FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: 8-ALKYL DERIVATIVES OF 3-FLUORO-10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS

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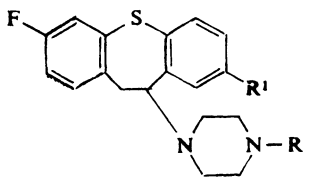
Reactions of (4-fluoro-2-iodophenyl)acetic or (2-bromo-4-fluorophenyl)acetic acid with 4-methylthiophenol, 4-ethylthiophenol and 4-isopropylthiophenol under various conditions afforded the acids *IIIa–c* which were cyclized with polyphosphoric acid to 8-alkyl-3-fluorodibenzo-[*b*,*f*]thiepin-10(11*H*)-ones *IVa–c*. The alcohols *Va–c*, which were obtained by reduction of the ketones with sodium borohydride, were transformed by treatment with hydrogen chloride to the chloro derivatives *VIa–c*. Their substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine afforded the title compounds *Ib*, *Ic* and *IIa*, The corresponding 2-alkyl-7-fluororodibenzo[*b*,*f*]thiepins *VIIa–c* were obtained as by-products. Reaction of the ketone *IVc* with 1-methylpiperazine in the presence of titanium tetrachloride gave the enamine *VIII*. The piperazine derivatives prepared are very potent neuroleptic agents with regard to their acute activities. Important prolongation of the effects was found mainly with the isopropyl compounds *Ic* and *VIII*.

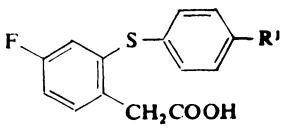
Our systematic investigations of fluorination in the series of the neuroleptic 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins[1,2] led to the conclusion that presence of the fluorine atom in position 3 of the skeleton with simultaneous presence of a "neuroleptic substituent" in position 8 results in the optimum profile from the point of view of intensity as well as duration of the effects. While 3-fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], lacking the "neuroleptic substituent" in position 8 of the skeleton, is a tranquillizer free of the neuroleptic activity, its 8-substituted derivatives and their N-(2-hydroxyethyl) analogues are very potent neuroleptics with a various degree of prolongation of the effects after the oral administration. As 8-substituents there were used chlorine[4], other halogen atoms[5], trifluoromethyl[6], hydroxyl and lower alkoxyl[7], methylthio[8], ethylthio[7], nitro and amino group, dimethylsulfamoyl and acetyl[9]. In the present communication we are describing the use of lower alkyls in this role: methyl, ethyl and isopropyl. All the three groups proved successful in the nonfluorinated series as typical "neuroleptic substituents" (ref.[10,11]). Therefore, we synthetized the title compounds *Ib*, *Ic* and *IIa*.

The synthesis started from 4-methylthiophenol, 4-ethylthiophenol[12] and 4-isopropylthiophenol[11] and proceeded analogously like in some of the cited cases[3,5,7,13]

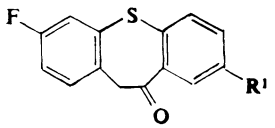


I, R = CH_3
II, R = CH_2CH_2OH

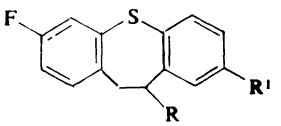
via the acids *IIIa–c*, ketones *IVa–c*, alcohols *Va–c* and the chloro compounds *VIa–c*. In series *a* and *b* 4-methylthiophenol and 4-ethylthiophenol[12] were reacted with (4-fluoro-2-iodophenyl)acetic acid[3] in a boiling aqueous solution of potassium hydroxide in the presence of copper. The acids *IIIa* and *IIIb* were obtained in very satisfactory yields. Their cyclization was carried our with polyphosphoric acid in the presence of boiling toluene; ketones *IVa* and *IVb* were obtained in yields of 80–90%. For reducing them to the alcohols *Va* and *Vb*, a boiling solution of sodium borohydride in aqueous ethanol was used. The transformation of the alcohols to the chloro compounds *VIa* and *VIb* by treatment with anhydrous hydrogen chloride in benzene proceeded with almost theoretical yields. In the final substitution reactions there were used in series *a* the chloro compound *VIa* and 1-(2-hydroxyethyl)piperazine and in series *b* the chloro compound *VIb* and 1-methylpiperazine. The reactions were carried out in a small volume of boiling chloroform and afforded mixtures of basic and neutral products. The prevailing basic products (60–70%) were isolated from the mixtures by shaking with hydrochloric acid. Solid hydrochlorides precipitated and their decomposition with aqueous ammonia gave the crude bases *IIa* and *Ib*



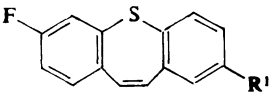
III



IV



V, R = OH
VI, R = Cl

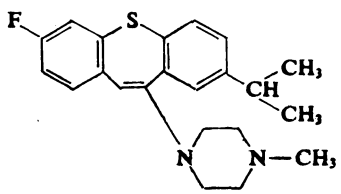


VII

In formulae *I–VII* *a*, $R^1 = CH_3$ *b*, $R^1 = CH_2CH_3$ *c*, $R^1 = CH(CH_3)_2$

which were purified by chromatography on alumina. The neutral product in series *a* was identified as 2-methyl-7-fluorodibenzo[*b*,*f*]thiepin (*VIIa*), in series *b* as 2-ethyl analogue *VIIb*.

In series *c* the acid *IIIc* was prepared on the one hand from (4-fluoro-2-iodophenyl)-acetic acid[3], and from (2-bromo-4-fluorophenyl)acetic acid[13] on the other, using various conditions. In the first case the reaction with 4-isopropylthiophenol[11] was first carried out under similar conditions like in series *a* and *b*, *i.e.* in a boiling aqueous solution of potassium hydroxide in the presence of copper; the acid *IIIc* was obtained in yields of 60–70%. In reactions of the same main components in a small volume of dimethylformamide, dimethyl sulfoxide or ethanol at 100–110°C (in the case of ethanol at the boiling point temperature of the mixture) in the presence of potassium carbonate and copper the acid *IIIc* was obtained in yields of about 65%. The use of (2-bromo-4-fluorophenyl)acetic acid[13] necessitated to work at higher temperatures (150°C); dimethylformamide was used as a diluent and the reaction proceeded in the presence of potassium carbonate and copper; in this case the yield was 50% at the maximum. The cyclization to the ketone *IVc* was carried out with polyphosphoric acid at 150°C with yields of 75–85%. The reduction to the alcohol *Vc* was performed with sodium borohydride in boiling ethanol either in the presence of water or without water; the yields were almost the same and very similar to those in series *a* and *b*. Transformation to the chloride *VIc* in toluene was carried out similarly like in series *a* and *b*. 1-Methylpiperazine was used as the amine component in the substitution reaction and the oily base *Ic* was obtained in a yield of 70%. It was transformed to the maleate. The neutral product was identified as 7-fluoro-2-isopropyldibenzo[*b*,*f*]thiepin (*VIIc*). Reaction of the ketone *IVc* with 1-methylpiperazine in boiling benzene in the presence of titanium tetrachloride gave the enamine *VIII*.



VIII

Compounds *Ib*, *Ic*, *IIa* and *VIII* were pharmacologically tested in the form of salts described in the Experimental; they were administrated orally and the doses given were calculated for bases. In addition to the intensity of effects, their duration was also followed. The acute toxicity was estimated in mice and is expressed as the medium lethal doses LD_{50}. The discoordinating effect was evaluated by the rotarod test in mice; medium effective doses eliciting ataxia in 50% animals (ED_{50}) in the time of maximum effect in the course of 2 h after the administration are given. The

influence on the spontaneous locomotor activity was evaluated by the photocell method (Dews) in mice; the doses D_{50} decrease the locomotor activity to 50% of the control values. The cataleptic effect was evaluated in rats; the medium effective doses ED_{50} 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 agitation was followed (the activity in both lines is expressed in percents and for the control group, which was administered only with apomorphine, these values for both parameters are 100%). The results are summarized in Table I which includes also data on clorothepin (octoclothepin) (ref.[14]). Data on prolonged activities are to be found in the notes to the Table.

The data in Table I and in the notes show that we are dealing here with a group of very potent neuroleptic agents having high discoordinating, central depressant, cataleptic as well as antipomorphine activities. With regard to the prolongation of the effects, both 8-isopropyl compounds (*Ic* and *VIII*) are most interesting: the dihydro compound *Ic* maintained clear activity in the interval of 24 h after the ad-

TABLE I

Pharmacological properties of the 8-alkyl derivatives of 3-fluoro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins

Compound	LD_{50} mg/kg	Rotarod ED_{50} mg/kg	Locomotor activity D_{50} mg/kg	Catalepsy ED_{50} mg/kg	Antiapomorphine effects		
					dose mg/kg	chewing %	agitation %
Ib	50	0·36[a]	0·17[b]	0·88[b]	2·5	16[b]	16[b]
Ic	57	0·7[c]	0·41[d]	2·0[e]	5·0	11[b]	11[b]
IIa	49	0·34[b]	—	1·1[b]	2·5	18[b]	28[b]
VIII	*c.* 200[f]	2·6[g]	0·89[h]	>5·0[i]	5·0	33[j]	29[j]
Oct.[k]	78	2·2[b]	1·9[b]	2·5[b]	4·1	50[b]	50[b,l]

[a] After the highest dose given ataxia appeared after 24 h with 70% animals. [b] No effect in 24 h after the administration. [c] After the highest dose given in 24 h after the administration ataxia with 60% animals and after 48 h with 20%. [d] In the interval of 24 h after the administration, ED_{50} = 0·53 mg/kg; no effect after 48 h. [e] After a dose of 5 mg/kg catalepsy persisted for 24 h in 40% animals; no effect after 48 h. [f] Due to instability of the administered solution, the value is only approximative. [g] After the highest dose used in 24 h after the administration ataxia with 40% animals and after 48 h with 30%. [h] In the interval of 24 h after the administration, ED_{50} = = 0·50 mg/kg, after 48 h ED_{50} = 1·4 mg/kg; no effect after 72 h. [i] The dose of 5 mg/kg brought about catalepsy in 40% animals. [j] After 24 h the stereotypies were still reduced to 69% and the agitation to 67%. [k] Octoclothepin (clorothepin). [l] Dose 4·5 mg/kg.

ministration (with the exception of the antiapomorphine effects) and in the rotarod test even after 48 h; the enamine *VIII* has a protracted effect even in the antiapomorphine test and the inhibition of locomotor activity reaches its maximum only after 24 h and is still significant after 48 h. These findings played an important role in the selection of the candidate for preclinical and clinical trials, *i.e.* isofloxythepin (*IIc*) (ref.[1,2]) whose chemistry will be the object of a further communication.

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentration in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *Ib* 6·25, *Va* 12·5, *VIII* 100; *Streptococcus faecalis*, *Ib* 25, *IIa* 50, *VIII* 50; *Staphylococcus pyogenes aureus*, *Ib* 25, *IIa* 25; *Escherichia coli*, *IIa* 25; *Mycobacterium tuberculosis* H37Rv, *Ib* 1·5, *IIa* 6·25, *VIII* 25; *Saccharomyces pasterianus*, *Ib* 50, *IIa* 50, *VIII* 6·2; *Trichophyton mentagrophytes*, *Ib* 25, *IIa* 50, *VIII* 25; *Candida albicans*, *VIII* 100; *Aspergillus niger*, *VIII* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined partly in a automatic Mettler FP-5 melting point recorder, partly in Kofler's block; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in C^2HCl_3) 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 homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

[4-Fluoro-2-(4-methylphenylthio)phenyl]acetic Acid (*IIIa*)

4-Methylthiophenol (9·75 g) was added to a solution of 14·6 g KOH in 130 ml water at 50°C, the mixture was stirred for 10 min and treated with 22·0 g (4-fluoro-2-iodophenyl)acetic acid[3] and 2·0 g Cu. It was then stirred and refluxed for 7 h, filtered while hot and the filtrate was acidified under cooling with 3M-HCl. The precipitated product was filtered after standing overnight, washed with water and dried; 20·6 g (95%), m.p. 86–90°C. Analytical sample, m.p. 115·5°C (aqueous ethanol). IR spectrum: 810, 824, 864, 869 (2 adjacent and solitary Ar—H), 910, 1 241, **1 710**, 2 560, 2 660, 2 745 (COOH), 1 489, 1 582, 1 604 cm^{-1} (Ar). For $C_{15}H_{13}FO_2S$ (276·3) calculated: 65·20% C, 4·74% H, 6·88% F, 11·60% S; found: 64·93% C, 4·67% H, 6·64% F, 11·49% S.

[2-(4-Ethylphenylthio)-4-fluorophenyl]acetic Acid (*IIId*)

A similar reaction of 10·4 g 4-ethylthiophenol[12], 21·0 g (4-fluoro-2-iodophenyl)acetic acid[3] and 14 g KOH in 120 ml water in the presence of 2·0 g Cu gave 16·0 g (74%) crude product, m.p. 94–97°C. Analytical sample, m.p. 108–109°C (aqueous ethanol). IR spectrum: 803, 829, 840, 861, 900 (2 adjacent and solitary Ar—H), 931, 1 233, **1 711**, 2 540, 2 645, 2 730 (COOH), 1 487, 1 575, 1 599 cm^{-1} (Ar). For $C_{16}H_{15}FO_2S$ (290·3) calculated: 66·18% C, 5·21% H, 6·54% F, 11·04% S; found: 66·24% C, 6·52% H, 6·40% F, 11·11% S.

[4-Fluoro-2-(4-isopropylphenylthio)phenyl]acetic Acid (*IIIc*)

A) 4-Isopropylthiophenol[11] (117 g), 196 g (4-fluoro-2-iodophenyl)acetic acid[3] and 7 g Cu were added to a stirred solution of 97 g KOH in 250 ml water and the mixture was refluxed

for 5·5 h under nitrogen. After standing overnight the mixture was diluted with 750 ml hot water, filtered and the filtrate was acidified with hydrochloric acid. The product was extracted with chloroform, the extract was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in 70 ml cyclohexane and the solution was treated with 700 ml light petroleum. Standing overnight gave 148 g (70%) product melting at 106—115°C. Analytical sample, m.p. 115—117°C (cyclohexane). IR spectrum: 822, 868 (2 adjacent and solitary Ar—H), 905, 1 239, **1 708**, 2 555, 2 660, 2 760 (COOH), 1 490, 1 579, 1 598 cm^{-1} (Ar). For $C_{17}H_{17}FO_2S$ (304·4) calculated: 67·08% C, 5·63% H; found: 67·37% C, 5·93% H.

B) A mixture of 28·0 g (4-fluoro-2-iodophenyl)acetic acid[3], 16·0 g 4-isopropylthiophenol[11] and 17 ml dimethylformamide was stirred and slowly treated with 28·3 g K_2CO_3. After 15 min stirring, 0·5 g Cu was added, the mixture was slowly heated to 100°C and stirred for 2·5 h at this temperature. After partial cooling 200 ml water were added and after 10 min stirring the mixture was filtered. The filtrate was acidified with 1 : 1 dilute hydrochloric acid and the oily product was extracted with chloroform. Processing of the extract gave 31·6 g oil which was dissolved in 15 ml warm cyclohexane and the solution was induced to crystallize by the addition of 150 ml light petroleum; 19·4 g (64%), m.p. 102—113°C.

C) Stirred mixture of 28·0 g (4-fluoro-2-iodophenyl)acetic acid[3], 16·0 g 4-isopropylthiophenol[11] and 30 ml dimethyl sulfoxide was treated at 50°C over 5 min with 28·3 g K_2CO_3, 0·5 g Cu was added and the mixture was stirred for 4 h at 110°C. It was then diluted with 200 ml warm water, filtered while hot, the filtrate was acidified with hydrochloric acid and after cooling extracted with benzene. The extract was dried with $MgSO_4$, filtered and evaporated. The residue was dissolved in 10 ml cyclohexane and the solution was diluted with 50 ml light petroleum; 19·3 g (64%), m.p. 108—113°C.

D) Mixture of 14·0 g (4-fluoro-2-iodophenyl)acetic acid[3], 8·0 g 4-isopropylthiophenol[11] and 15 ml ethanol was stirred and treated at 50°C with 14·0 g K_2CO_3 and 0·6 g Cu. The mixture was stirred for 7 h under reflux in a bath of 100°C, after standing overnight diluted with 100 ml hot water and filtered. Similar processing of the filtrate like in the preceding cases gave 10·3 g (68%) crude *IIIc*, m.p. 101—113°C.

E) Mixture of 75·9 g (2-bromo-4-fluorophenyl)acetic acid[13], 50·0 g 4-isopropylthiophenol[11], 140 ml dimethylformamide and 7·0 g Cu was heated under stirring to 100°C and treated over 3 min with 90 g K_2CO_3. It was then refluxed for 5 h (bath temperature 175°C), allowed to stand overnight, diluted with 400 ml water, heated to the boiling point and filtered while hot. The cooled filtrate was acidified with hydrochloric acid and the crude product was extracted with benzene. The acid was transferred by shaking with 5% NaOH into the aqueous layer which was separated and acidified with hydrochloric acid. The acid was extracted with benzene, the extract was dried and evaporated. The residue crystallized from a mixture of 50 ml cyclohexane and 60 ml light petroleum; 49·9 g (50%), m.p. 107—115·5°C.

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

Mixture of 5·0 g *IIIa*, 60 g polyphosphoric acid and 25 ml toluene was stirred and heated for 6·5 h to 130—135°C. After cooling the mixture was decomposed with 200 ml water and extracted with toluene. The extract was washed with water, 5% NaOH and water, dried with K_2CO_3 and evaporated; 4·23 g (91%), m.p. 108—111°C. Analytical sample, m.p. 113°C (ethanol). UV spectrum: λ_{max} 239 nm (log ε 4·30), 330 nm (3·60), infl. 256 nm (4·08). IR spectrum: 825, 879 (2 adjacent and solitary Ar—H), 1 471, 1 487, 1 600, 3 080 (Ar), **1 673** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·05 (bs, 1 H, 9-H), 6·90—7·60 (m, 5 H, remaining ArH), 4·34 (s, 2 H, $ArCH_2CO$), 2·35 (s, 3 H, $ArCH_3$). ^{19}F NMR spectrum: δ —115·2 (m). For $C_{15}H_{11}FOS$ (258·3) calculated: 69·75% C, 4·29% H, 7·36% F, 12·41% S; found: 70·01% C, 4·43% H, 7·21% F, 12·50% S.

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

Mixture of 14·5 g *IIIb*, 100 ml toluene and 200 g polyphosphoric acid was stirred and refluxed for 7 h. Similar processing like in the preceding case gave 11·1 g (83%) crude product melting at 71°C. Analytical sample, m.p. 74°C (ethanol). UV spectrum: λ_{max} 331 nm (log ε 3·61), infl. 254 nm (4·10), IR spectrum: 818, 836, 873 (2 adjacent and solitary Ar—H), 1 228, 1 240, **1 671** (ArCO), 1 489, 1 584, 1 599, 3 067, 3 080 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·95 (d, J = 2·0 Hz, 1 H, 9-H), 7·45 (d, J = 8·0 Hz, 1 H, 6-H), 6·80—7·40 (m, 4 H, remaining ArH), 4·25 (s, 2 H, $ArCH_2CO$), 2·58 (q, J = 7·0 Hz, 2 H, 8-$ArCH_2$), 1·15 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{16}H_{13}FOS$ (272·3) calculated: 70·56% C, 4·81% H, 6·98% F, 11·77% S; found: 70·53% C, 4·88% H, 7·15% F, 11·97% S.

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

Mixture of 88 g *IIIc* and 520 g polyphosphoric acid (prepared from 260 g P_2O_5 and 260 g 85% H_3PO_4) was stirred for 3 h and heated to 130°C (bath temperature 150°C). After cooling to 90°C it was poured under stirring to 2·5 l water. The oily product was extracted with toluene, the extract was washed with 500 ml 5% NaOH and 500 ml water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in 75 ml boiling ethanol and the solution was allowed to crystallize overnight; 68 g (82%), m.p. 69·5—72·5°C. Processing of the mother liquor raised the yield to 85%. Analytical sample, m.p. 76—78°C (needles from ethanol). UV spectrum λ_{max} 240 nm (log ε 4·64), 333 nm (4·27), infl. 255 nm (4·25). IR spectrum (KBr): 802, 827, 867, 902, 912 (2 adjacent and solitary Ar—H), 1 220, 1 255, **1 670** (ArCO), 1 479, 1 588 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·05 (d, J = 2·0 Hz, 1 H, 9-H), 6·90—7·60 (m, 5 H, remaining ArH), 4·30 (s, 2 H, $ArCH_2CO$), 2·90 (m, 1 H, 8-ArCH), 1·20 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{15}FOS$ (286·4) calculated: 71·30% C, 5·28% H, 6·63% F, 11·20% S; found: 70·95% C, 5·40% H, 6·76% F, 11·32% S.

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

Stirred solution of 3·7 g *IVa* in 50 ml ethanol was treated at 70°C with a solution of 1·8 g $NaBH_4$ in 10 ml water containing 0·5 ml 10% NaOH, added dropwise over 20 min. The mixture was refluxed for 4 h, evaporated under reduced pressure, the residue was diluted with 60 ml water and extracted with benzene. The extract was washed with 3% NaOH and water, dried with Na_2SO_4 and evaporated *in vacuo*; 3·6 g (97%), m.p. 130—135°C. Analytical sample, m.p. 138 to 139°C (cyclohexane). IR spectrum: 803, 818, 826, 880, 889 (2 adjacent and solitary Ar-H), 1 060 (CHOH in the ring), 1 493, 1 589, 1 600, 3 065 (Ar), 3 310, 3 375 cm^{-1} (OH). For C_{15}·$H_{13}FOS$ (260·3) calculated: 69·21% C, 5·03% H, 7·30% F, 12·31% S; found: 69·58% C, 4·76% H, 7·26% F, 12·60% S.

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

A similar reduction of 10·0 g *IVb* in 150 ml ethanol with 2·78 g $NaBH_4$ in 20 ml water (containing 1 ml 5% NaOH) gave 10·0 g (99%) crude product melting at 92—94·5°C. Analytical sample, m.p. 97°C (cyclohexane). IR spectrum: 794, 800, 828, 833, 873, 890 (2 adjacent and solitary Ar—H), 1 000, **1 044**, **1 054**, 1 230, 1 260 (CHOH in the ring), 1 489, 1 582, 1 598, 3 070 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70—7·40 (m, 6 H, ArH), 5·22 (m, after ^2H_2O *dd*, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·62 and 3·22 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·56 (q, J = 7·0 Hz, 2 H, 8-$ArCH_2$), 2·20 (d, J = 8·0 Hz, 1 H, disappears after ^2H_2O, OH), 1·26 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{16}H_{15}FOS$ (274·3) calculated: 70·04% C, 5·51% H, 6·93% F, 11·69% S; found: 70·39% C, 5·46% H, 6·80% F, 11·77% S.

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

A) Solution of 67 g *IVc* in 850 ml ethanol was treated under stirring at 70°C over 30 min with a solution of 5·0 g $NaBH_4$ in 25 ml water containing 0·5 ml 10% NaOH. The mixture was refluxed for 3 h, ethanol was evaporated *in vacuo* and the residue was distributed between 600 ml toluene and 450 ml water. The toluene layer was washed with 300 ml 3% NaOH and 300 ml water, dried with K_2CO_3, filtered with charcoal and evaporated; 66 g (98%), m.p. 106 to 108°C. Analytical sample, m.p. 110–112°C (cyclohexane). IR spectrum: 800, 830, 882 (2 adjacent and solitary Ar—H), 997, **1 040, 1 057**, 1 230, 1 260 (CHOH in the ring), 1 486, 1 582, 1 596 (Ar), 3 380 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70–7·40 (m, 6 H, ArH), 5·25 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·82 (m, 1 H, 8-ArCH), 2·10 (s, 1 H, OH), 1·20 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{17}FOS$ (288·4) calculated: 70·80% C, 5·94% H, 6·59% F, 11·12% S; found: 71·14% C, 6·10% H, 6·61% F, 10·94% S.

B) Stirred solution of 41·5 g *IVc* in 400 ml ethanol was slowly treated at 70°C with 7·7 g $NaBH_4$ and the mixture was refluxed for 30 h. Ethanol was evaporated *in vacuo*, the residue was distributed between chloroform and water, the organic layer was dried with K_2CO_3 and evaporated; 40·2 g (96%), crude product which was crystallized from 120 ml cyclohexane and gave 38·2 g product melting at 108–109°C.

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

Powdered $CaCl_2$ (3·0 g) was added to a solution of 2·8 g *Va* in 40 ml benzene and the suspension was stirred and saturated for 45 min with HCl. After standing overnight the mixture was filtered with charcoal and the filtrate was evaporated under reduced pressure; 2·9 g (97%), m.p. 90–92° C. Analytical sample, m.p. 92·5°C (light petroleum). ^1H NMR spectrum: δ 6·70–7·40 (m, 6 H, ArH), 5·71 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·62 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·25 (s, 3 H, $ArCH_3$). For $C_{15}H_{12}ClFS$ (278·8) calculated: 64·62% C, 4·34% H, 12·72% Cl, 6·82% F, 11·50% S; found: 64·42% C, 4·46% H, 12·89% Cl, 6·95% F, 11·32% S.

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

Solution of 9·4 g *Vb* in 120 ml benzene, containing 9·0 g $CaCl_2$, was similarly saturated with HCl and then processed giving 9·8 g (98%) crude product, m.p. 65–67°C. Analytical sample, m.p. 68–70°C (light petroleum). ^1H NMR spectrum: δ 6·70–7·50 (m, 6 H, ArH), 5·70 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·55 (q, J = 7·0 Hz, 2 H, 2-$ArCH_2$), 1·20 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). ^{19}F NMR spectrum: δ −115·5 (dt). For $C_{16}H_{14}ClFS$ (292·8) calculated: 65·63% C, 4·82% H, 12·11% Cl, 6·49% F, 10·95% S; found: 65·69% C, 4·58% H, 12·40% Cl, 6·75% F, 11·07% S.

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

Vc (65 g) was dissolved in 600 ml toluene at 50–60°C, 40 g $CaCl_2$ were added, the suspension was cooled to 18°C and saturated under stirring for 3 h with HCl. After standing overnight the mixture was filtered with charcoal and the filtrate was evaporated *in vacuo*. The residue (69 g, 100%) was dissolved in 100 ml boiling hexane and the solution was allowed to stand in a refrigerator for 4 h; 61 g (88%), m.p. 80–81°C. Analytical sample, m.p. 82–83°C (cyclohexane–light petroleum). ^1H NMR-spectrum: δ 6·70–7·40 (m, 6 H, ArH), 5·70 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—Cl), 3·91 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the

ring), 2·80 (m, 1 H, 2-ArCH), 1·18 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{16}ClFS$ (306·8) calculated: 66·54% C, 5·26% H, 11·56% Cl, 10·45% S; found: 66·75% C, 5·49% H, 11·70% Cl, 10·56% S.

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

Mixture of 63· g *VIa*, 6·3 g 1-(2-hydroxyethyl)piperazine and 7 ml chloroform was stirred and refluxed for 8 h and evaporated under reduced pressure. The residue was diluted with 150 ml water and extracted with benzene. The extract was washed with water and shaken with 70 ml 3M-HCl. After 1 h standing the precipitated hydrochloride was filtered and washed with benzene. It was suspended in 150 ml water, the suspension was made alkaline with NH_4OH and the base was extracted with benzene. The extract was washed with water, dried with K_2CO_3, evaporated *in vacuo* and the residue was chromatographed on a column of 130 g neutral Al_2O_3 (activity II). The homogeneous oily base (4·93 g, 59%) was obtained by elution with benzene containing 3% ethanol. It crystallized from light petroleum and for analysis it was recrystallized from aqueous ethanol, m.p. 114°C. IR spectrum: 817, 826, 833, 875 (2 adjacent and solitary Ar—H), 1 054 (CH_2OH), 1 489, 1 584, 1 598, 3 025, 3 058 (Ar), 3 165 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70—7·40 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, J = 6·0 Hz, 2 H, CH_2O), 2·80 (bs, 1 H, OH), 2·58 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·48 (m, 6 H, 3 CH_2N^4), 2·18 (s, 3 H, $ArCH_3$). ^{19}F NMR spectrum: δ −117·2 [dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz]. For $C_{21}H_{25}FN_2OS$ (372·5) calculated: 67·71% C, 6·76% H, 5·10% F, 7·52% N, 8·61% S; found: 67·95% C, 6·78% H, 4·97% F, 7·58% N, 8·42% S.

Succinate, m.p. 154·5°C (ethanol). For $C_{25}H_{31}FN_2O_5S$ (490·6) calculated: 61·20% C, 6·37% H, 3·87% F, 5·71% N, 6·54% S; found: 61·22% C, 6·71% H, 4·05% F, 5·70% N, 6·74% S.

The benzene layer of the filtrate after the hydrochloride was washed with dilute hydrochloric acid and water, dried with $CaCl_2$ and evaporated *in vacuo*. The residue was crystallized from 7 ml ethanol; 0·5 g (9%) 7-fluoro-2-methyldibenzo[*b,f*]thiepin (*VIIa*), m.p. 110°C (ethanol). UV spectrum: λ_{max} 263 nm (log ε 4·41), 296 nm (3·69), infl. 339 nm (3·05). ^1H NMR spectrum: δ 6·80—7·40 (m, 6 H, ArH), 6·86 (s, 2 H, CH=CH), 2·21 (s, 3 H, $ArCH_3$). ^{19}F NMR spectrum: δ −114·4 [dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz]. For $C_{15}H_{11}FS$ (242·3) calculated: 74·35% C, 4·58% H, 7·84% F, 13·23% S; found: 73·97% C, 4·74% H, 7·98% F, 13·03% S.

2-Ethyl-7-fluoro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

Mixture of 9·4 g *VIb*, 9·4 g 1-methylpiperazine and 15 ml chloroform was stirred and refluxed for 8 h. A similar processing like in the preceding case gave 8·3 g (72%) crude oily base which was chromatographed on 220 g Al_2O_3. Elution with benzene and benzene containing 2% ethanol gave 6·24 g (55%) homogeneous base *Ib* which was transformed to the maleate, m.p. 156°C (ethanol–ether). For $C_{25}H_{29}FN_2O_4S$ (472·6) calculated: 63·54% C, 6·19% H, 4·02% F, 5·93% N, 6·78% S; found: 63·70% C, 6·05% H, 4·15% F, 6·31% N, 6·85% S.

Pure oily base *Ib* was prepared from the crystalline maleate by decomposition with aqueous NH_3 and extraction with benzene. ^1H NMR spectrum: δ 7·40 (d, J = 2·5Hz, 1 H, 1-H), 6·70 to 7·40 (m, 5 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·55 (q, J = 7·0 Hz, 2 H, 2-$ArCH_2$), 2·44 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3), 1·18 (t, J = 7·0 Hz, CH_3 of ethyl). ^{19}F NMR spectrum: δ −117·1 (dt).

The neutral by-product, 2-ethyl-7-fluorodibenzo[*b,f*]thiepin (*VIIb*), was isolated similarly like in the preceding case; 1·6 g (20%) oil. For purification it was chromatographed on 40 g Al_2O_3 using elution with light petroleum. The first fraction (0·35 g) contained impurities, the second one (0·75 g) was homogeneous and was used for analysis and spectra. UV spectrum: λ_{max} 262·5 nm

(log ε 4·42), 296 nm (3·70), infl. 339 nm (2·94). IR spectrum (film): 760, 775, 788, 819, 854, 871 (2 adjacent and solitary Ar—H), 1 209, 1 259 (C—F), 1 487, 1 569, 1 593, 3 014 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60—7·50 (m, 8 H, ArH and CH=CH), 2·55 (q, J = 7·0 Hz, 2 H, 2-ArCH_2), 1·20 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{16}H_{13}FS$ (256·3) calculated: 74·97% C, 5·11% H, 7·41% F, 12·51% S; found: 74·93% C, 5·06% H, 7·64% F, 12·27%S .

7-Fluoro-2-isopropyl-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ic*)

Mixture of 3·9 g *VIc*, 6·0 g 1-methylpiperazine and 8 ml chloroform was stirred and refluxed for 5 h. After cooling it was diluted with water and extracted with benzene. The benzene layer was washed with water and shaken with excessive 2% H_2SO_4. The precipitated sulfate was filtered, washed with benzene, combined with the aqueous layer of the filtrate, and the suspension was made alkaline with NH_4OH. The base was extracted with benzene, the extract was dried with K_2CO_3 and evaporated *in vacuo*; 4·3 g (70%) oily *Ic*. Neutralization with 1·3 g maleic acid in 10 ml ethanol and addition of 60 ml ether gave 4·5 g maleate, m.p. 174—176°C (ethanol–ether). For $C_{26}H_{31}FN_2O_4S$ (486·6) calculated: 64·17% C, 6·42% H, 3·90% F, 5·76% N, 6·59% S; found: 64·17% C, 6·34% H, 3·92% F, 5·74% N, 6·88% S.

The benzene layer from the filtrate after the *Ic* sulfate was washed with water, dried and evaporated; 1·0 g (30%) 7-fluoro-2-isopropyldibenzo[*b,f*]thiepin (*VIIc*). The oily compound was first chromatographed on 35 g Al_2O_3 and the benzene eluate was distilled, b.p. 140°C/1·3 Pa. ^1H NMR spectrum: δ 7·47 (d, J = 8·0 Hz, 1 H, 4-H), 7·00—7·30 (m, 4 H, 1,6,8,9-H_4), 6·96 (s, 2 H, ArCH=CHAr), 6·88 (q, J = 8·0; 2·0 Hz, 1 H, 3-H), 2·82 (m, 1 H, 2-ArCH), 1·20 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{17}H_{15}FS$ (270·4) calculated: 75·52% C, 5·59% H, 7·03% F,11·86% S; found: 75·72% C, 5·65% H, 6·92% F, 11·79% S.

7-Fluoro-2-isopropyl-11-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*VIII*)

Stirred solution of 8·0 g *IVc* and 14 g 1-methylpiperazine in 55 ml benzene was treated dropwise with 2·8 g $TiCl_4$ in 14 ml benzene and the mixture was refluxed for 15 h. After cooling it was slowly decomposed with 80 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was neutralized with 2·8 g maleic acid in 30 ml ethanol, the precipitated salt was dissolved by heating and the warm solution was slowly treated with 200 ml ether; 6·2 g (46%) maleate, m.p. 183—184°C with decomposition (ethanol). For $C_{26}H_{29}FN_2O_4S$ (484·8) calculated: 64·44% C, 6·03% H, 3·92% F, 5·78% N, 6·62% S; found: 64·11% C, 6·01% H, 3·95% F, 5·87% N, 6·34% S.

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