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

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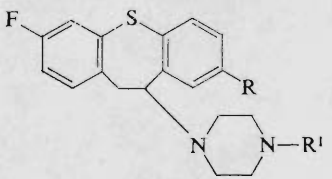
Reactions of (4-fluoro-2-iodophenyl)acetic acid with 4-fluoro and 4-bromothiophenol gave the acids *IIIa* and *IIIc* which were cyclized to 3-fluoro-8-halogenodibenzo[*b*,*f*]thiepin-10(11*H*)--ones *IVa* and *IVc*. The title compounds *Ia* and *IIc* were obtained *via* the intermediates *VIac* and *VIIac*. Reactions of (4-fluoro-2-mercaptophenyl)acetic acid or 6-fluorobenzo[*b*]thiophen--2(3*H*)-one with 4-chloronitrobenzene afforded the nitro acid *IIIe* which was reduced to the amino acid *IIIf*. Cyclization gave the amino ketone *IVf* which was transformed to the iodo ketone *IVd*. Proceeding *via* the intermediates *VId* and *VIId* led to the final product *IId*. Compounds *Ia* and *IIcd* have strong central depressant and cataleptic activity; prolongation of the effect is connected merely with the central depressant component of the action.

In several of the preceding communications of this series[1-3] we described the synthesis of variously N-substituted 8-chloro-3-fluoro derivatives of 10-piperazino--10,11-dihydrodibenzo[*b*,*f*]thiepin and reported a high degree of central depressant and neuroleptic activity of compounds *Ib* (ref.[1]) and *IIb* (ref.[2]); the effects were partly protracted and could be proven still on the other day after the administration. Within a systematic search after 3-fluoro derivatives of this series with prolonged action, based on the hypothesis about the blockade of metabolic hydroxylation by fluorination[4], we considered useful to estimate the influence of further halogen



a, R = F
b, R = Cl
c, R = Br
d, R = I
e, R = NO_2
f, R = NH_2

I, $R^1 = CH_3$
II, $R^1 = CH_2CH_2OH$

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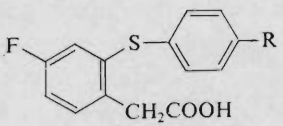
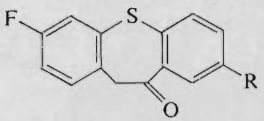
atoms in position 8 on the intensity and duration of effects. In the present paper we are dealing with the syntheses of the 3,8-difluoro compound *Ia*, 8-bromo-3-fluoro compound *IIa* and 3-fluoro-8-iodo compound *IId*, as well as with results of their orientation pharmacological evaluation.

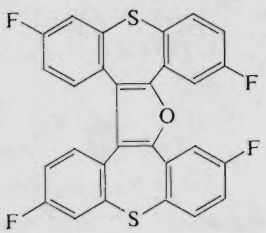
In the synthesis of the fluoro derivative *Ia* we used as starting compound (4-fluoro--2-iodophenyl)acetic acid, the preparation of which has recently been described by our group[5]. A reaction with 4-fluorothiophenol[1] in a boiling aqueous potassium hydroxide solution in the presence of copper gave the acid *IIIa* which was cyclized with polyphosphoric acid at 125–130°C. 3,8-Difluorodibenzo[*b*,*f*]thiepin-10(11*H*)--one (*IVa*) was obtained in a high yield and was accompanied by a small amount of a little soluble and high-melting substance, the composition of which was determined by means of the mass spectrum as $C_{28}H_{12}F_4OS_2$. The UV and IR spectra are not at variance with formulating the compound as the pentacyclic furan derivative *V*; it is a further case of isolation of this type of compound as a by-product of cyclization of (2-arylthiophenyl)acetic acids[5,6]. Reduction of the ketone *IVa* with sodium borohydride in boiling ethanol afforded in an almost theoretical yield the alcohol *VIa*, which was transformed by treatment with anhydrous hydrogen chloride in benzene to the chloro derivative *VIIa*. A substitution reaction of this compound with 1-methylpiperazine in boiling chloroform resulted in 72% of the base *Ia* which was transformed to the methanesulfonate. We are dealing here with a stoichiometrically unusual salt containing 3 molecules of methanesulfonic acid per 2 molecules of the base *Ia* (sesquimethanesulfonate); this phenomenon was already observed by us with the 3,8-disubstituted derivatives of the perathiepin series[7] so that we have to assume that it is determined by a special arrangement of the crystal lattice of methanesulfonates of bases with the corresponding shape of molecules.



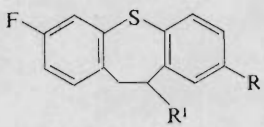
III



IV

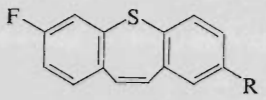


V



VI, $R^1 = OH$
VII, $R^1 = Cl$

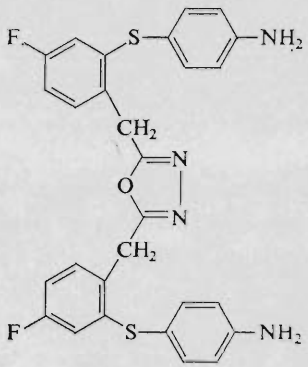
The synthesis of the 8-bromo-3-fluoro derivative *IIc* proceeded similarly. The starting step was again a reaction of potassium salts of (4-fluoro-2-iodophenyl)acetic acid[5] and 4-bromothiophenol (prepared by reduction of 4-bromobenzenesulfonyl chloride[8] using the Wagner method[9], *cf.*[10,11]). The obtained acid *IIIc* cyclized smoothly with polyphosphoric acid in the presence of boiling toluene to the ketone *IVc*. The preparation of intermediates *VIc* and *VIIc* proceeded similarly like in the preceding case. The substitution reaction of the chloride *VIIc* with 1-(2-hydroxyethyl)-piperazine in boiling chloroform afforded a relatively low yield of the crystalline base *IIc* which was transformed to the succinate. The substitution reaction was accompanied in a rather important extent by elimination resulting in 2-bromo--7-fluorodibenzo[*b*,*f*]thiepin (*VIIIc*).



VIII

The synthesis of the 3-fluoro-8-iodo derivative *IId* required a longer way leading to intermediates useful in the synthesis of further 8-substituted analogues. The first step was the synthesis of the nitro acid *IIIe* using reactions of 4-chloronitrobenzene either with (4-fluoro-2-mercaptophenyl)acetic acid[12] or its thiolactone, *i.e.* 6-fluorobenzo[*b*]thiophen-2(3*H*)-one[12]. The reactions were carried out in aqueous ethanol in the presence of potassium carbonate and a small amount of potassium iodide and led in excellent yield to compound *IIIe*. Its reduction resulted in the amino acid *IIIf*. The reduction was carried out with hydrazine hydrate in ethanol in the presence of ferric chloride; the alternative reduction method used iron and acetic acid in water. While the product obtained by the latter method was completely pure, the product prepared by the former method was contaminated by the corresponding N,N'-diacylhydrazine which was shown by its further processing by cyclization with polyphosphoric acid at 125°C. The pure amino acid *IIIf* afforded in 85% yield the pure amino ketone *IVf*. The amino acid, obtained by the hydrazine reduction, resulted in an inhomogeneous product; crystallization gave a low yield of the amino ketone *IVf* and chromatography of the mother liquor separated a more polar compound, characterized by the mass spectrum to be $C_{28}H_{22}F_2N_4OS_2$. This composition corresponds to the structure of the 2,5-disubstituted 1,3,4-oxadiazole *IX* confirmed by the ^{1}H-NMR spectrum. The formation of this compound can only be explained by dehydration of the corresponding N,N'-diacylhydrazine and represents thus the proof of the presence of this substance in the crude amino acid *IIIf* obtained by hydrazine reduction of the nitro acid *IIIe*. Dehydration of N,N'-diacylhydrazines is a preparative method for 2,5-disubstituted 1,3,4-oxadiazoles[13–15]. The amino ketone *IVf* was diazotized and the diazonium salt was transformed by reaction with potassium

iodide to the iodo ketone *IVd*. The final steps were similar to those used in the preceding cases: reduction with sodium borohydride in a mixture of dioxane and aqueous ethanol to the alcohol *VId*, conversion to the chloride *VIId* by treatment with hydrogen chloride in chloroform and finally the substitution reaction with 1-(2-hydroxyethyl)piperazine in boiling chloroform. The oily base *IId* was obtained in a yield of 67% and was transformed to the bis(hydrogen maleate); a by-product was isolated and characterized as 7-fluoro-2-iododibenzo[*b*,*f*]thiepin (*VIIId*), formed by the elimination reaction.



IX

Compounds *Ia*, *IIc* and *IId* were pharmacologically evaluated in the form of salts described in the Experimental; the doses given were calculated for bases. The substances were administered orally and tested especially for the central depressant and neuroleptic effects; in addition to the intensity of effects, their duration was noted. 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 in the time of maximum effect are given. The influence on the spontaneous locomotor activity was evaluated by the photo-cell method in mice; the dose D_{50} decreases the locomotor activity to 50% of the control values. The cataleptic effect was evaluated in rats; the medium effective dose ED_{50} brings about catalepsy in 50% animals and was calculated from the optimum values obtained in the course of the experiment lasting for 5 h. The anti-apomorphine activity was tested in rats and the influence on apomorphine stereotypies (chewing) as well as on the 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%).

Compound *Ia*: Acute toxicity, LD_{50} = 20 mg/kg. Rotarod, ED_{50} = 0·55 mg/kg; the effect is protracted since 24 h after the administration of the highest dose, ataxia is still present in 90% animals, and after 48 h in 20% animals. Locomotor activity,

D_{50} = 0·29 mg/kg; the effect disappears after 24 h. Catalepsy: ED_{50} = 3·1 mg/kg; the effect is practically without any protraction since in 24 h after the adminstration catalepsy is present only with 10% animals. The antiapomorphine effect: a dose of 5 mg/kg decreases the stereotypies to 89% and agitation to 75%; the effect disappears within 24 h. Compound *IIc*: Acute toxicity, LD_{50} = 64 mg/kg. Rotarod, ED_{50} = 0·71 mg/kg; the effect is strongly protracted since even after 24h the ED_{50} is still 2·5 mg/kg; after the highest dose given, ataxia lasts after 24h with 90% animals, after 48 h with 30% animals. Catalepsy, ED_{50} = 3·0 mg/kg; the effect disappears, within 1 day (after 24 h catalepsy in 10% animals). Compound *IId*: Acute toxicity, LD_{50} = 125 mg/kg. Rotarod, ED_{50} = 0·67 mg/kg; the effect is mildly protracted – the highest dose administered maintains ataxia after 24 h with 30% animals. Catalepsy, ED_{50} = 0·68 mg/kg; the effect is mildly protracted – after the highest dose given catalepsy persists after 24 h in 40% animals.

In comparison with analogues lacking the fluorine atom in position 3 of the skeleton[16], the fluorinated compounds are more toxic, more active in the rotarod test and have stronger cataleptic activity. The atom of halogen in position 8 influences the properties in the same way like within the 3-non-fluorinated series: the 8-fluoro derivative is the most toxic one and has the highest central depressant effects, the 8-iodo compound has the lowest toxicity and exhibits the most significant cataleptic action. Similarly like with the heretofore described 8-chloro-3-fluoro compounds[1,2], the prolongation of effects appears significantly in the line of central depressant action and is insignificant with the true neuroleptic effects.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Ia* 25, *IIc* 12·5; *Streptococcus faecalis*, *Ia* 100, *IIc* 12·5; *Staphylococcus pyogenes aureus*, *Ia* 25, *IIc* 12·5; *Pseudomonas aeruginosa*, *Ia* 100; *Escherichia coli*, *IIc* 12·5; *Mycobacterium tuberculosis* H37Rv, *Ia* 6·25; *IIc* 12·5; *Saccharomyces pasterianus*, *IIc* 25; *Trichophyton mentagrophytes*, *Ia* 25, *IIc* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block (not corrected) and partly in an automatic Mettler FP-5 melting point recorder; 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 (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer and ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CHCl_3} = 0$) with the same instrument. The mass spectra were recorded on a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

4-Bromothiophenol

A solution of 68 g 4-bromobenzenesulfonyl chloride[8] in 100 ml acetic acid was added dropwise to a stirred and refluxing mixture of 130 ml acetic acid, 29 g red phosphorus and 1·5 g iodine.

The mixture was refluxed for 3 h. After standing overnight, 25 ml water were slowly added, the mixture was refluxed for 1 h and subjected to steam distillation. The distillate (2 l) deposited after cooling the product which was filtered, washed with water and dried *in vacuo* over P_2O_5; 48 g (95%), m.p. 74°C. Lit.[10,11], m.p. values of 73–75°C, and 74°C, respectively.

[2-(4-Fluorophenylthio)-4-fluorophenyl]acetic Acid (*IIIa*)

4-Fluorothiophenol[1] (6·4 g) was added to a solution of 9·8 g KOH in 40 ml water, the stirred solution was treated with 14·0 g (4-fluoro-2-iodophenyl)acetic acid[5] and 0·3 g Cu and the mixture was refluxed for 10 h. It was diluted with 60 ml hot water, filtered wigh charcoal and the cooled filtrate acidified with 1 : 1 dilute hydrochloric acid; 11·8 g (84%), m.p. 100–104°C. Analytical sample, m.p. 112–114°C (aqueous ethanol). IR spectrum (KBr): 800, 835, 861, 897 (2 adjacent and solitary Ar—H), 1 230, 1 693, 2 650, 2 720 (RCOOH), 1 478, 1 489, 1 574, 1 589 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 11·25 (bs, 1 H, COOH), 6·70–7·50 (m, 7 H, Ar—H), 3·82 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ −113·5 (m, F in 4-fluorophenyl), −113·9 (m, the remaining Ar—F). For $C_{14}H_{10}F_2O_2S$ (280·3) calculated: 59·99% C, 3·60% H, 13·55% F, 11·44% S; found: 60·28% C, 3·63% H, 13·29% F, 11·58% S.

[2-(4-Bromophenylthio)-4-fluorophenyl]acetic Acid (*IIIc*)

A stirred solution of 14·6 g KOH in 130 ml water was successively treated at 50°C with 14·8 g 4-bromothiophenol, 22 g (4-fluoro-2-iodophenyl)acetic acid[5] and 2 g Cu and the mixture was refluxed for 7 h. It was filtered while hot and the cooled filtrate was acidified with 3M-HCl. The separated product was filtered, washed with water and dried *in vacuo*; 25·7 g (95%) crude product, m.p. 100–115°C. Analytical sample, m.p. 117–118°C (Mettler) (aqueous ethanol). IR spectrum: 809, 820, 861, 880, 900 (2 adjacent and solitary Ar—H), 945, 1 250, 1 704, 2 535, 2 620, 2 715, infl. 3 100 (RCOOH), 1 474, 1 485, 1 574, 1 600 cm^{-1} (Ar). For $C_{14}H_{10}BrFO_2S$ (341·2) calculated: 49·28% C, 2·95% H, 23·42% Br, 5·57% F, 9·40% S; found: 48·73% C, 2·95% H, 23·65% Br, 5·48% F, 9·35% S.

[4-Fluoro-2-(4-nitrophenylthio)phenyl]acetic Acid (*IIIe*)

A) (4-Fluoro-2-mercaptophenyl)acetic acid[12] (3·0 g) was added to a solution of 4·5 g K_2CO_3 in 20 ml water, the mixture was heated to 80°C, treated with 0·2 g KI and a solution of 4·0 g 4-chloronitrobenzene in 40 ml ethanol and refluxed under stirring for 7 h. Ethanol was partly evaporated, the residue diluted with water and the mixture allowed to stand overnight at room temperature. The excessive 4-chloronitrobenzene was filtered off and the filtrate was acidified with hydrochloric acid; 4·6 g (93%), m.p. 159–163°C. Analytical sample, m.p. 162–164°C, (ethanol). UV spectrum: λ_{max} 236 nm (infl.) (log ε 4·02), 313 nm (4·07). IR spectrum: 805, 842, 856, 880 (2 adjacent and solitary Ar—H), 960, 1 249, 1 709, 2 560, 2 640, 2 750 (RCOOH), 1 349, 1 505 ($ArNO_2$), 1 583, 1 600, 3 075, 3 112 cm^{-1} (Ar). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·02 (d, J = 8·0 Hz, 2 H, 2 Ar—H adjacent to NO_2), 7·20–7·60 (m, 3 H, 3 Ar-H in the phenylacetic acid residue), 7·18 (d, J = 8·0 Hz, 2 H, 2,6-H_2 in the 4-nitrophenylthio group), 3·70 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}FNO_4S$ (307·3) calculated: 54·72% C, 3·28% H, 4·56% N, 10·43% S; found: 54·63% C, 3·34% H, 4·66% N, 10·68% S.

B) 6-Fluorobenzo[*b*]thiophen-2(3*H*)-one[12] (10·2 g) was dissolved in a warm solution of 16·8 g K_2CO_3 in 80 ml water, the solution was treated at 80°C with 0·8 g KI and a solution of 15·8 g 4-chloronitrobenzene in 160 ml ethanol and the mixture was refluxed for 12 h. Ethanol was

evaporated, the residue diluted with water, filtered and the filtrate acidified with hydrochloric acid; 16·9 g (92%) crude product which was crystallized from ethanol, m.p. 160—164°C.

[2-(4-Aminophenylthio)-4-fluorophenyl]acetic Acid (*IIIf*)

A) A solution of 31·3 g *IIIe* in 250 ml ethanol was treated with 20 ml 80% hydrazine hydrate, 4·0 g charcoal and 1·0 g $FeCl_3$ in 20 ml ethanol and the mixture was refluxed for 6·5 h. After filtration the filtrate was evaporated, the residue diluted with water and acidified with acetic acid; 27·4 g (97%) crude product, m.p. 145—153°C. Crystallization from a mixture of benzene and light petroleum did not lead to a change of the melting point and the TLC suggested erroneously homogeneity. The analysis, however, indicated the presence of a nitrogen-rich impurity. For $C_{14}H_{12}FNO_2S$ (277·3) calculated: 6·85% F, 5·05% N, 11·56% S; found: 6·79% F, 5·62% N, 11·46% S.

B) A solution of 19 g *IIIe* in 60 ml acetic acid was added dropwise to a mixture of 300 ml water and 30 g Fe powder and the mixture was refluxed for 6 h under stirring. After cooling it was treated with 200 ml 20% NaOH, filtered and the filtrate was acidified with acetic acid; 9·5 g (55%), m.p. 151—155°C. Analytical sample, m.p. 154—156°C (benzene–light petroleum). IR spectrum: 838, 874 (2 adjacent and solitary Ar—H), 912, 1 256, 1 700 (COOH), 1 497, 1 509, 1 610 (Ar), 1 645 ($ArNH_2$), 3 395, 3 480 cm^{-1} (NH_2). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·10 (d, J = 8·0 Hz, 2 H, 2,6-H_2 of the 4-aminophenylthio residue), 6·58 (d, J = 8·0 Hz, 2 H, 2 Ar—H adjacent to NH_2), 6·70—7·30 (m, 2 H, 5,6-H_2 in the phenylacetic acid residue), 6·38 (mcd, J_{H-H} = 2·5 Hz, J_{H-F} = 10·0 Hz, 1 H, 3-H in the phenylacetic acid residue), 3·64 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{12}FNO_2S$ (277·3) calculated: 60·63% C, 4·36% H, 6·85% F, 5·05% N, 11·56% S; found: 60·41% C, 4·22% H, 6·77% F, 4·92% N, 11·40% S.

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

A mixture of 8·5 g *IIIa* and 85 g polyphosphoric acid was stirred and heated to 125—130°C for 6 h. After partial cooling, the mixture was decomposed with ice and water and extracted with benzene. The extract was washed with water, 5% NaOH and water, dried with $MgSO_4$, filtered with charcoal and evaporated. Crystallization of the residue from ethanol separated first a small qauntity of insoluble 3,8,12,17-tetrafluorofuro[2,3-*m*;4,5-*m'*]bis(dibenzo[*b*,*f*]thiepin) (*V*), m.p. 377—380°C (benzene). Mass spectrum, *m*/*z* (%): 504·0257 (M^+ corresponding to $C_{28}H_{12}F_4OS_2$, 100%), 472 (40), 440 (33). UV spectrum (saturated solution): λ_{max} 268 nm, inflexes at 327 and 302 nm. IR spectrum (KBr): 822, 868, 897 (2 adjacent and solitary Ar—H), 1 190, 1 211, 1 254 (ArOAr), 1 500, 1 563, 1 601 cm^{-1} (Ar). For $C_{28}H_{12}F_4OS_2$ (504·5) calculated: 66·66% C, 2·40% H, 15·06% F, 12·71% S; found: 66·86% C, 2·56% H, 15·20% F, 12·85% S.

The filtrate gave by crystallization 7·7 g (97%) crude *IVa*, m.p. 120—123°C. Analytical sample, m.p. 128—129°C (ethanol). UV spectrum: λ_{max} 232·5 nm (log ε 4·22), infl. 250 nm (4·00), 307·5 nm (3·54). IR spectrum (KBr): 811, 833, 859, 890, 910 (2 adjacent and solitary Ar—H), 1 222, 1 255, 1 265 (CO), 1 482, 1 566, 1 600 (Ar), 1 684 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·88 (mcd, J = 10·0; 2·5 Hz, 1 H, 9-H), 6·90—7·70 (m, 5 H, remaining Ar—H), 4·30 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —113·9 (m, 8-F), —114·5 (dt, 3-F). For $C_{14}H_8F_2OS$ (262·3) calculated 64·11% C, 3·07% H, 14·49% F, 12·23% S; found: 64·17% C, 3·16% H, 14·48% F, 11·97% S.

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

A mixture of 6·5 g *IIIc*, 75 g polyphosphoric acid and 35 ml toluene was stirred and refluxed for 7 h (bath temperature 130—135°C). After decomposition with ice and water, the mixture

was extracted with toluene and the extract processed similarly like in the preceding case; 6·0 g (97%) crude product, m.p. 117—120°C. Analytical sample, m.p. 121°C (Mettler) (ethanol). UV spectrum: λ_{max} 240 nm (log ε 4·31), infl. 263 nm (4·07), 335 nm (3·61). IR spectrum: 811, 829, 881, 915 (2 adjacent and solitary Ar—H), 1 239, 1 240, 1 280, 1 285 (CO), 1 488, 1 573, 1 597, 1 600 (Ar), 1 673 (ArCO), 3 048, 3 070 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·29 (mcs, J = 2·5 Hz, 1 H, 9-H), 6·80—7·70 (m, 5 H, remaining Ar—H), 4·31 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ −114·5 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_8BrFOS$ (323·2) calculated: 52·03% C, 2·49% H, 24·73% Br, 5·88% F, 9·92% S; found: 52·27% C, 2·68% H, 24·88% Br, 5·72% F, 9·89% S.

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

A) A mixture of polyphosphoric acid (prepared from 150 ml 85% H_3PO_4 and 300 g P_2O_5) and 20·4 g pure *IIIf* was stirred and heated for 1·5 h to 125°C, decomposed by pouring on ice, the solid product extracted with chloroform, the extract washed with 5% Na_2CO_3 and evaporated; 16·1 g (85%) crude product, m.p. 198—203°C. Analytical sample, m.p. 206—210°C (benzene). UV spectrum: λ_{max} 244 nm (log ε 4·41), infl. 267 nm (4·10), 362 nm (3·74). IR spectrum (KBr): 810, 832, 880, 914 (2 adjacent and solitary Ar—H), 1 497, 1 600, 3 070 (Ar), 1 642 ($ArNH_2$), 1 670 (ArCO), 3 220, 3 340, 3 435 cm^{-1} (NH_2). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·00 to 7·60 (m, 5 H, 1,2,4,6,9-H_5), 6·70 (mcd, J = 8·0; 2·5 Hz, 1 H, 7-H), 5·50 (bs, 2 H, NH_2), 4·20, (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}FNOS$ (259·3) calculated: 64·85% C, 3·89% H, 7·33% F, 5·40% N, 12·36% S; found: 65·21% C, 4·07% H, 7·25% F, 5·30% N, 12·06% S.

B) Impure *IIIf* (28·4 g, obtained by procedure *A*) was similarly cyclized and gave 25·3 g inhomogeneous product which crystallized from chloroform; 8·4 g *IVf*, m.p. 200—208°C. The mother liquor was chromatographed on a column of 500 g neutral Al_2O_3 (activity II). Chloroform eluted 5·3 g *IVf*, m.p. 200—207°C (benzene). The total yield is thus 13·7 g (52%). Continuation of the chromatography by elution with a mixture of chloroform and ethanol gave 3·36 g 2,5-bis[2-(4-aminophenylthio)-4-fluorobenzyl]-1,3,4-oxadiazole (*IX*), m.p. 170—172°C (benzene–ethanol). Mass spectrum, *m/z*: 532·1220 (M^+ corresponding to $C_{28}H_{22}F_2N_4OS_2$), 430·1793, 295, 258, 245, 230, 197. UV spectrum: λ_{max} 264 nm (log ε 4·62). IR spectrum: 827, 859, 897 (2 adjacent and solitary Ar—H), 1 475, 1 483, 1 500, 1 600 (Ar), 1 636 ($ArNH_2$), 1 656 (C=N), 3 240, 3 350, 3 420 cm^{-1} (NH_2). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·70—7·30 (m, 4 H, 5,6,5′,6′-H_4 in the fluorobenzyl residues), 7·00 (d, J = 8·0 Hz, 4 H, 2,6,2′,6′-H_4 in the aminophenylthio residues), 6·50 (d, J = 8·0 Hz, 4 H, 4 Ar—H adjacent to NH_2), 6·35 (mcd, J_{H-F} = = 10·0 Hz, J_{H-H} = 3·0 Hz, 2 H, 3,3′-H_2 in the fluorobenzyl residues), 6·50 (bs, 4 H, 2 NH_2), 4·20 (s, 4 H, 2 $ArCH_2$). For $C_{28}H_{22}F_2N_4OS_2$ (532·6) calculated: 63·14% C, 4·16% H, 7·13% F, 10·52% N, 12·04% S; found: 63·92% C, 4·43% H, 7·13% F, 10·38% N, 11·99% S.

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

A stirred suspension of 11·4 g *IVf* in 45 ml acetic acid and 45 ml hydrochloric acid was treated at 0—5°C with a solution of 4·3 g $NaNO_2$ in 10 ml water, the mixture stirred for 1 h and the solution formed treated with a solution of 20 g KI in 200 ml water. The stirring was continued for 1 h at room temperature, 200 ml benzene were added and the mixture stirred for 1·5 h and allowed to stand overnight. The benzene layer was separated, washed with 5% NaOH and a solution of $NaHSO_3$, dried with $MgSO_4$ and evaporated. The residue crystallized after the addition of a small amount of ethanol; 11·3 g (69%), m.p. 135—139°C. Analytical sample, m.p. 136 to 139°C (ethanol). UV spectrum: λ_{max} 243 nm (log ε 4·37), infl. 265 nm (4·16), 340 nm (3·64). IR

spectrum (KBr): 819, 827, 878 (2 adjacent and solitary Ar—H), 1 230, 1 260, 1 287 (CO), 1 489, 1 568, 1 599, 3 070 (Ar), 1 670 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 8·44 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·68 (mcd, J = 8·0; 2·0 Hz, 1 H, 7-H), 6·85—7·50 (m, 4 H, remaining Ar—H), 4·28 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ −114·5 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_8FIOS$ (370·2) calculated: 45·42% C, 2·18% H, 5·13% F, 34·28% I, 8·66% S; found: 46·22% C, 2·49% H, 4·76% F, 33·41% I, 9·10% S.

3,8-Difluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*VIa*)

A suspension of 7·0 g *IVa* in 110 ml ethanol was stirred and slowly treated at 70°C with a solution of 0·35 g $NaBH_4$ in 3·5 ml water containing 0·1 ml 20% NaOH. The mixture was stirred and refluxed for 3·5 h, ethanol was evaporated under reduced pressure, the residue was diluted with water and extracted with benzene. The extract was washed with water and 3% NaOH, dried with $MgSO_4$ and evaporated. The oily residue (7·0 g, 99%) crystallized on standing, m.p. 99—103°C. Analytical sample, m.p. 106—109°C (cyclohexane). IR spectrum (KBr): 810, 867, 903 (2 adjacent and solitary Ar—H), 1 055 (CHOH), 1 207, 1 260 (OH), 1 486, 1 575, 1 583, 1 601 (Ar), 3 280, 3 370 cm^{-1} (OH). For $C_{14}H_{10}F_2OS$ (264·3) calculated: 63·62% C, 3·81% H, 14·38% F 12·13% S; found: 63·71% C, 3·92% H, 14·25% F, 12·35% S.

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

A solution of 5·0 g *IVc* in 70 ml ethanol was reduced similarly like in the preceding case with a solution of 1·2 g $NaBH_4$ in 15 ml water containing 0·5 ml 10% NaOH. There were obtained 4·0 g (80%) crude product which was crystallized from cyclohexane, m.p. 148·5°C (Mettler). IR spectrum: 814, 827, 881 (2 adjacent and solitary Ar-H), 1 058 (CHOH), 1 490, 1 581, 1 589, 1 600, 3 060 (Ar), 3 300, 3 368 cm^{-1} (OH). For $C_{14}H_{10}BrFOS$ (325·2) calculated: 51·70% C, 3·10% H, 24·58% Br, 5·84% F, 9·86% S; found: 52·05% C, 3·15% H, 24·81% Br, 5·90% F, 9·97% S.

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

A solution of 11·2 g *IVd* in a mixture of 100 ml dioxane and 50 ml ethanol was slowly treated with a solution of 1·15 g $NaBH_4$ in 3 ml water containing 1 drop 20% NaOH, the mixture (warmed spontaneously) was stirred for 2 h, allowed to stand overnight, evaporated, the residue was diluted with water and extracted with chloroform. Processing of the extract gave 11·2 g (almost 100%) crude product, m.p. 155—162°C. Analytical sample, m.p. 157—162°C (benzene). IR spectrum: 816, 823, 883 (2 adjacent and solitary Ar—H), 1 057 (CHOH), 1 490, 1 583, 1 590, 1 600, 3 060 (Ar), 3 288, 3 360 cm^{-1} (OH). For $C_{14}H_{10}FIOS$ (372·2) calculated: 45·18% C, 2·71% H, 5·10% F, 34·10% I, 8·61% S; found: 45·57% C, 2·83% H, 5·18% F, 32·95% I, 9·00% S.

11-Chloro-2,7-difluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIa*)

A solution of 6·5 g *VIa* in 80 ml benzene was treated with 6·0 g pulverized $CaCl_2$ and saturated with anhydrous HCl for 4·5 h. The mixture was diluted with 60 ml benzene, warmed to 45°C and filtered with charcoal. The filtrate was evaporated; 6·5 g (93%), m.p. 127—132°C. Analytical sample, m.p. 146—148°C (benzene). For $C_{14}H_9ClF_2S$ (282·7) calculated: 59·47% C, 3·21% H, 12·54% Cl, 13·44% F, 11·34% S; found: 59·76% C, 3·22% H, 12·33% Cl, 13·73% F, 11·58% S.

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

A solution of 3·3 g *VIc* in 60 ml benzene was saturated with HCl for 2 h in the presence of 3·0 g $CaCl_2$ and the mixture was processed similarly like in the preceding case; 2·85 g (82%), m.p. 114–115°C. Analytical sample, m.p. 115°C (Mettler) (light petroleum). ^{1}H-NMR spectrum: δ 8·65 (bs, 1 H, 1-H), *c.* 8·20 (m, 4 H, 3,4,6,9-H_4), 6·90 (mct, 1 H, 8-H), 5·65 (dd, 1 H, Ar—CH—Cl), 3·90 and 3·58 (2 dd, 2 H, $ArCH_2$). For $C_{14}H_9BrClFS$ (343·6) calculated: 48·93% C, 2·64% H, 23·25% Br, 10·32% Cl, 5·53% F, 9·33% S; found: 48·82% C, 2·81% H, 23·17% Br, 10·28% Cl, 5·98% F, 9·28% S.

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

A solution of 1·8 g *VId* in 80 ml chloroform was saturated for 1 h with HCl in the presence of 2·0 g $CaCl_2$. The mixture was allowed to stand overnight, filtered and evaporated; 1·9 g (100%), m.p. 105–120°C. The product obtained by crystallization from cyclohexane withholds a small and non-stoichiometric amount of this solvent (as crystal solvent evidently) which was not possible to remove by drying the sample, m.p. 105–107°C and 117–121°C, ^{1}H-NMR spectrum: δ 8·32 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·45 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 6·80–7·35 (m, 4 H remaining Ar—H), 5·64 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 1·38 (s, cyclohexane). For $C_{14}H_9ClFIS$ (390·7) calculated: 43·04% C, 2·32% H, 9·08% Cl, 4·86% F, 32·49% I, 8·21% S; found: 44·90% C, 2·69% H, 8·74% Cl, 4·74% F, 30·29% I, 8·29% S.

2,7-Difluoro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*)

A mixture of 4·8 g *VIIa*, 15 ml chloroform and 5·1 g 1-methylpiperazine was refluxed for 7 h. Chloroform was evaporated, the residue diluted with 40 ml 3% NaOH and extracted with benzene. The extract was washed with water and the base was transferred into the aqueous layer by shaking with excessive 1·25M-H_2SO_4. The solution of the sulfate was separated, made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with $MgSO_4$, filtered with charcoal and evaporated; 4·2 g (72%) base *Ia*, m.p. 120–122°C. Analytical sample, m.p. 121–123°C (benzene). ^{1}H-NMR spectrum: δ 6·50–7·50 (m, 6 H, Ar—H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·21 (s, 3 H, NCH_3). ^{19}F-NMR spectrum: δ −114·9 (m, 2-F), −116·5 (dt, 7-F). For $C_{19}H_{20}F_2N_2S$ (346·4) calculated: 65·87% C, 5·82% H, 10·97% F. 8·09% N, 9·25% S; found: 65·83% C, 5·83% H, 11·03% F, 8·03% N, 9·48% S.

Sesquimethanesulfonate, m.p. 211–214°C (ethanol). For $C_{19}H_{20}F_2N_2S + 1{\cdot}5\ CH_4O_3S$ (490·6) calculated: 50·18% C, 5·34% H, 7·74% F, 5·71% N, 16·34% S; found: 50·02% C, 5·57% H, 8·06% F, 5·73% N, 16·69% S.

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

A mixture of 2·5 g *VIIc*, 5 ml chloroform and 2·5 g 1-(2-hydroxyethyl)piperazine was refluxed for 10 h under stirring. Chloroform was evaporated, the residue diluted with water and extracted with benzene. The extract was washed with water and shaken with 25 ml 3M-HCl. The solid hydrochloride was filtered, washed with benzene, decomposed with NH_4OH and the base extracted with benzene. Processing of the extract gave 1·7 g (54%) oily base which was chromatographed on a column of 45 g neutral Al_2O_3 (activity II). Benzene with 2% ethanol eluted 1·35 g purified base which crystallized, m.p. 119–121°C (Mettler) (aqueous ethanol). IR spectrum:

816, 830, 880, 911 (2 adjacent and solitary Ar—H), 1 049, 1 060 (CH_2OH), 1 490, 1 500, 1 582, 1 595, 3 065, 3 087(Ar), 1 233 (Ar—F), 3 175 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·70 (bs, H 1 1-H), 6·70—7·30 (m, 5 H, remaining Ar-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, J = = 6·0 Hz, 2 H, CH_2O), 2·75 (bs, 1 H, OH), *c.* 2·50 (m, 10 H, 5 NCH_2). ^{19}F-NMR spectrum: δ —116·6 (dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz). For $C_{20}H_{22}BrFN_2OS$ (437·4) calculated: 54·92% C, 5·07% H, 18·27% Br, 4·34% F, 6·40% N, 7·33% S; found: 55·28% C, 5·12% H,18·42% Br, 4·19% F, 6·88% N, 7·55% S.

Succinate, m.p. 169°C (Mettler) (ethanol). For $C_{24}H_{28}BrFN_2O_5S$ (555·5) calculated: 51·89% C, 5·08% H, 14·39% Br, 3·42% F, 5·04% N, 5·77% S; found: 51·97% C, 5·21% H, 14·61% Br. 3·44% F, 5·11% N, 6·04% S.

The benzene layer, which was separated from the filtrate after the filtration of *IIc*-HCl, was washed with water, dried with $CaCl_2$ and evaporated; 1·1 g crude 2-bromo-7-fluorodibenzo-[*b,f*]thiepin (*VIIIc*), m.p. 90—100°C. Several crystallizations from ethanol gave the analytical sample, m.p. 125—126°C (Mettler). UV spectrum: λ_{max} 263 nm (log ε 4·47), infl. 297 nm (3·68). ^{1}H-NMR spectrum: δ 6·70—7·40 (m, Ar—H and CH=CH). ^{19}F-NMR spectrum: δ —113·4 (dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_8BrFS$ (307·2) calculated: 54·74% C, 2·62% H, 26·02% Br, 6·18% F, 10·44% S; found: 55·09% C, 3·00% H, 26·36% Br, 6·12% F, 10·61% S.

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

A mixture of 1·9 g *VIId*, 10 ml chloroform and 5 ml 1-(2-hydroxyethyl)piperazine was refluxed for 8 h and processed similarly like in the preceding case; 1·65 g (67%) oily base. Neutralization with 0·9 g maleic acid in acetone gave 1·94 g bis(hydrogen maleate), m.p. 141—145°C. Analytical sample, m.p. 145—147°C (acetone). Mass spectrum, *m/z* (%): 484·0516 (M^+ corresponding to $C_{20}H_{22}FIN_2OS$, 5·5%), 452 (2), 355 (7), 227 (5·5), 195 (3·6), 183 (3·6), 98 (61), 72 (100), 58 (81), 55 (100). IR spectrum: 814, 821, 869 (2 adjacent and solitary Ar—H), 1 049 (CH_2OH), 1 467, 1 532, 1 573 (Ar), 2 300, 2 420 (NH^+), 3 320, 3 485 cm^{-1} (OH). For $C_{28}H_{30}FIN_2O_9S$ (716·5) calculated: 46·93% C, 4·22% H, 2·65% F, 17·71% I, 3·91% N, 4·48% S; found: 47·67% C, 4·43% H, 2·56% F, 16·79% I, 3·92% N, 4·79% S.

The benzene layer, containing neutral products, was processed similarly like in the preceding case; 0·4 g (23%) 7-fluoro-2-iododibenzo[*b,f*]thiepin (*VIIId*), m.p. 139—142°C (ethanol). UV spectrum: λ_{max} 264 nm (log ε 4·48), infl. 300 nm (3·71). ^{1}H-NMR spectrum: δ 7·50 (m, 2 H, 1,3-H_2), 6·60—7·30 (m, 6 H, remaining Ar—H and CH=CH). ^{19}F-NMR spectrum: δ —113·4 (dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz). For $C_{14}H_8FIS$ (354·2) calculated: 47·48% C, 2·28% H, 5·36% F, 35·83% I, 9·05% S; found: 48·10%C, 2·50% H, 5·14% F, 34·99% I, 9·32% S.

The analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs J. Kropáčová in the analytical department of this institute.

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