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(11H)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(3H)-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 series¹⁻³ 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 fluorination⁴, we considered useful to estimate the influence of further halogen



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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 group⁵. A reaction with 4-fluorothiophenol¹ in a boiling aqueous potassium hydroxide solution in the presence of copper gave the acid IIIa which was cyclized with polyphosphoric acid at $125 - 130^{\circ}$ C. 3,8-Difluorodibenzo b, f thiepin-10(11H)--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 series⁷ 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.









 $VI, R^{1} = OH$ $VII, R^{1} = CI$

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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 acid⁵ and 4-bromothiophenol (prepared by reduction of 4-bromobenzenesulfonyl chloride⁸ using the Wagner method⁹, $cf.^{10,11}$). 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*).

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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 acid¹² or its thiolactone, *i.e.* 6-fluorobenzo b]thiophen-2(3H)-one¹². 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 C₂₈H₂₂F₂N₄OS₂. This composition corresponds to the structure of the 2,5-disubstituted 1,3,4-oxadiazole IX confirmed by the ¹H-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-oxadiazoles¹³⁻¹⁵. 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.



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 LD₅₀. 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 D₅₀ decreases the locomotor activity to 50% of the control values. The cataleptic effect was evaluated in rats; the medium effective dose ED₅₀ 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 antiapomorphine 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, $LD_{50} = 20 \text{ mg/kg}$. Rotarod, $ED_{50} = 0.55 \text{ mg/kg}$; 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,

 $D_{50} = 0.29 \text{ mg/kg}$; the effect disappears after 24 h. Catalepsy: $ED_{50} = 3.1 \text{ mg/kg}$; 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, $LD_{50} = 64 \text{ mg/kg}$. Rotarod, $ED_{50} = 0.71 \text{ mg/kg}$; 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, $ED_{50} = 3.0 \text{ mg/kg}$; the effect disappears, within 1 day (after 24 h catalepsy in 10% animals). Compound *IId*: Acute toxicity, $LD_{50} = 125 \text{ mg/kg}$. Rotarod, $ED_{50} = 0.67 \text{ mg/kg}$; the effect is mildly protracted — the highest dose administered maintains ataxia after 24 h with 30% animals. Catalepsy, $ED_{50} = 0.68 \text{ mg/kg}$; 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 skeleton¹⁶, 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 μ g/ml (unless they exceed 100 μ g/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

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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, ¹H-NMR spectra (in CDCl₃ unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer and ¹⁹F-NMR spectra (in CHCl₃, $\delta_{CHCl_3} = 0$) 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 chloride⁸ 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 (21) 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-Fluorothiophenol¹ (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 acid⁵ 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). ¹H-NMR spectrum: δ 11·25 (bs, 1 H, COOH), 6·70–7·50 (m, 7 H, Ar–H), 3·82 (s, 2 H, ArCH₂CO). ¹⁹F-NMR spectrum: δ –113·5 (m, F in 4-fluorophenyl), –113·9 (m, the remaining Ar–F). For C₁₄H₁₀F₂O₂S (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 acid⁵ 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 C₁₄H₁₀BrFO₂S (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 acid¹² (3·0 g) was added to a solution of 4·5 g K₂CO₃ 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 $\varepsilon 4\cdot02$), 313 nm (4·07). IR spectrum: 805, 842, 856, 880 (2 adjacent and solitary Ar—H), 960, 1 249, <u>1</u>709, 2 560, 2 640, 2 750 (RCOOH), 1 349, 1 505 (ArNO₂), 1 583, 1 600, 3 075, 3 112 cm⁻¹ (Ar). ¹H-NMR spectrum (C²H₃SOC²H₃): $\delta 8\cdot02$ (d, $J = 8\cdot0$ Hz, 2 H, 2 Ar—H adjacent to NO₂), 7·20–7·60 (m, 3 H, 3 Ar-H in the phenylacetic acid residue), 7·18 (d, $J = 8\cdot0$ Hz, 2 H, 2,6-H₂ in the 4-nitrophenylthio group), 3·70 (s, 2 H, ArCH₂CO). For C₁₄H₁₀FNO₄S (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(3H)-one¹² (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. $160-164^{\circ}C$.

[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 FeCl₃ 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 (ArNH₂), 3 395, 3 480 cm⁻¹ (NH₂). ¹H-NMR spectrum (C²H₃SOC²H₃): δ 7·10 (d, J = 8.0 Hz, 2 H, 2,6-H₂ of the 4-aminophenylthio residue), 6·58 (d, J = 8.0 Hz, 2 H, 2 Ar—H adjacent to NH₂), 6·70–7·30 (m, 2 H, 5,6-H₂ 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, ArCH₂CO). For C₁₄H₁₂FNO₂S (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(11H)-one (IVa)

A mixture of 8.5 g *IIIa* and 85 g polyphosphoric acid was stirred and heated to $125-130^{\circ}$ 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 MgSO₄, 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 C₂₈H₁₂F₄OS₂, 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 C₂₈H₁₂F₄OS₂ (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), <u>1 684</u> cm⁻¹ (ArCO). ¹H-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, ArCH₂CO). ¹⁹F-NMR spectrum: δ –113·9 (m, 8-F), –114·5 (dt, 3-F). For C₁₄H₈F₂OS (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(11H)-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 $130-135^{\circ}$ C). After decomposition with ice and water, the mixture

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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). ¹H-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, ArCH₂CO). ¹⁹F-NMR spectrum: δ -114.5 (dt, $J_{F(o-H)} = 8.0$ Hz; $J_{F(m-H)} = 5.5$ Hz). For C₁₄H₈BrFOS (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(11H)-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% Na₂CO₃ 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 (ArNH₂), 1 670 (ArCO), 3 220, 3 340, 3 435 cm⁻¹ (NH₂). ¹H-NMR spectrum (C²H₃SOC²H₃): δ 7·00 to 7·60 (m, 5 H, 1,2,4,6,9-H₅), 6·70 (mcd, $J = 8\cdot0$; 2·5 Hz, 1 H, 7-H), 5·50 (bs, 2 H, NH₂), 4·20, (s, 2 H, ArCH₂CO). For C₁₄H₁₀FNOS (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 Al₂O₃ (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 C₂₈H₂₂F₂N₄OS₂), 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 (ArNH₂), 1 656 (C=N), 3 240, 3 350, 3 420 cm⁻¹ (NH₂). ¹H-NMR spectrum (C²H₃SOC²H₃): δ 6·70–7·30 (m, 4 H, 5,6,5',6'-H₄ in the fluorobenzyl residues), 7·00 (d, $J = 8\cdot0$ Hz, 4 H, 2,6,2',6'-H₄ in the aminophenylthio residues), 6·50 (d, $J = 8\cdot0$ Hz, 4 H, 4 Ar—H adjacent to NH₂), 6·35 (mcd, $J_{H-F} = 10\cdot0$ Hz, $J_{H-H} = 3\cdot0$ Hz, 2 H, 3,3'-H₂ in the fluorobenzyl residues), 6·50 (bs, 4 H, 2 NH₂), 4·20 (s, 4 H, 2 ArCH₂). For C₂₈H₂₂F₂N₄OS₂ (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(11H)-one (IVd)

A stirred suspension of 11.4 g IVf in 45 ml acetic acid and 45 ml hydrochloric acid was treated at $0-5^{\circ}$ C with a solution of 4.3 g NaNO₂ 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 NaHSO₃, dried with MgSO₄ 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

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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). ¹H-NMR spectrum: δ 8·44 (mcs, $J = 2 \cdot 0$ Hz, 1 H, 9-H), 7·68 (mcd, $J = 8 \cdot 0$; 2·0 Hz, 1 H, 7-H), 6·85–7·50 (m, 4 H, remaining Ar—H), 4·28 (s, 2 H, ArCH₂CO). ¹⁹F-NMR spectrum: δ –114·5 (dt, $J_{F(0-H)} = 8 \cdot 0$ Hz; $J_{F(m-H)} = 5 \cdot 5$ Hz). For C₁₄H₈FIOS (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)

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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 NaBH₄ 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 MgSO₄ 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 C₁₄H₁₀F₂OS (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 NaBH₄ 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 C₁₄H₁₀BrFOS (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. $155-162^{\circ}$ C. Analytical sample, m.p. $157-162^{\circ}$ 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 C₁₄H₁₀FlOS (372.2) calculated: $45\cdot18\%$ C, $2\cdot71\%$ H, $5\cdot10\%$ F, $34\cdot10\%$ I, $8\cdot61\%$ S; found: $45\cdot57\%$ C, $2\cdot83\%$ H, $5\cdot18\%$ F, $32\cdot95\%$ I, $9\cdot00\%$ 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 CaCl₂ 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 C₁₄H₉ClF₂S (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 CaCl₂ 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). ¹H-NMR spectrum: δ 8.65 (bs, 1 H, 1-H), c. 8.20 (m, 4 H, 3,4,6,9-H₄), 6.90 (mct, 1 H, 8-H), 5.65 (dd, 1 H, Ar—CH—Cl), 3.90 and 3.58 (2 dd, 2 H, ArCH₂). For C₁₄H₉BrClFS (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 CaCl₂. 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, ¹H-NMR spectrum: $\delta 8.32$ (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, ArCH₂), 1.38 (s, cyclohexane). For C₁₄H₉CIFIS (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-H₂SO₄. The solution of the sulfate was separated, made alkaline with NH₄OH and the base extracted with benzene. The extract was dried with MgSO₄, filtered with charcoal and evaporated; 4.2 g (72%) base *Ia*, m.p. 120–122°C. Analytical sample, m.p. 121–123°C (benzene). ¹H-NMR spectrum: $\delta 6.50-7.50$ (m, 6 H, Ar–H), 3.00-4.00 (m, 3 H, ArCH₂CHAr), 2.60 (def. t, 4 H, CH₂N¹CH₂ of piperazine), 2.40 (def. t, 4 H, CH₂N⁴CH₂ of piperazine), 2.21 (s, 3 H, NCH₃). ¹⁹F-NMR spectrum: $\delta -114.9$ (m, 2-F), -116.5 (dt, 7-F). For C₁₉H₂₀F₂N₂S (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. $211-214^{\circ}$ C (ethanol). For $C_{19}H_{20}F_2N_2S + 1.5 CH_4O_3S$ (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 NH₄OH 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 Al₂O₃ (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 (CH₂OH), 1 490, 1 500, 1 582, 1 595, 3 065, 3 087(Ar), 1 233 (Ar—F), 3 175 cm⁻¹ (OH). ¹H-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, ArCH₂CHAr), 3·58 (t, $J = 6\cdot0$ Hz, 2 H, CH₂O), 2·75 (bs, 1 H, OH), c. 2·50 (m, 10 H, 5 NCH₂). ¹⁹F-NMR spectrum: δ –116·6 (dt, $J_{F(o-H)} = 8\cdot0$ Hz, $J_{F(m-H)} = 5\cdot5$ Hz). For C₂₀H₂₂BrFN₂OS (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 CaCl₂ 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). ¹H-NMR spectrum: δ 6·70–7·40 (m, Ar—H and CH=CH). ¹⁹F-NMR spectrum: δ –113·4 (dt, $J_{F(o-H)} = 8\cdot0$ Hz, $J_{F(m-H)} = 5\cdot5$ Hz). For C₁₄H₈BrFS (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 C₂₀H₂₂FIN₂OS, 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 (CH₂OH), 1 467, 1 532, 1 573 (Ar), 2 300, 2 420 (NH⁺), 3 320, 3 485 cm⁻¹ (OH). For C₂₈H₃₀FIN₂O₉S (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). ¹H-NMR spectrum: δ 7.50 (m, 2 H, 1,3-H₂), 6.60–7.30 (m, 6 H, remaining Ar—H and CH=CH). ¹⁹F-NMR spectrum: δ –113.4 (dt, $J_{F(0-H)} = 8.0$ Hz, $J_{F(m-H)} = 5.5$ Hz). For C₁₄H₈FIS (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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