FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: 8-METHOXY, 8-ETHOXY, 8-ETHYLTHIO AND 8-HYDROXY DERIVATIVES OF 3-FLUORO-10-(4-METHYLPIPERAZINO)--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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Acids *IIa—c* were prepared by reactions of (4-fluoro-2-iodophenyl)acetic acid with 4-methoxythiophenol, 4-ethoxythiophenol and 4-(ethylthio)thiophenol and cyclized with polyphosphoric acid in boiling toluene to dibenzo[*b*,*f*]thiepin-10(11*H*)-ones *IIIa—c*. Reduction with sodium borohydride afforded the alcohols *IVa—c* which were treated with hydrogen chloride and gave the chloro derivatives *Va—c*. Substitution reactions with 1-methylpiperazine resulted in the title compounds *Ia—c* out of which the methoxy derivative *Ia* was transformed by demethylation with boron tribromide to the phenol *Id*. Compounds *Ia—d* are very potent neuroleptics exhibiting a clear prolongation of the central depressant and some prolongation of the cataleptic activity.

Our systematic investigations of the influence of fluorination in molecules of neuroleptic agents derived from 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin on the activity[1] proved that from the point of view of the intensity, as well as of the prolongation of the effects, the most successful is the combination of fluorination in position 3 with substitution in position 8 by some of the renowned neuroleptic substituents (as "neuroleptic" substituents we designate such atoms or groups whose presence in the corresponding position of molecules of neuroleptics derived from phenothiazine, thioxanthene, dibenzo[*b*,*f*]thiepin, morphanthridine and its hetero analogues[2] have a favourable influence on the activity). Until present we have described the synthesis and pharmacological properties of substances of this type substituted in position 8 with some of the halogen atoms[3-5], with trifluoromethyl[6] and methylthio group[7]. The present communication deals with the synthesis and pharmacology of similar compounds substituted in position 8 by methoxyl (*Ia*), ethoxyl (*Ib*), ethylthio group (*Ic*) and hydroxyl (*Id*). Analogous compounds, lacking the fluorine atom in position 3, have been shown to be highly potent neuroleptic agents[8-10].

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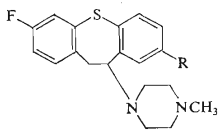
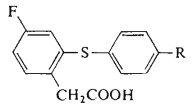


I

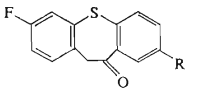
a, R = OCH_3
b, R = OC_2H_5
c, R = SC_2H_5
d, R = OH

The synthesis of compound *Ia–c* used similar methods like the synthesis of analogical 8-fluoro and 8-bromo derivatives[5] and of the corresponding compounds free of the fluorine atom in position 3 (ref.[8,10]). (4-Fluoro-2-iodophenyl)acetic acid[11] was the starting material which was transformed in the first step by reactions with 4-methoxythiophenol[12], 4-ethoxythiophenol[13] and 4-(ethylthio)thiophenol[10] (the last two thiophenols have now been prepared by the Wagner method[14], *i.e.* by reduction of 4-ethoxybenzenesulfonyl chloride[13] and 4-ethylthiobenzenesulfonyl chloride[10] with iodine and red phosphosphorus in boiling acetic acid) in a boiling aqueous solution of potassium hydroxide in the presence of copper to the acids *IIa–c*. These acids were cyclized by heating with polyphosphoric acid in boiling toluene to dibenzo[*b*,*f*]thiepin-10(11*H*)-ones *IIIa–c*. By reduction of the ketones with sodium borohydride in boiling aqueous ethanol the alcohols *IVa–c* were obtained which afforded by treatment with hydrogen chloride in benzene the chloro derivatives *Va–c*. The final steps of the syntheses were substitution reactions of these chloro derivatives with 1-methylpiperazine in boiling chloroform; in addition to the desired bases *Ia–c* the 2-substituted 7-fluorodibenzo[*b*,*f*]thiepins (*VIa–c*) were obtained as by-products resulting from the simultaneous elimination. The methoxy derivative *Ia* was demethylated by a reaction with boron tribromide in chloroform (method, *cf.*[11,15–17]) and the primary product was hydrolyzed with boiling aqueous ethanol; there resulted the 8-hydroxy derivative *Id* showing the character of an amphion (high melting point, amphoteric character, the band at 2 700 cm^{-1} in the IR spectrum). For pharmacological tests, all the four bases *Ia–d* were transformed to the maleates.

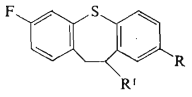
Compounds *Ia–d* were pharmacologically evaluated in the form of maleates which were administered orally; the doses given were calculated for bases. The testing was concentrated to the expected central depressant and neuroleptic effects; in addition to the intensity of effects, their duration was observed. The acute toxicity was estimated in mice and is expressed as the medium lethal doses LD_{50}. The incoordinating effect was evaluated in the rotarod test in mice; medium effective doses eliciting ataxia in 50% animals (ED_{50}) in the time of maximum effect in the course of 2 h after the administration are given. The cataleptic effect was evaluated in rats; the medium effective doses 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



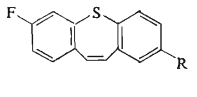
II



III



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



VI

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%). The results are summarized in Table I which includes also data on the 8-chloro derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (octoclothepin, ref.[18,19]).

Compounds *Ib* and *Ic* were also tested for the influence on the spontaneous locomotor activity which was evaluated by the photocell method in mice; the doses D_{50} decrease the locomotor activity to 50% of the control values. Compound *Ib*, D_{50} = = 0·29 mg/kg (the inhibiting action after a dose of 0·8 mg/kg still apparent after

TABLE I

Pharmacological properties of compounds *Ia*—*Id*

Compound	LD_{50} mg/kg	Rotarod ED_{50} mg/kg			Catalepsy ED_{50} mg/kg		Antiapomorphine effect				
							dose mg/kg	chewing %		agitation %	
		2 h	24 h[a]	48 h[a]	5 h	24 h[a]		4 h	24 h	4 h	24 h
Ia	24	0·26	6	3	0·88	3	2·5	62·9[b]	100	64·5[b]	96·2
Ib	91	0·36	3	0	2·0	0	5·0	72·0[b]	100	75·0[b]	100
Ic	67	0·68	7	[c]	5·4	4	10·0	11·0[b]	100	19·0[b]	100
Id	160	0·72	0	[c]	5·4	2	10·0	72·7	94	72·2	92·8
Oct.[d]	78	2·2	0	[c]	2·5	0	4·1	50[b]	100	50[b,e]	100[e]

[a] The maximum number of animals in the groups of 10 showing the effect in the interval indicated after the highest dose included into the calculation of the ED_{50}. [b] Statistical significance. [c] The experiment was interrupted after 24 h. [d] Octoclothepin. [e] Dose 4·5 mg/kg.

24 h with statistical significance); *Ic*, D_{50} = 0·52 mg/kg (the effect of a dose of 0·8 mg/kg persists after 24 h with statistical significance). For octoclothepin as a standard, D_{50} = 1·9 mg/kg (after 24 h the effect is not apparent).

The values in the Table indicate the very high incoordinating activity of compounds *Ia–d* and the high cataleptic activity of compounds *Iab*. Under the conditions of acute testing these compounds are more active than octoclothepin[19]. Compounds *Ia* and *Ic* show a clear prolongation of the effects. The antiapomorphine activity of compounds *Ia–c* is comparable with that of octoclothepin; there is not a clear evidence of any significant protraction of this effect. The phenolic derivative *Id*, which is rather active under the conditions of acute testing (with the exception of the antiapomorphine activity) and has the lowest toxicity, does not show any protraction of the effects probably due to its rather high hydrophilicity and rapid elimination.

Compounds *Ib* and *Ic* were also tested for antimicrobial activity in vitro (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Ib* 25, *Ic* 12·5; *Streptococcus faecalis*, *Ib* 50, *Ic* 25; *Staphylococcus pyogenes aureus*, *Ib* 25, *Ic* 25; *Mycobacterium tuberculosis* H37Rv, *Ib* 6·2, *Ic* 3·1; *Saccharomyces pasterianus*, *Ic* 25; *Trichophyton mentagrophytes*, *Ic* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined 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 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-Ethoxythiophenol

A solution of 170 g 4-ethoxybenzenesulfonyl chloride[13] in 220 ml acetic acid was added dropwise over 1 h to a refluxing mixture of 330 ml acetic acid, 77 g red P and 12 g I_2. The mixture was refluxed and stirred for 5 h, allowed to stand overnight, diluted with 90 ml water and refluxed for 1 h. After cooling the mixture was filtered, the filtrate diluted with water and the separated oily product isolated by extraction with benzene. The extract was dried with $MgSO_4$ and distilled; 80·7 g (68%), b.p. 125–130°C/2·3 kPa. Lit.[13], b.p. 110–112°C/1·3 kPa.

4-(Ethylthio)thiophenol

Was prepared similarly from 126 g 4-ethylthiobenzenesulfonyl chloride[10], 53 g P and 8·3 g I_2 in 400 ml acetic acid; 57·8 g (64%), b.p. 138–144°C/1·3 kPa. Lit[10], b.p. 140–142°C/10 kPa.

[4-Fluoro-2-(4-methoxyphenylthio)phenyl]acetic Acid (*IIa*)

4-Methoxythiophenol[12] (14·8 g) was added to a stirred solution of 19·7 g KOH in 170 ml water

at 50°C, 29·5 g (4-fluoro-2-iodophenyl)acetic acid[11] and 2 g Cu were added and the mixture was stirred and refluxed for 8·5 h. It was filtered while hot and the filtrate was acidified under cooling with 1 : 1 diluted hydrochloric acid. The aqueous layer was separated from the oily product by decantation and the oil crystallized after mixing with water. It was filtered, washed with water and dried *in vacuo*; 17·1 g (57%), m.p. 105—108°C. Analytical sample, m.p. 110°C (aqueous ethanol). IR spectrum: 800, 816, 840, 870, 900 (2 adjacent and solitary Ar—H), 909, 1 246, **1 705**, 2 650, 2 740 (COOH), 1 030, 1 172, 1 185, 1 290 ($ArOCH_3$), 1 485, 1 497, 1 578, **1** 592 cm^{-1} (Ar). For $C_{15}H_{13}FO_3S$ (292·3) calculated: 61·63% C, 4·48% H, 6·50% F, 10·97% S; found: 61·48% C, 4·77% H, 6·52% F, **11**·07% S.

[2-(4-Ethoxyphenylthio)-4-fluorophenyl]acetic Acid (*IIb*)

4-Ethoxythiophenol (11·6 g), 21 g (4-fluoro-2-iodophenyl)acetic acid[11], 2·0 g Cu, 14·0 g KOH and 120 ml water were refluxed for 7·5 h and processed similarly like in the preceding case; 20·1 g (88%), m.p. 106—107°C. Analytical sample, m.p. 108°C (aqueous ethanol). IR spectrum: 802, 840, 859, 906 (2 adjacent and solitary Ar—H), 928, **1 691**, 2 550, 2 650, 2 735, infl. 3 140 (COOH), 1 176, 1 233, 1 250 (ArOR, COOH), 1 483, 1 500, 1 571, 1 600 cm^{-1} (Ar). For $C_{16}H_{15}FO_3S$ (306·3) calculated: 62·73% C, 4·94% H, 6·20% F, 10·46% S; found: 62·90% C, 4·99% H, 6·18% F, 10·79% S.

[2-(4-Ethylthiophenylthio)-4-fluorophenyl]acetic Acid (*IIc*)

A mixture of 12·7 g KOH in 100 ml water, 11·74 g 4-(ethylthio)thiophenol, 19·3 g (4-fluoro--2-iodophenyl)acetic acid[11] and 1 g Cu was refluxed for 7 h and processed similarly like in the preceding cases; 15·5 g (70%), m.p. 92—95°C. Analytical sample, m.p. 99°C (aqueous ethanol). IR spectrum: 786, 799, 812, 829, 850 (2 adjacent and solitary Ar—H), 929, 1 233, **1 692**, 2 530, 2 630, 2 720 (COOH), 1 480, 1 575, 1 592, 1 600 cm^{-1} (Ar). For $C_{16}H_{15}FO_2S_2$ (322·4) calculated: 59·60% C, 4·69% H, 5·89% F, 19·89% S; found: 59·50% C, 4·73% H, 5·69% F, 19·55% S.

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

A mixture of 16·0 g *IIa*, 220 g polyphosphoric acid and 110 ml toluene was stirred and refluxed for 8 h. After cooling it was decomposed by pouring into 600 ml water and extracted with toluene. The extract was washed with water, 5% NaOH and water, dried with K_2CO_3 and evaporated. The residue crystallized on standing: 13·5 g (90%), m.p. 123—127°C. Analytical sample, m.p. 129—130°C (ethanol). UV spectrum: λ_{max} 237·5 nm (log ε 4·37), 346 nm (3·60), inflexes at 256 nm (4·05), 275 nm (3·80) and 281·5 nm (3·67). IR spectrum: 806, 819, 830, 870, 910 (2 adjacent and solitary Ar—H), 1 026, 1 293 ($ArOCH_3$), 1 487, 1 560, 1 600, 3 147 (Ar), **1 676** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 7·62 (d, J = 3·0 Hz, 1 H, 9-H), 7·40 (d, J = 8·0 Hz, 1 H, 6-H), 6·80 to 7·40 (m, 4 H, remaining Ar—H), 4·30 (s, 2 H, $ArCH_2O$), 3·76 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ −114·9 (dt). For $C_{15}H_{11}FO_2S$ (274·3) calculated: 65·68% C, 4·04% H, 6·93% F, 11·68% S; found: 65·68% C, 4·30% H, 6·70% F, 11·86% S.

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

IIb (19·0 g) was cyclized with 270 g polyphosphoric acid in 130 ml toluene (refluxed for 7·5 h) similarly like in the preceding case; 14·7 g (82%), m.p. 97—103°C. Analytical sample, m.p. 107 to 108°C (ethanol). UV spectrum: λ_{max} 238 nm (log ε 4·45), 342 nm (3·65), inflexes at 253·5 nm (4·13) and 281 nm (3·71). IR spectrum (KBr): 808, 827, 874, 904 (2 adjacent and solitary Ar—H),

1 041, 1 222 (ArOR), 1 484, 1 595 (Ar), **1 665** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 7·70 (d, J = = 3·0 Hz, 1 H, 9-H), 7·45 (d, J = 8·0 Hz, 1 H, 6-H), 6·80–7·50 (m, 4 H, remaining Ar—H), 4·34 (s, 2 H, $ArCH_2CO$), 4·02 (q, J = 7·0 Hz, 2 H, OCH_2), 1·40 (t, J = 7·0 Hz, 3 H, C—CH_3). ^{19}F NMR spectrum: δ −115·1 (dt). For $C_{16}H_{13}FO_2S$ (288·3) calculated: 66·65% C, 4·54% H, 6·59% F, 11·12% S; found: 66·69% C, 4·56% H, 6·43% F, 11·21% S.

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

IIc (5·0 g) was cyclized with 65 g polyphosphoric acid in 30 ml toluene (refluxed for 6·5 h) similarly like in the preceding cases; 4·3 g (91%), m.p. 70–75°C. Analytical sample, m.p. 82°C (ethanol). UV spectrum: λ_{max} 249 nm (log ε 4·35), 281 nm (4·23), 354 nm (3·89). IR spectrum: 795, 819, 856, 894, 909 (2 adjacent and solitary Ar—H), 1 225, 1 251, 1 269, 1 271 (C—O of ketone), 1 482, 1 571, 1 592 (Ar), **1 680** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·08 (d, J = 3·0 Hz, 1 H, 9-H), 6·80–7·60 (m, 5 H, remaining Ar—H), 4·30 (s, 2 H, $ArCH_2CO$), 2·95 (q, J = 7·0 Hz, 2 H, SCH_2), 1·30 (t, J = 7·0 Hz, 3 H, C—CH_3). ^{19}F NMR spectrum: δ −114·6 (dt). For $C_{16}H_{13}$· .FOS_2 (304·4) calculated: 63·13% C, 4·30% H, 6·24% F, 21·06% S; found: 62·94% C, 4·32% H, 6·41% F, 21·10% S.

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

A solution of 12·4 g *IIIa* in 200 ml ethanol was stirred and treated at 80°C over 20 min with a solution of 3·40 g $NaBH_4$ in 20 ml water containing 1 ml 10% NaOH. The mixture was refluxed for 3·5 h and evaporated under reduced pressure. The residue was diluted with 200 ml water and extracted with benzene. The extract was washed with 150 ml 3% NaOH and 150 ml water, dried with $MgSO_4$ and evaporated; 12·0 g (97%), m.p. 112–115°C. Analytical sample, m.p. 118°C (ethanol). IR spectrum: 800, 808, 813, 874 (2 adjacent and solitary Ar—H), 1 059 (CHOH in the cycle), 1 229, 1 239, 1 260, 1 278 ($ArOCH_3$), 1 473, 1 484, 1 561, 1 583, 1 597, 3 025, 3 062, 3 100 (Ar), 3 330, 3 390 cm^{-1} (OH). For $C_{15}H_{13}FO_2S$ (276·3) calculated: 65·20% C, 4·74% H, 6·88% F, 11·60% S; found: 65·37% C, 4·99% H, 6·73% F, 11·78% S.

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

IIIb (13·0 g) in 200 ml ethanol was similarly reduced with 3·40 g $NaBH_4$ in 20 ml water; 12·4 g (95%), m.p. 77–78°C. Analytical sample, m.p. 81–82°C (cyclohexane). IR spectrum: 795, 831, 870, 880 (2 adjacent and solitary Ar—H), 1 046, 1 056 (CHOH in the cycle), 1 226, 1 233 (ArOR), 1 471, 1 487, 1 577, 1 583, 1 600, 3 061 (Ar), 3 300 cm^{-1} (OH). For $C_{16}H_{15}FO_2S$ (290·3) calculated: 66·18% C, 5·21% H, 6·55% F, 11·04% S; found: 66·51% C, 5·39% H, 6·47% F, 11·16% S.

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

Was prepared similarly like in the preceding cases from 3·8 g *IIIc* and 0·9 g $NaBH_4$ in 60 ml ethanol and 10 ml water; 3·44 g (90%), m.p. 98–103°C. Analytical sample, m.p. 104–105°C (cyclohexane). IR spectrum: 793, 852, 879 (2 adjacent and solitary Ar—H), 1 056 (CHOH in the cycle), 1 485, 1 587, 1 600 (Ar), 3 300, 3 370 cm^{-1} (OH). ^1H NMR spectrum: δ 7·45 (d, J = 2·0 Hz, 1 H, 9-H), 7·30 (d, J = 8·0 Hz, 1 H, 6-H), 6·70–7·30 (m, 4 H, remaining Ar-H), 5·25 (m, 1 H, Ar—CH—O), 3·60 and 3·20 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·88 (q, J = 7·0 Hz, 2 H, SCH_2), 2·30 (d, J = 7·0 Hz, 1 H, OH), 1·28 (t, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −116·2 (dt). For $C_{16}H_{15}FOS_2$ (306·4) calculated: 62·72% C, 4·93% H, 6·20% F, 20·93% S; found: 62·94% C, 4·92% H, 6·31% F, 20·63% S.

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

A solution of 12·0 g *IVa* in 150 ml benzene was treated with 10 g $CaCl_2$ and the suspension was saturated under stirring for 2 h with HCl. After 2 h standing the mixture was filtered with charcoal and the filtrate evaporated; 12·4 g (97%), m.p. 127–128°C. Analytical sample, m.p. 129°C, (cyclohexane). ^{1}H NMR spectrum: δ 7·28 (d, J = 8·0 Hz, 1 H, 4-H), 6·80–7·20 (m, 4 H, 1,6,8,9-H_4), 6·68 (q, J = 8·0; 3·0 Hz, 1 H, 3-H), 5·75 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·58 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·72 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ −115·5 (dt). For $C_{15}H_{12}ClFOS$ (294·8) calculated: 61·12% C, 4·10%H, 12·03%Cl, 6·45% F, 10·87% S; found: 61·42% C, 4·13% H, 12·39% Cl, 6·18% F, 11·12% S.

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

Was prepared similarly like *Va* from 10·0 g *IVb*; 10·6 g (100%), m.p. 107–111°C. Analytical sample, m.p. 110–111°C (ethanol). ^{1}H NMR spectrum: δ 7·30 (d, J = 8·0 Hz, 1 H, 4-H), 7·05 (d, J = 3·0 Hz, 1 H, 1-H), 6·68 (q, J = 8·0; 3·0 Hz, 1 H, 3-H), 6·90–7·30 (m, 3 H, remaining Ar—H), 5·80 (dd, J = 8·0; 4·0 Hz, 1 H, Ar-CH-Cl), 3·97 (q, J = 7·0 Hz, 2 H, OCH_2), *c.* 3·75 (m, 2 H, $ArCH_2$), 1·38 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{16}H_{14}ClFOS$ (308·8) calculated: 62·23% C, 4·57% H, 11·48% Cl, 6·15% F, 10·38% S; found: 62·42% C, 4·66% H, 11·58% Cl, 6·33% F, 10·32% S.

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

Was prepared similarly like *Va* from 3·2 g *IVc*; 3·0 g (94%), m.p. 107–108°C. Analytical sample, m.p. 110°C (cyclohexane). ^{1}H NMR spectrum: δ 7·40 (d, J = 2·5 Hz, 1 H, 1-H), 6·80–7·35 (m, 5 H, remaining Ar—H), 5·69 (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, 2 H, $ArCH_2$), 2·90 (q, J = 7·0 Hz, 2 H, SCH_2), 1·28 (t, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −115·1 (dt). For $C_{16}H_{14}ClFS_2$ (324·8) calculated: 59·16% C, 4·34% H, 10·91% Cl, 5·85% F, 19·74% S; found: 59·30% C, 4·36% H, 11·05% Cl, 5·95% F, 19·60% S.

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

A mixture of 11·5 g *Va*, 11·5 g 1-methylpiperazine and 20 ml chloroform was stirred and refluxed for 8 h. Chloroform was evaporated, the residue was diluted with 150 ml water and extracted with benzene. The organic layer was washed with water and then shaken with 85 ml 3M-HCl. The precipitated hydrochloride was filtered off after 1 h standing, washed with benzene and combined with the aqueous layer of the filtrate. The suspension was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried and evaporated; 11·5 g (82%) oil. Neutralization with maleic acid gave the maleate, m.p. 172°C (ethanol). For $C_{24}H_{27}FN_2O_5S$ (474·5) calculated: 60·74% C, 5·74% H, 4·00% F, 5·90% N, 6·76% S; found: 60·82% C, 5·97% H, 4·00% F, 6·04% N, 6·84% S.

Decomposition of the maleate with NH_4OH gave the pure base which was isolated by extraction with benzene and crystallized, m.p. 81°C (light petroleum). IR spectrum (KBr): 809, 869, 879, 909 (2 adjacent and solitary Ar—H), 1 231 ($ArOCH_3$), 1 480, 1 488, 1 597, 3 000, 3 028, 3 075 (Ar), 2 745, 2 765, 2 795 cm^{-1} (N—CH_3). ^{1}H NMR spectrum: δ 7·28 (d, J = 8·0 Hz, 1 H, 4-H), 6·70–7·20 (m, 4 H, 1,6,8,9-H_4), 6·60 (q, J = 8·0; 3·0 Hz, 1 H, 3-H), 3·00–4·00 (m, 3 H, $ArCH_2$.CHAr), 3·70 (s, 3 H, OCH_3), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, CH_2N^4.CH_2 of piperazine), 2·20 (s, 3 H, NCH_3). ^{19}F NMR spectrum: δ −117·1 (dt). For $C_{20}H_{23}FN_2$.

.OS (358·5) calculated: 67·01% C, 6·47% H, 5·30% F, 7·81% N, 8·95% S; found: 66·61% C, 6·52% H, 4·97% F, 7·69% N, 9·28% S.

The benzene layer after the extraction with 3M-HCl was washed with water, dried with K_2CO_3 and evaporated; 1·5 g 7-fluoro-2-methoxydibenzo[*b,f*]thiepin (*VIa*), m.p. 106°C (ethanol–light petroleum). UV spectrum: λ_{max} 223 nm (log ε 4·43), 264·6 nm (4·47), 297 nm (3·68), infl. 340 nm (2·83). IR spectrum: 778 (*cis*-CH=CH), 802, 810, 838, 880, 901 (2 adjacent and solitary Ar—H), 1 030, 1 207, 1 250, 1 262, 1 278 ($ArOCH_3$), 1 488, 1 563, 1 570, 1 591, 3 022, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·40—7·40 (m, 6 H, Ar—H), 6·88 (s, 2 H, ArCH=CHAr), 3·70 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ −114·0 (dt). For $C_{15}H_{11}FOS$ (258·3) calculated: 69·74% C, 4·29% H, 7·36% F, 12·41% S; found: 69·58% C, 4·41% H, 7·08% F, 12·15% S.

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

A similar reaction of 8·4 g *Vb* with 8·4 g 1-methylpiperazine in 15 ml boiling chloroform gave 6·8 g (67%) oily base which was transformed to the maleate, m.p. 130—131°C (ethanol–ether). For $C_{25}H_{29}FN_2O_5S$ (488·6) calculated: 61·46% C, 5·98% H, 3·89% F, 5·73% N, 6·56% S; found: 60·98% C, 6·08% H, 3·96% F, 5·79% N, 6·61% S.

Decomposition of the maleate with NH_4OH and extraction with ether afforded the homogeneous oily base which was used for recording the spectra. ^1H NMR spectrum: δ 6·50—7·40 (m, 6 H, Ar—H), 3·88 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·68 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3), 1·39 (t, J = 7·0 Hz, 3 H, C—CH_3). ^{19}F NMR spectrum: δ −117·0 (dt).

There were further obtained 1·45 g neutral by-product identified as 2-ethoxy-7-fluorodibenzo-[*b,f*]thiepin (*VIb*), m.p. 72°C (light petroleum). UV spectrum: λ_{max} 223 nm (log ε 4·45), 264 nm (4·34), 297 nm (3·64). IR spectrum (KBr): 774 (*cis*-CH=CH), 793, 805, 831, 879 (2 adjacent and solitary Ar—H), 1 033, 1 249, 1 259, 1 270 (ArOR), 1 484, 1 508, 1 538 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60—7·50 (m, 8 H, Ar—H and CH=CH), 3·95 (q, J = 7·0 Hz, 2 H, OCH_2), 1·40 (t, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −114·1 (dt). For $C_{16}H_{13}FOS$ (272·3) calculated: 70·56% C, 4·81% H, 6·98% F, 11·77% S; found: 70·94% C, 5·00% H, 6·40% F, 11·56% S.

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

A similar reaction of 6·2 g *Vc* with 6·2 g 1-methylpiperazine in 12 ml boiling chloroform gave 5·9 g (80%) oily base which was transformed to the maleate, m.p. 124—125°C (ethanol–ether). For $C_{25}H_{29}FN_2O_4S_2$ (504·6) calculated: 59·50% C, 5·79% H, 5·55% N, 12·71% S; found: 59·53% C, 5·83% H, 5·58% N, 12·88% S.

Decomposition of the maleate with NH_4OH and extraction with ether afforded the pure base *Ic* (oil). ^1H NMR spectrum: δ 7·60 (d, J = 2·5 Hz, 1 H, 1-H), 7·25 (d, J = 8·0 Hz, 1 H, 4-H), 6·80—7·30 (m, 4 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·88 (q, J = 7·0 Hz, 2 H, SCH_2), 2·63 and 2·40 (2 t, 8 H, 4 NCH_2 of piperazine), 2·22 (s, 3 H, NCH_3), 1·28 (t, J = 7·0 Hz, 3 H, C—CH_3). ^{19}F NMR spectrum: δ −116·7 (dt).

2-*Ethylthio-7-fluorodibenzo*[*b,f*]*thiepin* (VIc) was obtained as the neutral by-product (0·95 g), m.p. 85°C (ethanol). UV spectrum: λ_{max} 268 nm (log ε 4·59), infl. 315 nm (3·57). ^1H NMR spectrum: δ 6·95—7·40 (m, 6 H, Ar—H), 6·88 (s, 2 H, CH=CH), 2·85 (q, J = 7·0 Hz, 2 H, SCH_2), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −113·9 (dt.) For $C_{16}H_{13}FS_2$ (288·4) calculated: 66·63% C, 4·54% H, 6·59% F, 22·24% S; found: 66·04% C, 4·69% H, 6·61%F, 21·75% S.

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

A solution of 4·0 g *Ia* in 40 ml chloroform was stirred and treated at 15°C over 15 min with a solution of 8·42 g BBr_3 in 10 ml chloroform. The mixture was stirred for 5 h at room temperature and allowed to stand overnight. Chloroform was then evaporated, the residue treated with 120 ml ethanol and 45 ml water and the mixture refluxed for 5 h. After standing overnight the precipitated solid was filtered, washed with 50% ethanol, suspended in 100 ml 5% Na_2CO_3 and the product extracted with chloroform. Processing of the extract gave 2·8 g amorphous product which crystallized after treatment with 20 ml light petroleum; 2·44 g (64%), m.p. 234—234·5°C (ethanol). UV spectrum: λ_{max} 247 nm (log ε 3·89), 280 nm (3·66). IR spectrum (KBr): 795, 800, 820, 870 (2 adjacent and solitary Ar—H), 1 006, 1 237, 1 240, 1 252 (ArOH), 1 471, 1 576, 1 600, 3 060 (Ar), 2 700 cm^{-1} (OH...N, NH^+). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·45 (bs, 1 H, OH), 6·80 to 7·50 (m, 5 H, 1,4,6,8,9-H_s), 6·48 (q, J = 8·0; 3·0 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 2·45 and 2·20 (2 bs, 8 H, 4 NCH_2 of piperazine), 2·03 (s, 3 H, NCH_3). ^{19}F NMR spectrum ($C^2H_3SOC^2H_3$): δ −118·1 (m). For $C_{19}H_{21}FN_2OS$ (344·4) calculated: 66·25% C, 6·15% H, 5·52% F, 8·13% N, 9·31% S; found: 65·91% C, 6·34% H, 5·35% F, 8·06% N, 9·37% S.

Maleate, m.p. 175°C (ethanol). For $C_{23}H_{25}FN_2O_5S$ (460·5) calculated: 59·98% C, 5·47% H, 4·13% F, 6·08% N, 6·96% S; found: 60·42% C, 5·67% H, 3·70% F, 6·04% N, 7·23% S.

The preparation of the starting thiophenols was carried out by Mr Z. Šedivý. Spectra were recorded and interpreted by Drs E. Svátek and J. Holubek (physico-chemical department of this institute). The analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech (analytical laboratory of this institute).

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