FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: DERIVATIVES AND ANALOGUES OF 2-(4-(7-FLUORO--2-ISOPROPYL-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN-11-YL)-PIPERAZINE-1-YL)ETHANOL

Miroslav PROTIVA, Jiří JÍLEK, Miroslav RAJŠNER, Karel ŠINDELÁŘ, Václav BÁRTL, Miroslav RYSKA, Ivan KORUNA, Jiří HOLUBEK, Emil SVÁTEK, Jiřina METYŠOVÁ, Antonín DLABAČ, Josef POMYKÁČEK and František MIKŠÍK

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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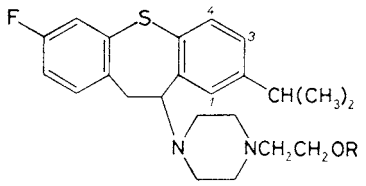
The preparation of 4-fluoro-2-nitrobenzonitrile (*V*), an intermediate in the synthesis of the title compound *I*, from 4-fluoro-2-nitroaniline *via* 5-fluoro-2-iodonitrobenzene (*VII*) was elaborated. Syntheses of 1,1,1,3,3,3-hexadeutero-2-propyl (*XX*) and 1,3,4-trideutero (*XXVIII*) analogues of compound *I* from hexadeuteroacetone, and pentadeuterobromobenzene, respectively, were carried out. Compound *I* was esterified with acetic anhydride, decanoic acid and 3,4,5-trimethoxybenzoyl chloride to give the esters *II*—*IV*. Acylation of compound *XXX* with acetyl chloride, 4-fluorophenoxyacetyl chloride and (4-fluorophenylthio)acetyl chloride and the following reduction of the amides with lithium aluminium hydride gave compounds *XXXII*, *XXXIX* and *XL*. Substitution reactions of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin with the corresponding N-monosubstituted piperazines resulted in compounds *XXXIII*—*XXXV*, *XXXVII*, *XXXVIII*, *XLI* and *XLII*. Alkylation of *XXX* with 2-(2-chloroethyl)-1,3-dioxolane afforded compound *XXXVI*. Pharmacological testing of the new compounds, derivatives and analogoues of the neuroleptic agent isofloxythepin (*I*), for discoordinating and cataleptic activities, showed especially for compounds *II*, *XXXIV* and *XXXVI* very intensive and long-lasting effects. The decanoate *III* has properties of a depot neuroleptic agent.

In a recent communication[1], the synthesis of the title compound *I* (the neuroleptic agent isofloxythepin) has been described and the recent state of the knowledge of its properties has been reviewed. This communication included also report on the resolution of racemic *I* and on the synthesis of several S- and N-oxidated derivatives of *I* as potential metabolites. The present paper describes further amendment of the synthesis of *I*, synthesis of two deuterated analogues of *I*, and finally synthesis of some esters and piperazine-N-substituted analogues of *I* with their pharmacological properties.

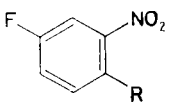
The preparation of 4-fluoro-2-nitrobenzonitrile (*V*), an intermediate in the synthesis of *I*, was described[1] by diazotization of 4-fluoro-2-nitroaniline[1,2] with nitrosylsulfuric acid and by the following reaction with a solution of cuprous cyanide under simulta-



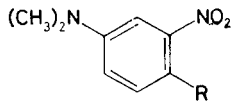
I, R = H
II, R = $COCH_3$
III, R = $CO(CH_2)_8CH_3$

neous neutralization of the mixture with sodium carbonate. A similar synthesis of *V*, using nickel(II) cyanide, was described[3] after the termination of the first series of our experiments. The process was favourable for preparing *V* in laboratory scale but working in larger quantities showed the evolution of considerable amounts of hydrogen cyanide, which was entrained by carbon dioxide and nitrogen formed, and passed into the exhalations in the stage of reaction with cuprous cyanide and neutralization with sodium carbonate. Attempts to modify this step by substituting sodium carbonate with sodium acetate or by neutralization of the diazonium sulfate solution with sodium carbonate before the reaction with cuprous cyanide (*cf.*[4-6]) were not successful. For these reasons an alternative method for preparing *V* was considered necessary; reactions of 5-fluoro-2-halogenonitrobenzenes with metal cyanides were suggested as a possibility. Diazotization of 4-fluoro-2-nitroaniline[1,2] in dilute hydrochloric acid and the following treatment with a solution of cuprous chloride in 3M-HCl (method[7]) led to an improved procedure for preparing 2-chloro-5-fluoronitrobenzene (*VI*) (refs[1,8]). The use of cupric chloride instead of cuprous chloride, which was recommended for similar cases[9], was found unfavourable in our case (the yield dropped to about 25%). Compound *VI*, however, was found not of use to the purpose followed: it does react neither with cuprous cyanide in dimethylformamide at room temperature or at 100°C, nor with potassium cyanide in dimethylformamide at 150°C. The reaction with cuprous cyanide in hexamethylphosphoric triamide at 150°C gave as the only product to be isolated a small amount (below 10%) of 4-dimethylamino-2-nitrobenzonitrile (*VIII*) (ref.[10]). The substitution of the chlorine atom by the cyano group was accompanied by interaction with the solvent which resulted in substitution of the nonactivated fluorine atom by the dimethylamino group. It was clear that a more reactive 5-fluoro-2-halogenonitrobenzene is needed and the known 5-fluoro-2-iodonitrobenzene (*VII*) (refs[11,12]) was selected to this purpose. Its preparation by diazotization of 4-fluoro-2-nitroaniline[1,2] in dilute sulfuric acid and by the following treatment with a solution of potassium iodide was elaborated to give 79% of crude *VII* which could be used without purification for the following step. From the alkaline washings 4-iodo-3-nitrophenol (*XI*) (ref.[13])

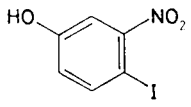
was isolated in the yield of 15% as a by-product. Compound *VII* reacted with cuprous cyanide in hexamethylphosphoric triamide (method[14]) first at room temperature and finally at 100°C, and gave in a high yield the nitrile *V*. The reaction proceeded under similar conditions in dimethylformamide and this version was found most suitable for the preparation of *V*. From the mother liquors *VIII* (ref.[10]) was isolated in the yield of 8% as a by-product. The displacement of the fluorine atom by the dimethylamino group proceeds thus not only by interaction with hexamethylphosphoric triamide but also with dimethylformamide. The iodo compound *VII* does not react with sodium cyanide in dimethylformamide at 150–160°C. For characterization the compound *VIII* was hydrated with dilute sulfuric acid at 100°C and the amide *IX* was obtained. A similar reaction under more severe conditions gave N,N-dimethyl-3-nitroaniline (*X*); the easy decarboxylation of 4-dimethylamino-2-nitrobenzoic acid to compound *X* was described[15].



V, R = CN
VI, R = Cl
VII, R = I

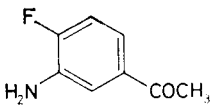


VIII, R = CN
IX, R = $CONH_2$
X, R = H



XI

Preliminary metabolic studies with isofloxythepin (*I*) in animals[16,17] showed that most of the metabolites detected contain hydroxyl group in unknown positions of the aromatic nuclei. Authentic samples of the individual hydroxylated derivatives of *I* were not available. For this reason we started an attempt at synthesizing the 8-hydroxy derivative of isofloxythepin (*I*). One of the intermediates, 3-amino-4-fluoroacetophenone (*XII*) (ref.[18]), has now been prepared by reduction of 4-fluoro-3-nitroacetophenone[18] not only with tin(II) chloride[18] but also by catalytic hydrogenation on Raney nickel at normal conditions in methanol and less favourably in acetone. Trials to transform compound *XII* to 4-fluoro-3-hydroxyacetophenone by diazotization and following heating led only to resinous products.



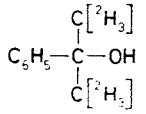
XII

It has been suggested that the availability of specifically deuterated isofloxythepin analogues could be helpful in the effort to localize the hydroxyl groups in metabolites

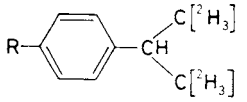
by means of mass spectrometry. Moreover, these analogues could be useful for the detection of metabolites of *I* using the "ion pair" technique. For these reasons the total syntheses of 2-(4-(7-fluoro-2-(1,1,1,3,3,3-hexadeutero-2-propyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yl)piperazine-1-yl)ethanol (1,1,1,3,3,3-hexadeutero-2-propyl analogue of isofloxythepin) (*XX*) and of 2-(4-(1,3,4-trideutero-7-fluoro-2-isopropyl--10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yl)piperazine-1-yl)ethanol (1,3,4-trideutero analogue of isofloxythepin) (*XXVIII*) have been carried out. With the exception of the starting deuterated intermediates, the syntheses used similar methods like those leading to nonlabeled intermediates[19,20] and to the final product[1]. The critical point was the evaluation of the isotopic purity of the deuterated intermediates as well as of the final products. The deuterated compounds were not homogeneous and, therefore, it was necessary to calculate the distribution of the individual components (according to the number of deuterium atoms in molecules) which was done on the basis of relative intensities of peaks of the multiplet in the range of molecular ions, or of the intensities of characteristic fragments $(M - CH_n{}^2H_{3-n})^+$, where $n = 0-3$. With intermediates containing atoms of sulfur and especially chlorine, the calculations must be considered only semi-quantitative due to the overlapping of the molecular ions containing on the one hand ^2H, and ^{34}S and ^{37}Cl isotopes on the other. Corrections on the overlapping of peaks of molecular ions and fragments $(M - H)^+$, and $(M - {}^2H)^+$, respectively, could not be considered due to the lack of knowledge of isotopic effect and of the fragmentation of the individual components with various number of deuterium atoms in molecules.

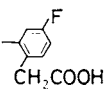
The synthesis of the hexadeutero analogue of *I* (*XX*) started from hexadeuteroacetone and its reaction with phenylmagnesium bromide in ether. The product, after separation on the GC column, gave an intensive peak whose mass spectrum corresponded to the expected structure *XIII* and with regard to deuterium content, the substance was useful for the synthesis. It was contaminated with 2-phenyl-1,1,3, 3,3-pentadeutero-1-propene and its less deuterated analogues. Reduction of *XIII* using the $AlCl_3$/Pd-catalyzed hydrogen transfer from cyclohexene (method[21]) led to a 1 : 1 mixture of hexadeuterocumene (*XIV*) and the mentioned 2-phenyl-1,1,3, 3,3-pentadeutero-1-propene; the very poor isotopic purity of *XIV* made it useless for further synthesis. On the other hand, reduction of *XIII* with lithium and liquid ammonia in tetrahydrofuran (method[22]) gave a very good yield of hexadeuterocumene (*XIV*) (content of the $^2H_6$ component over 90%). Treatment of *XIV* with chlorosulfonic acid in chloroform and the following reduction of the crude sulfonyl chloride by the Wagner method (analogy in the nonlabeled series[19]) gave 4-(1,1,1, 3,3,3-hexadeutero-2-propyl)thiophenol (*XV*) of good quality (over 90% of the $^2H_6$ component). Reaction of *XV* with (4-fluoro-2-iodophenyl)acetic acid[23] in the boiling aqueous potassium hydroxide (analogy[20]) in the presence of copper afforded the acid *XVI* (over 91% of the $^2H_6$ component). The next step was the cyclization of this acid with polyphosphoric acid at 130°C (analogy[20]) to the ketone *XVII*. This product

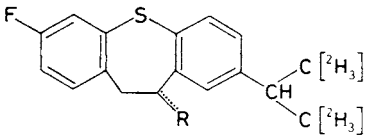
contains only about 58% of the $^2H_6$ component and surprisingly a rather great quantity (about 18%) of the unlabeled ($^2H_0$) component, the formation of which is obscure. Reduction of *XVII* with sodium borohydride in ethanol (analogy[20]) gave the alcohol *XVIII* which was transformed by treatment with hydrogen chloride in benzene to the chloro compound *XIX* (analogy[20]). The final substitution reaction with 2-(1-piperazinyl)ethanol in boiling chloroform (analogy[1]) gave the hexadeutero analogue of isofloxythepin (*XX*) which was transformed to the methanesulfonate. The distribution of deuterium in *XVIII*, *XIX*, and *XX* is similar like in compound *XVII*, *i.e.* about 60% of the $^2H_6$ component and the surprisingly high content of the $^2H_0$ component. Nevertheless, the final product *XX* is considered still useful for the purpose mentioned.



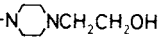
XIII



XIV, R = H
XV, R = SH
XVI, R = 

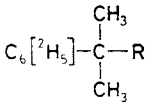


XVII, R = =O
XVIII, R = OH

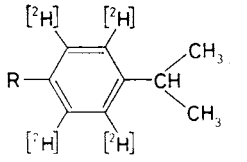
XIX, R = Cl
XX, R = 

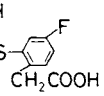
The synthesis of the trideutero analogue of *I* (*XXVIII*) started from pentadeuterobromobenzene which was transformed to the Grignard reagent and this was treated with acetone in ether. The obtained 2-(pentadeuterophenyl)-2-propanol (*XXI*) was of good quality (about 92% of the $^2H_5$ component). The reduction was carried out again with lithium and ammonia in tetrahydrofuran (method[22]) and afforded Ar-pentadeuterocumene (*XXII*) (about 50% of the $^2H_5$ component). The synthesis of compound *XXVIII* continued than similarly like in the preceding case, *i.e. via* *XXIII*–*XXVII*. The synthesis of thiophenol *XXIII* was accompanied by a considerable loss of deuterium (the ratio of the $^2H_4 : {}^2H_3 : {}^2H_2 : {}^2H_1 : {}^2H_0$ approximately 100 : 55 : 20 : 5 : 3). The acid *XXIV* was about of the same quality (57% of the $^2H_4$ component). The cyclization of the acid *XXIV* to the ketone *XXV* was connected

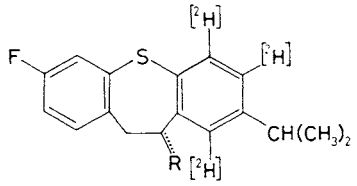
with further loss of deuterium (about 21% of the $^2H_3$ component and predominance of the $^2H_2$ (37%) and $^2H_1$ (30%) components). The same distribution of deuterium remains in the alcohol *XXVI* and in the final product *XXVIII* which, also, was transformed to the methanesulfonate (about 19% $^2H_3$ component, 35% $^2H_2$, 31% $^2H_1$ and 14% $^2H_0$). The product has been considered useful for the metabolic study.



XXI, R = OH
XXII, R = H



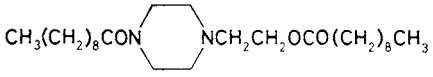
XXIII, R = SH
XXIV, R = 



XXV, R = =O
XXVI, R = OH
XXVII, R = Cl
XXVIII, R =

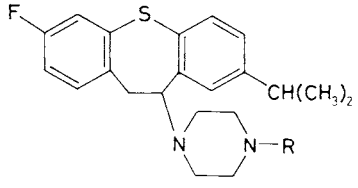
The base *I* (ref.[1]) was transformed to succinate and dihydrochloride. Three esters of *I* were prepared: *II*–*IV*. The acetate *II* was obtained by treatment of *I* with acetic anhydride in chloroform at room temperature. The oily base was transformed to the bis(hydrogen maleate) and the ^1H NMR spectrum of the purified base was recorded. The decanoate *III* was prepared by esterification of *I* with decanoic acid in boiling xylene with distillation of the azeotropic mixture of xylene and water. The crude oily base gave the bis(hydrogen maleate) which was purified by crystallization. The free base was released from the pure maleate, the ^1H NMR spectrum was recorded and the base was dissolved in the neutral oil "Miglyol 812" for pharmacological testing. An attempt to prepare the decanoate *III* by treatment of *I* with an excess of decanoyl chloride[24] in chloroform at room temperature led to complete cleavage of the molecule like observed in experiments dealing with the synthesis of 3-(4-(2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yl)piperazine-1-yl)propyl decanoate (oxyprothepin decanoate) (ref.[25]). The basic product was isolated, characterized as the hydrogen oxalate and identified as 2-(4-decanoylpiperazine-1-yl)ethyl

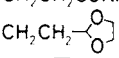
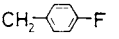
decanoate (*XXIX*), prepared previously[25] by acylation of 2-(1-piperazinyl)ethanol with decanoyl chloride[24]. Esterification of *I* with a slight excess of 3,4,5-trimethoxybenzoyl chloride[26] in chloroform at room temperature led in a moderate yield to the ester *IV* which was characterized as the oxalate. Cleavage of the type like just described, was not observed.

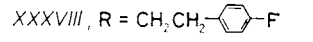
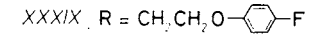
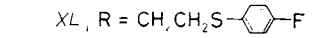
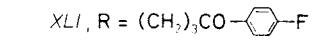
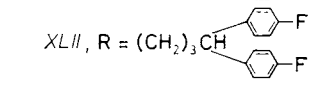


XXIX

The synthesis of isofloxythepin analogues was needed for completing the picture of the structure–activity relations. In general, they can be designated as 7-fluoro-2--substituted-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins. Variously 2-substituted compounds were described in a series of previous articles[20,27–32]; in this line the knowledge of structure–activity relationships seems to be sufficient. The gap of knowledge was in the line of the influence of various piperazine-N-substituents. Until now, only the N-methyl analogue of *I* (ref.[20]) and the secondary amine *XXX* (ref.[1]) have been investigated. Now, a series of twelve analogues of this type (*XXXI* to *XLII*) is being described. The compounds were prepared partly by N-acylation of compound *XXX* (ref.[1]) and by the following reduction of the amides with lithium aluminium hydride. The other possibility is the substitution reaction of 11-chloro-7--fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[20] with N-monosubstituted piperazines. The reactions were carried out mostly in boiling chloroform with an excess of the piperazine component; the processing of the reaction mixtures varied



XXX, R = H
XXXI, R = $COCH_3$
XXXII, R = CH_2CH_3
XXXIII, R = $CH(CH_3)_2$
XXXIV, R = $(CH_2)_3OH$
XXXV, R = $CH_2CH_2CONH_2$
XXXVI, R = 
XXXVII, R = 

XXXVIII, R = 
XXXIX, R = 
XL, R = 
XLI, R = 
XLII, R = 

according to the degree of hydrophilic or lipophilic character of the starting piperazines. In one case (*XXXVI*), alkylation of compound *XXX* was used. All the products were characterized by spectra and with the exception of compounds *XXXI* and *XXXV*, they were transformed to maleates which were used for characterization as well as for pharmacological testing.

Compound *XXX* was acetylated with acetyl chloride in chloroform and the amide *XXXI* was reduced with lithium aluminium hydride in tetrahydrofuran to give the N-ethyl compound *XXXII*. The syntheses of the N-isopropyl analogue *XXXIII*, N-(3-hydroxypropyl) analogue *XXXIV*, the N-(2-aminocarbonylethyl) analogue *XXXV*, and the 4-fluoroaralkyl analogues *XXXVII* and *XXXVIII* used the mentioned substitution reaction; the following N-monosubstituted piperazines were used as reaction components: 1-isopropylpiperazine[33], 3-(1-piperazinyl)propanol[34], 3-(1-piperazinyl)propionamide[35-37], 1-(4-fluorobenzyl)piperazine[38] and 1-(2-(4-fluorophenyl)ethyl)piperazine[38]. Compound *XXXVI* was obtained by alkylation of *XXX* (ref.[1]) with 2-(2-chloroethyl)-1,3-dioxolane[39] in boiling dimethylformamide in the presence of potassium carbonate. Compounds *XXXIX* and *XL* were prepared *via* amides which were used for reduction as oily crude products and were not characterized. The acylating agents were 4-fluorophenoxyacetyl chloride[40] and (4-fluorophenylthio)acetyl chloride which was obtained from (4-fluorophenylthio)-acetic acid[41,42] by treatment with thionyl chloride. Syntheses of *XLI* and *XLII* consisted in reactions of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]-thiepin[20] with 1-(3-(4-fluorobenzoyl)propyl)piperazine[43], and 1-(4,4-bis(4-fluorophenyl)butyl)piperazine[38], respectively.

Most of the isofloxythepin analogues prepared were pharmacologically tested for discoordinating and cataleptic activity in the form of maleates, described in Experimental; they were administered orally and the doses given were calculated for bases. In addition to the intensity of effects, their duration was also followed. The discoordinating effect was evaluated by the rotarod test in mice; medium effective doses eliciting ataxia in 50% animals (ED_{50}) are assembled in Table I for the course of 2 h after the administration, and then for the intervals of 3, 4, 24, 48, 72 and 96 h so long as the activity persisted. The cataleptic effect was evaluated in rats; the medium effective doses ED_{50} brought 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 second value in Table I related to the effect in 24 h after the administration: The dose and its effect, expressed as % of the cataleptic animals, are given.

Table I includes isofloxythepin (*I*) (ref.[44]). Some of the analogues are well comparable with this standard in the line of discoordinating activity and its duration, especially the acetate *II* (VÚFB-12 475), the hydroxypropyl homologue *XXXIV* (VÚFB-12 473) and the dioxolane *XXXVI* (VÚFB-12 474), which are also highly cataleptic and even this effect is detectable in 24 h after the administration. On the

other hand, the ethyl (*XXXII*), the isopropyl analogue (*XXXIII*) and the trimethoxybenzoate *IV*, which are also long-acting in the rotarod test, are inactive in the test of catalepsy after 24 h. The hydrophilicity of the side chain seems to play a role; the acetate *II* may be considered a prodrug of isofloxythepin (*I*). The bulkier 4-fluorophenyl containing side chains diminish considerably the activity. Ataxia appears in doses 20–40 times higher than those of *I*; the effect, however, is protracted. In most of the compounds, a latentiation of the effect is apparent: in 24 h after the administration it is higher than in the first 2 h. In the test of catalepsy, only the 4-fluorobenzyl (*XXXVII*) and 4-fluorophenylethyl (*XXXVIII*) compounds have some activity with protraction until the 24 h interval. The other compounds of this type are in this test almost inactive. Compound *XLII* with a fragment of the penfluridol[45] molecule is inactive in both tests. Combining fragments of two different structural types of long-acting neuroleptic agents in one molecule does not seem a good approach for designing new structures.

TABLE I

Discoordinating and cataleptic activity of isofloxythepin analogues and their duration (oral administration)

Compound	Rotarod ED_{50} mg/kg in the time interval							Catalepsy[a] ED_{50} mg/kg		
	2 h	3 h	4 h	24 h	48 h	72 h	96 h	5 h	24 h	%
I	1·0	0·8	0·88	4·1	>10[b]	>10	—	2·1	4·0	50
II	1·3	0·78	0·5	2·3	4·1	5[c]	—	3·7	25	30
IV	2·1	2·7	1·1	2·0	5·9	10[b]	10[d]	8·4	inactive	
XXXII	2·0	—	—	2·4	4·2	7·0	—	1·6	inactive	
XXXIII	1·5	0·84	0·94	1·95	—	—	—	3·7	inactive	
XXXIV	1·4	0·7	1·1	1·1	3·8	5·0[e]	—	2·1	10	40
XXXVI	1·3	0·96	0·98	2·2	3·0	4·2	5·0	5·6	25	40
XXXVII	44	24·5	26	37	50	50	100	70	50	40
XXXVIII	38	21	21·5	29·5	46	38	—	52	100	50[f]
XXXIX	26	16·5	14·5	22	—	—	—	>100	—	30[g]
XL	20	10·2	11·5	31	47	60	—	>100	—	40[g]
XLI	30	14·5	9·8	19	30	29·5	—	>100	—	30[g]
XLII	>100	—	—	—	—	—	—	>100	—	—

[a] In the last column (the effect in 24 h interval after the administration) the dose is given and its response, *i.e.* % of cataleptic animals after this dose. [b] After this dose ataxia in 40% animals. [c] After this dose ataxia in 6 out of 9 animals. [d] Ataxia in 30% animals. [e] After this dose, ataxia in 60% of the animals. [f] The same dose (100 mg/kg) was still cataleptic for 40% animals after 48 h. [g] Per cent of cataleptic animals in the first 5 h after the administration of the dose of 100 mg/kg.

Isofloxythepin decanoate (VÚFB-13 707) (*III*) was tested as a potential depot neuroleptic agent in rats and dogs. It was administered intramuscularly in the form of a solution of the base *III* in Miglyol 812 containing 25 mg of the substance in 1 ml solution. In rats, the doses of 25 mg/kg significantly inhibited the apomorphine-induced stereotypies (chewing) as well as the agitation until the 7th day after the administration. On the 9th day, only the agitation was significantly inhibited and on the 13th day the effect disappeared completely. These results are well comparable with those obtained with oxyprothepin decanoate[46]. In dogs, the effect of the dose of 5 mg/kg on the apomorphine-induced emesis was followed with a group of 6 animals. Although the complete blockade of emesis was not attained even in the first week after the application, in a part of the animals the blockade of emesis lasted longer than 4 weeks, and with one animal the blockade lasted still on the sixth week after the administration. Isofloxythepin decanoate (*III*) has thus evidently properties of a depot neuroleptic agent.

Antimicrobial screening ***in vitro*** (number of compounds and the minimum inhibiting concentrations in μg/ml, unless they exceed 100 μg/ml, are given): *Streptococcus β-haemolyticus, XXXII* 3·12, *XXXIII* 6·25, *XXXIV* 12·5, *XXXVI* 25; *Streptococcus faecalis, XXXII* 12·5, *XXXIII* 12·5, *XXXIV* 12·5, *XXXVI* 100; *Staphylococcus pyogenes aureus, II* 12·5, *XXXII* 3·12, *XXXIII* 6·25, *XXXIV* 12·5, *XXXVI* 25; *Escherichia coli, IV* 100, *XXXII* 12·5, *XXXIII* 50, *XXXIV* 12·5, *XXXVI* 100, *XLII* 100; *Mycobacterium tuberculosis* H37Rv, *II* 12·5, *XXXII* 12·5, *XXXIII* 6·25, *XXXIV* 12·5, *XXXVI* 25, *XXXVIII* 50, *XXXIX* 50, *XL* 50, *XLI* 25; *Saccharomyces pasterianus, II* 50, *XXXII* 25, *XXXIII* 25, *XXXIV* 25, *XXXVI* 50; *Trichophyton mentagrophytes, II* 25, *XXXII* 25, *XXXIII* 50, *XXXIV* 25, *XXXVI* 50, *XXXVII* 50, *XXXVIII* 50, *XXXIX* 50, *XL* 50, *XLI* 50; *Candida albicans, XXXIII* 50.

EXPERIMENTAL

The melting points were determined partly in Kofler block (these are not corrected), partly in the 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 recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with Unicam SP 200G and Perkin–Elmer 298 spectrophotometers, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) mostly with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F NMR spectra (in $CHCl_3$, $\delta(CFCl_3) = 0$) with the same instrument, and the mass spectra with MCH 1 320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol), and in the case of liquids by gas chromatography. The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

2-Chloro-5-fluoronitrobenzene (*VI*)

4-Fluoro-2-nitroaniline[1,2] (100 g) was dissolved in a stirred mixture of 160 ml water, 80 ml hydrochloric acid and 170 ml 3M-HCl by heating to 70°C. The solution was cooled under vigorous stirring and diazotized at 0—5°C with a solution of 45 g $NaNO_2$ in 100 ml water. The mixture was stirred at this temperature for 2 h, filtered, and the cooled filtrate was added under stirring

to a solution of 77 g CuCl in 300 ml 3M-HCl at 65°C. It was cooled under stirring, the precipitated solid was filtered, suspended in 100 ml 1·5M-HCl, and the suspension was distilled with steam. The distillate (1·2 l) was cooled, the crystalline product was filtered, washed with water, and dried over P_2O_5; 83·5 g (75%), m.p. 37—37·5°C. Ref.[1,8], m.p. 38·5—39·5°C, and 37·2°C, respectively.

4-Dimethylamino-2-nitrobenzonitrile (*VIII*)

A mixture of 10·0 g *VI*, 5·0 g CuCN and 20 ml hexamethylphosphoric triamide was stirred and heated to 150°C for 16 h. After cooling, the mixture was treated with 80 ml NH_4OH and 80 ml water, and extracted at 50°C with 250 ml benzene. The insoluble part was filtered off, the benzene layer was dried with $CaCl_2$ and evaporated; the separated solid was filtered and crystallized from 30 ml benzene by standing for 24 h; 1·0 g (9%) red needles, identified as *VIII*, m.p. 185 to 186°C (benzene). Mass spectrum, *m/z* (%): 191 (M^+ corresponding to $C_9H_9N_3O_2$, 72%), 145 (32), 130 (22), 118 (17), 103 (18), 91 (12), 76 (22), 42 (100). UV spectrum: λ_{max} 260·6 nm (log ε 4·33), 302·8 nm (4·20), 400 nm (3·43). IR spectrum: 824, 881 (2 adjacent and solitary Ar—H), 1 350, 1 549 ($ArNO_2$), 1 512, 3 100 (Ar), 1 623 (NO_2), 2 215 (Ar—CN), 2 790, 2 825 cm^{-1} ($N—CH_3$). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·68 (d, J = 9·0 Hz, 1 H, 6-H), 7·39 (d, J = 3·0 Hz, 1 H, 3-H), 7·00 (dd, J = 9·0; 3·0 Hz, 1 H, 5-H), 3·09 (s, 6 H, $N(CH_3)_2$). Ref.[10], m.p. 182—185°C.

5-Fluoro-2-iodonitrobenzene (*VII*)

4-Fluoro-2-nitroaniline[1,2] (200 g) was added to a stirred mixture of 1·0 l water and 430 g H_2SO_4 at 60°C, the suspension was cooled to 0—5°C, and diazotized with a solution of 96 g $NaNO_2$ in 200 ml water over 1 h. The diazonium solution was stirred for 3 h at 0—5°C, filtered, and the cooled filtrate was slowly added to a stirred solution of 310 g KI in 570 ml dilute H_2SO_4 (130 g H_2SO_4 and 500 ml water) over 20 min. The temperature rose spontaneously from 20 to 40°C. The mixture was then heated to 80—85°C under reflux, maintained at this temperature with stirring for 1·5 h, cooled to 40°C, and extracted with toluene (1·4 l). The extract was washed with a solution of 215 g $Na_2S_2O_3.5\ H_2O$ in 800 ml water, divided to two parts, and then with a solution of 35 g NaOH in 700 ml water (also divided to two parts). It was then dried with $CaCl_2$ and evaporated under reduced pressure; 270 g (79%) crude oily *VII* which could be used for transformation to *V*. Purification of a sample was carried out by distillation with steam or by simple distillation *in vacuo*, b.p. 126—128°C/1·3 kPa. UV spectrum: λ_{max} 222 nm (log ε 3·46), 315 nm (2·60), infl. 262 nm (2·73). IR spectrum (film): 782, 810, 870 (2 adjacent and solitary Ar—H), 1 213, 1 264 (Ar—F), 1 351, 1 530 ($ArNO_2$), 1 511, 1 579, 1 590, 3 085 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·00 (dd, J_{H-H} = 8·5 Hz; J_{H-F} = 5·0 Hz, 1 H, 3-H), 7·65 (dd, J_{H-H} = = 3·0 Hz; J_{H-F} = 8·0 Hz, 1 H, 6-H), 7·10 (m, J_{H-H} = 8·5; 3·0 Hz; J_{H-F} = 8·0 Hz, 1 H, 4-H). Refs[11,12], b.p. 162—163°C/4·7 kPa, m.p. 22·5°C.

The alkaline washings were acidified under cooling with hydrochloric acid, the separated solid was filtered after standing overnight, washed with water, and dried *in vacuo*; 53 g (15%) 4-iodo-3-nitrophenol (*XI*), m.p. 148—154°C. Analytical sample, m.p. 158—159°C (water). Mass spectrum, *m/z* (%): 265 (M^+ corresponding to $C_6H_4INO_3$, 100%), 219 (32), 191 (18), 127 (5), 108 (20), 92 (62), 64 (56). UV spectrum: λ_{max} 340 nm (log ε 3·22), 228 nm (4·25). IR spectrum: 820, 895 (2 adjacent and solitary Ar—H), 1 215, 1 295 (ArOH), 1 350, 1 520 ($ArNO_2$), 1 605, 3 085 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 11·25 (bs, 1 H, OH), 7·85 (d, J = 8·5 Hz, 1 H, 5-H), 7·33 (d, J = 3·0 Hz, 1 H, 2-H), 6·88 (dd, J = 8·5; 3·0 Hz, 1 H, 6-H). Ref.[13], m.p. 156°C.

4-Fluoro-2-nitrobenzonitrile (*V*)

A) A stirred solution of 10·0 g *VII* in 15 ml hexamethylphosphoric triamide was treated with 4·5 g CuCN, heated for 3 h to 90—100°C, cooled, treated under stirring with a solution of 10·0 g $FeCl_3.6\,H_2O$ in 20 ml 3M-HCl and 80 ml water, heated with 150 ml benzene to 50°C, shaken and filtered. The benzene layer of the filtrate was washed twice with 60 ml 10% Na_2SO_3, filtered, dried with $CaCl_2$, and evaporated; 6·2 g (almost 100%) crude *V*, m.p. 60—67°C. The crude product was dissolved in 10 ml benzene and the solution was filtered through a column of 80 g silica gel which was washed with benzene. Evaporation of the filtrate gave the pure nitrile *V*, m.p. 71—73°C (benzene–light petroleum). Refs[1,3], m.p. 69—71°C, and 73—74°C, respectively.

B) Stirred suspension of 197 g CuCN in 1·5 l dimethylformamide was treated with 492 g *VII*. The temperature rose spontaneously from 20°C over 20 min to 65°C and remained at this temperature for further 20 min. When it dropped to 50°C, the mixture was heated to 90—95°C and maintained for 2 h at this temperature; it was then allowed to stand overnight at room temperature. The solid was filtered off, was washed with dimethylformamide, and the filtrate was poured under stirring to 7·2 l 1 : 1 dilute NH_4OH. The mixture was stirred for 1 h, the product was filtered, washed with water, dissolved at 60°C in 2 l toluene (stirring for 30 min), the solution was cooled to 40°C, filtered, and the toluene layer of the filtrate (a small quantity of the aqueous layer was separated) was evaporated *in vacuo*; 285 g (93%) crude *V*, m.p. 67—72°C. Crystalization from a mixture of benzene and light petroleum gave the pure product melting at 71—73°C, identical with that, obtained under *A*.

The aqueous mother liquor and the washings were allowed to stand at 15—20°C for 48 h. The separated red compound was filtered, washed with water, and dried *in vacuo* at 70—90°C; 32·0 g (8%) *VIII*, m.p. 183—185°C. Crystallization from benzene gave the pure compound, m.p. 185—186°C, identical with that described above.

4-Dimethylamino-2-nitrobenzamide (*IX*)

A mixture of 28 ml water, 35 ml H_2SO_4 and 5·0 g *VIII* was stirred and heated to 95—100°C for 6 h. After cooling, the mixture was diluted with 30 ml water and treated with NH_4OH (about 200 ml) until pH 10. The clear solution deposited by standing 4·80 g (91%) of the yellow *IX*, m.p. 207—220°C. Analytical sample, m.p. 236—237°C (benzene–ethanol). UV spectrum: λ_{max} 257 nm (log ε 4·20), 284 nm (4·08). IR spectrum: 800, 830, 882 (2 adjacent and solitary Ar—H), 1 368, 1 392, 1 524 ($ArNO_2$), 1 499, 1 610 (Ar), 1 656 ($ArCONH_2$), 3 170, 3 445 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·83 and 7·28 (2 bs, 1 + 1 H, $CONH_2$), 7·54 (d, J = = 8·5 Hz, 1 H, 6-H), 6·97 (d, J = 2·5 Hz, 1 H, 3-H), 6·81 (dd, J = 8·5; 2·5 Hz, 1 H, 5-H), 3·00. (s, 6 H, $N(CH_3)_2$). For $C_9H_{11}N_3O_3$ (209·2) calculated: 51·67% C, 5·30% H, 20·09% N; found: 51·35% C, 5·20% H, 20·09% N.

N,N-Dimethyl-3-nitroaniline (*X*)

A mixture of 10 ml water, 10 ml H_2SO_4 and 5·0 g *V* was refluxed in a bath of 160—170°C for 6 h. After cooling it was diluted with 20 ml water and under stirring made alkaline with NH_4OH (pH 10). The precipitated dark solid (4·5 g) was dissolved in 25 ml benzene, the solution was filtered, and the filtrate was evaporated; 3·9 g (90%), m.p. 50—55°C, which was shown to be crude *X*. Crystallization from 95% ethanol gave pure *X*, m.p. 58—59°C. UV spectrum: λ_{max} 250·5 nm (log ε 4·27), 400 nm (3·11). IR spectrum: 775, 786, 878 (3 adjacent and solitary Ar—H), 1 340, 1 538 ($ArNO_2$), 1 570, 1 619, 3 090 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80—7·50 (m, 4 H, ArH), 3·00 (s, 6 H, $N(CH_3)_2$). Ref.[15], m.p. 60—61°C.

3-Amino-4-fluoroacetophenone (*XII*)

A) 4-Fluoro-3-nitroacetophenone[18] (35 g) was reduced by a described procedure[18] with 135 g $SnCl_2.2\,H_2O$ in 200 ml hydrochloric acid. The very exothermic reaction followed by treatment with 30% NaOH (to pH 13) and extraction with toluene gave 24·6 g (84%) crude *XII*, m.p. 50—57°C. A single crystallization from a mixture 1 : 1 of benzene and light petroleum gave the homogeneous product melting at 58—59°C. This melting point did not change upon repeated crystallization. Because ref.[18] gave the m.p. 70—72°C, it was considered necessary to characterize our product. UV spectrum: λ_{max} 231·5 nm (log ε 4·37), 326 nm (3·32), infl. 258 nm (3·80). IR spectrum: 770, 805, 880 (2 adjacent and solitary Ar—H), 1 200 (Ar—F), 1 512, 1 592, 1 610, 3 070 (Ar), 1 630, 1 668 (ArC=O...HN), 3 210, 3 320, 3 395 cm^{-1} (NH_2). ^1H NMR spectrum: δ 6·80—7·50 (m, 3 H, ArH), 3·95 (bs, 2 H, NH_2), 2·48 (s, 3 H, $COCH_3$). For C_8H_8FNO (153·2) calculated: 62·74% C, 5·26% H, 12·41% F, 9·15% N; found: 62·89% C, 5·19% H, 12·24% F, 9·05% N. The substance appears to be a crystal modification of *XII*.

B) 4-Fluoro-3-nitroacetophenone[18] (10·0 g) was hydrogenated in 200 ml methanol in a hydrogenation reactor with vibrating stirrer under normal conditions in the presence of 10 g wet Raney Ni. The theoretical consumption of hydrogen (3·6 l) was attained in 90 min and the temperature rose spontaneously from 20° to 37°C. After the mentioned consumption was reached, the reaction stopped. The catalyst was filtered off and the filtrate was evaporated; 8·2 g (98%). Crystallization from 15 ml benzene and the final addition of 10 ml light petroleum gave 6·7 g substance melting at 69—71°C. This product was dissolved in 15 ml benzene and the solution was filtered through a column of 40 g neutral Al_2O_3 (activity II). This procedure removed the coloured impurities. Washing with benzene and evaporation gave 5·9 g product, m.p. 72°C (benzene–light petroleum). The UV and ^1H NMR spectra in solutions are completely identical with those of the lower melting modification. Even the IR spectrum in Nujol does not show important differences. We are dealing here evidently with the Oelschläger's crystal form[18]. Inoculation of a clear solution of the lower melting form in a mixture 1 : 1 of benzene and light petroleum with the higher melting form afforded the form melting at 71—72°C which is, evidently, the stable form. This transformation is considered a proof of existence of the new lower melting crystal modification of *XII*.

1,1,1,3,3,3-Hexadeutero-2-phenylpropan-2-ol (*XIII*)

Grignard reagent prepared from 2·5 g Mg and 32 g bromobenzene in 150 ml ether was slowly treated under stirring with 8·7 g hexadeuteroacetone, the mixture was refluxed for 1 h, allowed to stand overnight at room temperature, decomposed with 100 ml 20% NH_4Cl, and the ether layer was processed to give 17·9 g (93%) product boiling at 90—92°C/1·3 kPa or at 98—103°C/2·4 kPa. Mass spectrum, *m/z* (%): 142 (M^+ corresponding to $C_9H_6{}^2H_6O$, 1·8%), 141 (0·13), 125 (5·6), 124 (40), 123 (2·3), 122 (0·63), 121 (0·29), 46 (100). Ref.[47] gave for the unlabeled analogue the b.p. 94°C/1·7 kPa.

2-(Pentadeuterophenyl)propan-2-ol (*XXI*)

Grignard reagent was prepared from 3·0 g Mg and 20 g pentadeuterobromobenzene in 150 ml ether. It was treated under stirring with a solution of 8·9 g acetone in 20 ml ether, added dropwise over 20 min. Similar processing like in the preceding case gave 15·1 g (87%) *XXI*, b.p. 104 to 106°C/3 kPa. Mass spectrum, *m/z* (%): 141 (M^+ corresponding to $C_9H_7{}^2H_5O$, 5·4%), 140 (0·28), 126 (43), 125 (2·4), 43 (100). Ref.[47] gave for the unlabeled analogue the b.p. 94°C/1·7 kPa.

(1,1,1,3,3,3-Hexadeutero-2-propyl)benzene (*XIV*)

Li (3·3 g) was added to a mixture of 200 ml liquid NH_3 and 60 ml tetrahydrofuran, the mixture was stirred for 30 min, treated with 18·2 g *XIII* in 60 ml tetrahydrofuran, stirred for 20 min, and over 20 min treated with 25 g NH_4Cl. NH_3 was allowed to evaporate, the mixture was diluted with water and extracted with ether. Processing of the extract gave 14·1 g (87%) product boiling at 150—160°C. Mass spectrum, *m/z* (%): 126 (M^+ corresponding to $C_9H_6{}^2H_6$, 24%), 125 (1·9), 124 (0·15), 108 (100), 107 (5·3), 106 (4·8), 105 (4·3), 104 (1·3). Ref.[48] gave for the unlabeled cumene the b.p. 152—153°C.

(2-Propyl)pentadeuterobenzene (*XXII*)

XXI (15·1 g) was similarly reduced with 3·5 g Li in a mixture of 200 ml NH_3 and 60 ml tetrahydrofuran; 11·7 g (87%), b.p. 150—160°C. Mass spectrum, *m/z* (%): 125 (M^+ corresponding to $C_9H_7{}^2H_5$, 21%), 124 (2), 110 (100), 109 (9·6), 108 (4), 107 (5·2), 106 (1·6). Ref.[48] gave for the unlabeled analogue the b.p. 152—153°C.

4-(1,1,1,3,3,3-Hexadeutero-2-propyl)thiophenol (*XV*)

A solution of 14·0 g *XIV* in 60 ml chloroform was added over 30 min under stirring to 5 g chlorosulfonic acid, the mixture was stirred at 10—15°C for 75 min, poured on ice, extracted with chloroform and the extract was processed; 22·8 g (91%) crude 4-(1,1,1,3,3,3-hexadeutero--2-propyl)benzenesulfonyl chloride (analogy in the unlabeled series[49]). It was dissolved in 25 ml acetic acid and the solution was added dropwise over 15 min to a stirred mixture of 50 ml acetic acid, 9·0 g P and 0·7 g I, heated to 100°C. The mixture was then refluxed for 3 h, cooled, diluted with 10 ml water, refluxed for 1 h, cooled, filtered, the filtrate was diluted with 400 ml water, and extracted with chloroform; 11·35 g (71%), b.p. 105—115°C/2 kPa (similar preparation of the unlabeled compound[19]). Mass spectrum, *m/z* (%): 160 (2·3), 159 (6·2), 158 (M^+ corresponding to $C_9H_6{}^2H_6S$, 42%), 157 (6·1), 156 (1·1), 155 (0·67), 142 (5·1), 141 (13), 140 (100), 139 (9·8), 138 (11), 137 (9·3), 136 (2·3), 135 (0·52). Ref.[19] gave for the unlabeled analogue the b.p. 100—103°C/ /1·6 kPa.

2,3,5,6-Tetradeutero-4-(2-propyl)thiophenol (*XXIII*)

Similarly like in the preceding case (analogies in the unlabeled series[19,49]), *XXII* (11·7 g) in 60 ml chloroform was treated with 52 g $ClSO_3H$ and the crude sulfonyl chloride (16·8 g) was reduced with 9·0 g P and 0·7 g I in 70 ml boiling acetic acid. There were obtained 8·9 g (61%) *XXIII* b.p. 110—120°C/2·4 kPa. Mass spectrum, *m/z* (%): 159 (0·52), 158 (3·5), 157 (9·0), 156 (M^+ corresponding to $C_9H_8{}^2H_4S$, 51%), 155 (27), 154 (9·6), 153 (2·9), 152 (1·3), 141 (100). Ref.[19] gave for the unlabeled analogue the b.p. 100—103°C/1·6 kPa.

(2-(4-(1,1,1,3,3,3-Hexadeutero-2-propyl)phenythio)-4-fluorophenyl)acetic Acid (*XVI*)

In analogy to the unlabeled series[20], a solution of 9·7 g KOH in 25 ml water was treated with 11·7 g *XV*, 19·6 g (4-fluoro-2-iodophenyl)acetic acid[23] and 0·7 g Cu, the mixture was refluxed with stirring under nitrogen for 5·5 h. It was diluted with 75 ml water, filtered, the filtrate was acidified with hydrochloric acid, and the product extracted with chloroform; 15·8 g (69%) *XVI*, m.p. 109—114°C (cyclohexane–hexane). Mass spectrum, *m/z* (%): 312, (5·4), 311 (17), 310 (M^+ corresponding to $C_{17}H_{11}{}^2H_6FO_2S$, 70%), 309 (5·2), 308 (1·1), 307 (0·49), 306 (0·16), 305 (0·04), 45 (100). Ref.[20] gave for the pure unlabeled analogue the m.p. 115—117°C.

(2-(2,3,5,6-Tetradeutero-4-(2-propyl)phenylthio)-4-fluorophenyl)acetic Acid (*XXIV*)

In analogy to the preceding case and to the nonlabeled series[20], *XXIII* (8·9 g) was reacted with 15·1 g (4-fluoro-2-iodophenyl)acetic acid[23] in a solution of 7·5 g KOH in 20 ml water and in the presence of 0·6 g Cu, and gave 11·7 g (70%) *XXIV*, m.p. 108—114°C (cyclohexane–hexane). Mass spectrum, *m/z* (%): 310 (2·1), 309 (4·8), 308 (M^+ corresponding to $C_{17}H_{13}{}^2H_4FO_2S$, 21%), 307 (9·9), 306 (3·7), 305 (1·2), 304 (0·44), 40 (100). Ref.[20] gave for the pure unlabeled analogue the m.p. 115—117°C.

8-(1,1,1,3,3,3-Hexadeutero-2-propyl)-3-fluoro
dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVII*)

In analogy to the unlabeled series[20], *XVI* (15·7 g) was stirred and heated to 130°C for 3 h with polyphosphoric acid, prepared from 35 g 85% H_3PO_4 and 35 g P_2O_5. The mixture was poured into ice and water, and the product was extracted with benzene; 12·4 g (84%) *XVII*, m.p. 72 to 73·5°C (ethanol). Mass spectrum, *m/z* (%): 294 (11), 293 (36), 292 (M^+ corresponding to $C_{17}.H_9{}^2H_6FOS$, 100%), 291 (19), 290 (2·9), 289 (2·2), 288 (5·7), 287 (16), 286 (31), 285 (4·0). Ref.[20] gave for the pure unlabeled analogue the m.p. 76—78°C.

6,7,9-Trideutero-3-fluoro-8-(2-propyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXV*)

In analogy to the preceding case and to the nonlabeled series[20], *XXIV* (11·6 g) was treated with polyphosphoric acid (from 30 g P_2O_5 and 30 g 85% H_3PO_4) at 130°C, and gave 9·1 g (84%) *XXV*, m.p. 72—73·5°C (ethanol). Mass spectrum, *m/z* (%): 292 (0·55), 291 (2·6), 290 (8·9), 289 (M^+ corresponding to $C_{17}H_{12}{}^2H_3$ FOS, 22%), 288 (38), 287 (31), 286 (13), 40 (100). Ref.[20] gave for the pure unlabeled analogue the m.p. 76—78°C.

8-(1,1,1,3,3,3-Hexadeutero-2-propyl)-3-fluoro-10,11-
-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XVIII*)

In analogy to the nonlabeled series[20], *XVII* (12·4 g) in 150 ml ethanol was treated with 1·0 g $NaBH_4$ in 5 ml water containing 0·1 ml 20% NaOH, and the mixture was refluxed for 3 h. Ethanol was evaporated, the residue was diluted with 100 ml water and extracted with benzene; 12·4 g (89%) *XVIII*, m.p. 107—108·5°C. Mass spectrum, *m/z* (%): 296 (4·6), 295 (16), 294 (M^+ corresponding to $C_{17}H_{11}{}^2H_6FOS$, 55%), 293 (5·5), 292 (1·4), 291 (1·1), 290 (2·6), 289 (7·7), 288 (16), 287 (0·77), 45 (100). Ref.[20] gave for the pure unlabeled analogue the m.p. 110—112°C.

6,7,9-Trideutero-3-fluoro-8-(2-propyl)-10,11-dihydro-
dibenzo [*b*,*f*]thiepin-10-ol (*XXVI*)

In analogy to the preceding case and to the nonlabeled series[20], *XXV* (8·75 g) was reduced with 0·8 g $NaBH_4$ in a mixture of 100 ml ethanol and 4 ml water, and gave 8·65 g (98%) *XXVI*, m.p. 107—108·5°C. Mass spectrum, *m/z* (%): 294 (1·2), 293 (5·0), 292 (17), 291 (M^+ corresponding to $C_{17}H_{14}{}^2H_3FOS$, 48%), 290 (100), 289 (80), 288 (31), 287 (1·3). Ref.[20] gave for the pure unlabeled analogue the m.p. 110—112°C.

11-Chloro-2-(1,1,1,3,3,3-hexadeutero-2-propyl)-7-fluoro-10,11-
-dihydrodibenzo[*b*,*f*]thiepin (*XIX*)

In analogy to the nonlabeled series[20], *XVIII* (12·4 g) was dissolved in 20 ml benzene and saturated with HCl for 3 h in the presence of 6·0 g $CaCl_2$. After standing overnight it was filtered, the filtrate was evaporated, and the residue was crystallized from 15 ml hexane; 12·2 g (93%) *XIX*,

m.p. 77·5—79°C. Mass spectrum, *m/z* (%): 316 (0·80), 315 (3·3), 314 (12), 313 (9·2), 312 (M^+ corresponding to $C_{17}H_{10}{}^2H_6ClFS$, 31%), 311 (2·7), 310 (0·96), 309 (1·9), 308 (4·3), 307 (4·3), 306 (9·4), 305 (0·21), 49 (100). Ref.[20] gave for the pure unlabeled analogue the m.p. 82—83°C.

2-(4-(2-(1,1,1,3,3,3-Hexadeutero-2-propyl)-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazine-1-yl)ethanol (*XX*)

In analogy to the nonlabeled series[1], *XIX* (12·2 g) was refluxed with 11·1 g 2-(1-piperazinyl)-ethanol in 20 ml chloroform for 6·5 h. After cooling, the mixture was distributed between benzene and water, the organic layer was washed with water and extracted with excessive 10% solution of methanesulfonic acid. The acid aqueous layer was made alkaline with NH_4OH and the base *XX* (12·1 g) was extracted with benzene. The crude base was neutralized with 2·8 g methanesulfonic acid in a mixture of 12 ml ethanol and 12 ml hexane; 11·1 g (57%) methanesulfonate of *XX*, m.p. 189·5—190·5°C. Mass spectrum, *m/z* (%): 408 (0·10), 407 (0·27), 406 (M^+ corresponding to $C_{23}H_{23}{}^2H_6FN_2OS$, 0·87%), 405 (0·22), 402 (0·02), 401 (0·08), 400 (0·22), 399 (0·02), 56 (100). Ref.[1] gave for the pure unlabeled analogue the m.p. 193·5—194·5°C.

2-(4-(1,3,4-Trideutero-7-fluoro-2-(2-propyl)-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazine-1-yl)ethanol (*XXVIII*)

In analogy to the preceding case and to the nonlabeled series[1,20], *XXVI* (8·65 g) was transformed to the crude *XXVII* (m.p. 77—79°C) which was processed by the substitution reaction with 7·0 g 2-(1-piperazinyl)ethanol in 15 ml boiling chloroform to give 8·3 g crude *XXVIII* base. This was transformed to 6·1 g (41%) methanesulfonate melting at 190—191·5°C. Mass spectrum, *m/z* (%): 405 (0·09), 404 (0·40), 403 (M^+ corresponding to $C_{23}H_{26}{}^2H_3FN_2OS$, 1·6%), 402 (2·9), 401 (2·6), 400 (1·2), 399 (0·18), 100 (100). Ref.[1] gave for the pure unlabeled analogue the m.p. 193·5—194·5°C.

2-(3-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazine-1-yl)ethanol (*I*)

Succinate, m.p. 99—102°C (ethanol–ether). For $C_{27}H_{35}FN_2O_5S$ (518·6) calculated: 62·53% C, 6·80% H, 3·66% F, 5·40% N, 6·18% S; found: 62·42% C, 7·00% H, 3·65% F, 5·42% N, 6·42% S.

Dihydrochloride, m.p. 179—182°C (aqueous ethanol). For $C_{23}H_{31}Cl_2FN_2OS$ (473·5) calculated: 58·34% C, 6·60% H, 14·98% Cl, 4·01% F, 5·92% N, 6·77% S; found: 58·67% C, 6·72% H, 14·97% Cl, 4·28% F, 5·82% N, 6·48% S.

2-(4-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine-1-yl)ethyl Acetate (*II*)

A solution of 2·5 g *I* (ref.[1]) in 12·5 ml chloroform was treated with 1·25 g acetic anhydride and the mixture was allowed to stand overnight at room temperature. It was then washed with water, 20% NaOH and water, dried and evaporated *in vacuo*. The residue (2·7 g crude base *II*) was dissolved in 10 ml acetone and the solution was treated with 1·4 g maleic acid; 3·3 g (78%) bis-(hydrogen maleate), m.p. 153—156°C (acetone). For $C_{33}H_{39}FN_2O_{10}S$ (674·7) calculated: 58·74% C, 5·83% H, 2·82% F, 4·15% N, 4·75% S; found: 58·35% C, 6·09% H, 2·79% F, 4·29% N, 4·82% S.

The pure oily base *II* was obtained from the recrystallized maleate by treatment with aqueous solution of $NaHCO_3$ and by extraction with ether. ^1H NMR spectrum: δ 7·49 (d, $J = 2·5$ Hz,

1 H, 1-H), 6·70—7·40 (m, 5 H, remaining ArH), 4·18 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·85 (m, 1 H, ArCH of isopropyl), 2·60 (m, 10 H, 5 CH_2N), 2·02 (s, 3 H, $COCH_3$), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl).

2-(4-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine-1-yl)ethyl Decanoate (*III*)

A mixture of 4·0 g *I* (ref.[1]), 5·5 g decanoic acid and 40 ml xylene was distilled for 7 h and the distillate was substituted with dry xylene. Then it was distilled off, the residue was dissolved in 50 ml benzene and the solution was washed with 5% NaOH. After drying with K_2CO_3, benzene was evaporated; 5·30 g (96%) crude base *III*. This base was dissolved in a boiling solutionof 2·3 g maleic acid in 6 ml acetone; cooling gave the crude bis(hydrogen maleate) which was crystallized from a mixture of 50 ml acetone and 50 ml ether; 3·8 g (48%), m.p. 112—113°C. For $C_{41}H_{55}FN_2O_{10}S$ (786·9) calculated: 62·57% C, 7·05% H, 2·41% F, 3·56% N, 4·08% S; found: 62·06% C, 7·22% H, 2·34% F, 3·58% N, 4·33% S.

The released oily base was used for recording the ^{1}H NMR spectrum: δ 7·49 (d, J = 2·5 Hz, 1 H, 1-H), 6·60—7·40 (m, 5 H, remaining ArH), 4·20 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·50 (m, 10 H, 5 CH_2N), 2·29 (t, J = 7·0 Hz, 2 H, CH_2CO), 1·90 (m, 1 H, ArCH of isopropyl), 1·65 (m) and 1·25 (bs) (2 + 12 H, $(CH_2)_7$ in the decanoyl chain), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl), 0·89 (def. t, 3 H, terminal CH_3 of decanoyl).

2-(4-Decanoylpiperazine-1-yl)ethyl Decanoate (*XXIX*)

A solution of 4·0 g *I* (ref.[1]) in 10 ml chloroform was treated with 3·3 g decanoyl chloride[24] and the mixture was allowed to stand overnight at room temperature. It was stirred for 1 h with a solution of 1·0 g NaOH in 20 ml water, diluted with chloroform, the chloroform layer was separated, dried and evaporated. The residue was dissolved in a boiling solution of 1·2 g oxalic acid dihydrate; *XXIX* hydrogen oxalate; 4·2 g (80%), m.p. 127°C. Analytical sample, m.p. 126—129°C (acetone). For $C_{28}H_{52}N_2O_7$ (528·7) calculated: 63·60% C, 9·91% H, 5·30% N; found: 64·07% C, 10·10% H, 5·63% N.

2-(4-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine-1-yl)ethyl 3,4,5-Trimethoxybenzoate (*IV*)

3,4,5-Trimethoxybenzoyl chloride[26] (5·2 g) was added to a solution of 5·7 g *I* (ref.[1]) in 20 ml chloroform and the solution formed was allowed to stand overnight at room temperature. The mixture was stirred for 1 h with 5 ml 20% NaOH, diluted with chloroform, the chloroform layer was separated and evaporated. The residue was dissolved in benzene and the solution was chromatographed on a column of 60 g neutral Al_2O_3 (activity II). Elution with benzene gave 4·3 g base *IV*. It was dissolved in a boiling solution of 0·9 g oxalic acid dihydrate in 10 ml ethanol; *IV* oxalate (4·3 g, 59%) crystallized, m.p. 188—192°C with decomposition. IR spectrum: 1 000, 1 133, 1 230, 1 339 ($ArOCH_3$), 1 510, 1 596 (Ar), 1 649 (COO^-), 1 720 (ArCOOR), 2 600 cm^{-1} (NH^+). For $C_{35}H_{41}FN_2O_9S$ (684·8) calculated: 61·39% C, 6·04% H, 2·77% F, 4·09% N, 4·68% S; found: 61·13% C, 6·15% H, 2·72% F, 3·93% N, 4·81% S.

1-Acetyl-4-(7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]-thiepin-11-yl)piperazine (*XXXI*)

A solution of 5·0 g *XXX* (ref.[1]) in 20 ml chloroform was treated with 2·2 g acetyl chloride (added under stirring over 5 min). The spontaneously warmed mixture was allowed to stand overnight

at room temperature. The precipitated solid (*XXXI* hydrochloride) was filtered, suspended in water, treated with 10% NaOH, and the base extracted with chloroform; 5·4 g (97%), m.p. 163—164·5°C. Analytical sample, m.p. 164·5—166°C (benzene–light petroleum). IR spectrum: 812, 826, 875, 909 (2 adjacent and solitary Ar—H), 1 490, 1 586, 1 599, 3 020 (Ar), 1 645 cm^{-1} (CON<). ^1H NMR spectrum: δ 6·70—7·50 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·55 and 3·45 (2 m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·80 (m, 1 H, ArCH of isopropyl), 2·58, (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·04 (s, 3 H, $COCH_3$), 1·18 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −116·8 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{23}H_{27}FN_2OS$ (398·5) calculated: 69·31% C, 6·83% H, 4·77% F, 7·03% N, 8·05% S; found: 69·40% C, 7·00% H, 4·78% F, 7·31% N, 8·18% S.

1-Ethyl-4-(7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]-thiepin-11-yl)piperazine (*XXXII*)

A solution of 4·8 g *XXXI* in 25 ml tetrahydrofuran was added dropwise to a stirred suspension of 0·6 g $LiAlH_4$ in 12 ml tetrahydrofuran, and the mixture was stirred and refluxed for 5 h. After standing overnight it was decomposed by the addition of 0·6 ml water, 0·7 ml 20% NaOH and 1·7 ml water, the mixture was stirred for 30 min, the solid was filtered off and washed with tetrahydrofuran. The filtrate was evaporated to give 4·3 g (93%) crude oily *XXXII*. Neutralization with 1·3 g maleic acid in 11 ml ethanol gave 5·1 g maleate, m.p. 201—203°C (ethanol). For $C_{27}H_{33}FN_2O_4S$ (500·6) calculated: 64·77% C, 6·64% H, 3·80% F, 5·60% N, 6·41% S; found: 64·96% C, 6·79% H, 3·58% F, 5·63% N, 6·64% S.

The base was released from the pure salt with NH_4OH and was isolated by extraction with ether; oil. ^1H NMR spectrum: δ 7·49 (d, J = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 5 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·64 (def. t, 5 H, $CH_2N^4CH_2$ of piperazine and ArCH of isopropyl), 2·45 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (q, J = 7·0 Hz, 2 H, CH_2N of N-ethyl), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl), 1·10 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl).

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibeno[*b*,*f*]thiepin-11-yl)-4-isopropylpiperazine (*XXXIII*)

A solution of 4·4 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[20] and 3·7 g 1-isopropylpiperazine[33] in 7·5 ml chloroform was refluxed for 5 h. It was diluted with chloroform, washed with dilute NH_4OH and water, and the base was extracted with 150 ml 5% H_2SO_4. Chloroform layer was separated, the aqueous layer was combined with the oily sulfate, the mixture was made alkaline with NH_4OH, and the base was extracted with chloroform; 4·3 g (75%) crude oily base. Neutralization with 1·3 g maleic acid in 10 ml ethanol gave 4·8 g maleate, m.p. 196—197·5°C (ethanol). For $C_{28}H_{35}FN_2O_4S$ (514·7) calculated: 65·34% C, 6·86% H, 3·69% F, 5·44% N, 6·23% S; found: 65·27% C, 7·17% H, 3·96% F, 5·44% N, 6·48% S.

The pure oily base, released from th salt with NH_4OH and isolated by extraction with ether, was used for recording the ^1H NMR spectrum: δ 7·50 (d, J = 2·5 Hz, 1 H, 1-H), 6·60—7·40 (m, 5 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·90 (m, 1 H, ArCH of 2-isopropyl), c. 2·50 (m, 9 H, 4 CH_2N and CH—N), 1·21 (d, J = 7·0 Hz, 6 H, 2 CH_3 of 2-isopropyl), 1·05 (d, J = 6·0 Hz, 6 H, 2 CH_3 of N-isopropyl).

3-(4-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin--11-yl)piperazine-1-yl)propanol (*XXXIV*)

11-Chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[20] (4·0 g) and 4·0 g 3-(1-piperazinyl)propanol[34] were reacted in 7 ml boiling chloroform similarly like in the preceding case

and the reaction mixture was similarly processed; 4·4 g (76%) crude oily base. Neutralization with 2·2 g maleic acid in 20 ml ethanol and addition of ether gave 5·9 g bis(hydrogen maleate), m.p. 106—108°C (ethanol). For $C_{32}H_{39}FN_2O_9S$ (646·7) calculated: 59·43% C, 6·08% H, 2·94% F, 4·33% N, 4·96% S; found: 59·60% C, 6·18% H, 2·96% F, 4·68% N, 5·16% S.

3-(4-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazine-1-yl)propionamide (*XXXV*)

A solution of 9·2 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[20] and 9·5 g 3-(1-piperazinyl)propionamide[37] in 25 ml chloroform was stirred and refluxed for 15 h. After cooling the mixture was filtered, and the filtrate was evaporated. The residue was diluted with 100 ml warm (40°C) water and the mixture extracted with warm benzene. From the benzene layer the product was extracted twice with 50 ml 10% solution of methanesulfonic acid. The combined acid extracts were made alkaline with 30 ml NH_4OH. The separated base was filtered after standing overnight; 8·0 g (61%) hemihydrate, m.p. 108—111°C (ethanol–light petroleum). IR spectrum: 820, 869 (2 adjacent and solitary Ar—H), 1 483, 1 580, 1 595, 3 075 (Ar), 1 660 ($RCONH_2$), 3 180, 3 300, 3 400 cm^{-1} (NH_2 and H_2O). ^1H NMR spectrum (BS 567A, 100 MHz): δ 8·05 and 5·75 (2 bs, 1 + 1 H, $CONH_2$), 6·90—7·50 (m, 6 H, ArH), 3·00—4·10 (m, 3 H, $ArCH_2CHAr$), 2·82 (m, 1 H, ArCH of isopropyl), 2·20—2·80 (bm, 12 H, 5 CH_2N and CH_2CO), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{24}H_{30}FN_3OS + 0{\cdot}5\ H_2O$ (436·6) calculated: 66·03% C, 7·16% H, 4·35% F, 9·62% N, 7·34% S; found: 66·21% C, 7·22% H, 4·65% F, 9·45% N, 7·52% S.

1-(2-(1,3-Dioxolan-2-yl)ethyl)-4-(7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazine (*XXXVI*)

A mixture of 3·5 g *XXX* (ref.[1]), 2·1 g 2-(2-chloroethyl)-1,3-dioxolane[39], 1·4 g K_2CO_3 and 5 ml dimethylformamide was stirred and refluxed for 5 h. After cooling the mixture was diluted with 30 ml water and extracted with chloroform. The extract was washed with water, dried and evaporated. The residue was chromatographed on 200 g neutral Al_2O_3 (activity II). Benzene eluted 2·6 g (59%) oily base which was neutralized with 1·4 g maleic acid in 10 ml ethanol; 3·5 g bis(hydrogen maleate), m.p. 127—129°C (ethanol). Mass spectrum, m/z: 456 (M^+ corresponding to $C_{26}H_{33}FN_2O_2S$). For $C_{34}H_{41}FN_2O_{10}S$ (688·8) calculated: 59·29% C, 6·00% H, 2·76% F, 4·07% N, 4·65% S; found: 59·83% C, 6·19% H, 2·59% F, 4·17% N, 4·80% S.

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)-4-(4-fluorobenzyl)piperazine (*XXXVII*)

A mixture of 2·5 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[20], 3·2 g 1-(4-fluorobenzyl)piperazine[38] and 7 ml chloroform was stirred and refluxed for 8 h. It was then diluted with chloroform, washed with water, and the organic layer was dried and evaporated. The residue was chromatographed on 150 g neutral Al_2O_3 (activity II). Elution with benzene and then with chloroform gave 3·1 g (82%) homogeneous oily product. Bis(hydrogen maleate), m.p. 171—173°C (acetone). For $C_{36}H_{38}F_2N_2O_8S$ (696·8) calculated: 62·06% C, 5·50% H, 5·45% F, 4·02% N, 4·60% S; found: 62·01% C, 5·78% H, 5·24% F, 4·02% N, 4·82% S.

The base, released from the salt by treatment with NH_4OH and isolated by extraction with ether, was used for recording the ^1H NMR spectrum: δ 6·70—7·50 (m, 10 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·44 (s, 2 H, $ArCH_2N$), 2·80 (m, 1 H, ArCH of isopropyl), 2·60 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·48 (def. t, 4 H, $CH_2N^4CH_2$ od piperazine), 1·20 (d, J = = 7·0 Hz, 6 H, 2 CH_3 of isopropyl).

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)-4-(2-(4-fluorophenyl)ethyl)piperazine (*XXXVIII*)

The preparation was carried out similarly like in the preceding case from 3·0 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[20] and 4·1 g 1-(2-(4-fluorophenyl)ethyl)piperazine[38] in 7 ml boiling chloroform. Similar processing gave 2·2 g (47%) chromatographed oily base which was transformed to the bis(hydrogen maleate), m.p. 171–175° (acetone). Mass spectrum, *m/z* (%): 478·2248 (M^+ corresponding to $C_{29}H_{32}F_2N_2S$, 13%), 369 (55), 271 (100), 229 (15), 178 (13), 123 (27), 72 (31). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80–7·50 (m, 10 H, ArH), 6·10 (s, 4 H, 2 CH=CH of maleic acid), 4·10 (m, 1 H, Ar—CH—NH^+), 1·12 (d, 6 H, 2 CH_3 of isopropyl), 2·40–3·90 (m, remaining 7 CH_2 and CH). For $C_{37}H_{40}F_2N_2O_8S$ (710·8) calculated: 62·52% C, 5·67% H, 5·35% F, 3·94% N, 4·51% S; found: 62·79% C, 5·95% H, 5·09% F, 3·87% N, 4·68% S.

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)-4-(2-(4-fluorophenoxy)ethyl)piperazine (*XXXIX*)

A solution of 2·60 g *XXX* (ref.[1]) in 15 ml chloroform was treated with 1·7 g 4-fluorophenoxyacetyl chloride[40] and the mixture was allowed to stand overnight at room temperature. It was then washed with diluted NaOH, dried with K_2CO_3 and evaporated. The residue (3·7 g, 100% crude amide) was dissolved in 20 ml ether and the solution was slowly added to a stirred suspension of 0·5 g $LiAlH_4$ in 20 m ether. The mixture was refluxed for 4 h, allowed to stand overnight at room temperature, decomposed by successive addition of 0·4 ml water, 0·6 ml 5M-NaOH and 1·4 ml water, the solid was filtered off, washed with ether, and the filtrate was dried and evaporated; 3·2 g (89%) crude base which was transformed to the bis(hydrogen maleate), m.p. 155·5–157·5°C (ethanol). Mass spectrum, *m/z* (%): 494·2198 (M^+ corresponding to $C_{29}H_{32}F_2N_2OS$, 16%), 383 (33), 271 (100), 196 (22), 194 (33), 99 (91), 72 (100), 71 (55). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80–7·60 (m, 10 H, ArH), 6·12 (s, 4 H, 2 CH=CH of maleic acid), 1·11 (d, 6 H, 2 CH_3 of isopropyl), 2·40–4·30 (m, 7 CH_2 and 2 CH). For $C_{37}H_{40}F_2N_2O_9S$ (726·8) calculated: 61·14% C, 5·55% H, 5·23% F, 3·86% N, 4·41% S; found: 61·71% C, 5·67% H, 4·89% F, 4·10% N, 4·58% S.

(4-Fluorophenylthio)acetic Acid

A solution of 10·1 g 4-fluorothiophenol[50] in 40 ml ethanol was treated with a solution of 7·2 g NaOH in 7·5 ml water and the solution was then treated slowly under efficient stirring with a solution of 8·2 g chloroacetic acid in 20 ml ethanol. An exothermic reaction took place which brought the mixture to boiling. After this was over, the mixture was stirred and refluxed for 2 h, and evaporated *in vacuo*. The residue was distributed between water and ether, the aqueous layer was acidified with hydrochloric acid and the separated oily acid was extracted with ether. Processing of the extract gave 13·0 g solid residue which was crystallized from 15 ml benzene; 7·8 g (53%),m.p. 73–75·5°C. Ref.[42], m.p. 70°C for a product, prepared differently.

(4-Fluorophenylthio)acetyl Chloride

A mixture of 5·3 g (4-fluorophenylthio)acetic acid and 6·8 g $SOCl_2$ was refluxed for 2 h, evaporated, and the residue was distilled; 5·1 g (88%), b.p. 76–77°C/33 Pa. For C_8H_6ClFOS (204·7) calculated: 9·28% F, 15·67% S; found: 9·07% F, 15·05% S.

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-
-11-yl)-4-(2-(4-fluorophenylthio)ethyl)piperazine (*XL*)

Similarly like in the preparation of *XXXIX*, 3·56 g *XXX* (ref.[1]) was reacted with 2·66 g (4-fluorophenylthio)acetyl chloride in 18 ml chloroform, and 5·2 g (100%) of the crude amide were obtained. This was reduced with 0·5 g $LiAlH_4$ in 35 ml ether to give 4·9 g (96%) crude base *XL* which was transformed to 4·1 g (65%) maleate, m.p. 184—186·5°C (ethanol). Mass spectrum, *m/z* (%): 510·1959 (M^+ corresponding to $C_{29}H_{32}F_2N_2S_2$, 7%), 383 (40), 369 (36), 271 (100), 227 (16), 155 (25), 127 (27), 72 (36). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80—7·60 (m, 10 H, ArH), 6·02 (s, 2 H, CH=CH of maleic acid), 1·10 (d, 6 H, 2 CH_3 of isopropyl), 2·40—4·20 (m, remaining 7 CH_2 and 2 CH). For $C_{33}H_{36}F_2N_2O_4S_2$ (626·8) calculated: 63·23% C, 5·79% H, 6·06% F, 4·47% N, 10·23% S; found: 63·44% C, 6·00% H, 6·28% F, 4·60% N, 10·00% S.

1-(4-Fluorophenyl)-4-(4-(7-fluoro-2-isopropyl-10,11-dihydro-
dibenzo[*b,f*]thiepin-11-yl)piperazine-1-yl)butan-1-one (*XLI*)

A mixture of 3·0 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[20], 5·3 g 1-(3-(4-fluorobenzoyl)propyl)piperazine[43] and 10 ml chloroform was stirred and refluxed for 8 h. It was diluted with 100 ml chloroform and washed with a solution of 1·0 g NaOH in 100 ml water, dried and evaporated. The residue was chromatographed on 150 g neutral Al_2O_3 (activity II), Elution with light petroleum removed 7-fluoro-2-isopropyldibenzo[*b,f*]thiepin[1,20] (product of elimination), and benzene eluted 3·57 g (70%) base *XLI* which crystallized, m.p. 104—106°C (acetone). UV spectrum: λ_{max} 242·5 nm (log ε 4·38), 295 nm (3·59), infl. 270 nm (3·90). IR spectrum: 825, 840, 914 (2 adjacent and solitary Ar—H), 1 509, 1 589, 1 600, 3 035, 3 050, 3 065 (Ar), 1 684 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·00 (dd, J_{H-H} = 8·0 Hz; J_{H-F} = 6·0 Hz, 2 H, 2,6-H_2 in 4-fluorophenyl), 7·49 (d, J = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 7 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·98 (t, J = 7·0 Hz, 2 H, CH_2CO), 2·45 (m, 6 H, $CH_2N^1CH_2$ of piperazine and CH_2N in the chain), 1·98 (m, 2 H, CH_2 in the middle of $(CH_2)_3$), 1·85 (m, 1 H, ArCH of isopropyl), 1·56 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ —106·5 (m, F in 4-fluorophenyl), —117·2 (dt, 7-F, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz). For $C_{31}H_{34}F_2N_2OS$ (520·7) calculated: 71·51% C 6·58% H, 7·30% F, 5·38% N, 6·16% S; found: 71·85% C, 6·79% H, 7·49% F, 5·42% N, 6·18% S.

Bis(hydrogen maleate), m.p. 145—147°C (acetone). For $C_{39}H_{42}F_2N_2O_9S$ (752·8) calculated: 62·22% C, 5·62% H, 5·05% F, 3·72% N, 4·26% S; found: 62·82% C, 5·93% H, 4·91% F, 3·68% N, 4·27% S.

1-(7-Fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-
-11-yl)-4-(4,4-bis(4-fluorophenyl)butyl)piperazine (*XLII*)

A similar reaction of 2·5 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[20] with 5·5 g 1-(4,4-bis(4-fluorophenyl)butyl)piperazine[38] in 7 ml chloroform gave 3·9 g (80%) of chromatographed oily base which was transformed to the maleate crystallizing from ethanol or acetone as a dihydrate, m.p. 185—187°C. Mass spectrum, *m/z* (%): 600·2784 (M^+ corresponding to $C_{37}H_{39}F_3N_2S$, 20%), 372 (17), 299 (12), 271 (22), 203 (10), 108 (20), 98 (12), 72 (100). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80—7·50 (m, 14 H, ArH) 6·00 (s, 2 H, CH=CH, of maleic acid), 1·11 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl), 1·20—4·20 (remaining 8 CH_2 and 3 CH). For $C_{41}H_{43}F_3N_2O_4S + 2\ H_2O$ (752·9) calculated: 65·40% C, 6·29% H, 7·57% F, 3·72% N, 4·26% S; found: 65·57% C, 6·26% H, 8·01% F, 3·90% N, 4·55% S.

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