# FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: 3-FLUORO-10-[4-(2-HYDROXYETHYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b,f*]THIEPINS WITH LESS COMMON SUBSTITUENTS IN POSITION 8*

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Cyclization of [4-fluoro-2-(4-nitrophenylthio)phenyl]acetic acid resulted in 3-fluoro-8-nitrodibenzo[*b,f*]thiepin-10(11*H*)-one (*IIa*) which was transformed *via* the intermediates *IVa* and *Va* to the compound *Ia*. Its reduction gave the amino alcohol *Ib*. 8-Amino-3-fluorodibenzo-[*b,f*]thiepin-10(11*H*)-one (*IIb*) was diazotized and the diazonium salt was converted by treatment with sulfur dioxide and cuprous chloride, followed by dimethylamine, to the N,N-dimethylsulfonamide *IIc*. Its processing *via* the intermediates *IVc* and *Vc* afforded *Ic*. Reduction of the amino ketone *IIb* gave the amino alcohol *IVb* which was transformed by the Beech method to the hydroxy ketone *IVd*. *Id* was obtained *via* the chloro derivative *Vd*. A reaction of 3-fluoro-8-iodo--10,11-dihydrodibenzo[*b,f*]thiepin-10-ol with cuprous cyanide in dimethylformamide led to the cyano alcohol *IVe* which was used for concluding the synthesis of *Ie*. Compounds *Ia*—*Id* are neuroleptics with central depressant and cataleptic activity; the sedative effects reveal protraction in all cases. In the test of catalepsy the least active compound *Ib* shows, however, a clear prolongation of this effect. Compound *Ia* is the most active one in the test of antiapomorphine activity but its effects are not protracted.

In one of the recent communications[1] we have enhanced the knowledge of the 3-fluoro-8-substituted 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins as potential neuroleptic agents with prolonged action[2] by compounds having as the 8-substituents hydroxyl, methoxyl, ethoxyl and the ethylthio group. In the present communication we are describing the synthesis and pharmacology of further compounds of this type (*Ia*—*Ie*) containing as neuroleptic substituents in position 8 the less common (in this context) groups, *i.e.* nitro, amino, dimethylsulfamoyl, acetyl and cyano[3,4]. The N-methyl analogues of the corresponding compounds lacking the atom of fluorine in position 3 were described previously[5–8] and were found altogether very potent neuroleptic agents.

The syntheses of compounds *Ia*—*Ie* used mostly methods similar to those described in our previous communications[1,5–8] as well as intermediates previously described.

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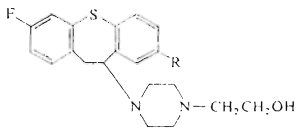
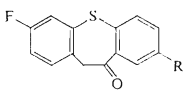
In the synthesis of the nitro compound *Ia* it was [4-fluoro-2-(4-nitrophenylthio)-phenyl]acetic acid[9] which was cyclized with polyphosphoric acid at 150–155°C to 3-fluoro-8-nitrodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*IIa*). The pure compound was obtained by chromatography of the crude product which separated a small amount of a less polar substance melting above 360°C which was characterized by analysis and mas spectrum to have the composition $C_{28}H_{12}F_2N_2O_5S_2$. On the basis of a num-



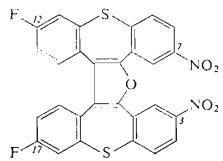
*I*

In formulae *I*, *II*, *IV*–*VI*: *a*, R = $NO_2$; *b*, R = $NH_2$; *c*, R = $SO_2N(CH_3)_2$; *d*, R = $COCH_3$; *e*, R = CN; *f*, R = $CONH_2$

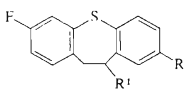
ber of analogies[9–13] we ascribe to it the structure of 12,17-difluoro-3,7-dinitrobis-dibenzo[2,3;6,7]thiepino[4,5-*b*;4′,5′-*d*]furan (*III*) (for the nomenclature, *cf*[12]). Reduction of the nitro ketone *IIa* with sodium borohydride in aqueous dioxane gave the alcohol *IVa* which was subjected to treatment with thionyl chloride affording the chloro derivative *Va*. The desired piperazine derivative *Ia* was obtained by the substitution reaction with 1-(2-hydroxyethyl)piperazine in boiling acetonitrile. As the neutral by-product there was isolated in small quantity 7-fluoro-2-nitrodibenzo-[*b*,*f*]thiepin (*VIa*) resulting from a simultaneously proceeding elimination. Reduc-



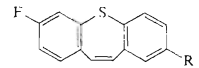
*II*



*III*



*IV*, $R^1$ = OH
*V*, $R^1$ = Cl



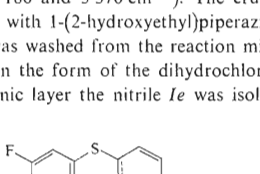
*VI*

tion of the nitro compound *Ia* with hydrazine in boiling ethanol in the presence of ferric chloride resulted in the primary amine *Ib*.

In series *c* we used 8-amino-3-fluorodibenzo[*b*,*f*]thiepin10(11*H*)-one (*IIb*) (ref.[9]) as the starting compound. The substance was diazotized and the solution of the diazonium salt subjected to treatment with sulfur dioxide and cuprous chloride (formed by reduction of cupric chloride with excessive sulfur dioxide) in acetic acid (method, *cf*.[6,14]); the crude sulfonyl chloride was immediately reacted with dimethylamine in dioxane to give the dimethylsulfamoyl derivative *IIc*. Reduction with sodium borohydride in a mixture of ethanol, dioxane and tetrahydrofuran in the presence of water led to the alcohol *IVc* giving by treatment with thionyl chloride the chloro derivative *Vc*. The substitution reaction with 1-(2-hydroxyethyl)-piperazine in boiling chloroform resulted in the base *Ic* and in a small amount of N,N--dimethyl-7-fluorodibenzo[*b*,*f*]thiepin-2-sulfonamide (*VIc*). The identity of both products was corroborated by spectra and the base *Ic* was transformed to the dihydrochloride.

The amino ketone *IIb* (ref.[9]) was likewise used in series *d*; it was first reduced with sodium borohydride to the amino alcohol *IVb*. Then the Beech method[7,15,16] was applied consisting in diazotization, reaction of the diazonium salt with acetaldehyde semicarbazone[17] and hydrolysis; the product was the hydroxy ketone *IVd*. Its reaction with hydrogen chloride in chloroform gave the chloro ketone *Vd* whose substitution reaction with 1-(2-hydroxyethyl)piperazine in boiling chloroform led to the base *Id* and to a small quantity of 2-acetyl-7-fluorodibenzo[*b*,*f*]thiepin (*VId*).

In the synthesis of the cyano derivative *Ie* we started from the previously described[9] 3-fluoro-8-iodo-10,11-dihydrodibenzo [*b*,*f*]thiepin-10-ol which was subjected to a reaction with cuprous cyanide in boiling dimethylformamide resulting in the nitrile *IVe* in a good yield. Treatment with hydrogen chloride in chloroform gave the crude chloronitrile *Ve*. The mass spectrum proved the contamination with the ethyl ester *VII* (its source was apparently the hydrochloride of the ethyl carboximidate formed by a reaction of the nitrile with hydrogen chloride and ethanol present in the chloroform used) and the IR spectrum indicated clearly the presence of the amide *Vf* (bands at 1 630, 1 657, 3 180 and 3 370 $cm^{-1}$). The crude product was subjected to a substitution reaction with 1-(2-hydroxyethyl)piperazine in boiling chloroform. A highly polar product was washed from the reaction mixture with water, isolated in crystalline state (also in the form of the dihydrochloride) and identified as the amide *If*. From the organic layer the nitrile *Ie* was isolated as the basic product




*VII*

(the crystalline solvate of the dimethanesulfonate) and 7-fluorodibenzo[*b,f*]thiepin--2-carbonitrile (*VIe*) as the neutral product; the identity of both substances was confirmed by spectra.

Compounds *Ia – Id* were pharmacologically evaluated in the form of salts described in the Experimental; they were administered orally and the doses given were calculated for bases. The testing was concentrated to the expected central depressant and neuroleptic effects; in addition to the intensity of effects, their duration was observed. The acute toxicity was estimated in mice and is expressed as the medium lethal doses $LD_{50}$. The incoordinating effect was evaluated in the rotarod test in mice; medium effective doses eliciting ataxia in 50% animals ($ED_{50}$) at the time of maximum effect in the course of 2 h after the administration are given. The cataleptic effect was evaluated in rats; the medium effective doses bring about catalepsy in 50% animals and were calculated from the optimum values obtained in the course of the first 5 h after the administration. The antiapomorphine activity was tested in rats and the influence on apomorphine stereotypies (chewing) as well as on the agitation was examined (the activity in both lines is expressed in percents of the values found for the control group which was administered only with apomorphine). The results are summarized in Table I which includes also data on the 8-chloro derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (octoclothepin, clorothepin) (ref.[18,19]) as the standard drug. The values in the Table I indicate very high incoordinating activity of compounds *Ia*, *Ib* and *Id* and high cataleptic activity of compound *Id*. Under the conditions of acute testing these compounds are more active than octoclothepin[19]. Compounds *Ib* and *Ic* show a prolongation of the effect. The antiapomorphine activity was found only with compounds *Ia* and *Ib*; it was not protracted.

Compounds *Ia*, *Ic* and *Id* were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl, 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*, *Ia* 25, *Ic* 50, *Id* 25; *Streptococcus faecalis*, *Ia* 100, *Id* 50; *Staphylococcus pyogenes aureus*, *Ia* 10, *Id* 50; *Escherichia coli*, *Ia* 50, *Ic* 50, *Id* 100; *Mycobacterium tuberculosis* H37Rv, *Ia* 25, *Ic* 25, *Id* 25; *Trichophyton mentagrophytes*, *Ia* 50, *Ic* 50, *Id* 50.

## EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and are not corrected; the samples were dried at about 60 Pa over $P_2O_5$ at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, $^1H$ NMR spectra (mostly in $C^2HCl_3$) were produced with a Tesla BS 487C (80 MHz) spectrometer and $^{19}F$ NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument. The mass spectra were recorded with MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral $Al_2O_3$ (activity II).

3-Fluoro-8-nitrodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*IIa*)

A mixture of polyphosphoric acid, prepared from 60 ml 85% $H_3PO_4$ and 100 g $P_2O_5$, and 17·6 g [4-fluoro-2-(4-nitrophenylthio)phenyl]acetic acid[9] was stirred and heated to 150—155°C for 2 h and then poured into a mixture of ice and water. The product was extracted with warm benzene, the solution was washed with a solution of $Na_2CO_3$, filtered and evaporated. The residue was dissolved in benzene and the solution was chromatographed on a column of 420 g $Al_2O_3$. Benzene eluted first 0·41 g solid crystallizing from a mixture of toluene and dioxane and melting above 360°C. It is considered to be 12,17-difluoro-3,7-dinitrobisdibenzo[2,3;6,7]thiepino-[4,5-*b*;4′,5′-*d*]furan (*III*). Mass spectrum, *m*/*e*: 558·0150 ($M^+$ corresponding to $C_{28}H_{12}F_2N_2O_5S_2$). For $C_{28}H_{12}F_2N_2O_5S_2$ (558·6) calculated: 60·21% C, 2·17% H, 5·02% N, 11·48% S; found: 59·81% C, 2·48% H, 4·82% N, 10·85% S.

The elution was continued with benzene and then with a mixture of benzene and chloroform and gave 7·25 g (44%) *IIa*, m.p. 161—163°C (benzene–light petroleum). UV spectrum: $\lambda_{max}$ 335 nm (log $\varepsilon$ 4·04), 225 nm (4·26), infl. 255 nm (4·10). IR spectrum (KBr): 787, 814, 841, 865, 894 (2 adjacent and solitary Ar—H), 1 348, 1 524 ($NO_2$), 1 489, 1 605, 3 112 (Ar), 1687 $cm^{-1}$ (ArCOR). For $C_{14}H_8FNO_3S$ (289·3) calculated: 58·13% C, 2·79% H, 6·57% F, 4·84% N, 11·08% S; found: 58·30% C, 2·61% H, 6·40% F, 4·82% N, 11·28% S.

3-Fluoro-8-(dimethylsulfamoyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*IIc*)

A suspension of 7·8 g 8-amino-3-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)one[9] in 30 ml acetic acid and 30 ml hydrochloric acid was diazotized at 5°C with a solution of 2·8 g $NaNO_2$ in 5 ml water, added dropwise under stirring, and the mixture was stirred for 1 h at 0—5°C. It was then poured at 0°C into a solution of 30 g $SO_2$ in 60 ml acetic acid and 20 ml benzene containing 3·0 g $CuCl_2$.

TABLE I

Pharmacological properties of compounds *Ia*—*Id*

| Compound | $LD_{50}$ mg/kg | Rotarod $ED_{50}$ mg/kg | | | Catalepsy $ED_{50}$ mg/kg | | Antiapomorphine effect[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | dose | chewing | | agitation | |
| | | 2 h | 24 h[a] | 48 h[a] | 5 h | 24 h[a] | mg/kg | 4 h | 24 h | 4 h | 24 h |
| Ia | 33 | 0·27 | 2 | 0 | 3·5 | 2 | 10 | 13·6+ | 91·1 | 13·9+ | 97·6 |
| Ib | 34 | 0·95 | 4 | 3 | 13·5 | 5[c] | 40 | 36·4+ | 100 | 32·9+ | 100 |
| Ic | 120 | 13·5 | 6 | 2 | 6·5 | 2 | — | [d] | [d] | [d] | [d] |
| Id | 78 | 0·4 | 3 | 0 | 1·4 | 0 | 5·0 | 100 | [d] | 100 | [d] |
| Oct.[e] | 78 | 2·2 | 0 | 0 | 2·5 | 0 | 4·1 | 50+ | 100 | — | — |
| Oct.[e] | — | — | — | — | — | — | 4·5 | — | — | 50+ | 100 |

[a] The maximum number of animals in the group of 10 showing the effect in the interval indicated after the highest dose included into the calculation of the $ED_{50}$. [b] + means statistical significance. [c] The same number of rats was cataleptic after 48 h. [d] Not estimated. [e] Octoclothepin.

The mixture was warmed to 40°C, stirred for 3 h at room temperature, allowed to stand overnight, diluted with water and extracted with benzene, the extract was washed with 10% $Na_2CO_3$, dried with $MgSO_4$ and evaporated. The residue was dissolved in 60 ml dioxane and the solution was treated at 0°C with 15 g dimethylamine, stirred for 3 h at room temperature, diluted with 60 ml water and allowed to stand overnight. The product was filtered, washed with ethanol and dried; 6·55 g (62%), m.p. 194–198°C. Analytical sample, m.p. 195–199°C (ethanol–benzene). UV spectrum: $\lambda_{max}$ 242 nm (log ε 4·33), 280 nm (4·08), 328 nm (3·74). IR spectrum: 831, 843, 869 (2 adjacent and solitary Ar–H), 1 170, 1 349 ($SO_2NR_2$), 1 490, 1 592, 1 600, 3 050, 3 088, 3 110 (Ar), 1 688 $cm^{-1}$ (ArCOR). $^1H$ NMR spectrum: δ 8·50 (d, 1 H, 9-H), 7·75 (s, 2 H, 6,7-$H_2$), 6·90–7·50 (m, 3 H, remaining Ar–H), 4·30 (s, 2 H, $ArCH_2CO$), 2·68 (s, 6 H, $CH_3NCH_3$). For $C_{16}H_{14}FNO_3S_2$ (351·4) calculated: 54·68% C, 4·02% H, 5·41% F, 3·99% N, 18·25% S; found: 54·63% C, 4·22% H, 5·56% F, 4·30% N, 17·99% S.

3-Fluoro-8-nitro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IVa*)

A stirred solution of 6·9 g *IIa* in 90 ml dioxane was treated dropwise with a solution of 0·8 g $NaBH_4$ in 30 ml water containing 1 drop of 20% NaOH, the mixture was stirred for 2 h at room temperature and allowed to stand overnight. The solvent was evaporated under reduced pressure, the residue was diluted with water, acidified with hydrochloric acid and extracted with chloroform. The extract was dried with $MgSO_4$ and evaporated. The residue crystallized from benzene and yielded 4·1 g (60%) product melting at 131–134°C. Analytical sample, m.p. 133–135°C (benzene–light petroleum). IR spectrum (KBr): 810, 831, 887 (2 adjacent and solitary Ar–H), 1 052 (CHOH in a cycle), 1 346, 1 519 ($NO_2$), 1 496, 1 576, 1 602, 3 070, 3 120 (Ar), 3 518 $cm^{-1}$ (OH). For $C_{14}H_{10}FNO_3S$ (291·3) calculated: 57·72% C, 3·46% H, 6·52% F, 4·81% N, 11·01% S; found: 58·05% C, 3·54% H, 6·46% F, 4·78% N, 11·28% S.

N,N-Dimethyl-7-fluoro-11-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-2-sulfonamide (*IVc*)

A solution of 6·3 g *IIc* in a mixture of 50 ml ethanol, 50 ml dioxane and 40 ml tetrahydrofuran was treated with a solution of 0·74 g $NaBH_4$ in 2 ml water containing 1 drop 20% NaOH, added dropwise under stirring. The mixture was refluxed for 4 h, evaporated, the residue was mixed with diluted hydrochlorid acid and extracted with chloroform. The extract was dried with $MgSO_4$, evaporated and the residue was induced to crystallize by treatment with benzene; 5·5 g (88%), m.p. 160–161°C (benzene). IR spectrum: 803, 821, 876 (2 adjacent and solitary Ar–H), 1 050, 1 067 (CHOH in the ring), 1 163, 1 340 [$SO_2N(CH_3)_2$], 1 493, 1 558, 1 590, 1 601, 3 065 (Ar), 3 530 $cm^{-1}$ (OH). For $C_{16}H_{16}FNO_3S_2$ (353·5) calculated: 54·37% C, 4·56% H, 5·38% F, 3·96% N, 18·14% S; found: 54·27% C, 4·75% H, 5·13% F, 3·87% N, 18·18% S.

8-Amino-3-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IVb*)

A solution of 11·5 g 8-amino-3-fluorodibenzo[*b,f*]thiepin-10(11*H*)one[9] in a mixture of 100 ml dioxane and 50 ml ethanol was stirred and slowly treated with a solution of 1·9 g $NaBH_4$ in 5 ml water containing 1 drop 20% NaOH. The mixture was refluxed for 1·5 h, allowed to stand overnight, evaporated under reduced pressure, the residue was diluted with water and extracted with chloroform. The extract was dried with $MgSO_4$, evaporated and the residue was crystallized from benzene; 7·6 g *IVb*, m.p. 125–128°C. Processing of the mother liquor yielded further 3·85 g product increasing the total yield to 11·45 g (99%). Analytical sample, m.p. 128·5–129°C (benzene). IR spectrum (KBr): 818, 862 (2 adjacent and solitary Ar–H), 1 050, 1 060 (CHOH in the ring), 1 496, 1 578, 1 607 (Ar), 1 623 ($ArNH_2$), 3 340, 3 385, 3 420 $cm^{-1}$ ($NH_2$). $^1H$ NMR

spectrum ($C^2H_3SOC^2H_3$): $\delta$ 6·90—7·30 (m, 4 H, 1,2,4,6-$H_4$), 6·80 (d, $J$ = 3·0 Hz, 1 H, 9-H), 6·30 (q, $J$ = 8·0; 3·0 Hz, 1 H, 7-H), 5·45 (bs, 1 H, OH), 5·28 (bs, 2 H, $NH_2$), *c.* 5·30 (m, 1 H, Ar—CH—O), 2·80—3·50 (m, 2 H, $ArCH_2$). For $C_{14}H_{12}FNOS$ (261·3) calculated: 64·35% C, 4·63% H, 7·27% F, 5·36% N, 12·27% S; found: 64·95% C, 4·90% H, 7·29% F, 5·42% N, 12·02% S.

8-Acetyl-3-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IVd*)

A suspension of 11·2 g *IVb* in 40 ml acetic acid and 40 ml hydrochloric acid was stirred and diazotized at 0—5°C with a solution of 3·5 g $NaNO_2$ in 10 ml water. The mixture was stirred for 1 h at 0°C, treated with 1 g urea, stirred for 10 min, then treated over 15 min with a solution of 35 g $Na_2CO_3$ in 150 ml water and the mixture added at 5°C to a stirred mixture of 25 g acetaldehyde semicarbazone[17], 25 g sodium acetate trihydrate, 1·5 g $CuSO_4.5\ H_2O$ and 0·2 g $Na_2SO_3$ in 130 ml water. The mixture was stirred for 3 h at room temperature, acidified with 30 ml hydrochloric acid, the separated solid was filtered with suction and refluxed for 4 h with a solution of 30 g oxalic acid dihydrate in 200 ml water. After cooling the product was extracted with chloroform, the extract was dried with $MgSO_4$ and evaporated. The residue (12·4 g) was dissolved in a mixture of benzene and chloroform and chromatographed on a column of 500 g $Al_2O_3$. The mixture of benzene and chloroform eluted 2·92 g of less polar components and chloroform eluted then 2·88 g (23%) *IVd*, m.p. 125—127°C. Analytical sample, m.p. 126·5—127·5°C (benzene–light petroleum). UV spectrum: $\lambda_{max}$ 238 nm ($\log \varepsilon$ 4·09), 303 nm (4·08), infl. 252 nm (3·91). IR spectrum (KBr): 803, 838, 880 (2 adjacent and solitary Ar—H), 1 050, 1 061 (CHOH in the ring), 1 493, 1 551, 1 594, 3 015, 3 040, 3 058, 3 080 (Ar), 1 669 ($ArCOCH_3$), 3 480 $cm^{-1}$ (OH). $^1H$ NMR spectrum: $\delta$ 8·08 (d, $J$ = 2·0 Hz, 1 H, 9-H), 7·65 (q, $J$ = 8·0; 2·0 Hz, 1 H, 7-H), 7·42 (d, $J$ = 8·0 Hz, 1 H, 6-H), 7·10—7·35 (m, 2 H, 1,4-$H_2$), 6·90 (tt, $J_{H(o-H)} = J_{H-F} = 8{\cdot}0$; $J_{H(m-H)}$ = 2·0 Hz, 1 H, 2-H), 5·26 (dt, after $^2H_2O$ dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·32 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·72 (d, $J$ = 8·0 Hz, disappears after $^2H_2O$, 1 H, OH), 2·50 (s, 3 H, $COCH_3$). For $C_{16}H_{13}FO_2S$ (288·3) calculated: 66·65% C, 4·54% H, 6·59% F, 11·12% S; found: 66·59% C, 4·36% H, 6·38% F, 11·40% S.

7-Fluoro-11-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-2-carbonitrile (*IVe*)

A mixture of 9·4 g 3-fluoro-8-iodo-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol[9], 10 ml dimethylformamide and 7·2 g 90% CuCN wass refluxed under stirring for 5 h. After cooling it was treated with water and benzene, the solid was filtered off and extracted with chloroform. The organic solutions were combined, dried with $MgSO_4$ and evaporated. The oily residue was chromatographed on a column of 400 g $Al_2O_3$. A mixture of benzene and chloroform eluted 1·25 g starting iodo compound and elution with chloroform yielded 5·18 g (87% per conversion) *IVe*, m.p. 130·5 to 131°C (benzene–light petroleum). IR spectrum (KBr): 801, 828, 877 (2 adjacent and solitary Ar—H), 1 059 (CHOH in the ring), 1 493, 1 597, 1 605 (Ar), 2 241 (ArCN), 3 508 $cm^{-1}$ (OH). $^1H$ NMR spectrum: $\delta$ 7·80 (d, $J$ = 2·5 Hz, 1 H, 1-H), 6·70—7·60 (m, 5 H, remaining Ar—H), 5·20 (m, 1 H, Ar—CH—O), 3·60 and 3·25 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·52 (d, $J$ = 8·0 Hz, 1 H, OH). For $C_{25}H_{10}FNOS$ (271·3) calculated: 66·40% C, 3·72% H, 7·00% F, 5·16% N, 11·82% S; found: 66·71% C, 3·88% H, 6·88% F, 5·24% N, 12·10% S.

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

A solution of 6·8 g *IVa* in 25 ml $SOCl_2$ was refluxed for 1 h, allowed to stand overnight at room temperature, $SOCl_2$ was evaporated *in vacuo* and the residue induced to crystallize by light petroleum; 6·8 g (94%), m.p. 149—155°C. Analytical sample, m.p. 151—154°C (benzene–light

petroleum). $^1$H NMR spectrum: $\delta$ 8·38 (d, $J$ = 3·0 Hz, 1 H, 1-H), 8·00 (q, $J$ = 8·0; 3·0 Hz, 1 H, 3-H), 7·58 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·80–7·45 (m, 3 H, remaining Ar—H), 5·75 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·00 and 3·68 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). $^{19}$F NMR spectrum: $\delta$ = 114·5 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_9$-$ClFNO_2S$ (309·8) calculated: 54·29% C, 2·93% H, 11·45% Cl, 6·13% F, 4·52% N, 10·35% S; found: 55·19% C, 3·08% H, 11·33% Cl, 6·21% F, 4·28% N, 10·38% S.

N,N-Dimethyl-11-chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-2-sulfonamide (*Vc*)

A solution of 6·2 g *IVc* in 50 ml benzene and 15 ml $SOCl_2$ was refluxed for 1 h and the volatile components were evaporated *in vacuo*. The residue crystallized from benzene as a solvate (6·2 g) melting at 67–77°C. A further crystallization from the same solvent raised the m.p. to 148 to 150°C (solvent-free product). $^1$H NMR spectrum: $\delta$ 7·86 (bs, 1 H, 1-H), 7·50 (bs, 2 H, 3,4-H$_2$), 6·80–7·40 (m, 3 H, remaining Ar-H), 5·70 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·00 and 3·60 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·64 (s, 6 H, $CH_3NCH_3$). For $C_{16}H_{15}$-$ClFNO_2S_2$ (371·9) calculated: 9·53% Cl, 5·11% F, 3·77% N, 17·24% S; found: 10·06% Cl, 5·18% F, 3·80% N, 17·48% S.

2-Acetyl-11-chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*Vd*)

A solution of 2·35 g *IVd* in 100 ml chloroform was saturated at room temperature for 1 h with HCl in the presence of 3·0 g powdered $CaCl_2$. The mixture was allowed to stand for 48 h, filtered and evaporated. The residue crystallized from cyclohexane; 2·22 g (89%), m.p. 112–114°C. UV spectrum: $\lambda_{max}$ 239 nm (log $\varepsilon$ 4·15), 302 nm (4·09). IR spectrum (KBr): 822, 873 (2 adjacent and solitary Ar—H), 1 230, 1 249, 1 260 (CO), 1 490, 1 590, 3 062 (Ar), 1 690 cm$^{-1}$ ($ArCOCH_3$). $^1$H NMR spectrum: $\delta$ 8·04 (d, $J$ = 2·5 Hz, 1 H, 1-H), 7·69 (q, $J$ = 8·0; 2·5 Hz, 1 H, 3-H), 7·45 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·80–7·40 (m, 3 H, remaining Ar—H), 5·72 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·94 and 3·59 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·52 (s, 3 H, $COCH_3$). For $C_{16}H_{12}ClFOS$ (306·8) calculated: 62·64% C, 3·94% H, 11·56% Cl, 6·19%F, 10·45% S; found: 63·26% C, 4·09% H, 11·64% Cl, 6·25% F, 10·63% S.

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

A solution of 5·0 g *IVe* in 120 ml chloroform was saturated at room temperature with HCl for 1 h in the presence of 5·0 g $CaCl_2$. The mixture was allowed to stand overnight at room temperature, filtered and the filtrate evaporated *in vacuo*. The residue crystallized from ethanol; 3·75 g (70%) crude *Ve*, m.p. 197–199°C. Mass spectrum, *m/z*: 289·0108 ($M^+$ of *Ve* corresponding to $C_{15}H_9ClFNS$), 336·0385 ($M^+$ corresponding to $C_{17}H_{14}ClFO_2S$, *i.e. VII*). IR spectrum: 812, 844, 878 (2 adjacent and solitary Ar—H), 1 498, 1 558, 1 600 (Ar), 2 241 cm$^{-1}$ (ArCN); the bands at 1 630, 1 657, 3 180 and 3 370 cm$^{-1}$ indicate the presence of the amide *Vf*. For $C_{15}H_9ClFNS$, (289·8) calculated: 12·24% Cl, 6·56% F, 4·83% N, 11·07% S; found: 11·31% Cl, 6·25% F, 4·35% N 10·29% S.

7-Fluoro-11-[4-(2-hydroxyethyl)piperazino]-2-nitro-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

A mixture of 6·7 g *Va*, 15 ml 1-(2-hydroxyethyl)piperazine and 20 ml acetonitrile was refluxed for 8 h, cooled, diluted with water and extracted with benzene. The benzene layer was washed with water and the basic product was extracted into 10% hydrochloric acid. The precipitated hydrochloride was filtered and combined with the aqueous layer of the filtrate. The benzene layer

was washed with water, dried and evaporated. The residue was crystallized from a mixture of ethanol and benzene; 1·2 g (20%) 7-fluoro-2-nitrodibenzo[*b,f*]thiepin (*VIa*), m.p. 143–145°C (benzene–light petroleum). $^1$H NMR spectrum: $\delta$ 8·08 (q, $J$ = 8·0; 2·5 Hz, 1 H, 3-H), 8·03 (d, 1 H, 1-H), 7·58 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·90–7·40 (m, 5 H, remaining 3 ArH and CH=CH). $^{19}$F NMR spectrum $\delta$ −112·4 (dt, $J_{F-(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_8FNO_2S$ (273·3) calculated: 61·53% C, 2·95% H, 6·95% F, 5·13% N, 11·73% S; found: 61·65% C, 3·07% H, 6·73% F, 4·94% N, 11·84% S.

The aqueous suspension of the hydrochloride was made alkaline with 20% NaOH and the base was extracted with a mixture of ether and benzene. Drying and evaporation of the extract gave 5·9 g (68%) *Ia* which crystallized from ethanol, m.p. 134–137°C. $^1$H NMR spectrum: $\delta$ 8·68 (d, $J$ = 2·5 Hz, 1 H, 1-H), 7·92 (q, $J$ = 8·0; 2·5 Hz, 1 H, 3-H), 7·59 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·90–7·40 (m, 3 H, remaining Ar–H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·64 (t, 2 H, $CH_2O$), 2·60 (m, 11 H, 5 $NCH_2$ and OH). $^{19}$F NMR spectrum: $\delta$ −116·0 (dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz). For $C_{20}H_{22}FN_3O_3S$ (403·5) calculated: 59·54% C, 5·50% H, 4·71% F, 10·41% N, 7·95% S; found: 59·50% C, 5·51% H, 4·54% F, 10·61% N, 7·73% S.

*Bis*(*hydrogen maleate*), m.p. 75–78°C (acetone–ether). For $C_{28}H_{30}FN_3O_{11}S$ (635·6) calculated: 52·91% C, 4·76% H, 2·99% F, 6·61% N, 5·04% S; found: 53·10% C, 4·96% H, 3·01% F, 6·72% N, 5·25% S.

2-Amino-7-fluoro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

A solution of 2·6 g *Ia* in 25 ml ethanol was treated with 0·4 g charcoal, 2·5 ml $N_2H_4.H_2O$, 0·1 g $FeCl_3$ and 5 ml ethanol. The mixture was refluxed for 6 h and filtered, the filtrate was evaporated, the residue was diluted with water and extracted with benzene. The extract was dried with $K_2CO_3$ and evaporated. The crude *Ib* was neutralized with methanesulfonic acid in acetone to give 1·98 g (44%) trimethanesulfonate dihydrate, m.p. 184–186°C (95% ethanol–ether). Mass spectrum, *m/z* (%): 373·1618 ($M^+$ corresponding to $C_{20}H_{24}FN_3OS$, 23%), 245 (71), 244 (90), 243 (100), 211 (95), 183 (57). For $C_{23}H_{36}FN_3O_{10}S_4 \cdot 2\,H_2O$ (697·9) calculated: 39·58% C, 5·78% H, 2·72% F, 6·02% N, 18·38% S; found: 39·53% C, 5·57% H, 2·72% F, 6·12% N, 18·75% S.

N,N-Dimethyl-7-fluoro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin-2-sulfonamide (*Ic*)

A mixture of 6·0 g *Vc*, 20 ml chloroform and 20 g 1-(2-hydroxyethyl)piperazine was refluxed for 6 h, cooled, diluted with water and extracted with benzene. The extract was washed with water and shaken with an excess of 5% hydrochloric acid. The precipitated hydrochloride was filtered and combined with the aqueous layer of the filtrate. The benzene layer was washed with water, dried with $MgSO_4$ and evaporated; 1·2 g (22%) N,N-dimethyl-7-fluorodibenzo[*b,f*]thiepin-2-sulfonamide (*VIc*), m.p. 145–146°C (ethanol). UV spectrum: $\lambda_{max}$ 270 nm (log $\varepsilon$ 4·46), infl. 300 nm (3·70). IR spectrum: 811, 839, 846, 877 (2 adjacent and solitary Ar–H), 1 159, 1 170, 1 348 ($SO_2N$), 1 490, 1 570, 1 592 cm$^{-1}$ (Ar). $^1$H NMR spectrum: $\delta$ 7·60 (s, 3 H, 1,3,4-$H_3$), 6·90–7·30 (m, 5 H, remaining Ar–H) and CH=CH), 2·68 (s, 6 H, $CH_3NCH_3$). For $C_{16}H_{14}FNO_2S_2$ (335·4) calculated: 57·29% C, 4·21% H, 5·66% F, 4·18% N, 19·12% S; found: 56·92% C, 4·32% H, 5·79% F, 4·26% N, 18·91% S.

The aqueous suspension of the hydrochloride was made alkaline with $NH_4OH$ and extracted with benzene. The extract was dried with $K_2CO_3$ and evaporated *in vacuo*; 5·7 g (76%) oily *Ic*. Neutralization with HCl in ether gave the crude dihydrochloride which was crystallized from 95% ethanol; the obtained monohydrate melted at 215°C with softening starting from

165°C. For $C_{22}H_{30}Cl_2FN_3O_3S_2 \cdot H_2O$ (556·6) calculated: 47·48% C, 5·76% H, 12·74% Cl, 3·41% F, 7·57% N, 11·52% S; found: 47·87% C, 5·71% H, 12·70% Cl, 3·22% F, 7·71% N, 11·68% S.

The purified oily base *Ic* was released from the hydrochloride with $NH_4OH$ and isolated by extraction with ether. $^1$H NMR spectrum: $\delta$ 8·15 (bs, 1 H, 1-H), 7·45 (bs, 2 H, 3,4-$H_2$), 6·80–7·40 (m, 3 H, remaining Ar–H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, 2 H, $CH_2O$), 2·68 (s, 6 H, $CH_3NCH_3$), 2·20–2·80 (m, 11 H, 5 $NCH_2$ and OH).

2-Acetyl-7-fluoro-11-[4-(2-hydroxyethyl)piperazino]-
-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

A mixture of 2·4 g *IId*, 5 g 1-(2-hydroxyethyl)piperazine and 10 ml chloroform was refluxed for 7 h. After cooling it was mixed with water and extracted with benzene. The extract was washed with water and the base was transferred into the aqueous layer by shaking with an excess of 5% hydrochloric acid. The benzene layer was washed with water, dried with $MgSO_4$ and evaporated giving 0·35 g (17%) 2-acetyl-7-fluorodibenzo[*b,f*]thiepin (*IId*), m.p. 132·5–134·5°C (ethanol). UV spectrum: $\lambda_{max}$ 241 nm ($\log \varepsilon$ 4·39), 276 nm (4·37), inflexes at 255 nm (4·34) and 305 nm (3·71). IR spectrum: 832, 881 (2 adjacent and solitary Ar–H), 1 210, 1 262 (Ar–F), 1 490, 1 583, 1 594 (Ar), 1 678 $cm^{-1}$ ($ArCOCH_3$). $^1$H NMR spectrum: $\delta$ 7·80 (m, 2 H, 1,3-$H_2$), 7·49 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·70–7·30 (m, 5 H, remaining Ar–H and CH=CH), 2·51 (s, 3 H, $COCH_3$). $^{19}$F NMR spectrum: $\delta$ −113·4 (dt, $J_{H(m-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz). For $C_{16}H_{11}FOS$ (270·3) calculated: 71·09% C, 4·10% H, 7·03% F, 11·86% S; found: 71·20% C, 4·11% H, 7·13% F, 12·10% S.

The acid aqueous layer was made alkaline with 20% NaOH and the base was isolated by extraction with benzene; 2·6 g (83%) oil. Neutralization with maleic acid in a mixture of acetone and ether yielded 3·9 g bis(hydrogen maleate), m.p. 72–75°C (acetone–ether). Mass spectrum, *m/z* (%): 400·1604 ($M^+$ corresponding to $C_{22}H_{25}FN_2O_2S$, 20%), 369 (13), 281 (14), 270 (47), 209 (18), 100 (54), 99 (50), 98 (41), 88 (25), 72 (100), 58 (36). For $C_{30}H_{33}FN_2O_{10}S$ (632·7) calculated: 56·95% C, 5·26% H, 3·00% F, 4·43% N, 5·07% S; found: 56·82% C, 5·42% H, 3·08% F, 4·42% N, 5·06% S.

A sample of the purified base was obtained by decomposition of the maleate with $NH_4OH$ and extraction with ether. $^1$H NMR spectrum: $\delta$ 8·18 (d, $J$ = 2·5 Hz, 1 H, 1-H), 7·65 (q, $J$ = 8·0; 2·5 Hz, 1 H, 3-H), 7·40 (d, $J$ = 8·0 Hz, 1 H, 4-H), 6·80–7·40 (m, 3 H, remaining Ar–H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, $J$ = 5·0 Hz, 2 H, $CH_2O$), 3·05 (bs, 1 H, OH), 2·55 (m, 10 H, 5 $NCH_2$), 2·52 (s, 3 H, $COCH_3$).

7-Fluoro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin-2-carbonitrile (*Ie*)

A mixture of 3·6 g crude *Ie*, 10 ml chloroform and 10 ml 1-(2-hydroxyethyl)piperazine was refluxed for 8 h. After standing overnight it was diluted with benzene and washed with water. The aqueous layer deposited on standing 2·14 g (41%) crystalline product which was identified as 7-fluoro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin-2-carboxamide (*If*) monohydrate, m.p. 100–102°C (aqueous ethanol). Mass spectrum, *m/z*: 401·1585 ($M^+$ corresponding to $C_{21}H_{24}FN_3O_2S$; calculated 401·1573), 383 ($M-H_2O$), 370 ($M-CH_2OH$), 272, 188. IR spectrum: 820, 881 (2 adjacent and solitary Ar–H), 1 053 ($CH_2OH$), 1 491, 1 551, 1 597 (Ar), 1 615, 3 200 ($NH_2$), 1 668 ($ArCONH_2$), 3 358 $cm^{-1}$ (OH). $^1$H NMR spectrum: $\delta$ 8·09 (bs, 1 H, 1-H), 6·70–7·60 (m, 5 H, remaining Ar–H), 6·45 (bs, 2 H, $CONH_2$), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, $J$ = 6·0 Hz, 2 H, $CH_2O$), 2·90 (bs, $H_2O$), *c.* 2·50 (m, 10 H,

5 $NCH_2$). For $C_{21}H_{24}FN_3O_2S + H_2O$ (419·5) calculated: 60·12% C, 6·25% H, 4·53% F, 10·02% N, 7·64% S; found: 60·38% C, 6·26% H, 4·39% F, 10·17% N, 7·51% S.

*Dihydrochloride*, m.p. 209–212°C (aqueous ethanol–ether). For $C_{21}H_{26}Cl_2FN_3O_2S$ (474·4) calculated: 53·16% C, 5·52% H, 14·95% Cl, 4·00% F, 8·86% N, 6·76% S; found: 52·82% C, 5·76% H, 15·03% Cl, 4·25% F, 8·56% N, 6·90% S.

The benzene layer was shaken with an excess of 5% hydrochloric acid, washed with water, dried with $MgSO_4$ and evaporated giving 0·51 g (16%) 7-fluorodibenzo[*b*,*f*]thiepin-2-carbonitrile (*IVe*), m.p. 206–207°C (ethanol–benzene). UV spectrum: $\lambda_{max}$ 230 nm ($\log \varepsilon$ 4·50), 272·5 nm (4·43), infl. 303 nm (3·66). IR spectrum: 812, 832, 869, 908 (2 adjacent and solitary Ar–H), 1 475, 1 493, 1 538, 1 556, 1 600, 3 032, 3 073 (Ar), 2 240 $cm^{-1}$ (Ar–CN). For $C_{15}H_8$. .FNS (253·3) calculated: 71·12% C, 3·19% H, 7·50% F, 5·53% N, 12·66% S; found: 71·05% C, 3·53% H, 7·40% F, 5·43% N, 12·82% S.

The acid aqueous solution was treated with $NH_4OH$. The crude base *Ie* (containing some *If*) was isolated by extraction with benzene and purified by chromatography on 300 g $Al_2O_3$; elution with chloroform gave 1·5 g (32%) homogeneous oily *Ie*. Neutralization with methanesulfonic acid in a mixture of ethanol and ether resulted in the dimethanesulfonate which is solvated with $C_2H_5OH$ and $H_2O$, m.p. 122–125°C (ethanol–ether). Mass spectrum, *m/z*: 383 ($M^+$ corresponding to $C_{21}H_{22}FN_3OS$), 352 ($M-CH_2OH$), 254 (100%). IR spectrum (KBr): 778, 910 (2 adjacent and solitary Ar–H), 1 050 ($CH_2OH$), 1 491, 1 598, 3 030 (Ar), 2 242 (ArCN), 2·588, 2 670 ($NH^+$), 3 412 $cm^{-1}$ (OH). For $C_{23}H_{30}FN_3O_7S_3 + C_2H_5OH + H_2O$ (639·8) calculated: 46·94% C, 5·98% H, 2·97% F, 6·57% N, 15·03% S; found: 47·50% C, 5·77% H, 2·75% F, 6·33% N, 14·90% S.

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