NEUROLEPTICS WITH PROTRACTED ACTION: 3-FLUORO DERIVATIVES OF METHIOTHEPIN AND OXYPROTHEPIN AND THEIR 2-FLUORO ANALOGUES*

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3-Fluoro-8-(methylthio)dibenzo[*b,f*]thiepin-10(11*H*)-one (*XIIa*) and 2-fluoro-8-(methylthio)-dibenzo[*b,f*]thiepin-10(11*H*)-one (*XIIb*) were synthesized in six steps from 2-bromo-4-fluorobenzoic acid and 2-bromo-5-fluorobenzoic acid. In two further steps they yielded the chloro derivatives *XIVa* and *XIVb*. Substitution reactions with 1-methylpiperazine and 1-(3-hydroxypropyl)-piperazine led to 3-fluoro and 2-fluoro derivatives of the neuroleptics methiothepin and oxyprothepin (*Vab*, *VIab*). While the 2-fluoro derivatives do not much differ pharmacologically from the nonfluorinated prototypes, the 3-fluoro derivatives are more toxic and more effective as incoordinating and cataleptic agents and their effects are distinctly protracted.

In connection with the attempts to elucidate the antipsychotic effect of tricyclic neuroleptics, first of all "chlorpromazine", emphasis is being placed on the understanding of the metabolism of these compounds and of the contribution of their metabolites to the general pattern of pharmacodynamic and clinical effects[1,2]. In this context the metabolites resulting from an enzymic hydroxylation of benzene rings seem to be of special importance; in the case of chlorpromazine it is first of all the 7-hydroxy derivative *I* (ref.[3-6]). To simplify the situation arising from the multiplicity of mechanisms of biotransformation of most drug molecules it would be of interest if some of the mechanisms could be blocked by suitably modifying the structure of the effective substances[7]. Fluorination in the positions of metabolic hydroxylation in the series of 4-(4-arylpiperidino)butyrophenones as used by Janssen[8] led to a set of effective compounds. A similar procedure was suggested for the chlorpromazine series[9]. Before this suggestion was published our group set out along a similar route in other series of tricyclic neuroleptics[10,11]. The first positive result was the 6-fluoro derivative of chlorprothixene (*II*) which shows a higher incoordinating and cataleptic effect than chlorprothixene and, at the same time, shows signs of protraction of these effects after oral application[12-14]. Independently, the problem of 6-fluorinated 2-substituted thioxanthenes was tackled by Danish investigators[15] who selected "tefluxitol" (*III*) (ref.[16]) for detailed tests. In parallel with this, our work in the series of 10-piperazinodibenzo[*b,f*]thiepin neuroleptics provided the first evidence of the correctness of the concept by the 3-fluoro derivative of octoclothepin (*IV*); in comparison with octoclothepin, the compound is more effective in the rotating-rod test as well as in catalepsy, it is almost equivalent in the antiapomorphine tests in rats, it is more toxic and its effects are distinctly protracted[13,14,17]. Fluorination in different positions of aromatic rings

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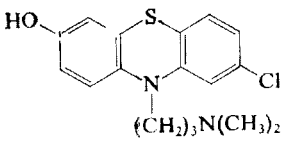
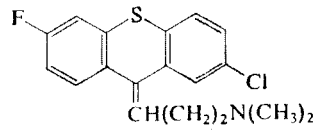


I



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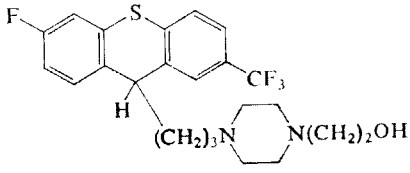
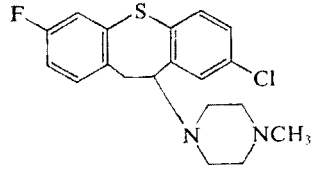


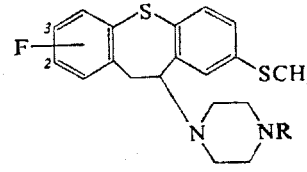
III



IV

of 10-piperazinodibenzo[*b*,*f*]thiepins was then taken up systematically, resulting in compounds fluorinated in position 2 (ref.[13,14,17–19]), 3 (ref.[13,14,17]), 7 (ref.[18–20]) and 8 (ref.[18–22]). The whole area of structures of 2,7-, 2,8-, 3,7- and 3,8-dihalogeno derivatives of perathiepin and of their N-(hydroxyalkyl) analogues where one or both halogen atoms are fluorine, is covered by our basic patent[23]. Our existing work in the series of fluorinated 10-piperazinodibenzo[*b*,*f*]-thiepins makes it possible to formulate in a preliminary way some relationships between structure and pharmacodynamic properties: *a*) If the "neuroleptic substituent" in position 8 is preserved, fluorination in position 2 serves to retain the general profile[14], fluorination in position 3 increases toxicity, sedative and neuroleptic effects and protracts these effects on oral application[14]; fluorination in position 7 distinctly decreases toxicity while preserving both types of activity and slightly protracting their effects[20]; *b*) in the presence of the "sedative substituent" in position 2 of the series of noncataleptic neuroleptics, fluorination in position 7 leads to a clear decrease in toxicity, a slight decrease of sedative effects and in a clear sign of cataleptic effects; fluorination in position 8 then leads to distinct cataleptic activity while toxicity and sedative activity is preserved[18,19].

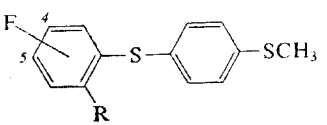
In this paper we describe the synthesis of 3-and 2-fluoro derivatives of further two potent neuroleptics of our series, namely 10-(4-methylpiperazino)-8-(methylthio)--10,11-dihydrodibenzo[*b*,*f*]thiepin (methiothepin, metitepin)[24–29] (for further ref.[30]) and 10-[4-(3-hydroxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo--[*b*,*f*]thiepin (oxyprothepin)[31–39] (for further ref.[40]) of formulae *Va*, *Vb*, *VIa* and



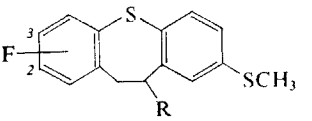
Va, R = CH_3; 3-F
Vb, R = CH_3; 2-F
VIa, R = $(CH_2)_3OH$; 3-F
VIb, R = $(CH_2)_3OH$; 2-F

VIb. The syntheses used methods repeatedly described for analogous compounds[6,14,19,21,22].

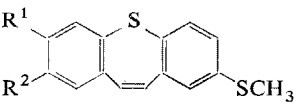
Heating of 2-bromo-4-fluorobenzoic acid[14] or of 2-bromo-5-fluorobenzoic acid[41] with 4-(methylthio)thiophenol[30] and anhydrous potassium carbonate in dimethylformamide led to acids *VIIa* and *VIIb* which were reduced with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene to alcohols *VIIIa* and *VIIIb*. Treatment with thionyl choride in boiling benzene led to chlorides *IXa* and *IXb* which were transformed in a reaction with sodium cyanide in dimethylformamide to nitriles *Xa* and *Xb*. Alkaline hydrolysis resulted in phenylacetic acids *XIa* and *XIb* which were cyclized in boiling toluene[24] by treatment with polyphosphoric acid to ketones *XIIa* and *XIIb*. Reaction with sodium borohydride in aqueous ethanol reduced the ketones to alcohols *XIIIa* and *XIIIb* and these were converted to chlorides *XIVa* and *XIVb* by treatment with hydrogen chloride in benzene. Reactions of these chlorides with 1-methylpiperazine and 1-(3-hydroxypropyl)piperazine[42] were done in boiling chloroform; bases *Vab* and *VIab* resulted in 70–80% yields. The by-products obtained included 7-fluoro-2-(methylthio)dibenzo[*b*,*f*]thiepin (*XV*) and 2-fluoro-8-(methylthio)dibenzo[*b*,*f*]thiepin (*XVI*) which were formed through a parallel elimination reaction.



a, 4-F; *b*, 5-F
VII, R = COOH
VIII, R = CH_2OH
IX, R = CH_2Cl
X, R = CH_2CN
XI, R = CH_2COOH



a, 3-F; *b*, 2-F
XII, F = =O
XIII, R = OH
XIV, R = Cl



XV, R^1 = F, R^2 = H
XVI, R^1 = H, R^2 = F

Fluorinated derivatives of methiothepin (*Vab*) and oxyprothepin (*VIab*) were evaluated pharmacologically, the results being shown in Table I, which includes for comparison methiothepin[24,30] and oxyprothepin[31,40]. The compounds were applied per os as maleates, oxyprothepin being administered as methanesulfonate, in doses referring to the base. Using mice, the acute toxicity and the incoordinating effects of the compounds in the rotating-rod test were evaluated, taking the latter as an indicator of the central depressant effect. With rats, the cataleptic effect was evaluated as a criterion of neuroleptic action.

Table I shows that the 3-fluoro derivatives *Va* and *VIa* are 1·5–2 times more toxic, 4 times more effective as central depressants and 2–4 times more effective cataleptically than the nonfluorinated prototypes. The protraction of the effects is significant. Thus, with *Va* the incoordinating effect on the rotating rod persists so long that even 24 h after administration one can estimate the mean effective dose (ED_{50} = = 1·15 mg/kg); the effect disappears only 48 h after application. The situation is similar in the catalepsy test; after 24 h the cataleptic effect is so developed that the mean effective dose can be estimated (ED_{50} = 6·9 mg/kg), the effect disappearing by 48 h. With compound *VIa* the protraction of the effects is even more pronounced. In the rotating-rod test, the ED_{50} after 24 h is 2·95 mg/kg, after 48 h ataxia is still apparent in 4 mice out of 10 and still after 72 h in 1 mouse out of 10. In the catalepsy test, ED_{50} after 24 h is 3·6 mg/kg; the effect disappears before 48 h. With the 2-fluoro derivatives *Vb* and *VIb* the differences in properties in comparison with the nonfluorinated standards are by far not as significant. As to the activity in the two tests the fluorinated compounds resemble the nonfluorinated analogues. Mention should be made of the twice lower toxicity of *VIb* in comparison with oxyprothepin. These compounds show no distinct prolongation of their effects. With *Vb* the effect in both tests completely disappears by 24 h. With *VIb*, only a slight indication of prolongation may be observed in the rotating-rod test where ataxia was observed in 3 mice out of 10 after 24 h.

The results are in fine agreement with the conclusion formulated in the introduction: If a "neuroleptic substituent" is present in position 8 (the methylthio group is un-

TABLE I

Pharmacological Effects of Fluorinated Derivatives of Methiothepin (*Vab*) and Oxyprothepin (*VIab*) on Oral Application (mg/kg)

Compound	Mice		Rats
	acute toxicity LD_{50}	rotating rod ED_{50}[a]	catalepsy ED_{50}[b]
Va	50	0·54	2·5
VIa	42	0·96	1·6
Vb	56	2·5	6·8
VIb	126	3·6	4·5
Methiothepin[24,30]	94	1·9	10·5
Oxyprothepin[31,40]	68	4·6	3·3

[a] Mean effective doses at the time of maximum effect of substance tested. [b] Doses bringing about catalepsy in 50% animals.

doubtedly such a substituent), 3-fluorination results in a rise of toxicity and of both types of activity, their duration being clearly protracted. On the other hand, fluorination in position 2 does not result in any substantial change of the pharmacodynamic profile.

Compounds *Va* a *VIa* were tested as maleates by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) for the antimicrobial activity *in vitro* toward a standard set of typical microorganisms. The compounds were found to show a wide spectrum of inhibitory activity which is rather common in this series. The individual microorganisms and the minimum inhibitory concentrations of the tested compounds in μg/ml are shown: *Streptococcus β-haemolyticus*, *Va* 10, *VIa* 20; *Streptococcus faecalis*, *Va* 20, *VIa* 20; *Staphylococcus pyogenes aureus*, *Va* 12·5, *VIa* 12·5; *Pseudomonas aeruginosa*, *Va* 100, *VIa* 100; *Escherichia coli*, *Va* 100, *VIa* 100; *Proteus vulgaris*, *Va* 100, *VIa* 100; *Mycobacterium tuberculosis* H37Rv, *Va* 5·25, *VIa* 12·5; *Saccharomyces pasterianus*, *Va* 100, *VIa* 100; *Trichophyton mentagrophytes*, *Va* 25, *VIa* 50; *Candida albicans*, *Va* 100, *VIa* 100; *Aspergillus niger*, *Va* 100, *VIa* 100.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in an Infrascan (Hilger and Watts) or a Unicam SP 200G spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) or a Tesla BC 487 (80 MHz) spectrometer. The homogeneity of the compounds was tested by chromatography on a thin layer of silica gel.

4-Fluoro-2-(4-methylthiophenylthio)benzoic Acid (*VIIa*)

A mixture of 50·0 g 2-bromo-4-fluorobenzoic acid[14], 120 ml dimethylformamide, 53·2 g 4-(methylthio)thiophenol[30], 39·0 g anhydrous K_2CO_3 and 3·5 g copper was heated under stirring for 2·5 h to 150–165°C. After partial cooling, it was diluted with water, the solution was filtered with charcoal and the filtrate made acid with hydrochloric acid. After standing overnight, the product was filtered, washed with water and dried; 52·2 g (79%), m.p. 217–219°C (ethanol). IR spectrum: 820, 865 (2 adjacent and solitary Ar—H), 940, 1 280 (COOH), 1 575, 1 610 (Ar), 1 700 (ArCOOH), 2 530, 2 570, 2 670 cm^{-1} (COOH). For $C_{14}H_{11}FO_2S_2$ (294·4) calculated: 57·12% C, 3·77% H, 6·45% F; found: 56·69% C, 4·06% H, 6·26% F.

5-Fluoro-2-(4-methylthiophenylthio)benzoic Acid (*VIIb*)

Like in the preceding case, reaction of 22·0 g 2-bromo-5-fluorobenzoic acid[41] and 20·0 g 4-(methylthio)thiophenol[30] in the presence of 17 g K_2CO_3 and 1·0 g Cu in dimethylformamide yielded 28·5 g (96%) product melting at 190–192°C which was recrystallized from ethanol for analysis; m.p. 192–194°C. UV spectrum: λ_{max} 213 nm (log ε 4·41), 265 nm (4·23), infl. 285 nm (4·11), 330 nm (3·68). IR spectrum (Nujol): 809, 812, 890 (2 adjacent and solitary Ar—H), 940, 1257, 1690, 2 600 (ArCOOH), 1 569, 1 606 cm^{-1} (Ar). For $C_{14}H_{11}FO_2S_2$ (294·4) calculated: 57·12% C, 3·77% H, 6·45% F, 21·79% S; found: 57·32% C, 4·02% H, 6·25% F, 21·49% S.

4-Fluoro-2-(4-methylthiophenylthio)benzyl Alcohol (*VIIIa*)

A suspension of 15·2 g acid *VIIa* in 300 ml benzene was treated dropwise with 42·5 g of a 50% benzene solution of sodium dihydrido-bis(2-methoxyethoxy)aluminate under stirring at 45—50°C. After 5 h of stirring at room temperature it was left to stand overnight, decomposed under external cooling with ice by slowly adding 130 ml 2M-NaOH, the benzene layer was separated, washed with water, dried with $MgSO_4$ and evaporated. A total of 12·4 g (65%) product melting at 78—84°C was obtained. The analytical sample melts at 83·5—86·5°C (cyclohexane). For $C_{14}H_{13}FOS_2$ (280·4) calculated: 59·97% C, 4·69% H, 6·77% F, 22·87% S; found: 60·54% C, 5·01% H, 6·67% F, 22·72% S.

5-Fluoro-2-(4-methylthiophenylthio)benzyl Alcohol (*VIIIb*)

In analogy with the preceding case, 20·3 g acid *VIIb* was reduced, yielding 17·0 g (89%) oil, a sample of which was redistilled for analysis; b.p. 177—179°C/0·25 Torr. IR spectrum (film): 810, 872 (2 adjacent and solitary Ar—H), 1011, 1032 (CH_2OH), 1102 (Ar—F), 1478, 1580, 1600 (Ar), 3390 cm^{-1} (OH). For $C_{14}H_{13}FOS_2$ (280·4) calculated: 59·97% C, 4·69% H, 6·77% F, 22·87% S; found: 60·03% C, 4·64% H, 6·76% F, 22·70% S.

4-Fluoro-2-(4-methylthiophenylthio)benzyl Chloride (*IXa*)

Thionyl chloride (11·9 g) was added dropwise under stirring to a refluxing solution of 27·5 g *VIIIa* in 250 ml benzene. The mixture was refluxed for 1·5 h, the volatile fractions were distilled *in vacuo*, the residue was dissolved in benzene, the solution was filtered with charcoal and the filtrate was evaporated. A total of 24·6 g (84%) product melting at 70—73°C was obtained, the analytical product melted at 72—74°C (cyclohexane). For $C_{14}H_{12}ClFS_2$ (298·8) calculated: 56·26% C, 4·05% H, 11·87% Cl, 6·36% F; found: 56·67% C, 4·25% H, 11·63% Cl, 6·26% F.

5-Fluoro-2-(4-methylthiophenylthio)benzyl Chloride (*IXb*)

Like in the preceding case, 11·8 g *VIIIb* yielded 12·3 g (99%) oil, a sample of which was redistilled for analysis; b.p. 172°C/1·5 Torr. NMR spectrum: δ 6·90—7·50 (m, 7 H, aromatic protons), 4·72 (s, 2 H, $ArCH_2Cl$), 2·40 (s, 3 H, SCH_3). For $C_{14}H_{12}ClFS_2$ (298·8) calculated: 21·46% S; found: 20·88% S.

4-Fluoro-2-(4-methylthiophenylthio)phenylacetonitrile (*Xa*)

A solution of 24·6 g *IX*a was prepared in 300 ml warm dimethylformamide; at 40°C, 7·6 g NaCN was then added under stirring (a slightly exothermic reaction). The mixture was stirred for 30 min without heating and then for 4 h at 80°C. On the following day, the solvent was distilled *in vacuo*, the residue was diluted with water and the product was isolated by extraction with benzene; 19·8 g (84%) oil which slowly crystallized, m.p. 74—84°C. Recrystallization from cyclohexane yielded the pure product which melts first at 84—86°C, the melt solidifies on further heating in the form of needles which melt again at 93—94°C. For $C_{15}H_{12}FNS_2$ (289·4) calculated: 62·25% C, 4·18% H, 4·84% N; found: 62·23% C, 4·30% H, 4·37% N.

5-Fluoro-2-(4-methylthiophenylthio)phenylacetonitrile (*Xb*)

In analogy with the preceding case, 29·5 g *IXb* yielded 25·7 g (90%) oil, a sample of which was purified for analysis by chromatography on a column of alumina (activity II), using elution with

benzene, and distilled; b.p. 194°C/1·5 Torr. IR spectrum (film): 809, 858 (2 adjacent and solitary Ar—H), 1575, 1596 (Ar), 2225 cm^{-1} (R—CN). For $C_{15}H_{12}FNS_2$ (289·4) calculated: 62·25% C, 4·18% H, 4·84% N; found: 62·82% C, 4·17% H, 4·81% N.

4-Fluoro-2-(4-methylthiophenylthio)phenylacetic Acid (*XIa*)

A solution of 19 g KOH in 45 ml water was added to a solution of 19·8 g *Xa* in 90 ml ethanol and the mixture was refluxed for 6 h. After evaporation of ethanol at reduced pressure, the residue was diluted with water, the solution was washed with benzene, filtered while hot with charcoal and the filtrate was acidified with hydrochloric acid; 16·4 g (78%), m.p. 137—140°C (aqueous ethanol). For $C_{15}H_{13}FO_2S_2$ (308·4) calculated: 58·42% C, 4·25% H, 6·16% F, 20·80% S; found: 58·21% C, 4·34% H, 5·78% F, 20·95% S.

5-Fluoro-2-(4-methylthiophenylthio)phenylacetic Acid (*XIb*)

Like in the preceding case, 16·9 g *Xb* was hydrolyzed, the alkaline solution was acidified, the product separated as an oil which was isolated by extraction with ether; 14.5 g (82%), m.p. 112 to 113·5°C (aqueous ethanol). IR spectrum: 798, 815, 868 (2 adjacent and solitary Ar—H), 919, 1175, 1230, 1265 (COOH), 1571, 1601 (Ar), 1720, 3170 cm^{-1} (COOH). For $C_{15}H_{13}FO_2S_2$ (308·4) calculated: 58·42% C, 4·25% H, 6·16% F, 20·80% S; found: 58·91% C, 4·27% H, 5·79% F, 20·66% S.

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

A mixture of 410 g polyphosphoric acid, 39·6 g *XIa* and 320 ml toluene was stirred under a reflux condenser for 6 h at 130°C. After cooling, it was decomposed by pouring into 2 litres ice-cold water and extracted with benzene. The extract was washed with water, 5% solution of NaOH and again with water, dried with K_2CO_3 and evaporated; 28·2 g (76%) product melting at 113—120°C which was purified for analysis by crystallization from benzene, m.p. 120—123°C. UV spectrum: λ_{max} 248 nm (log ε 4·41), 280 nm (4·24), 357 nm (3·60). IR spectrum: 820, 830, 850, 870 (2 adjacent and solitary Ar—H), 1230 (Ar—F), 1490, 1585 (Ar), 1675 cm^{-1} (ArCO). For $C_{15}H_{11}FOS_2$ (290·4) calculated: 62·04 % C, 3·82% H, 6·54% F, 22·09% S; found: 62·10% C, 3·88% H, 6·56% F, 21·73% S.

2-Fluoro-8-(methylthio)dibenzo[*b,f*]thiepin-10(11*H*)-one (*XIIb*)

Like in the preceding case, 8·0 g acid *XIb* was cyclized yielding 7·1 g (95%) neutral product, m.p. 173—175°C. On crystallization from benzene the m.p. did not change. IR spectrum: 811, 877 (2 adjacent and solitary Ar—H), 1223 (Ar—F), 1570, 1578, 1595 (Ar), 1669 cm^{-1} (ArCO). For $C_{15}H_{11}FOS_2$ (290·4) calculated: 62·04% C, 3·82% H; found: 62·06% C, 3·95% H.

3-Fluoro-10-hydroxy-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIa*)

A solution of 5·5 g $NaBH_4$ in 75 ml water with 2 drops of 5% NaOH was added dropwise to a suspension of 26·5 g *XIIa* in 80 ml ethanol. The mixture was refluxed under stirring for 3 h, ethanol was evaporated, the residue was diluted with water and the product isolated by extraction with benzene; 24·5 g (92%), m.p. 127—129°C (benzene). IR spectrum: 815, 885, 895 (2 adjacent and solitary Ar—H), 1065, 1130 (CHOH), 1240 (Ar—F), 1490, 1590, 1605 (Ar), 3320, 3370 cm^{-1} (OH). NMR spectrum: δ 6·70—7·50 (m, 6 H, aromatic protons), 6·25 (m, 1 H, Ar—CH—O),

3·58 and 3·16 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·41 (s, 3 H, SCH_3), *c.* 2·40 (bs, disappears after D_2O, 1 H, OH). For $C_{15}H_{13}FOS_2$ (292·4) calculated: 61·61% C, 4·48% H, 6·50% F, 21·93% S; found: 61·82% C, 4·58% H, 6·41% F, 21·72% S.

2-Fluoro-10-hydroxy-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIb*)

Like in the preceding case, reduction of 9·2 g *XIIb* yielded 8·6 g (93%) practically pure product (m.p. 121—125°C); the analytical product melted at 123—125°C (benzene). IR spectrum: 810, 889 (2 adjacent and solitary Ar—H), 1048, 1114 (CHOH in a ring), 1573, 1579 (Ar), 3340 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 6·80—7·60 (m, 6 H, aromatic protons), 5·77 (d, J = 5·5 Hz, 1 H, OH), 5·32 (m, 1 H, Ar—CH—O), 3·53 and 3·19 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·48 (s, 3 H, SCH_3). For $C_{15}H_{13}FOS_2$ (292·4) calculated: 61·61% C, 4·48% H; found: 62·02% C, 4·52% H.

10-Chloro-3-fluoro-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVa*)

A warm solution of 24·9 g *XIIIa* was prepared in 800 ml benzene, it was cooled to 20°C, 5 g powdery $CaCl_2$ was added and the suspension was saturated for 5 h with anhydrous hydrogen chloride. After standing overnight, it was filtered and the filtrate was evaporated at reduced pressure. The residue (24·9 g) was recrystallized from cyclohexane; 17·3 g (65%), m.p. 112—114°C. NMR spectrum: δ 6·70—7·50 (m, 6 H, aromatic protons), 5·66 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·89 and 3·50 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·40 (s, 3 H, SCH_3). For $C_{15}H_{12}ClFS_2$ (310·8) calculated: 57·95% C, 3·89% H, 11·41% Cl, 6·11% F; found: 58·38% C, 4·07% H, 11·32% Cl, 6·22% F.

10-Chloro-2-fluoro-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVb*)

Like in the preceding case, 8·6 g *XIIIb* yielded 8·6 g product melting at 115—119°C; analytical product, m.p. 122—123°C (cyclohexane). NMR spectrum: δ 6·75—7·50 (m, 6 H, aromatic protons), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·58 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·39 (s, 3 H, SCH_3). For $C_{15}H_{12}ClFS_2$ (310·8) calculated: 57·95% C, 3·89% H; found: 58·27% C, 3·96% H.

3-Fluoro-10-(4-methylpiperazino)-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*Va*)

A mixture of 8·0 g *XIVa*, 20 ml chloroform and 8·0 ml 1-methylpiperazine was refluxed under stirring for 7 h. Chloroform was then evaporated, the residue mixed with 200 ml water and extracted with 300 ml benzene. The benzene solution was washed with water and shaken with 200 ml dilute hydrochloric acid (1 : 2). The precipitated hydrochloride was filtered and combined with the aqueous layer of the filtrate. Treatment with NH_4OH released the base which was isolated by extraction with benzene; 7·6 g (79%), a slowly crystallizing oil. Recrystallization from ethanol yielded a pure product melting at 108—110°C. NMR spectrum: δ 6·70—7·60 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·41 (s, 3 H, SCH_3), 2·26 (s, 3 H, NCH_3). For $C_{20}H_{23}FN_2S_2$ (374·5) calculated: 64·13% C, 6·19% H, 5·07% F, 7·48% N, 17·12% S; found: 64·13% C, 6·35% H, 5·42% F, 7·41% N, 17·03% S.

Neutralization of the base with maleic acid in warm ethanol and addition of ether resulted in a maleate, m.p. 136—138°C (ethanol–ether). For $C_{24}H_{27}FN_2O_4S_2$ (490·6) calculated: 58·75% C, 5·55% H, 5·71% N, 13·07% S; found: 58·88% C, 5·65% H, 5·62% N, 12·78% S.

2-Fluoro-10-(4-methylpiperazino)-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*Vb*)

Like in the preceding case, reaction of 4·0 g *XIVb* with 4·0 ml 1-methylpiperazine in 15 ml boiling chloroform yielded 3·3 g (69%) base, m.p. 91—93°C (ethanol). NMR spectrum: δ 6·50—7·60 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·32 (s, 3 H, SCH_3), 2·22 (s, 3 H, NCH_3). For $C_{20}H_{23}FN_2S_2$ (374·5) calculated: 64·14% C, 6·19% H, 7·48% N, 17·12% S; found: 63·78% C, 6·29% H, 7·56% N, 17·46% S.

Maleate, m.p. 151—153·5°C (ethanol). For $C_{24}H_{27}FN_2O_4S_2$ (490·6) calculated: 58·75% C, 5·55% H, 3·87% F, 5·71% N, 13·07% S; found: 58·88% C, 5·62% H, 3·69% F, 5·78% N, 13·29% S.

3-Fluoro-10-[4-(3-hydroxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*VIa*)

Like in the preceding cases, reaction of 5·0 g *XIVa* with 6·0 g 1-(3-hydroxypropyl)piperazine[42] in 15 ml chloroform resulted in 5·5 g crude base which crystallized only after conversion to oxalate, its recrystallization from 95% ethanol, its decomposition with ammonia and isolation by extraction with benzene; m.p. 90—92°C (ether). IR spectrum (Nujol): 809, 870 (2 adjacent and solitary Ar—H), 1067 (CH_2OH), 1580, 1595 (Ar), 3170 cm^{-1} (OH). For $C_{22}H_{27}FN_2OS_2$ (418·6) calculated: 63·12% C, 6·50% H, 4·54% F, 6·69% N, 15·32% S; found: 63·39% C, 6·71% H, 4·33% F, 6·56% N, 15·27% S.

Di(hydrogen maleate) (solvate with ethanol), m.p. 105—108°C (ethanol). For $C_{32}H_{41}FN_2O_{10}S_2$ (696·8) calculated: 55·15% C, 5·93% H, 2·73% F, 4·02% N, 9·21% S; found: 55·01% C, 5·92% H, 2·99% F, 4·18% N, 9·37% S.

From the original benzene solution from which the base had been removed by shaking with hydrochloric acid, a total of 3·8 g crystalline substance was obtained by evaporation (from 9·0 g *XIVa*) which was chromatographed on a column of 130 g alumina (activity II). Elution with light petroleum yielded 0·6 g homogeneous 7-fluoro-2-(methylthio)dibenzo[*b,f*]thiepin (*XV*) which crystallizes from cyclohexane and melts first at 81—83°C; after change in crystal form it melts again at 103°C. UV spectrum: λ_{max} 216 nm (log ε 4·34), 269 nm (4·47). IR spectrum (Nujol): 810, 816, 824, 833, 856, 861, 866, 886 (2 adjacent and solitary Ar—H), 1481, 1567, 1578, 1591 cm^{-1} (Ar). For $C_{15}H_{11}FS_2$ (274·4) calculated: 65·66% C, 4·04% H, 6·93% F, 23·37% S; found: 65·15% C, 4·14% H, 6·89% F, 23·70% S.

2-Fluoro-10-[4-(3-hydroxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin (*VIb*)

Like in the preceding case, 4·9 g *XIVb* yielded 5·1 g base which readily crystallized and was identified as a solvate with benzene, m.p. 79°C, softening from 61°C up (benzene). NMR spectrum: δ 6·60—7·60 (m, 6 H, aromatic protons of the skeleton), 7·26 (s, C_6H_6), 4·38 (bs, 1 H, OH), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·77 (t, 2 H, CH_2O—), c. 2·60 (m, 10 H, 5 NCH_2), 2·40 (s, 3 H, SCH_3), 1·70 (m, 2 H, middle CH_2 of propyl). For $C_{28}H_{33}FN_2OS_2$ (496·7) calculated: 67·70% C, 6·70% H, 5·64% N; found: 67·34% C, 6·87% H, 5·64% N.

Di(hydrogen maleate), m.p. 133—135°C (ethanol). For $C_{30}H_{35}FN_2O_9S_2$ (650·7) calculated: 55·37% C, 5·42% H, 2·92% F, 4·31% N, 9·85% S; found: 55·32% C, 5·58% H, 3·11% F, 4·54% N, 9·76% S.

Like in the preceding case, a neutral product of an elimination reaction was isolated and identified as 2-fluoro-8-(methylthio)dibenzo[*b,f*]thiepin (*XVI*), m.p. 68—69°C (cyclohexane).

UV spectrum: λ_{max} 222 nm (log ε 4·41), 268·5 nm (4·61). IR spectrum (Nujol): 823, 869, 877, 889 (2 adjacent and solitary Ar—H), 1572, 1595 cm^{-1} (Ar). NMR spectrum: δ 6·70—7·50 (m, 8 H, aromatic and olefinic protons), 2·38 (s, 3 H, SCH_3). For $C_{15}H_{11}FS_2$ (274·4) calculated: 65·66% C, 4·04% H, 6·93% F, 23·37% S; found: 65·64% C, 4·25% H, 7·22% F, 22·93% S.

Only as this paper was in press we obtained the text of a patent application[43] describing the preparation of our compound *Vb*. This application, which is completely dependent on our previous papers by its topic, as well as the methods used, describes a total of 13 final products from which 6 are dihalogeno derivatives belonging into the scope of our former basic patent[23]. Of the intermediates of the synthesis of *Vb*, the application does not characterize at all substances *VIIIb*, *IXb*, *Xb*, as well as the base *Vb*. For the remaining intermediates (*VIIb*, *XIb—XIVb*) the application gives melting points by 6—10°C lower than values given in this paper for the analytical products. For the maleate of the final compound (*Vb*), the application gives the m.p. of 150—151°C being almost in agreement with our value.

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