FLUORINATED TRICYCLIC NEUROLEPTICS: SYNTHESIS AND PHARMACOLOGY OF 2-CHLORO-8-FLUORO--4-(4-METHYLPIPERAZINO)-4,5-DIHYDROTHIENO[2,3-*b*]--1-BENZOTHIEPIN*

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Diazotization of 4-fluoroanthranilic acid (*V*) and the following reaction with sodium disulfide gave the dithio diacid *VII* which was reduced with lithium aluminium hydride to 4-fluoro-2-mercaptobenzyl alcohol (*XI*). Its reaction with 2-chloro-5-iodothiophene afforded the alcohol *XIII* which was transformed *via* the chloride *XIV* and the nitrile *XV* to [2-(5-chloro-2-thienylthio)--4-fluorophenyl]acetic acid (*XVI*). Cyclization with phosphorus pentoxide in toluene resulted in 2-chloro-8-fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*XVIII*) which was converted *via* the alcohol *XIX* to the chloro derivative *XX*. The substitution reaction with 1-methylpiperazine led to the title compound *IV* which is a long-acting and very potent tranquillizer but did not reveal, in the animal tests performed, the properties of a neuroleptic agent.

Simultaneously with our synthetic investigations in the series of derivatives of the tranquillizing and neuroleptic agent 10-(4-methylpiperazino)-10,11-dihydrodibenzo-[*b*,*f*]thiepin (perathiepin) (ref.[1–4]), our attention was paid to their thieno analogues, *i.e.* to the more tediously accessible derivatives of 4,5-dihydrothieno[2,3-*b*]-1-benzothiepin. The nuclearly unsubstituted 4-(4-methylpiperazino) derivative of this system (peradithiepin, *I*) (ref.[5]) revealed a significantly stronger incoordinating action than perathiepin and its cataleptic activity was also more intensive. Since the thiophene sulfur atom in *I* substitutes the grouping —CH=CH— present in the perathiepin molecule[1] we presumed that introduction of a chlorine atom to position 2 of the skeleton will affect the activity in a similar manner like the introduction of the "neuroleptic substituent" in the analogous benzo series into the *para*-position towards the sulfur atom of the central ring. The compound *II* (ref.[6]) exhibits really cataleptic action of a similar intensity like that of the 8-chloro derivative of perathiepin (clorothepin, octoclothepin) (ref.[2]); its incoordinating action, however, is nearly 10 times lower than a similar effect of clorothepin and of the compound *I*. Compound *II*, in fact, is a more selective neuroleptic agent than the other substances mentio-

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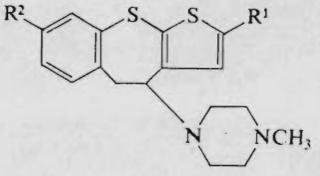
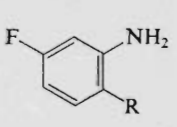
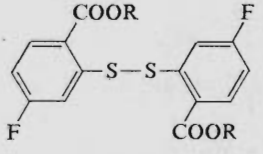
ned[1,2,5]. More recently, we have carried out the synthesis of the 8-fluoro derivative of peradithiepin (*III*) (ref.[7]) which is an analogue of the 3-fluoro derivative of perathiepin[3]; in comparison with this compound, the thiophene derivative *III* is a little more active in the rotarod test (incoordination) and enormously potent in the test of catalepsy. It shows further an unusual separation of the cataleptic and antiapomorphine activity (does not influence the apomorphine stereotypies in rats). After the finding of a high degree of neuroleptic activity with the 8-chloro-3-fluoro derivative of perathiepin[4] we considered useful to investigate also the influence of a combination of the chlorine and fluorine atoms in the corresponding positions in the thieno-[2,3-*b*]-1-benzothiepin series on this type of activity. To this end, the synthesis of the title compound *IV* has been carried out, the description of which is the object of the present communication.



I, $R^1 = R^2 = H$ *III*, $R^1 = H$, $R^2 = F$
II, $R^1 = Cl$, $R^2 = H$ *IV*, $R^1 = Cl$, $R^2 = F$

In the synthesis of *IV*, similar procedure like previously in the synthesis of *II* (ref.[6]) was used. 4-Fluoroanthranilic acid (*V*) (ref.[8]) was the starting material; its diazotization followed by a reaction with sodium disulfide gave 2,2'-dithiobis-(4-fluorobenzoic) acid (*VII*) in analogy with the preparation of the non-fluorinated compound[9]. The acid *VII* proved very resistant in attempts at its reduction – due probably to the very low solubility of its salts in nonpolar solvents. Under the use of a large excess of lithium aluminium hydride in boiling tetrahydrofuran and 6 h reaction time, only the reduction of the disulfide bond proceeded in some 15% and resulted in 4-fluoro-2-mercaptobenzoic acid (*IX*). The reduction of carboxyl did not take place at all and the prevailing quantity of the starting *VII* was recovered unchanged. Likewise in a attempt at a reduction of the mixed anhydride, prepared

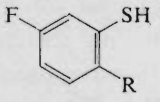




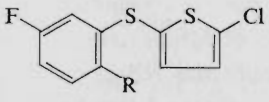
V, R = COOH *VII*, R = H
VI, R = CH_2OH *VIII*, R = CH_3

in situ by reaction of the acid *VII* with ethyl chloroformate in dioxane (for analogy, *cf.*[10]), with sodium borohydride, only the reduction of the disulfide bond took place and *IX* was obtained in an excellent yield. Its reduction with 2-chloro-5-iodothiophene[6] in dimethylformamide in the presence of potassium carbonate and copper gave the acid *XII* which, however, did not find further use in our synthesis.

In the effort to make the reduction of the acid *VII* easier by working with some of its more soluble derivative, its dimethyl ester *VIII* was prepared by treatment of the acid with dimethyl sulfate in a mixture of acetone and methanol in the presence of potassium carbonate. Its reduction was attempted again with lithium aluminium hydride but even in this case the reduction of carboxyl did not take place and the product obtained was characterized as methyl 4-fluoro-2-mercaptobenzoate (*X*). The reduction of carboxyl in the free diacid *VII* was finally achieved under the use of a large volume of a mixture of tetrahydrofuran and ether as the medium; a chromatographically homogeneous product was obtained (characterized by the ^{1}H-NMR spectrum) which could not be induced to crystallize and which decomposed in attempts at distillation. Its further processing, however, confirmed that we were dealing here with the desired 4-fluoro-2-mercaptobenzyl alcohol (*XI*) which was treated in crude state with 2-chloro-5-iodothiophene[6] at 125°C in the presence of potassium carbonate and copper. The alcohol *XIII* was obtained in a satisfactory yield. The attempt at finding an alternative procedure, in which the acid *V* was first reduced with lithium aluminium hydride in ether to 2-amino-4-fluorobenzyl alcohol (*VI*) (for analogy, *cf.*[11]) which was transformed to the crude thiol *XI* by the aryl xanthate method[12] and this was condensed with 2-chloro-5-iodothiophene, gave a less satisfactory result: the product obtained consists mainly of *XIII* (characterization by thin layer chromatography) but we did not succeed in obtaining it in crystalline state.



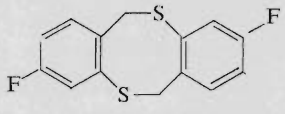
IX, R = COOH
X, R = $COOCH_3$
XI, R = CH_2OH



XII, R = COOH
XIII, R = CH_2OH
XIV, R = CH_2Cl
XV, R = CH_2CN
XVI, R = CH_2COOH

The alcohol *XIII* was processed by reaction with thionyl chloride in benzene to give the chloro derivative *XIV* which was treated with potassium cyanide in aqueous ethanol and afforded the nitrile *XV*. Hydrolysis with potassium hydroxide in aqueous ethanol resulted in [2-(5-chloro-2-thienylthio)-4-fluorophenyl]acetic acid (*XVI*). A neutral substance was isolated as by-product; it crystallized from

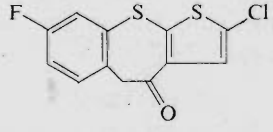
a mixture of chloroform and hexane and was obtained in two forms differing in melting points (A, 146–148°C; B, 244–246·5°C). Both forms correspond according to the analyses to the empirical formula $C_{14}H_{10}F_2S_2$ and are chromatographically indistinguishable. For the higher melting form, the composition was confirmed by the mass spectrum, and the ^{1}H-NMR spectrum of the lower melting form proved the structure of 2,8-difluoro-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin (*XVII*). The compound must have been formed already in the stage of processing of the crude chloride *XIV* which was evidently contaminated with 4-fluoro-2-mercaptobenzyl chloride.



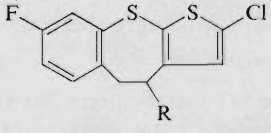
XVII

Intermediates of a similar type led in several instances to the unsubstituted 6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin[13–17]; the only derivatives described were the disulfone[16], the 6,12-dioxo derivative ("dithiosalicylide") (ref.[18]) and the 6,12-diethoxy-2,8-dimethyl derivative[19]. Our two forms of compound *XVII* are considered crystal modifications. In the case of the unsubstituted 6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin, the existence of two conformers could be established at low temperatures[16], their stability under normal conditions, however, can hardly be expected possible. A further alternative for the synthesis of the acid *XVI*, the reaction of (4-fluoro-2-iodophenyl)acetic acid[3] with 5-chlorothiophene-2-thiol was taken under consideration: the unstability of the latter compound, described in the literature[20], prevented us to attempt at investigating experimentally this approach.

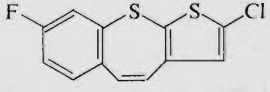
Cyclization of the acid *XVI* with phosphorus pentoxide in boiling toluene (method, *cf.*[6]) proceeded smoothly under the formation of 2-chloro-8-fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*XVIII*); its reduction with sodium borohydride in a mix-



XVIII



XIX, R = OH
XX, R = Cl



XXI

ture of ethanol and tetrahydrofuran resulted in the alcohol *XIX*. The following treatment with hydrogen chloride in benzene led to the chloro derivative *XX* which was treated with an excess of 1-methylpiperazine at 100°C. The substitution reaction gave the title compound *IV*; the simultaneously proceeding elimination resulted in 2-chloro-8-fluorothieno[2,3-*b*]-1-benzothiepin (*XXI*) which was isolated as the neutral by-product. The base *IV* was transformed for characterization and for the purpose of pharmacological testing to salts [bis(methanesulfonate), bis (hydrogen maleate)].

Compound *IV* was pharmacologically evaluated in the form of the bis(hydrogen maleate) using similar methods as mentioned in the preceding communications[1-4]; it was administered orally and the doses given were calculated for the base. Acute toxicity in mice, LD_{50} = 91 mg/kg. The incoordinating activity was evaluated by the rotarod test in mice with following the time-course of this effect after a single administration of various doses. The medium effective dose in 2 h after the administration, ED_{50} = 0·61 mg/kg; the optimum effect was reached in 3 h after the administration, ED_{50} = 0·54 mg/kg. The effect is significantly protracted: in 24 h after the administration, ED_{50} = 1·1 mg/kg; in 48 h, ED_{50} = 2·5 mg/kg; after 72 h ataxia appeared in 10% mice after the highest dose used. In the test of catalepsy, a dose of 10 mg/kg brought about the cataleptic state in 20% animals, a dose of 50 mg/kg in 40%; a dose of 100 mg/kg was lethal for 50% rats (the used strain of rats was evidently less sensible towards the cataleptic action than that used in the preceding investigations). When evaluating the antiapomorphine effect in rats it was established that doses of 20 and 40 mg/kg are inactive (evaluated in 4 h after the administration) and a dose of 80 mg/kg inhibits mildly the apomorphine stereotypies and inhibits to 50% the apomorphine agitation (simultaneously perishing of 10% animals). In comparison with the previously described 8-fluoro analogue *III* (ref.[7]), compound *IV* has similar toxicity, a similar intensity of the incoordinating activity in the short time interval (2–3 h) – which, however, is importantly protracted, cataleptically is substantially less active (partly due to a change of the used strain of rats) and similarly like compound *III* it is inactive in the test of antiapomorphine activity in rats. It reveals thus surprisingly the character of a long-acting tranquillizer or of a non-cataleptic neuroleptic.

The compound *IV* was also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, 6·25; *Streptococcus faecalis*, 12·5; *Staphylococcus pyogenes aureus*, 12·5; *Escherichia coli*, 12·5; *Proteus vulgaris*, 50; *Trichophyton mentagrophytes*, 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or

at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument, and the mass spectra with MCH-1320 and Varian MAT 311 spectrometers. The homogeneity of the compounds and composition of the reaction mixtures was checked by chromatography on thin layers of silica gel (Silufol).

2-Amino-4-fluorobenzyl Alcohol (*VI*)

A solution of 15·5 g 4-fluoroanthranilic acid[8] in 450 ml ether was added dropwise over 30 min to a stirred suspension of 8·35 g $LiAlH_4$ in 150 ml ether and the mixture was stirred and refluxed for 3 h. After cooling it was decomposed by a slow addition of 8·5 ml water, 8·5 ml 15% NaOH and 25 ml water, the precipitated solid was filtered off, washed with ether, the filtrate was dried with K_2CO_3 and evaporated; 14·2 g (100%) crude product. Crystallization from a mixture of benzene and hexane gave 70% product melting at 103—103·5°C. Further crystallization did not change the melting point. IR spectrum: 815, 850 (2 adjacent and solitary Ar—H), 1 511, 1 600 (Ar), 1 615 ($ArNH_2$), 3 270 (OH), 3 260, 3 345 cm^{-1} (NH_2). ^{1}H-NMR spectrum (CD_3.$SOCD_3$): δ 7·00 (t, $J_{H-H} = J_{H-F} = 8{\cdot}0$ Hz, 1 H, 6-H), 6·10—6·50 (m, 2 H, remaining Ar—H), 5·20 (bs, 2 H, NH_2), 4·99 (t, $J = 5{\cdot}5$ Hz, 1 H, OH), 4·35 (d, $J = 5{\cdot}5$ Hz, 2 H, $ArCH_2O$). For C_7H_8FNO (141·2) calculated: 59·56% C, 5·71% H, 13·46% F, 9·92% N; found: 59·69% C, 5·68% H, 13·57% F, 10·18% N.

2,2′-Dithiobis(4-fluorobenzoic) Acid (*VII*)

A solution of 170 g 4-fluoroanthranilic acid[8] in a mixture of 1 100 ml water and 220 ml hydrochloric acid was diazotized at 0°C with a solution of 76 g $NaNO_2$ in 310 ml water, added dropwise. The solution was stirred for 1 h at 0°C and then added to a solution of Na_2S_2·(prepared by heating 285 g $Na_2S.9\,H_2O$ and 37 g S in 340 ml water, treating the clear solution with 43·5 g NaOH in 110 ml water and cooling) containing 600 g ice. The mixture was allowed to stand for 3 h at room temperature, acidified with 200 ml hydrochloric acid and the precipitated crude product was filtered. It was dissolved in a warm solution of 140 g Na_2CO_3 in 2 l water, filtered with charcoal and the filtrate acidified again with hydrochloric acid. The precipitated product was filtered, washed with water, dried *in vacuo* and crystallized from a mixture of chloroform and ethanol; 136 g (73%), m.p. 311—312°C. Further crystallization from the same mixture did not change the melting point. UV spectrum: λ_{max} 256 nm (log ε 4·26), 297 nm (3·78). IR spectrum: 771, 783, 833, 869, 877 (2 adjacent and solitary Ar—H), 918, 1 260, 1 684, 2 500, 2 545, 2 635, 2 700, 2 790 (ArCOOH), 1 480, 1 569, 1 580, 1 600, 3 035 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3.$SOCD_3$): δ 8·01 (dd, $J_{H-H} = 8{\cdot}5$ Hz, $J_{H-F} = 6{\cdot}0$ Hz, 2 H, 6,6′-H_2), 7·28 (mcd, $J_{H-F} = 8{\cdot}5$ Hz, $J_{H-H} = 2{\cdot}5$ Hz, 2 H, 3,3′-H_2), 7·10 (mct, $J_{H-H} = 8{\cdot}5$; 2·5 Hz, $J_{H-F} = 8{\cdot}5$ Hz, 2 H, 5,5′-H_2), For $C_{14}H_8F_2O_4S_2$ (342·3) calculated: 49·12% C, 2·36% H, 11·10% F, 18·73% S; found: 49·02% C, 2·30% H, 11·21% F, 18·63% S.

Dimethyl 2,2′-Dithiobis(4-fluorobenzoate) (*VIII*)

A suspension of 5·0 g *VII* in a mixture of 40 ml methanol and 25 ml acetone was stirred and treated with 4·2 g dimethyl sulfate and 4·6 g K_2CO_3. The mixture was stirred and refluxed for 6·5 h, allowed to stand overnight at room temperature, the solvents were evaporated *in vacuo*, the residue was diluted with 50 ml 5% $NaHCO_3$ and extracted with chloroform. The extract

was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure; 4·3 g (80%) crude product. Crystallization from a mixture of ethanol and benzene gave the pure substance, m.p. 115—116°C. UV spectrum: λ_{max} 222 nm (log ε 4·64), 255 nm (4·27), 298 nm (3·89). IR spectrum (KBr): 771, 855, 871, 899 (2 adjacent and solitary Ar—H), 1 265, 1 710 (ArCOOR), 1 480, 1 570, 1 580, 1 600 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·12 (dd, J_{H-H} = 8·5 Hz, J_{H-F} = = 8·5 Hz, 2 H, 6,6′-H_2), 7·50 (mcd, J_{H-H} = 2·5 Hz, J_{H-F} = 10·0 Hz, 2 H, 3,3′-H_2), 6·92 (mcdd, J_{H-H} = 8·5; 2·5 Hz, J_{H-F} = 10·0 Hz, 2 H, 5,5′-H_2), 4·05 (s, 6 H, 2 OCH_3). ^{19}F-NMR spectrum: δ −104·75 (m). For $C_{16}H_{12}F_2O_4S_2$ (370·4) calculated: 51·88% C, 3·27% H, 10·26% F, 17·31% S; found: 52·07% C, 3·20% H, 10·00% F, 17·08% S.

4-Fluoro-2-mercaptobenzoic Acid (*IX*)

A) A solution of 20·0 g *VII* in 110 ml tetrahydrofuran was added dropwise to a stirred suspension of 10·6 g $LiAlH_4$ in 120 ml tetrahydrofuran over 75 min. The mixture was stirred and refluxed for 6 h and allowed to stand overnight at room temperature. It was decomposed by a slow addition of 30 ml water under stirring and external cooling and finally treated with a mixture of 110 ml hydrochloric acid and 160 ml water. The mixture obtained was extracted with benzene and the extract was shaken with 200 ml 5M-NaOH. The alkaline aqueous layer was separated and acidified with 1 : 1 dilute hydrochloric acid; the acids released were extracted with a mixture of benzene and ether. The extract was dried with $MgSO_4$ and evaporated. The residue was heated *in vacuo* of 1·73 kPa in a bath of 190°C; there were obtained 2·8 g (14%) sublimate crystallizing from benzene and melting at 169—172°C in a sealed capillary. The non-sublimating residue (17·2 g, 86%) was recrystallized from ethanol and found identical with the starting *VII*, m.p. 309—312°C. The sublimate was identified as *IX*. UV spectrum: λ_{max} 252 nm (log ε 3·97), 282 nm (3·46), infl. 300 nm (3·40). IR spectrum: 772, 860 (2 adjacent and solitary Ar---H), 910, 1 238, 1 265, 1 324, 1 670, 2 550, 2 625, 2 720, 2 795, infl. 3 160 (ArCOOH), 1 570, 1 598 cm^{-1} (Ar). For $C_7H_5FO_2S$ (172·2) calculated: 48·83% C, 2·93% H, 11·03% F, 18·62% S; found: 49·02% C, 2·89% H, 11·27% F, 18·43% S.

B) A suspension of 5·0 g *VII* in 30 ml dioxane was treated over 15 min with a solution of 3·2 g ethyl chloroformate in 10 ml dioxane. The mixture was stirred and refluxed for 3 h, allowed to stand overnight at room temperature, heated to 60—70°C and treated under stirring with 4·35 g $NaBH_4$, added in small portions over 6 h. It was then stirred for 3 h at 100°C, cooled and decomposed by addition of 30 ml water and 25 ml 1 : 1 dilute hydrochloric acid. After 30 min stirring, the product was extracted with chloroform, the extract was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from 20 ml benzene; 4·3 g (92%) *IX* melting at 169—172°C (sealed capillary) and sublimating at 184—185°C. The product is identical with that obtained under *A*.

Methyl 4-Fluoro-2-mercaptobenzoate (*X*)

A solution of 3·2 g *VIII* in a mixture of 50 ml ether and 10 ml tetrahydrofuran was added over 60 min to a stirred suspension of 1·25 g $LiAlH_4$ in 30 ml ether and the mixture was stirred and refluxed for 12 h. After standing for 24 h, the mixture was cooled and decomposed by a slow addition of 10 ml water and 35 ml 20% hydrochloric acid. It was extracted first with ether and then with chloroform, the combined extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Distillation of the residue gave 1·9 g (70%) *X* boiling at 2·0 kPa in a bath of 145—150°C. The distillate solidified on standing, m.p. 45—47°C. UV spectrum: λ_{max} 223 nm (log ε 4·33), 252 nm (3·94), 300 nm (3·39). IR spectrum (film): 771, 860 (2 adjacent and solitary

Ar—H), 1 265, 1 710 (ArCOOR), 1 487, 1 571, 1 602, 3 040 (Ar), 2 530 cm^{-1} (SH). For $C_8H_7.FO_2S$ (186·2) calculated: 51·60% C, 3·79% H, 10·20% F, 17·22% S; found: 51·52% C, 3·90% H, 10·52% F, 17·55% S.

2-(5-Chloro-2-thienylthio)-4-fluorobenzoic Acid (*XII*)

A solution of 2·45 g *IX* in 15 ml dimethylformamide was stirred and treated with 2·95 g K_2CO_3, 5 ml water, 50 mg Cu, and with a solution of 3·50 g 2-chloro-5-iodothiophene[6] in 5 ml dimethylformamide, added dropwise over 15 min. The mixture was stirred for 2 h at room temperature and for 3 h at 100—110°C. After standing overnight the solid was filtered off, washed with dimethylformamide and the filtrate was diluted with water. It was washed with chloroform and evaporated *in vacuo*. The residue was dissolved in 20 ml water and the solution acidified with 10% hydrochloric acid. The separated product was extracted with ether; processing of the extract gave 2·4 g (59%) *XII*, m.p. 220—222°C. Analytical sample was obtained by crystallization from ethanol, m.p. 221—223°C. UV spectrum: λ_{max} 223 nm (log ε 4·39), 254 nm (4·29), 290 nm (3·78). IR spectrum (KBr): 792, 865, 905 (2 adjacent and solitary Ar—H), 920, 1 260, 1 678, 2 540, 2 625 (ArCOOH), 1 478, 1 568, 1 600 cm^{-1} (Ar). For $C_{11}H_6ClFO_2S_2$ (288·8) calculated: 45·75% C, 2·09% H, 12·28% Cl, 6·58% F, 22·21% S; found: 46·06% C, 2·07% H, 12·32% Cl, 6·90% F, 22·50% S.

4-Fluoro-2-mercaptobenzyl Alcohol (*XI*)

A solution of 34·2 g *VII* in a mixture of 400 ml tetrahydrofuran and 1 300 ml ether was added dropwise to a stirred suspension of 24·7 g $LiAlH_4$ in 300 ml ether over 75 min and the mixture was refluxed for 6 h. After standing overnight it was decomposed under stirring by successive addition of 75 ml water (added dropwise), 550 ml 1 : 2 dilute hydrochloric acid and 75 ml concentrated hydrochloric acid. The organic layer was separated, the aqueous one extracted with benzene and from the combined organic layers the product was extracted into 160 ml 10% NaOH. The aqueous solution of the thiolate was acidified with dilute hydrochloric acid and the released thiol was extracted with benzene. The extract was dried ($MgSO_4$) and evaporated under reduced pressure; 29·5 g (93%) oily *XI* which was chromatographically homogeneous. ^{1}H-NMR spectrum: δ 6·60—7·20 (m, 3 H, Ar—H), 4·52 (s, 2 H, $ArCH_2O$), 3·72 and 2·65 (2 bs, 2 H, OH and SH). The attempts at crystallization were unsuccessful and distillation of a sample proceeded with decomposition. The compound was used without further purification.

2-(5-Chloro-2-thienylthio)-4-fluorobenzyl Alcohol (*XIII*)

A) A mixture of 29·0 g crude *XI*, 37·2 g 2-chloro-5-iodothiophene[6], 0·8 g Cu and 25·6 g K_2CO_3 was stirred and heated in a nitrogen atmosphere for 2·5 h to 120—130°C. It was allowed to stand overnight at room temperature, diluted with 100 ml chloroform, the solid was filtered off and washed with chloroform. The filtrate was evaporated under reduced pressure; 37·0 g (89%) oil. A sample was distilled, b.p. 192—196°C/40 Pa, and the distillate crystallized. The crystals were used to induce crystallization of the remaining part of the product by inoculation, m.p. 57—61°C. Analytical sample, m.p. 59—61°C (hexane–chloroform). IR spectrum: 800, 860, 900 (2 adjacent and solitary Ar—H), 1 052 (CH_2OH), 1 215 (Ar—F), 1 453, 1 480, 1 515, 1 575, 1 587, 1 600, 3 030, 3 040 (Ar), 3 200, 3 280 cm^{-1} (OH). For $C_{11}H_8ClFOS_2$ (274·8) calculated: 48·08% C, 2·94% H, 12·90% Cl, 6·92% F, 23·34% S; found: 48·07% C, 2·93% H, 12·73% Cl, 6·94% F, 23·00% S.

B) A solution of 15·3 g *VI* in a mixture of 26·3 ml hydrochloric acid and 235 ml water was diazotized over 25 min with a solution of 8·2 g $NaNO_2$ in 20 ml water at 0°C. The mixture was stirred for 30 min and then added over 45 min to a stirred solution of 17·3 g potassium ethyl xanthate in 100 ml water at 60—70°C. The stirring was continued for 30 min, the mixture was cooled and extracted with ether. The extract was washed with 2M-NaOH, 5% hydrochloric acid and water, dried (Na_2SO_4) and evaporated. The residue was refluxed for 10 h with 16 g KOH, 90 ml ethanol and 6 ml water, the mixture was evaporated *in vacuo*, the residue was diluted with 150 ml water and washed with ether. The aqueous layer was acidified with 10% hydrochloric acid and the intermediate extracted with ether. Processing of the extract gave 11·8 g crude *XI* which was reacted with 13·9 g 2-chloro-5-iodothiophene[6], 9·4 g K_2CO_3 and 0·2 g Cu in 20 ml dimethylformamide and 5 ml water similarly like under *A*. Similar processing led to 9·05 g inhomogeneous product which was chromatographed on a column of 450 g Al_2O_3 (activity III). Benzene and first fractions of chloroform eluted 4·1 g less polar impurities; the main chloroform fractions contained 4·8 g (16%, calculated for the starting *VI*) *XIII* which, according to TLC contains a minor amount of a less polar impurity and does not crystallize even after distillation.

2-(5-Chloro-2-thienylthio)-4-fluorobenzyl Chloride (*XIV*)

A stirred solution of 71·5 g *XIII* in 700 ml benzene was treated dropwise over 10 min with 65·5 g $SOCl_2$ and the mixture was refluxed for 45 min. After standing overnight, the volatile components were completely evaporated *in vacuo*, the residue was dissolved in 60 ml benzene and the solution was filtered through a column of 40 g silica gel. Benzene eluted 75 g (98%) homogeneous product, m.p. 57—62°C. Analytical sample, m.p. 61—63°C (hexane). For $C_{11}H_7Cl_2FS_2$ (293·2) calculated: 45·06% C, 2·41% H, 6·48% F, 21·87% S; found: 45·44% C, 2·64% H, 6·90% F, 21·75% S.

[2-(5-Chloro-2-thienylthio)-4-fluorophenyl]acetonitrile (*XV*)

A solution of 73·5 g *XIV* in 400 ml ethanol was treated with a solution of 33·8 g KCN in 55 ml water and the mixture was stirred and refluxed for 5·5 h. After cooling, the solid was filtered off, washed with ethanol, the filtrate was evaporated under reduced pressure, the residue diluted with 600 ml water and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in 100 ml benzene and chromatographed on a column of 35 g silica gel. Elution with benzene gave 64·9 g (92%) product which crystallized from ethanol, m.p. 78—82°C. Analytical sample, m.p. 81—82°C (hexane–chloroform). IR spectrum: 808, 863, 900 (2 adjacent and solitary Ar—H), 1 480, 1 515, 1 587, 3 020, 3 050 (Ar), 2 230 cm^{-1} (R—CN). For $C_{12}H_7ClFNS_2$ (287·8) calculated: 50·79% C, 2·49% H, 12·49% Cl, 6·70% F, 4·94% N, 22·60% S; found: 51·05% C, 2·68% H, 12·48% Cl, 6·82% F, 4·82% N, 22·68% S.

[2-(5-Chloro-2-thienylthio)-4-fluorophenyl]acetic Acid (*XVI*)

A solution of 59·8 g *XV* in 130 ml ethanol was treated with a solution of 56·7 g KOH in 55 ml water and the mixture was refluxed for 4 h. After cooling it was diluted with 600 ml water and the neutral components were extracted with benzene. The aqueous layer was filtered with charcoal and the filtrate acidified with 1 : 1 dilute hydrochloric acid. The separated product was extracted with chloroform, the extract was dried with $MgSO_4$ and evaporated; 55·0 g (87%) homogeneous *XVI*, m.p. 99—102°C. Analytical sample, m.p. 102—103°C (hexane–ethanol). IR spectrum (KBr): 805, 853 (2 adjacent and solitary Ar—H), 902, 1 230, 1 690, 2 610 (R—COOH), 1 478, 1 572, 1 600 cm^{-1} (Ar). For $C_{12}H_8ClFO_2S_2$ (302·8) calculated: 47·60% C, 2·66% H, 11·71% Cl, 6·28% F, 21·18% S; found: 48·25% C, 3·11% H, 11·81% Cl, 6·40% F, 20·80% S.

The benzene extract, containing neutral compounds, was dried and evaporated. The residue (10·4 g) crystallized from a mixture of chloroform and hexane and was identified as 2,8-difluoro-6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin (*XVII*), m.p. 142—147°C. Analytical sample (modification A), m.p. 146—148°C. ^{1}H-NMR spectrum: δ 6·60—7·20 (m, 6 H, Ar—H), 4·30 (s, 4 H, 2 $ArCH_2S$). For $C_{14}H_{10}F_2S_2$ (280·4) calculated: 59·98% C, 3·60% H, 13·55% F, 22·87% S; found: 60·03% C, 3·55% H, 13·84% F, 22·76% S. In another experiment, a single crystallization of the crude product was connected with a change of crystal modification and with a raise of the melting point by 100°C; the final m.p. of the modification B was 244—246·5°C (chloroform–hexane). Mass spectrum, *m/z*: 280 (M^+ corresponding to $C_{14}H_{10}F_2S_2$), 247, 233, 214, 171, 152, 140 (base peak), 96. For $C_{14}H_{10}F_2S_2$ (280·4) calculated: 59·98% C, 3·60% H, 13·55% F, 22·87% S; found: 60·35% C, 3·72% H, 13·96% F, 22·76% S.

2-Chloro-8-fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*XVIII*)

A solution of 55·0 g *XVI* in 450 ml toluene was stirred and treated with 64·5 g P_2O_5 and the mixture was refluxed for 3 h. After standing overnight the solid was filtered off and washed with toluene, the filtrate was washed with 5% KOH, dried with K_2CO_3 and evaporated under reduced pressure. The inhomogeneous residue was dissolved in benzene and chromatographed on a column of 45 g silica gel. Elution with benzene gave 30·2 g (58%) of a product melting at 140—145°C. Analytical sample was obtained by crystallization from a mixture of ethanol and benzene, m.p. 146·5—148·5°C. UV spectrum: λ_{max} 236 nm (log ε 4·29), infl. 265 nm (3·88), 315 nm (3·71). IR spectrum (KBr): 810, 835, 860 (2 adjacent and solitary Ar—H), 1 482, 1 512, 1 591 (Ar), 1 670 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 3 H, 6,7,9-H_3), 7·30 (s, 1 H, 3-H), 4·20 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —114·36 (dt, $J_{F(o-H)}$ = 8·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{12}H_6ClFOS_2$ (284·8) calculated: 50·61% C, 2·12% H, 12·45% Cl, 6·67% F, 22·52% S; found: 50·89% C, 2·07% H, 12·46% Cl, 6·95% F, 22·25% S.

2-Chloro-8-fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin-4-ol (*XIX*)

A solution of 18·0 g *XVIII* in a mixture of 300 ml ethanol and 70 ml tetrahydrofuran was stirred and slowly treated with 1·7 g $NaBH_4$. The mixture was refluxed for 10 min, cooled, evaporated under reduced pressure, the residue diluted with 500 ml water and extracted with benzene. The extract was dried with K_2CO_3 and evaporated *in vacuo*. The residue was crystallized from 400 ml cyclohexane; 13·0 g (72%), m.p. 126—127·5°C. Further crystallization from the same solvent did not change the melting point. IR spectrum: 790, 830, 839, 875 (2 adjacent and solitary Ar—H), 1 050 (CHOH), 1 227 (Ar—F), 1 485, 1 537, 1 580, 1 598, 3 020 (Ar), 3 300 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·95—7·40 (m, 3 H, 6,7,9-H_3), 6·88 (s, 1 H, 3-H), 4·80 (bm, after D_2O dd, 1 H, Ar—CH—O), 3·68 and 3·30 (2 dd, 2 H, $ArCH_2$), 2·05 (bd, disappears after D_2O, 1 H, OH). ^{19}F-NMR spectrum: δ —115·19 (dt, $J_{F(o-H)}$ = 8·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{12}H_8ClFOS_2$ (286·8) calculated: 50·26% C, 2·81% H, 12·36% Cl, 6·63% F, 22·36% S; found: 50·58% C, 2·82% H, 11·96% Cl, 6·65% F, 21·67% S.

2,4-Dichloro-8-fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*XX*)

A solution of 3·5 g *XIX* in 35 ml benzene was treated with 0·8 g $CaCl_2$ powder and saturated for 30 min with anhydrous HCl. After standing overnight, $CaCl_2$ was filtered off, washed with benzene and evaporated to a small volume; 3·3 g (89%), m.p. 138—139°C. Analytical sample, m.p. 139—141°C (benzene). ^{1}H-NMR spectrum: δ 7·00—7·50 (m, 3 H, 6,7,9-H_3), 6·90 (s, 1 H, 3-H), 5·40 (dd, 1 H, Ar—CH—Cl), 3·85 and 3·61 (2 dd, J^3 = 14·0 Hz, 2 H, $ArCH_2$). ^{19}F-NMR

spectrum: δ −114·58 (dt, $J_{F(o-H)}$ = 8·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{12}H_7Cl_2FS_2$ (305·2) calculated: 47·22% C, 2·31% H, 23·23% Cl, 6·23% F, 21·01% S; found: 47·08% C, 2·35% H, 22·89% Cl, 6·23% F, 20·82% S.

2-Chloro-8-fluoro-4-(4-methylpiperazino)-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*IV*)

A mixture of 4·7 g *XX* and 4·5 ml 1-methylpiperazine was stirred and heated for 2 h to 95—105°C. After standing overnight it was diluted with 70 ml water and extracted with benzene. The extract was washed with water and the base was transferred into the aqueous layer by shaking with 70 ml 5% H_2SO_4. The benzene solution of the neutral components was washed with water, dried with $MgSO_4$ and evaporated. The residue (1·1 g, 27%) was identified as 2-chloro-8-fluorothieno[2,3-*b*]-1-benzothiepin (*XXI*). After several recrystallizations from a mixture of hexane and chloroform it melted at 83—85°C. UV spectrum: λ_{max} 218 nm (log ε 4·47), 262 nm (4·32). IR spectrum: 830, 869 (2 adjacent and solitary Ar—H), 1 488, 1 531, 1 597, 3 010, 3 080 cm^{-1} (Ar). For $C_{12}H_6ClFS_2$ (268·8) calculated: 53·63% C, 2·25% H, 13·19% Cl, 7·07% F, 23·86% S; found: 53·83% C, 2·39% H, 13·77% Cl, 7·27% F, 23·38% S.

The aqueous solution of the sulfate was made alkaline with dilute NH_4OH and the base extracted with benzene. The extract was dried with K_2CO_3 and evaporated; 3·7 g (65%) *IV*, m.p. 138—143°C. Analytical sample, m.p. 146·5—147·5°C (ethanol). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 3 H, 6,7,9-H$_3$), 6·96 (s, 1 H, 3-H), 3·00—4·00 (m, 3 H, ArCH_2CHAr), 2·70 (bm, 4 H, CH_2N^{1}CH_2 of piperazine), 2·45 (bm, 4 H, CH_2N^{4}CH_2 of piperazine), 2·30 (s, 3 H, NCH_3). ^{19}F-NMR spectrum: δ −116·41 (dt, $J_{F(o-H)}$ = 8·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For; $C_{17}H_{18}ClFN_2S_2$ (368·9) calculated: 55·35% C, 4·92% H, 9·61% Cl, 5·15% F, 7·59% N, 17·38% S; found: 55·98% C, 4·84% H, 9·56% Cl, 5·06% F, 7·58% N, 17·22% S.

Bis(methanesulfonate), m.p. 196·5—197·5°C (ethanol). For $C_{19}H_{26}ClFN_2O_6S_3$ (529·1) calculated: 43·13% C, 4·95% H, 3·59% F, 5·30% N; found: 43·40% C, 4·71% H, 3·36% F, 5·28% N.

Bis(hydrogen maleate), m.p. 144·5—145·5°C (ethanol). For $C_{25}H_{26}ClFN_2O_8S_2$ (601·1) calculated: 49·96% C, 4·36% H, 5·90% Cl, 3·16% F, 4·66% N, 10·67% S; found: 49·87% C, 4·38% H, 6·11% Cl, 3·49% F, 4·49% N, 10·38% S.

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