bath. After dilution with water, the base was liberated with 20% NaOH and extracted with chloroform. Processing of the extract produced a theoretical yield of an oily base which was converted to the hydrochloride by treatment with hydrogen chloride in ether solution; 3·95 g (55%), m.p. 233—240°C. Repeated crystallization from ethanol yielded an analytical product melting at 244—246°C which behaves as a homogeneous compound. UV spectrum: λ_{max} 269 nm (log ε 4·17), 328 nm (3·54). IR spectrum (KBr): 801, 811, 869, 883, 890 (2 adjacent and solitary Ar—H), 1486, 1554, 1593, 1610, 3023 (Ar), 2480, 2525, 2570 cm^{-1} (NH^+); in CS_2: 810, 823 (2 adjacent Ar—H), 886 (solitary Ar—H). For $C_{18}H_{17}Cl_2F_2NS$ (388·3) calculated: 55·67% C, 4·41% H, 18·26% Cl, 3·61% N, 8·26% S; found: 56·05% C, 4·56% H, 18·22% Cl, 3·30% N, 8·13% S.

4-Fluoro-2-methyl-5-nitrobenzoic Acid (*XXV*)

A mixture of 13·4 ml concentrated HNO_3 and 20 ml H_2SO_4 was added dropwise under stirring at −10 to 0°C to a mixture of 11·9 g *XIX* (it contains a minor amount of *XXII*) (prepared according to the literature[26], b.p. 206—209°C/740 Torr, m.p. of the oxime 84—86°C) and 50 ml H_2SO_4. Stirring was then continued for 20 min without cooling, the temperature rising up to 50°C. After cooling, stirring was continued for 20 min at 15°C and the mixture was decomposed by pouring onto a mixture of ice and water. The precipitate formed was extracted with chloroform and reprecipitated from the solution in 15% NaOH with hydrochloric acid. After filtration, washing with water and drying in air, the yield was 12·4 g (79%) inhomogeneous acid which was obtained in an analytically pure state only after many crystallizations from benzene and then from aqueous ethanol; m.p. 211—214°C. For $C_8H_6FNO_4$ (199·1) calculated: 48·25% C, 3·04% H, 7·03% N; found: 48·93% C, 3·47% H, 7·00% N.

5-Amino-4-fluoro-2-methylacetophenone (*XXI*)

Nitration of 7·6 g *XIX* (and XXII) (ref.[26]) in 15 ml H_2SO_4 was done with a mixture of 4·0 ml HNO_3 (d 1·4) and 6 ml H_2SO_4 at −5 to +3°C. After 10 min of stirring it was poured into ice an water and the product was extracted with ether. The extract was washed with 5% NaOH and water, dried and evaporated. The yield was 9·3 g (95%) yellow oily mixture (*XX* + *XXIII*) which gives a single spot in TLC on silica gel but which was shown to be inhomogeneous by the ^{1}H-NMR spectrum. The total amount was dissolved in 25 ml ethanol, combined with 6 ml water and 7·8 g powdered iron and, under stirring in a 100°C bath, it was refluxed while a solution of 1·0 ml hydrochloric acid in 10 ml ethanol and 4 ml water was added dropwise (25 min). The mixture was refluxed for 2 h, left to stand overnight at room temperature, neutralized with 20% NaOH and ethanol was evaporated at reduced pressure. The residue was diluted with water and the product was extracted with benzene; 5·58 g oil, which showed two spots in TLC, their R_F values being very close. Chromatography on a column of 150 g alumina (activity II) and

elution with benzene produced first 4·4 g of the less polar compound *XXI*, m.p. 115–117°C (benzene). IR spectrum (KBr): 1 514, 1 580, 1 640 (Ar) 1 676 (Ar—CO—R), 3 220, 3 270, 3 300 cm^{-1} (NH_2). ^{1}H-NMR spectrum (ZKR 60): δ 7·06 (d, J = 9·0 Hz, 1 H, 6-H), 6·75(d, J = 12·0 Hz, 1 H, 3-H), 3·61 (bs, disappears after D_2O, 2 H, NH_2), 2·42 (s, 3 H, $COCH_3$), 2·32 (s, 3 H, Ar—CH_3). For $C_9H_{10}FNO$ (167·2) calculated: 64·66% C, 6·03% H, 8·38% N; found: 64·32% C, 6·16% H, 8·06% N.

Continuation of the chromatography using elution with benzene and chloroform (4 : 1) produced 1·0 g 5-amino-2-fluoro-4-methylacetophenone (*XXIV*), m.p. 112·5–114°C (benzene). IR spectrum (KBr): 1 510, 1 580, 1 623 (Ar), 1 688 (Ar—CO—R), 3 215, 3 280, 3 310 cm^{-1} (NH_2). ^{1}H-NMR spectrum (ZKR 60): δ 7·04 (d, J = 6·5 Hz, 1 H, 6-H), 6·73 (d, J = 11·5 Hz, 1 H, 3-H), 3·45 (bs, disappears after D_2O, 2 H, NH_2), 2·50 (d, J = 4·5 Hz, 3 H, $COCH_3$), 2·10 (s, 3 H, Ar—CH_3). For $C_9H_{10}FNO$ (167·2) calculated: 64·66% C, 6·03% H, 8·38% N; found: 64·45% C, 6·09% H, 8·16% N.

3-Bromo-4-methyl-2,6-dinitrophenol (*XXVI*)

Fuming HNO_3 (d 1·50) (6·3 ml) was added dropwise at −3°C under stirring to 9·2 g 2-bromo-4-fluorotoluene[27] (b.p. 169°C/740 Torr.) Stirring was continued for 1 h at 0°C, the mixture was left to heat to 60°C and the content of the flask solidified. The solid was decomposed with ice and water and the product was extracted with chloroform. The extract was washed with water and with 100 ml 15% NaOH. An orange-red precipitate formed and was dissolved in 500 ml warm water. The aqueous layer was separated and acidified with hydrochloric acid. The precipitated yellow solid was filtered after cooling washed with water and dried in air; 4·3 g (38%), m.p. 99–116°C. Crystallization from a mixture of benzene and light petroleum or from aqueous ethanol yielded an analytical product melting at 113–116°C. ^{1}H-NMR spectrum (ZKR 60): δ 10·56 (s, disappears after D_2O, 1 H, OH), 8·04 (s, 1 H, 6-H), 2·44 (s, 3 H, Ar—CH_3). For $C_7H_5BrN_2O_5$ (277·0) calculated: 30·35% C, 1·82% H, 28·55% Br, 10·11% N; found: 30·62% C, 1·80% H, 28·77% Br, 10·14% N.

Drying of the chloroform layer with K_2CO_3 and evaporation yielded 2·3 g needles melting at 54–64°C; after recrystallization from methanol, the analytical product melted at 63·5–65·5°C and was identified as 2-bromo-4-fluoro-5-nitrotoluene (*XXVII*). ^{1}H-NMR spectrum (ZKR 60): δ 7·90 (d, J = 8·0 Hz, 1 H, 6-H), 7·45 (d, J = 10·0 Hz, 1 H, 3-H), 2·41 (s, 3 H, CH_3). For C_7H_5. $BrFNO_2$ (234·0) calculated: 35·92% C, 2·15% H, 34·15% Br, 8·12% F, 5·99% N; found: 35·18% C, 2·14% H, 33·89% Br, 8·05% F, 5·80% N.

2-Bromo-5-fluoro-4-methoxybenzonitrile (*XXVIII*)

A solution of 12·75 g crude IX in 100 ml methanol was added to a solution of $NaOCH_3$ (from 1·34 g Na and 50 ml methanol) and the mixture was refluxed for 3 h. After partial cooling, filtration isolated 1·3 g orange-coloured 2,2′-dibromo-5,5′-difluoro-4,4′-dimethoxyazobenzene (*XXX*). After recrystallization from benzene it melted at 243–245°C. The mass spectrum agrees with the suggested structure: molecular ion at m/e 434, intense fragments at m/e 231 and 203. UV spectrum: λ_{max} 255 nm (log ε 4·11) infl., 325 nm (3·83), 363 nm (4·21), 396·5 nm (4·17). IR spectrum: 893 (solitary Ar—H), 1 271 ($ArOCH_3$), 1 507, 3065, 3105, 3125 (Ar), 1 611 cm^{-1} (N=N in conjugation). For $C_{14}H_{10}Br_2F_2N_2O_2$ (436·1) calculated: 38·56% C, 2·31% H, 36·65% Br, 8·71% F, 6·42% N; found: 38·68% C, 2·27% H, 36·88% Br, 8·84% F, 6·56% N.

Filtrate after *XXX* was evaporated at reduced pressure to remove methanol, combined with 50 ml water and extracted with benzene. Processing of the extract yielded a residue which was recrystallized from 110 ml ethanol; 9·57 g (72%), m.p. 129–132°C. Further recrystallization did

not change the m.p. UV spectrum: λ_{max} 252·5 nm (log ε 4·20), 282·5 nm (3·41), 292 nm (3·42). IR spectrum: 851, 881 (solitary Ar—H), 1022, 1213 ($ArOCH_3$), 1502, 1518, 1570, 1602 (Ar), 2235 cm^{-1} (Ar—CN). ^{1}H-NMR spectrum: δ 7·28 (d, J = 10·0 Hz, 1 H, 6-H), 7·14 (d, J = 8·0 Hz, 1 H, 3-H), 3·90 (s, 3 H, OCH_3). For C_8H_5BrFNO (230·0) calculated: 41·76% C, 2·19% H, 34·74% Br, 8·26% F, 6·09% N; found: 42·26% C, 2·36% H, 34·50% Br, 8·12% F, 6·01% N.

2-Bromo-5-fluoro-4-methoxybenzoic Acid (*XXIX*)

A solution of 12·3 g *XXVIII* in 60 ml acetic acid was refluxed for 11 h with a solution of 6·2 ml H_2SO_4 in 6·2 ml water, poured into 750 ml water, the precipitated product was filtered on the following day, washed with water and dried in air; 11·4 g (85%), m.p. 174—198°C. Analytical product, m.p. 201—202°C (aqueous ethanol). For $C_8H_6BrFO_3$ (249·0) calculated: 38·58% C, 2·43% H, 32·09% Br, 7·63% F; found: 38·63% C, 2·45% H, 32·01% Br, 7·61% F.

2-(4-Chlorophenylthio)-5-fluoro-4-methoxybenzoic Acid (*XXXI*)

A solution of 6·22 g *XXIX* in 35 ml 3-methylbutanol was successively combined with 8·7 g K_2CO_3, 0·3 g Cu, 0·3 g CuI and 5·4 g 4-chlorothiophenol and the mixture was refluxed for 5 h in a 125°C bath. 3-Methylbutanol was steamdistilled, the remaining liquid was filtered, evaporated *in vacuo* to about 300 ml and acidified with dilute H_2SO_4 to pH 1. The precipitated product was filtered on the following day, washed with water and dried in air; 6·89 g (88%), m.p. diffuse at about 240°C. Analytical product, m.p. 236—239°C (methanol). UV spectrum: λ_{max} 236 nm (log ε 4·37), infl. 256·5 nm (4·12), 289 nm (3·82), 307 nm (3·77). IR spectrum: 822, 890 (2 adjacent and solitary Ar—H), 1182, 1190 ($ArOCH_3$), 921, 1265, 2510, 2585 (COOH), 1508, 1568, 1610 (Ar), 1683 cm^{-1} (Ar—COOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·60 (d, J = 11·0 Hz, 1 H, 6-H), 7·45 (s, 4 H, 4 Ar—H of *p*-phenylene), 6·30 (d, J = 8·0 Hz, 1 H, 3-H), 3·45 (s, 3 H, OCH_3). For $C_{14}H_{10}ClFO_3S$ (312·7) calculated: 53·76% C, 3·22% H, 11·34% Cl, 6·07% F, 10·25% S; found: 53·93% C, 3·30% H, 11·29% Cl, 6·22% F, 10·38% S.

2-(4-Chlorophenylthio)-5-fluoro-4-methoxybenzyl Alcohol (*XXXII*)

Like with the preparation of *XVI*, 11·4 g acid *XXXI* in 85 ml benzene was reduced with 23 ml 70% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate at room temperature. Crystallization of the crude product from hexane yielded 9·82 g (92%) substance melting at 48—58°; analytical product, m.p. 63—65°C (hexane). IR spectrum: 810, 880 (2 adjacent and solitary Ar—H), 1050 (CH_2OH), 1270 ($ArOCH_3$), 1505, 1619 (Ar), 3255 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 6 H, Ar—H), 4·65 (s, 2 H, Ar—CH_2—O), 3·82 (s, 3 H, OCH_3), 2·14 (bs, 1 H, OH). For $C_{14}H_{12}ClFO_2S$ (298·8) calculated: 56·28% C, 4·05% H, 11·86% Cl, 6·36% F, 10·73% S; found: 56·33% C, 4·09% H, 12·01% Cl, 6·64% F, 10·95% S.

2-(4-Chlorophenylthio)-5-fluoro-4-methoxyphenylacetic Acid (*XXXV*)

A mixture of 6·96 g *XXXII* and 30 ml concentrated hydrochloric acid was stirred for 30 min at room temperature and for 10 min at 70°C. After cooling, the crude *XXXIII* was extracted with benzene, the extract was dried with $CaCl_2$ and evaporated at reduced pressure at below 45°C. The residue was combined with 1·72 g NaCN, 0·38 g NaI and 17 ml acetone. The mixture was refluxed under stirring for 20 h, cooled, filtered and the filtrate was evaporated *in vacuo*. The crude nitrile obtained (*XXXIV*) was dissolved in 20 ml ethanol and refluxed for 5 h with a solution of 5·5 g KOH in 12 ml water. Ethanol was evaporated at reduced pressure, the residue

was dissolved in 75 ml hot water, the solution was washed with benzene and, after filtration with charcoal, acidified with hydrochloric acid; 4·79 g (62% per *XXXII*), m.p. 134—136°C (acetone). IR spectrum: 770, 820, 880 (2 adjacent and solitary Ar—H), 910, 1 210, 1 230, *1 705*, 2 540, 2 640, 2 740 (COOH), 1 275, 1 310 ($ArOCH_3$), 1 480, 1 500, 1 570, 1 610 cm^{-1} (Ar). For $C_{15}H_{12}$. .$ClFO_3S$ (326·8) calculated: 55·13% C, 3·70% H, 10·85% Cl, 5·81% F, 9·81% S; found: 55·46% C, 3·79% H, 11·01% Cl, 5·73% F, 9·99% S.

8-Chloro-2-fluoro-3-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XXXVI*)

A mixture of 20 g polyphosphoric acid and 3·50 g *XXXV* was heated under stirring for 5 h to 140—160°C. After cooling, it was decomposed with 50 ml ice-cold water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with Na_2SO_4 and evaporated. A total of 2·90 g (92%) neutral residue was obtained; this was crystallized from benzene; m.p. 183—185°C. UV spectrum: λ_{max} 265 nm ($\log \varepsilon$ 4·17) infl., 289 nm (3·51), 338 nm (3·58). IR spectrum: 813, 852, 896, 912 (2 adjacent and solitary Ar—H), 1 270 ($ArOCH_3$), 1 495, 1 579, 1 609, 3 038, 3 080 (Ar), 1 678 cm^{-1} (ArCO). For $C_{15}H_{10}ClFO_2S$ (308·8) calculated: 58·35% C, 3·26% H, 11·48% Cl, 6·15% F, 10·39% S; found: 58·75% C, 3·24% H, 11·45% Cl, 6·33% F, 10·30% S.

8-Chloro-2-fluoro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XXXVII*)

A solution of 0·12 g $NaBH_4$ in 1 ml water containing two drops of 15% NaOH was added to a solution of 1·80 g *XXXVI* in 30 ml ethanol and 20 ml benzene. The mixture was refluxed for 2·5 h, evaporated at reduced pressure, diluted with 20 ml water and extracted with benzene. Processing of the extract yielded 1·39 g (77%) product melting at 123—126°C; analytical product melted at 126—128°C (ethanol). IR spectrum: 806, 811, 872, 886 (2 adjacent and solitary Ar—H), 1 031 (CHOH), 1 196, 1 252 ($ArOCH_3$), 1 510, 1 537, 1 562, 1 581, 1 616 (Ar), 3 210 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·53 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·40 (d, J = 8·0 Hz, 1 H, 6-H), 6·90—7·30 (m, 3 H, remaining Ar—H), 5·80 (d, J = 6·0 Hz, 1 H, OH), 5·20 (m, 1 H, Ar—CH—O), 3·75 (s, 3 H, OCH_3), 2·80—3·50 (m, 2 H, $ArCH_2$). For $C_{15}H_{12}ClFO_2S$ (310·8) calculated: 11·41% Cl, 6·11% F, 10·32% S; found 11·12% Cl, 6·06% F, 10·22% S.

8,10-Dichloro-2-fluoro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXXVIII*)

A solution of 1·70 g *XXXVII* in 15 ml benzene was combined with 1·3 g $CaCl_2$ and the suspension was saturated with hydrogen chloride at room temperature. After standing overnight, it was filtered and the filtrate was evaporated. Crystallization from 10 ml acetone yielded 1·42 g (78%) compound melting at 133—134°C; analytical product melts at 134—137°C (acetone). For C_{15}. .$H_{11}Cl_2FOS$ (329·2) calculated: 21·54% Cl, 9·74% S; found: 20·94% Cl, 9·80% S.

8-Chloro-2-fluoro-3-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A mixture of 1·02 g *XXXVIII*, 1 ml 1-methylpiperazine and 1 ml chloroform was refluxed for 7 h, diluted with 20 ml benzene and washed with water. The organic phase was shaken with excess 3M-HCl, the precipitated hydrochloride was filtered, combined with the aqueous phase of the filtrate and the base was set free by treatment of the suspension with NH_4OH. The base was extracted with benzene, the extract was processed to yield 0·82 g (66%) crude base which was purified by crystallization from ethanol; m.p. 135—138°C. ^{1}H-NMR spectrum: δ 7·59 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·23 (s, J = 8·0 Hz, 1 H, 6-H), 6·80—7·15 (m, 3 H, remaining Ar—H), 2·80—3·80 (m, 3 H, $ArCH_2CHAr$), 3·76 (s, 3 H, OCH_3), 2·58 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (def. t. 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). For $C_{20}H_{22}ClFN_2OS$

(392·9) calculated: 61·13% C, 5·64% H, 9·02% Cl, 4·84% F, 7·13% N, 8·16% S; found: 61·46% C, 5·44% H, 9·27% Cl, 5·07% F, 6·97% N, 8·33% S.

Processing of the benzene layer after separation of the hydrochloride of the basic product gave rise to 0·23 g neutral 8-chloro-2-fluoro-3-methoxydibenzo[*b,f*]thiepin (*XXXIX*) melting at 168 to 170°C; analytical product, m.p. 169—171°C (benzene). UV spectrum: λ_{max} 268 nm (log ε 4·32), infl. 297 nm (3·68), infl. 337 nm (3·29). IR spectrum (KBr): 799, 819, 873, 879 (2 adjacent and solitary Ar—H, *cis*-CH=CH), 1043, 1266 ($ArOCH_3$), 1504, 1521, 1567, 1580, 1609, 3023, 3085 cm^{-1} (Ar). For $C_{15}H_{10}ClFOS$ (292·8) calculated: 61·54% C, 3·44% H, 12·11% Cl, 6·49 F, 10·95% S; found: 61·89% C, 3·58% H, 12·30% Cl, 6·65% F, 10·78% S.

8-Chloro-2-fluoro-3-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*II*)

A solution of 3·9 g BBr_3 in 5 ml dichloromethane was added dropwise over a period of 10 min to a solution of 2·01 g *III* in 10 ml dichloromethane. The mixture was stirred for 7 h at room temperature and, on the following day, for 1 h with 10 ml 20% Na_2CO_3. The dichloromethane layer was separated and evaporated. The residue was dissolved in 20 ml ethanol and, after adding 1 ml 20% NaOH, it was refluxed for 3 h. After evaporation of ethanol, the residue was divided between chloroform and water, the chloroform solution was shaken with 5% hydrochloric acid and the acid solution obtained was neutralized with 20% Na_2CO_3 and extracted with chloroform. The residue after evaporation of the extract (0·60 g, 31%) was crystallized from benzene for analysis, m.p. 123—125°C. According to analysis, we are dealing with a solvate with one-half molecule of benzene. IR spectrum (KBr): 672 (C_6H_6), 775, 810, 842, 873 (2 adjacent and solitary Ar—H), 1287 (Ar—OH), 1493, 1576, 1607 (Ar), 2580 cm^{-1} (NH^+). For $C_{19}H_{20}$. $ClFN_2OS + 0{\cdot}5\ C_6H_6$ (418·0) calculated: 63·22% C, 5·55% H, 8·48% Cl, 4·55% F, 6·69% N, 7·67% S; found: 64·09% C, 5·58% H, 8·24% Cl, 3·79% F, 6·04% N, 7·22% S.

Bis(hydrogen maleate) dihydrate, m.p. 102—104°C (95% ethanol–ether). For $C_{27}H_{32}Cl$. $FN_2O_{11}S$ (647·1) calculated: 50·11% C, 4·98% H, 4·33% N; found: 49·91% C, 4·74% H, 4·39% N.

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