FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: 7-FLUORO-11-[4-(2-HYDROXYETHYL)PIPERAZINO]--2-ISOPROPYL-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN

Miroslav PROTIVA, Jiří JÍLEK, Miroslav RAJŠNER, Josef POMYKÁČEK, Miroslav RYSKA, Jiří HOLUBEK, Emil SVÁTEK and Jiřina METYŠOVÁ

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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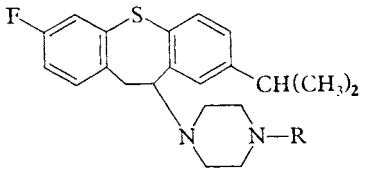
Substitution reaction of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin with 1-(2-hydroxyethyl)piperazine gave the title compound *I* which proved a very potent and long-acting oral neuroleptic agent („isofloxythepin"). Its resolution by means of dibenzoyl-(+)- and -(−)-tartaric acid led to (−)- and (+)-enantiomer out of which the former represents the neuroleptically active component. In the synthetic sequence leading to *I*, preparation of two key intermediates was re-elaborated using new partial sequences: 4-fluoro-2-iodobenzoic acid (*XIII*) from 4-fluoro-2-nitroaniline (*V*) *via* the nitrile *VI* and the acids *VIII* and *XII*, and [4-fluoro-2-(4-isopropylphenylthio)phenyl]acetic acid (*XVIII*) from *XIII via XIV* and the compounds *XV*—*XVII*. The sulfoxides and N-oxides *XIX*—*XXII* were prepared as potential metabolites of isofloxythepin (*I*).

In a recent communication[1] we described the synthesis of several 2-alkyl-7-fluoro-11--piperazino-10,11-dihydrodibenzo[*b,f*]thiepins out of which especially the 2-isopropyl derivatives exhibited outstanding neuroleptic effects with significant prolongation of their duration which led to the synthesis of the title compound *I*. This compound ("isofloxythepin") was selected on the basis of its properties for preclinical and clinical studies. In the present communication there are described the synthesis of isofloxythepin (*I*), resolution of the racemic compound to enantiomers, some new contributions to the synthesis of intermediates, and synthesis of several potential metabolites of isofloxythepin.

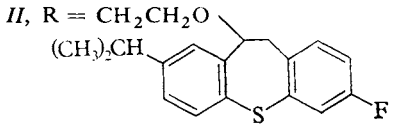
Compound *I* was obtained by substitution reaction of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin[1] with an excess of 1-(2-hydroxyethyl)piperazine in boiling chloroform (*cf.*[2]). This reaction resulted in a mixture, from which the excessive 1-(2-hydroxyethyl)piperazine was removed by washing with water, and from the benzene solution the base *I* was extracted into an excess of aqueous methanesulfonic acid solution. From the aqueous solution of the methanesulfonate the base *I* was obtained by treatment with aqueous ammonia and extraction with benzene in a yield of about 80%. It was characterized by spectra and transformed to salts (monomethanesulfonate, dimethanesulfonate, bis(hydrogen maleate)) which

were used in pharmacological tests and out of which the monomethanesulfonate was selected as the most suitable for clinical trials in the form of tablets.

The benzene solution after the extraction with methanesulfonic acid solution was considered solution of neutral by products of the substitution reaction. Its dilution with hexane resulted, however, in precipitation of a solid which was characterized as the methanesulfonate of a highly hydrophobic base. Decomposition of this salt with aqueous ammonia afforded an amorphous base which was used for recording the spectra. The mass spectrum showed the molecular ion with m/z 670 which corresponds to the empirical composition $C_{40}H_{44}F_2N_2OS_2$. This composition is in agreement with the analysis of the primarily isolated methanesulfonate. The molecule of the compound contains evidently two dibenzo[*b*,*f*]thiepin residues per one piperazine moiety. In the IR spectrum the band at 1 100 cm^{-1} was interpreted as indicating the presence of an aliphatic ether. In the ^1H NMR spectrum, the signals of protons on carbon atoms, which are adjacent to the ether oxygen in the fragment Ar—CH—O—CH_2—, are well differentiated. Consequently, the structure of the ether *II* was suggested for the product; it is plausible from the point of view of possibilities of its formation (product of reaction of compound *I* already formed with the starting 11-chloro-7-fluro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin) and the structure is in agreement with all experimental data available. It is a minor product, obtained in a yield of about 3%. Its molecule contains two chiral centres; the substance is thus a mixture of two racemates. Neutralization of the base *II* with maleic acid resulted in a neutral monomaleate which was crystalline. Only from the mother liquors of the *II* methanesulfonate it was possible to isolate by chromatography and distillation the product of the expected elimination reaction, i.e. 7-fluoro-2-isopropyldibenzo[*b*,*f*]-thiepin (ref.[1]) in a yield of about 7%.



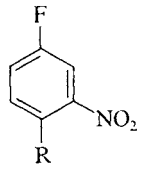
I, R = CH_2CH_2OH
III, R = H
IV, R = $COOC_2H_5$



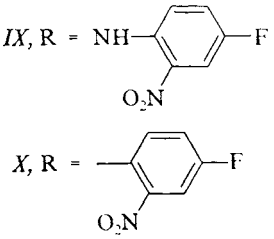
In the described synthesis of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[1,3], which is the immediate precursor of compound *I*, [4-fluoro-2-(4-isopropylphenylthio)phenyl]acetic acid (*XVIII*) was used as the key intermediate, which was cyclized to 3-fluoro-8-isopropyldibenzo[*b*,*f*]thiepin-10(11*H*) one[1,4]. This ketone was reduced to 3-fluoro-8-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-

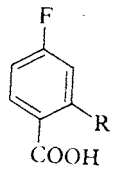
-ol[1,5] which was transformed by treatment with hydrogen chloride to the mentioned chloro compound. Together with the final substitution reaction these three steps are considered suitable for the synthesis of larger amounts of compound *I*. On the other hand, the preparation of the acid *XVIII* became the object of further experimentation; until now the synthesis of this acid was described[1,6] by reactions of (4-fluoro-2-iodophenyl)acetic acid[7-9] or (2-bromo-4-fluorophenyl)acetic acid[10] with 4-isopropylthiophenol[11], both of these acids being accessible by multistep syntheses including the Schiemann reaction[12], considered unsuitable for working in larger scale. A further disadvantage of both (fluorohalogenophenyl)acetic acids is the relatively low reactivity of the halogen atom (bromine, iodine), leading to the necessity of using more severe reaction conditions and further to lower yields on the acid *XVIII* which may be contaminated by the starting (fluorohalogenophenyl)acetic acid and requires purification by recrystallization (*cf.*[13]). It became the task to develop a synthesis of the acid *XVIII* from the more reactive 4-fluoro-2-iodobenzoic acid (*XIII*) (ref.[14]) without the necessity of using the Schiemann reaction in the preparation of the acid *XIII*.

4-Fluoro-2-nitroaniline (*V*), which was prepared by described procedures in five steps either from fluorobenzene or 4-chloronitrobenzene, was considered a suitable intermediate for our purpose. 4-Fluoronitrobenzene was obtained either by nitration of fluorobenzene[15] or by reaction of 4-chloronitrobenzene with potassium fluoride[16,17] Hydrogenation of 4-fluoronitrobenzene on Raney nickel[15] results in a high yield of 4-fluoroaniline affording 4-fluoroacetanilide by acetylation[18]. Further nitration[18] leads to 4-fluoro-2-nitroacetanilide which is hydrolyzed with hydrochloric acid[19,20] to compound *V*. This deacetylation has now been carried out by a method, not described for this case, *i.e.* by ethanolysis in the presence of sodium ethoxide (method[21]); the desired 4-fluoro-2-nitroaniline (*V*) was obtained in this way in a yield of 90% and ethyl acetate is the by-product.



V, R = NH_2
VI, R = CN
VII, R = Cl
VIII, R = COOH
XI, R = $CONH_2$





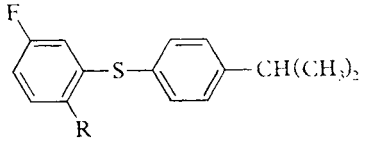
XII, R = NH_2
XIII, R = I

As a further intermediate 4-fluoro-2-nitrobenzonitrile (*VI*) was chosen; the compound has not been described up to present and it was the intention to prepare it from compound *V* by Sandmeyer reaction. Diazotization of compound *V* in dilute hydrochloric acid and decomposition of the diazonium salt by a solution of cuprous cyanide at 80–90°C resulted in a mixture which was separated by distillation into the wanted nitrile *VI* and the lower boiling 2-chloro-5-fluoronitrobenzene (*VII*) (ref.[22]); both products were formed in about equal yields (20%) and the procedure used was evidently unsuitable. References[23,24] described good experience with diazotization of weak amines, especially nitranilines, in anhydrous medium with nitrosylsulfuric acid; there were further described[25,26] substitutions of the diazonium group by the nitrile group by decomposition with solutions of cuprous or nickel(II) cyanide in neutral media. Combination of both methods led to elaboration of a favourable process for preparing nitrile *VI* which was obtained in crude state (suitable for the following step) in a yield of 85%. According to gas chromatography this product contains 95% *VI*; recrystallization gave the completely pure substance which was characterized by spectra. Gas chromatography indicated further the presence of two by-products in the crude product, both in amounts of about 1·5% which were isolated only in the further step, *i.e.* hydrolysis of the nitrile *VI* to 4-fluoro-2-nitrobenzoic acid (*VIII*). Their preparing in pure state enabled their characterization and identification. They were obtained as a fraction which was not hydrolyzed and not soluble in aqueous ammonia; their separation was carried out by fractional crystallization. More easily to be isolated was an orange substance melting at 193–194°C for which the mass spectrum and analysis estimated the formula $C_{12}H_7F_2N_3O_4$. The IR spectrum indicated the presence of NH group and the structure of the 4,4'-difluoro-2,2'-dinitrodiphenylamine (*IX*) is suggested for the compound; its formation could perhaps by explained by interaction of the aryl cation, postulated to be formed as an intermediate in the step of decomposition, with a small amount of unreacted starting amine *V* (however, no analogy could be found in the literature). From the mother liquors after the orange compound there was isolated the second by-product as a colourless substance melting at 168–169°C and corresponding to $C_{12}H_6F_2N_2O_4$. It was identified as 4,4'-difluoro-2,2'-dinitrodiphenyl (*X*). It is a known substance[27] which was obtained by different routes and whose formation by reduction of 4-fluoro-2-nitrobenzenediazonium sulfate with cuprous chloride or cyanide is not surprising (*cf.*[28,29]).

Reaction of the nitrile *VI* with dilute sulfuric acid at 100°C (*cf.*[30]) proceeds only as hydration and affords the amide *XI* which was isolated as a relatively hydrophilic substance in good yield. Hydrolysis of the nitrile *VI* to the desired 4-fluoro-2-nitrobenzoic acid (*VIII*) takes place only by using more severe reaction conditions: heating with a mixture of sulfuric and acetic acid to 150–160°C. The acid *VIII*, prepared until now only by oxidation procedures from 4-fluoro-2-nitrotoluene[31–33], was obtained in our case in a yield of 75% and was separated from the mixture of

compounds *IX* and *X* on the basis of its solubility in aqueous ammonia. The amide *XI* may also be transformed to the acid *VIII* using the Bouveault method[34-36] which consists in a reaction with nitrous acid. To this end it is not necessary to start from the isolated amide *XI*; quite satisfactory is to treat at 25–30°C with sodium nitrite the solution of the amide in dilute sulfuric acid which was obtained by the mentioned hydration of the nitrile *VI*. The following step is the transformation of the acid *VIII* to 4-fluoroanthranilic acid (*XII*) whose preparation was described on the one hand by oxidation of 2-acetamido-4-fluorotoluene and the following deacetylation[37], and from the acid *VIII* by reduction methods[31,33] (catalytic hydrogenation on palladium, reduction with ferrous sulfate in aqueous ammonia) on the other. With good results we reduced the acid *VIII* either with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and active carbon (method[38-40]), or with iron in boiling ethanol in the presence of a small amount of hydrochloric acid. Transformation of the acid *XII* to 4-fluoro-2-iodobenzoic acid (*XIII*) was carried out by the procedure we have already described[14].

Continuing the synthesis we have prepared 4-fluoro-2-(4-isopropylphenylthio)benzoic acid (*XIV*) by reaction of the acid *XIII* (ref.[14]) with 4-isopropylthiophenol[11] in an excess of boiling aqueous potassium hydroxide solution in the presence of copper. This method is preparatively more favourable than reaction of 2-bromo-4-fluorobenzoic acid with 4-isopropylthiophenol in dimethylformamide at 150–160°C in the presence of potassium carbonate and copper, described by us previously[41]. Further steps represented then the transformation of the acid *XIV* to the homologous acid *XVIII* under conditions suitable for preparing larger quantities of the material; these steps are close analogy of the reaction sequence used by us many times before (*e.g.*[11,14]). Reduction of the acid *XIV* with sodium dihydridobis(2-methoxyethoxy)-aluminate[42] in toluene gave the alcohol *XV*, which afforded by treatment with thionyl chloride at 60–80°C in aprotic solvents (benzene, toluene, chloroform) or in the presence of a small excess of pyridine at 20–40°C the chloro derivative *XVI*. For the following reaction with sodium cyanide, dimethylformamide at 100°C proved the most suitable solvent and the nitrile *XVII* was obtained in a yield of 82%. The hydrolysis of the nitrile to the acid *XVIII* was carried out by potassium hydroxide in boiling aqueous ethanol. In this way the task, formulated at the beginning of this communication, was achieved.

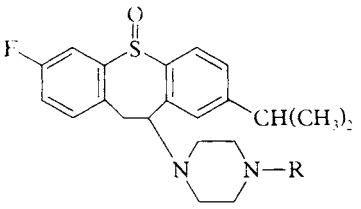


XIV, R = COOH *XVI*, R = CH_2Cl
XV, R = CH_2OH *XVII*, R = CH_2CN
XVIII, R = CH_2COOH

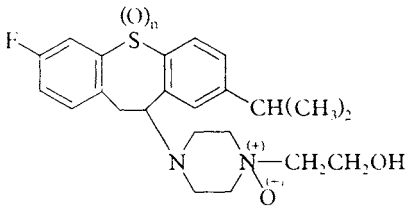
The molecule of the base *I* contains a chiral centre at $C_{(11)}$ of the tricyclic skeleton; the just described synthesis of isofloxythepin (*I*) afforded the racemate. With regard to the proven stereoselectivity of neuroleptic effects of clorothepin, *i.e.* 2-chloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[43], it was most desirable to confirm this property also with compound *I*. The resolution of the racemate was carried out by crystallization of the diastereoisomeric salts on the one hand with dibenzoyl-(+)-tartaric acid, and with dibenzoyl-(−)-tartaric acid on the other. In the first case there was obtained a homogeneous diastereoisomer whose decomposition resulted in the levorotatory base *I* with $[\alpha]_D^{20}$ −14·4°. In the second case, likewise, a homogeneous diastereoisomer crystallized which afforded the dextrorotatory base *I* with $[\alpha]_D^{20}$ +15·2°. Both enantiomers were transformed to monomethanesulfonates which were used in pharmacological tests.

With regard to the high neuroleptic potency of isofloxythepin (*I*) and its future use in pharmacotherapy of schizophrenia, it was evident that there will be necessary to investigate its pharmacokinetics and metabolism in animals as well as in patients. For such studies there was prepared a basic series of oxidation products which are formed in similar cases by oxidation with nonspecific liver enzymes. In the first line it was the compound lacking the 2-hydroxyethyl group on nitrogen N^4 of the piperazine residue, *i.e.* the secondary amine *III*. It was obtained by reaction of 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] with N-(ethoxycarbonyl)piperazine at 110°C and by hydrolysis of the formed carbamate *IV* (characterized as hydrogen maleate) with ethanolic potassium hydroxide (the base was characterized by spectra and the maleate was prepared for testing). For the preparation of the potential metabolites of isofloxythepin (*I*), oxygenated on the sulfur atom in position 5 and further on N^4 of the piperazine moiety, there were used similar reactions like described previously[44]. Oxidation of an aqueous solution of methanesulfonate of the base *I* at room temperature by excess of hydrogen peroxide gave sulfoxide *XIX* in a yield of 75% (mixture of two racemates), which was characterized as the maleate. The presence of the SO group was proven by the IR spectrum (band at 1 090 cm^{-1}) and by polarographic reduction ($E_{1/2}$ = −0·49 V). Similarly, the secondary amine *III* was also oxidized; in this case the sulfoxide *XX* was obtained as a homogeneous base (ν(SO) 1 060 cm^{-1}, $E_{1/2}$ = −0·71 V), which afforded the dimethanesulfonate solvated with ethanol. Oxidation of *I* with hydrogen peroxide in ethanol resulted in a base, containing one additional oxygen atom, whose IR spectrum does not display the sulfoxide band but a strong band at 911 cm^{-1}, attributed to the aliphatic N-oxide (polarographic reduction proceeds at $E_{1/2}$ = = −0·30 V). The product was thus identified as the N-oxide *XXI* (hemihydrate); neutralization with hydrogen chloride and crystallization from a mixture of ethanol and ether gave the dihydrochloride (hemihydrate). Oxidation of this salt with hydrogen peroxide in water at room temperature as well as oxidation of the sulfoxide base *XIX* with hydrogen peroxide in ethanol afforded the same high-melting base

containing by 2 atoms oxygen more than the base *I*; the assigned structure of the S,N⁴-dioxide *XXII* was confirmed by spectra and by the course of polarographic reduction (two reduction waves at −0·18 and −0·45 V).



XIX, R = CH_2CH_2OH
XX, R = H



XXI, n = 0
XXII, n = 1

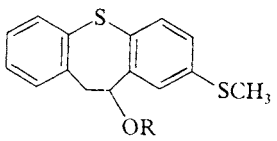
After identification of the ether *II* as a minor impurity of the crude base *I* we returned to a nonidentified impurity of the crude substance of oxyprothepin, *i.e.* 11-[4-(3-hydroxypropyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[43,45,46], which behaved chromatographically similarly like the ether *II* (twins of little spots of a similar R_F); it could now be assumed that we are dealing here with the ether *XXIII*. Similarly like in the case of the ether *II*, the molecule of the ether *XXIII* contains two chiral centers and could be a mixture of both possible racemates (the consequence is the appearing of twins of spots on the chromatograms). Because this impurity occurred in the oxyprothepin substance in too little amounts and we never were able to isolate it preparatively, we attempted now at its synthesis for getting material for comparison. An attempt to prepare the ether by reaction of the oxyprothepin base[43,45,46] with 8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XXIV*) (ref.[47]) in benzene and in the presence of boron trifluoride etherate (analogy[48]) was unsuccessful: the starting compounds were recovered. On the other hand a similar reaction of the alcohol *XXIV* with 3-chloropropanol in dichloromethane gave a mixture of the more polar ether *XXV* and a less polar substance which was separated by chromatography on silica gel. This less polar component was identified as 2-methylthiodibenzo[*b*,*f*]thiepin (*XXIX*); crystallization from ethanol gave the homogeneous substance melting constantly at 70−72°C. Its identity was corroborated by the ^{1}H NMR spectrum. Compound *XXIX* was described a longer time ago[47] as a substance crystallizing from a mixture of benzene and light petroleum and melting at 89−91°C. In spite of repeated efforts we never were able to prepare more recently this higher-melting substance which apparently was a crystal modification. A similar reaction of the alcohol *XXIV* with 3-bromopropanol resulted in a mixture of the ether *XXVI* and compound *XXIX* which, likewise, was separated by chromatography on silica gel. Ethers *XXV* and *XXVI* were oily and were analyzed

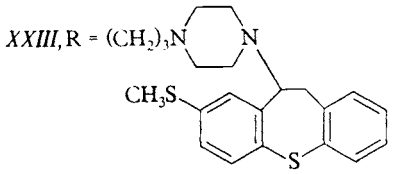
only as residues after evaporation of the chromatographic fractions. Both proved to be unsuitable for reaction with 2-methylthio-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[45,49] (in the presence of potassium carbonate in dimethylformamide at 100°C) probably due to their too low reactivity. Therefore, we transformed the chloropropyl ether *XXV* by the Finkelstein reaction[50,51] to the more reactive iodopropyl ether *XXVII*; even this substance was oily and it was necessary to use it in crude state (content of iodine by 2% lower than the theoretical). Reaction of compound *XXVII* with 2-methylthio-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[45,49] in boiling chloroform in the presence of potassium carbonate gave a mixture from which the less polar components were removed by chromatography on silica gel. The main component was a base which resisted to attempts at its crystallization. On the other hand it afforded a crystalline maleate whose analysis confirmed for the base the composition of the ether *XXIII*. The base released from the maleate remained amorphous but could be used for recording the spectra. It was not possible to register the mass spectrum because even at 325°C the substance did not afford a sufficient tension. IR spectrum exhibits a band at 1 100 cm^{-1} which indicated the structure of an aliphatic ether. The rather little differentiated ^1H NMR spectrum shows a clear signal of the proton at $C_{(11)}$ of the skeleton carrying simultaneously the oxygen atom of the ether. The structure of the ether *XXIII* is considered proven and its chromatographic comparison with the mentioned impurity of the crude oxyprothepin base[43,45,46] confirmed the identity of both compounds.

As a potential impurity of oxyprothepin decanoate, *i.e.* 11-[4-(3-decanoyloxypropyl)piperazino]-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[49,52,53], there was prepared the ester *XXVIII* by reaction of the alcohol *XXIV* with decanoyl chloride. With regard to the fact that its distillation was accompanied by a partial decomposition, the substance was analyzed as the residue after evaporation of a chromatographic fraction and the ^1H NMR spectrum was recorded. The chromatographic comparison showed that it does not represent an impurity of the oxyprothepin decanoate substance.

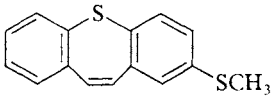
The basic pharmacological properties of racemic isofloxythepin (*I*) were determined in tests in mice, rats and dogs[54], and salts, described in the Experimental, were used; all doses given (in mg/kg) relate to oral administration and were calculated for the base. In addition to the intensity of effects in the time of maximum responses, the duration of the effects was also observed[55]. The acute toxicity in mice, LD_{50} = = 230. The incoordinating effect in mice in the rotarod test reached the maximum in 5 h after the administration, ED_{50} = 0·74; the effect is well apparent after 24 h (ED_{50} = 4·1). The inhibition of locomotor activity in mice, investigated by the photo-cell method of Dews, has, likewise, its maximum in 5 h after the administration, D_{50} = 0·41; the effect is almost unchanged after 24 h (D_{50} = 0·51) and is still considerable after 48 h (D_{50} = 2·1). In these tests the effects are comparable with those of clorothepin[56] which were evaluated in 1 h after the administration; after

12 h the effects of clorothepin already disappeared. The intensity and duration of these effects are comparable with those of tefluthixol[57]; on the other hand the duration of effects of pimozide[58] is shorter and the discoordinating activity weaker.





XXIV, R = H
XXV, R = $(CH_2)_3Cl$
XXVI, R = $(CH_2)_3Br$
XXVII, R = $(CH_2)_3I$
XXVIII, R = $CO(CH_2)_8CH_3$



XXIX

The cataleptic action of isofloxythepin in rats reached the maximum in the interval of 1–5 h after the administration, ED_{50} = 2·0; the effect is protracted because after 24 h ED_{50} = 4·0 (in the interval of 1–5 h are the values ED_{50} for clorothepin 4·3, tefluthixol 1·4 and pimozide 1·3; after 24 h the effects of clorothepin and tefluthixol already vanished and the effect of pimozide was weaker than that of compound *I*). In the test of inhibition of apomorphine-induced oral stereotypies (chewing) in rats in 4 h after the administration, compound *I* is fairly active, D_{50} = 2·7, after 24 h D_{50} = 8·4 (for comparison similar data for clorothepin: 2·2, 0; tefluthixol: 1·6, 2·0; pimozide: <1·0, 4·0). In the test of antiapomorphine action in dogs (inhibition of the emetic response to apomorphine) the dose of 1 mg/kg of compound *I* in the interval of 24 h after the administration elicited the complete blockade of the apomorphine effect in 88% of the animals, after 48 h in 38%. The analogous values for tefluthixol (1 mg/kg) were 100 and 88, and for pimozide (1 mg/kg) 100 and 75. In tests of the antiapomorphine actions tefluthixol and pimozide were somewhat more active than isofloxythepin (*I*).

The antidopaminergic effects of isofloxythepin (*I*) *in vivo* was evaluated by investigating its effects on the turnover and metabolism of dopamine in corpus striatum of the rat brain. Isofloxythepin in the dose of 5 mg/kg strongly increased the levels

of dopamine metabolites, *i.e.* 3,4-dihydroxyphenylacetic acid and homovanillic acid (4-hydroxy-3-methoxyphenylacetic acid, HVA), with attaining the maximum in 24 h after the administration; simultaneously the level of striatal dopamine is decreased until 96 h after the administration. The dose of 3 mg/kg (24 h) is the minimum active dose raising significantly the HVA level[55,59]. In 4–5 days after the administration of isofloxythepin there comes, however, to lowering of the HVA level under the control value which was explained by the induction of dopaminergic supersensitivity[60]. Isofloxythepin (*I*) exhibits also central antiserotonin action which was proven by lowering the 5-hydroxytryptamine level and raising the 5-hydroxyindole-3-acetic acid level in rat hypothalamus[61]. Similarly like haloperidol, isofloxythepin (*I*) inhibits significantly the hyperactivity of mice induced by compound H 77/77, *i.e.* the 3--hydroxy-4-methyl derivative of amphetamine[62]. Isofloxythepin raises significantly the prolactin level in blood serum of rats which is a typical effect of neuroleptics[63].

The pharmacokinetics and metabolism of isofloxythepin (*I*) were first investigated with the [10-^{14}C]-labeled substance using oral and intravenous administration to rats[64]. The radioactive metabolites were separated by means of thin-layer chromatography; 12 of them were detected in urine out of which the most important corresponded to the N,S-dioxide *XXII*. In bile 13 radioactive compounds were detected out of which one again appeared to be identical with the N,S-dioxide *XXII*. In faeces (25 metabolites) the least polar metabolite was identified as 7-fluoro-2-isopropyldibenzo[*b*,*f*]thiepin[1]. A further pharmacokinetic and metabolic study was carried out with nonlabeled isofloxythepin (*I*) in rats and monkeys[65]. The metabolites in urine and faeces were again separated but in this case their preliminary characterization by mass spectrometry was performed. One metabolite was characterized as the compound hydroxylated in one methyl of the isopropyl group and a further as a dihydroxy derivative with one hydroxyl in the isopropyl and the other on an aromatic nucleus. One of the metabolites appeared to be the dehydrogenated compound, *i.e.* the corresponding enamine. In the urine five S-oxides were detected, most of them being hydroxylated in unknown positions of the aromatic nuclei. The accurate identification was not possible due to the lack of synthetic standards.

Clinical testing of racemic isofloxythepin (*I*) was started in healthy volunteers on the one hand by a tolerance study[66] (a single oral dose of 3 mg was administered), and by a comparative study[67] in a different group, the members of which were administered either with a single dose of 2 mg isofloxythepin or 2 mg pimozide, on the other. In both cases isofloxythepin elicited changes and reactions (control by EEG and psychological tests) which are common after the administration of very strong neuroleptic agents. Contrary to classical tricyclic neuroleptics these reactions reached their maximum only in 24 h after the administration and lasted for about 3 days (the EEG changes after isofloxythepin lasted longer than those after pimozide). In the second phase of clinical trials[68–70], isofloxythepin was administered to hospitalized schizophrenic patients for 6 weeks in two psychiatric clinics. The medium

daily doses of 5·7 mg (administered in 24 or 48 h intervals) led in 58% of patients to a full remission of the disease and in most of the rest to improvement. The antipsychotic effect was clear even if the interval between the administrations was prolonged to 7 days. The intensity of the therapeutic effect was comparable with that of haloperidol or was even higher. The clinical testing of isofloxythepin is now being continued in the third phase.

Pharmacological[71] and biochemical[72] testing of isofloxythepin enantiomers proved the stereoselectivity of the neuroleptic and antidopaminergic activity of the substance. There were used usual tests in mice (inhibition of the amphetamine-induced hypermotility, inhibition of the spontaneous locomotor activity and rotarod test) and in rats (cataleptic and antiapomorphine actions). It was found that in tests, corresponding to neuroleptic activity (antiamphetamine, cataleptic and antiapomorphine actions), the (−)-enantiomer is about twice as active as the racemate and 10−20 times as active as the (+)-enantiomer. In tests, corresponding to the central depressant action (inhibition of the locomotor activity and rotarod test) the stereoselectivity does not appear. The stereoselectivity of the antidopaminergic action of isofloxythepin (*I*) was confirmed by investigating the influence of the enantiomers on the metabolism of dopamine in corpus striatum of the rat brain: the oral dose of the (−)-enantiomer, raising the HVA level in striatum to 200% of the control value (ED_{200} = 0·018 mg/kg in the interval of 3 h), is approximately one half of the ED_{200} of the racemate and is less than one tenth of the ED_{200} for the (+)-enantiomer. Contrary to clorothepin[43], where the (+)-enantiomer is the more active one, in the case of isofloxythepin (*I*) the (−)-enantiomer is the active component of the racemate. It is assumed that the configuration on the chiral centre of (−)-isofloxythepin (*I*) is the same like in the case of (+)-clorothepin[73], *i.e.* (*S*).

Further compounds, described in this communication, *i.e.* the ethers *II* and *XXIII* and the potential metabolites *III* and *XIX*−*XXII*, were also submitted to pharmacological testing. The results are assembled in Table I. All compounds were tested in the form of salts, described in the Experimental (with the exception of the base *XXII*); the compounds were administrated orally and the doses (in mg/kg) were calculated per bases. The table includes racemic isofloxythepin (*I*), both enantiomers and clorothepin[56] as a standard. The values of LD_{50} express the acute toxicity of the compounds in mice. The rotarod test in mice evaluates the discoordinating activity; the ED_{50} values relate to the interval of optimum activity. Inhibition of locomotor activity in mice was studied by the photo-cell method of Dews; values of D_{50} relate to the time of maximum effect. Cataleptic activity was evaluated in rats; values of ED_{50} were calculated for the interval of 4 h after the administration (with the exception of clorothepin with evaluation after 1 h). The antiapomorphine effect was studied also in rats and relates to the influence on the apomorphine oral stereotypies; the values D_{50} were calculated for the 4 h interval after the administration.

Table I shows clearly the high activity of racemic and levorotatory isofloxythepin (*I*) in all tests and the relatively low toxicity of the racemate. The nontoxicity and inactivity of the ethers *II* and *XXIII* is also apparent. Out of the potential metabolites the secondary amine *III* has considerable discoordinating and cataleptic activity (the discoordinating effect is protracted because still in the intervals of 24 and 48 h after the administration the ED_{50} values are 4·3, and 6·0 mg/kg, respectively; the cataleptic effect vanishes within 24 h). Also the N-oxide *XXI* is very active and its effects are also protracted: in the rotarod test the maximum effect appears in the interval of 4–5 h after the administration (ED_{50} = 1·4 mg/kg), after 24 h ED_{50} is still 2·6 mg/kg; cataleptic effect of doses 5 and 10 mg/kg appears after 24 h in 30% of the animals, it vanishes after 48 h. With the sulfoxide *XX* the significantly higher toxicity than with the sulfide *I* is apparent; otherwise both of the sulfoxides (*XX*, *XXII*) are little active in the tests shown.

The compounds prepared were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *I* 25, *III* 6·25, *XXI* 12·5, *XXII* 100; *Streptococcus faecalis*, *I* 25, *III* 6·25, *XX* 50, *XXI* 100; *Staphylococcus pyogenes aureus*, *I* 25, *III* 6·25, *XIX* 100, *XX* 50, *XXI* 25; *Escherichia coli*, *III* 6·25, *XIX* 100, *XXI* 25; *Proteus vulgaris*, *III* 25; *Mycobacterium tuberculosis*, *I* 5, *III* 6·25, *XIX* 50, *XXI* 25; *Saccharomyces pasterianus*, *I* 12·5, *III* 12·5; *Trichophyton mentagrophytes*, *I* 50, *II* 50, *III* 12·5; *XXIII* 50; *Candida albicans*, *I* 100. Compound *III* appears rather interesting because of the considerable activity towards a broad spectrum of microorganisms.

TABLE I

Pharmacological properties of isofloxythepin (*I*) and related compounds

Compound	LD_{50} mg/kg	Rotarod ED_{50} mg/kg	Locomotor activity D_{50} mg/kg	Catalepsy ED_{50} mg/kg	Antiapomorphine effect D_{50} mg/kg
(±)-*I*	230	1·0	0·68	2·1	2·7
(−)-*I*	—	1·3	0·78	1·5	1·2
(+)-*I*	—	1·5	0·94	9·2	26·6
II	>2 500	>300	—	—	—
III	—	2·4	—	2·0	—
XIX	170	11·5	—	29·0	—
XX	90	18·0	6·7	>50·0	>40·0
XXI	170	1·4	—	4·2	—
XXII	400	43·0	—	56·0	—
XXIII	>2 500	>300	—	>300	—
Clorothepin	78	2·2	1·9	4·3	2·2

EXPERIMENTAL

The melting points of analytical preparations were determined partly in the Mettler FP-5 melting point recorder, partly in Kofler's block (these are not corrected); 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 a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) 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 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

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

A solution of sodium ethoxide was prepared from 125 ml ethanol and 0·35 g Na, 10·0 g 4-fluoro-2-nitroacetanilide[18] were added, and the solution was refluxed for 4 h. After cooling it was filtered, the filtrate was evaporated *in vacuo*, the residue was distributed between water and ether, and the organic layer was evaporated; 7·0 g (90%), m.p. 92–93°C. Ref.[18], m.p. 90–92°C.

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

A) A suspension of 24·6 g *V* in a mixture of 38 ml hydrochloric acid and 25 ml water was treated dropwise with a solution of 12·5 g $NaNO_2$ in 20 ml water at 0–3°C (45 min), the mixture was stirred for 1 h at the temperature indicated and then added over 20 min to a stirred solution of CuCN (prepared from 19 g CuCl and 25 g NaCN in 115 ml water) at 80–90°C. The mixture was cooled, the precipitated solid filtered and extracted by boiling with 150 ml ethanol. The insoluble part was filtered off, the filtrate was evaporated and the residue was distilled *in vacuo*; 5·7 g (21%), b.p. 100–120°C/1·5 kPa, representing the crude 2-chloro-5-fluoronitrobenzene (*VII*). Crystallization from hexane gave pure yellow crystals melting at 38·5–39·5°C. Ref.[22], m.p. 37·2°C.

The distillation was continued and gave 5·1 g (20%) *VI*, b.p. 145–150°C/1·5 kPa, m.p. 69 to 71°C (benzene–light petroleum). UV spectrum: λ_{max} 255 nm (log ε 3·73), infl. 293 nm (3·32). IR spectrum: 812, 850, 888 (2 adjacent and solitary Ar—H), 1 350, 1 545 ($ArNO_2$), 1 490, 1 580, 1 609 (Ar), 2 220 (ArCN), 3 020, 3 048, 3 065 cm^{-1} (Ar). For $C_7H_3FN_2O_2$ (166·1) calculated: 50·61% C, 1·82% H, 11·44% F, 16·87% N; found: 50·38% C, 1·78% H, 11·68% F, 16·50% N.

B) Stirred H_2SO_4 (570 g) was treated over 1 h at 5–10°C with 50 g $NaNO_2$, the mixture was slowly heated to 70°C and the nitrosylsulfuric acid solution thus obtained was cooled to 10°C. It was then treated under stirring over 1 h with a solution of 90 g *V* in 560 ml acetic acid at 15–20°C. The mixture was stirred at this temperature for 3 h and added over 30 min under stirring to a solution of CuCN (prepared by treatment of a suspension of 99 g CuCl in 500 ml water with a solution of 200 g KCN in 700 ml water, by heating the mixture to 60°C and by the addition of a solution of 1·2 kg Na_2CO_3 in 2·8 l water) at 60°C. Under copious development of CO_2 the temperature rose spontaneously to 75°C. After the cessation of the exothermic reaction the mixture was heated to 85–90°C and maintained for 30 min. After cooling to 20°C and standing for 30 min the solid product was filtered and washed with water. It was then dissolved at 70°C in 1 l benzene (stirred for 30 min), a small quantity of undissolved material was filtered off and washed with benzene. The filtrate was dried and evaporated; 82 g (85%) *VI*, m.p. 66–70°C. Crystallization of a sample from a mixture of benzene and light petroleum gave needles melting at 69–71°C, identical with the product obtained under *A*.

4-Fluoro-2-nitrobenzamide (*XI*)

A mixture of 2·0 g *VI* and 20 ml 70% H_2SO_4 was stirred and heated for 6 h to 90—110°C, cooled and filtered through a sintered glass filter. The filtrate was diluted with 10 ml water and made alkaline by addition of K_2CO_3. After the addition of 50 ml ethanol and stirring, the crystallized K_2SO_4 was filtered off and washed with ethanol. The filtrate was evaporated *in vacuo* to a volume of about 15 ml and cooled which led to crystallization of 1·60 g (73%) *XI*, m.p. 152—154°C. Analytical sample, m.p. 154—155°C (water). UV spectrum: λ_{max} 245 nm (log ε 3·74), infl. 295 nm (3·16). IR spectrum: 812, 852, 885 (2 adjacent and solitary Ar—H), 1 360, 1 395, 1 410, 1 530 ($ArNO_2$), 1 582, 3 070 (Ar), 1 610, 1 622, 3 185, 3 365 (NH_2), 1 655 cm^{-1} ($ArCONH_2$). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·15 (bs, 2 H, $CONH_2$), 7·95 (dd, J_{H-F} = 9·0 Hz, J_{H-H} = 2·0 Hz, 1 H, 3-H), c. 7·65 (m, 2 H, 5,6-H_2). For $C_7H_5FN_2O_3$ (184·1) calculated: 45·66% C, 2·74% H, 10·32% F, 15·22% N; found: 45·44% C, 2·72% H, 10·43% F, 15·38% N.

4-Fluoro-2-nitrobenzoic Acid (*VIII*)

A) A solution of 76·3 g *VI* in 143 ml acetic acid was slowly added to a mixture of 145 ml water and 270 g H_2SO_4, and the mixture was refluxed under stirring for 8 h (bath of 150—160°C). After cooling to 60°C the mixture was poured into 1 l cold water and stirred for 3 h under cooling. The solid was filtered using a sintered glass filter and was extracted over 30 min at 75°C with a stirred 1 : 1 dilute NH_4OH solution. The insoluble part was filtered off while hot (after drying 6·1 g, m.p. 127—134°C), the filtrate was treated with 10 g active carbon and after stirring for 10 min at 60°C filtered again. The filtrate was cooled and acidified under stirring with 80 ml hydrochloric acid. The product was filtered after 2 h (cooled and stirred), washed with ice-cold water and dried; 65·0 g (76%), m.p. 142—144°C. Crystallization from water gave the pure substance melting at 147—148°C. Refs[31-33], m.p. values of 145, 149, and 140—141°C, respectively.

The NH_4OH-insoluble solid (6·1 g) was heated for 15 min with a mixture of 25 ml acetic acid and 7 ml acetic anhydride to the boiling point of the mixture, allowed to stand for 2 h and filtered. There were obtained 3·5 g orange-red substance, m.p. 192—194°C. Recrystallization from acetic acid or from benzene gave the pure substance, m.p. 193—194°C, for which the structure of 4,4'-difluoro-2,2'-dinitrodiphenylamine (*IX*) is suggested. Mass spectrum, *m/z*: 295 (M^+ corresponding to $C_{12}H_7F_2N_3O_4$). UV spectrum: λ_{max} 222 nm (log ε 4·16), 242 nm (4·25), 430 nm (3·98), inflexes at 257 nm (4·16), 287 nm (3·87) and 394 nm (3·89). IR spectrum: 821, 877, 896 (2 adjacent and solitary Ar—H), 1 210 (Ar—F), 1 332, 1 342, 1 530 ($ArNO_2$), 1 547, 1 588, 3 050 (Ar), 3 245 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·92 (q, J_{H-F} = 9·0 Hz, 2 H, 3,3'-H_2), 7·50 (m, 4 H, remaining ArH). For $C_{12}H_7F_2N_3O_4$ (295·2) calculated: 48·82% C, 2·39% H, 12·87% F, 14·23% N; found: 48·80% C, 2·39% H, 13·14% F, 14·42% N.

The mother liquor after the preceding substance was evaporated *in vacuo* giving 2·5 g of a solid which was recrystallized from benzene and melted at 168—169°C. It was identified as 4,4'-difluoro-2,2'-dinitrodiphenyl (*X*). Mass spectrum, *m/z* (%): 280 (M^+ corresponding to $C_{12}H_6F_2N_2O_4$, 0·9%), 234 (100), 204 (90), 175 (57), 158 (37), 151 (24), 131 (14), 81 (14), 57 (27). UV spectrum: λ_{max} 210 nm (log ε 4·32), 216 nm (4·32), 252·5 nm (4·02), 303 nm (3·57). IR spectrum: 812, 840, 878, 888 (2 adjacent and solitary Ar—H), 1 220, 1 272 (Ar—F), 1 360, 1 530 ($ArNO_2$), 1 583, 1 608, 3 005, 3 040, 3 050 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·20 (q, $^4J_{H-H}$ = 2·5 Hz, J_{H-F} = 8·5 Hz, 2 H, 3,3'-H_2), 7·80 (dt, $^4J_{H-H}$ = 2·5 Hz; J_{H-F} = = $^3J_{H-H}$ = 8·5 Hz, 2 H, 5,5'-H_2), 7·60 (dd, $^3J_{H-H}$ = 8·5 Hz; J_{H-F} = 5·5 Hz, 2 H, 6,6'-H_2). Ref.[27], m.p. 165 to 166°C.

B) *VI* (88 g) was added to a mixture of 450 ml water and 1 kg H_2SO_4, the mixture was stirred and heated to 95—100°C for 6 h, the brownish solution formed was allowed to stand overnight

at room temperature, the separated impurities were removed by filtration through a sintered glass filter, and were washed with 30 ml 70% H_2SO_4. The acid solution of *XI* formed was stirred and treated over 30—60 min at 25°C with a solution of 86 g $NaNO_2$ in 115 ml water (casual external cooling is necessary). The mixture was stirred for 30 min without cooling and then heated for 4 h in a boiling water bath. Nitrogen was formed and the product precipitated. It was filtered after standing overnight at 4°C using a sintered glass filter, and washed with 100 ml ice-cold water. It was then dissolved in a solution of 80 ml NH_4OH in 260 ml water, the solution was heated with 10 g active carbon to 50°C, and filtered. Acidification of the filtrate with 120 ml hydrochloric acid and crystallization for 12 h at 4°C gave 72 g (79%) crude *VIII*, m.p. 140—147°C. Single crystallization from water afforded the pure substance melting at 147—148°C, identical with the product obtained under *A*.

4-Fluoroanthranilic Acid (*XII*)

A) A suspension of 335 g *VIII* in 1·7 l ethanol was stirred and treated with 230 g 80% $N_2H_4 . H_2O$, 30 g active carbon and a solution of 8·0 g $FeCl_3 . 6 H_2O$ in 75 ml ethanol, and the mixture was refluxed for 10 h (nitrogen formation). After cooling ethanol was evaporated under reduced pressure, the cooled residue was treated with 1·3 l 20% NaOH, 3·4 l water and 30 g active carbon. It was stirred and heated to 70—75°C, filtered at 50°C, the filtrate was cooled to 20°C and under external cooling and stirring it was treated over 10 min with 580 g acetic acid. The suspension of the product formed was stirred for 2 h under cooling, the product was filtered with suction, washed with ice-cold water, and dried; 260 g (92%), m.p. 186—196°C. Single crystallization from water gave the pure substance melting at 196—197°C. Ref.[33,37], m.p. 190—191, and 192·5—193°C, respectively.

B) The boiling suspension of 70 g Fe powder in 500 ml water was slowly treated with 5 ml hydrochloric acid and after 10 min refluxing a solution of 40 g *VIII* in 200 ml 95% ethanol, containing 10 ml hydrochloric acid, was added over 2·5 h. The mixture was then stirred and refluxed for 1·5 h, cooled and slowly treated under stirring with 100 ml NH_4OH. It was stirred for 20 min at 70—80°C, and after cooling the undissolved substance was filtered. It was then extracted twice with a boiling mixture of 200 ml water and 20 ml NH_4OH, and filtered. The filtrates were combined, neutralized and slightly acidified with acetic acid. The product was filtered after standing overnight, washed with a small quantity of water, and dried; 25·0 g (76%) *XII*, m.p. 192—194°C. Single crystallization from water gave the pure *XII*, m.p. 196—197°C, identical with the product obtained under *A*.

4-Fluoro-2-(4-isopropylphenylthio)benzoic Acid (*XIV*)

4-Isopropylthiophenol[11] (25·4 g) was added to a stirred solution of 34·0 g 85% KOH in 350 ml water at 60°C, the mixture was stirred for 15 min and treated with 1·5 g Cu and 44·0 g 4-fluoro-2-iodobenzoic acid[14]. It was then stirred and refluxed for 8 h. After cooling to 80°C the mixture was diluted with 400 ml warm water (70°C) and filtered while hot. The filtrate was maintained at 60—70°C for preventing crystallization of the potassium salt of *XIV*. The solid on the filter was washed with 100 ml hot water and the filtrate was slowly treated under stirring with 36 ml hydrochloric acid at 60°C. Under stirring it was cooled to 10—15°C and the product was filtered after 2 h standing. It was washed twice with 100 ml cold water and dried; 47·0 g (98%) crude *XIV*, m.p. 190—196°C. Recrystallization from 70% aqueous ethanol gave the pure acid *XIV*, m.p. 201·5—202°C. UV spectrum: λ_{max} 257 nm ($\log \varepsilon$ 4·00), infl. 306 nm (3·60). IR spectrum: 835, 860 (2 adjacent and solitary Ar—H), 920, 1 260, 1 676, 2 550, 2 638, 2 710, 3 140 (COOH), 1 562, 1 600 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·12 (dd, $J_{H-H} = 9·0$ Hz; $J_{H-F} = 6·5$ Hz, 1 H, 6-H), 7·60 and 7·45 (ABq, $J = 8·5$ Hz, 2 + 2 H, 4 ArH of isopropyl-

phenylthio), 7·08 (dt, J_{H-H} = 9·0; 2·5 Hz; J_{H-F} = 9·0 Hz, 1 H, 5-H), 6·35 (q, J_{H-H} = 2·5 Hz; J_{H-F} = 10·0 Hz, 1 H, 3-H), 3·00 (m, 1 H, ArCH), 1·28 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). Ref.[41], m.p. 201–202°C.

4-Fluoro-2-(4-isopropylphenylthio)benzyl Alcohol (*XV*)

A stirred suspension of 29·0 g *XIV* in 200 ml toluene was treated dropwise over 1 h with 80 g 50% sodium dihydridobis(2-methoxyethoxy)aluminate in toluene at 45°C. The solution obtained was stirred for 3 h at room temperature, allowed to stand overnight and decomposed under stirring and cooling by a slow addition of a solution of 15 g NaOH in 150 ml water (30–35°C). The stirring was continued for 1 h at room temperature, the aqueous layer was extracted with 50 ml toluene, the organic layers were combined, dried and evaporated; 26·2 g 93% crude product (88%). Distillation gave the pure *XV*, b.p. 140°C/7 Pa. IR spectrum (film): 828, 859, 900 (2 adjacent and solitary Ar–H), 1 014, 1 037, 1 050 (CH_2OH), 1 480, 1 576, 1 600, 3 035 (Ar), 3 290 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·80–7·40 (m, 5 H, 3,5,6,3′,5′-H_5), 6·70 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), 4·62 (s, 2 H, $ArCH_2O$), 2·80 (m, 1 H, ArCH), 1·40 (s, 1 H, OH), 1·19 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −114·45 (dt, $J_{F-(o-H)}$ = 8·5 Hz; $J_{F-(m-H)}$ = = 6·0 Hz). For $C_{16}H_{17}FOS$ (276·4) calculated: 69·53% C, 6·20% H, 6·88% F, 11·60% S; found: 69·94% C, 6·19% H, 7·24% F, 11·55% S.

4-Fluoro-2-(4-isopropylphenylthio)benzyl Chloride (*XVI*)

A) A stirred and boiling solution of 30·0 g *XV* in 70 ml benzene was treated dropwise with 19·4 g $SOCl_2$ over 45 min, the mixture was refluxed for 30 min and evaporated *in vacuo*. The residue was diluted with 50 ml benzene and evaporation *in vacuo* was repeated. The residue (30·9 g, 97%) is the crude oily *XVI*. Distillation gave the pure substance; b.p. 137–139°C/65 Pa. ^{1}H NMR spectrum: δ 6·50–7·40 (m, 7 H, ArH), 4·68 (s, 2 H, $ArCH_2Cl$), 2·84 (m, 1 H, ArCH), 1·19 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −112·38 (dt, $J_{F-(o-H)}$ = = 8·5 Hz; $J_{F-(m-H)}$ = 6·0 Hz). For $C_{16}H_{16}ClFS$ (294·8) calculated: 65·18% C, 5·47% H, 12·03% Cl, 6·45% F, 10·87% S; found: 65·76% C, 5·41% H, 11·70% Cl, 6·51% F, 10·73% S.

B) A stirred solution of 26·2 g *XV* in 100 ml toluene was treated dropwise over 2 h with 16·0 g $SOCl_2$ at 80°C. Similar processing like under *A*) gave 28·6 g 90% *XVI* (99%) which was used in further step without purification.

C) A boiling solution of 48·5 g 93% *XV* in 125 ml chloroform was treated dropwise over 70 min with 20 ml $SOCl_2$. Similar processing like under *A*) gave 51 g 90% *XVI* which could be used for further step.

D) A mixture of 40 g *XV* and 15 ml pyridine was cooled to 10°C and treated under stirring and cooling over 1 h with 12·5 ml $SOCl_2$, added dropwise (temperature maintained below 20°C). It was stirred for 1 h at 20°C, diluted with 200 ml benzene and heated for 45 min to 40°C. After cooling to 10°C the mixture was decomposed by the slow addition of 70 ml water under stirring. Further 150 ml benzene were added, the organic layer was washed with 150 ml 1M-HCl, 5% $NaHCO_3$ and with water, it was dried with $CaCl_2$ and evaporated; 40·1 g (94%) crude *XVI* distilling without decomposition at 137–139°C/65 Pa. Using higher pressure and higher temperature led to partial decomposition.

4-Fluoro-2-(4-isopropylphenylthio)phenylacetonitrile (*XVII*)

A stirred solution of 161 g 90% *XVI* in 420 ml dimethylformamide was treated with 80 g NaCN. After 20 min stirring without heating (the reaction is exothermic and the temperature raised

spontaneously to 60°C and then began to drop) the mixture was heated on a boiling water bath and stirred for 7 h (temperature of the mixture 85–90°C). Dimethylformamide was distilled off *in vacuo*, the residue was cooled to 40°C and distributed between 750 ml toluene and 600 ml water. The toluene layer was washed with water, dried with $CaCl_2$ and filtered with 20 g active carbon. The filtrate was evaporated *in vacuo* giving 135 g 85% *XVII* (82%). The pure substance was obtained by distillation *in vacuo*; b.p. 148–150°C/13 Pa, m.p. 39–40°C. IR spectrum (film): 828, 860, 900 (2 adjacent and solitary Ar—H), 1 480, 1 600, 3 040 (Ar), 2 235 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·80–7·60 (m, 7 H, ArH), 3·84 (s, 2 H, $ArCH_2CN$), 2·95 (m, 1 H, ArCH), 1·30 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −112·28 (dt, $J_{F-(o-H)}$ = = 8·5 Hz; $J_{F-(m-H)}$ = 6·0 Hz). For $C_{17}H_{16}FNS$ (285·4) calculated: 71·55% C, 5·65% H, 6·66% F, 4·91% N, 11·23% S; found: 71·91% C, 5·58% H, 6·40% F, 4·98% N, 11·41% S.

[4-Fluoro-2-(4-isopropylphenylthio)phenyl]acetic Acid (*XVIII*)

A solution of 125 g 85% KOH in 270 ml water was added to a warm solution of 130 g 85% *XVII* in 800 ml ethanol and the mixture was stirred and refluxed for 9 h. Ethanol was evaporated under reduced pressure, the residue diluted with 2 l water at 50°C and the solution was filtered with 25 g charcoal. The filtrate was acidified under stirring and cooling by a slow addition of 160 ml hydrochloric acid. The separated semi-solid product was extracted with 500 and 400 ml toluene, the combined extracts were filtered with 15 g active carbon and the filtrate was evaporated under reduced pressure. The residue was treated at 65°C with 110 ml hexane and stirred under cooling until the crystallization. After 3 h cooling the product was filtered, washed with hexane and dried; 88·5 g (76%) *XVIII*, m.p. 110–115°C. Recrystallization from 65% ethanol, hexane or cyclohexane gave the pure *XVIII* melting at 115–117°C. ^1H NMR spectrum: δ 11·18 (bs, 1 H, COOH), 6·70–7·50 (m, 7 H, ArH), 3·88 (s, 2 H, $ArCH_2CO$), 2·90 (m, 1 H, ArCH), 1·28 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −114·27 (dt, $J_{F-(o-H)}$ = = 8·5 Hz; $J_{F-(m-H)}$ = 6·0 Hz). Ref.[1], m.p. 115–117°C.

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

A) A mixture of 198 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[1], 180 g 1-(2-hydroxyethyl)piperazine and 320 ml chloroform was stirred and refluxed for 7 h. Chloroform was removed by evaporation *in vacuo*, the residue was dissolved in 1·25 l benzene, the solution was washed twice with 1 l water, and then extracted with a solution of 125 g methanesulfonic acid in 1·25 l water. The organic layer was extracted once more with 150 ml 10% methanesulfonic acid, the acid aqueous layers were combined and made alkaline with 170 ml NH_4OH. The base was isolated by extraction with benzene; 213 g (83%) oily *I* which crystallized after having been triturated with 150 ml toluene, m.p. 93–97°C (toluene). Mass spectrum, *m/z*: 400 (M^+ corresponding to $C_{23}H_{29}FN_2OS$), 369, 271, 129, 99. IR spectrum: 780, 830, 835, 875 (2 adjacent and solitary Ar—H), 1 070, (CH_2OH), 1 485, 1 580, 1 596, 3 040 (Ar), 3 240, 3 415 cm^{-1} (OH). ^1H NMR spectrum: δ 7·45 (d, J = 2·0 Hz, 1 H, 1-H), 6·70–7·40 (m, 5 H, remaining ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, 2 H, CH_2O), 2·90 (s, 1 H, OH), 2·20–3·00 (m, 11 H, 5 CH_2N and ArCH), 1·15 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −117·2 (dt, $J_{F-(o-H)}$ = 7·5 Hz; $J_{F-(m-H)}$ = 6·0 Hz). For $C_{23}H_{29}FN_2OS$ (400·6) calculated: 68·97% C, 7·30% H, 4·74% F, 7·00% N, 8·00% S; found: 69·30% C, 7·58% H, 4·82% F, 7·00% N, 8·08% S.

Monomethanesulfonate was obtained by neutralization of 1·0 g base *I* with 0·24 g methanesulfonic acid in 5 ml acetone; m.p. 193·5–194·5°C (ethanol). For $C_{24}H_{33}FN_2O_4S_2$ (496·7) calculated: 58·04% C, 6·70% H, 3·83% F, 5·64% N, 12·91% S; found: 58·26% C, 6·96% H, 3·75% F, 5·36% N, 12·67% S.

Dimethanesulfonate was obtained by neutralization of 2·1 g base *I* with 1·0 g methanesulfonic acid in a mixture of ethanol and ether; m.p. 211–213°C (ethanol). For $C_{25}H_{37}FN_2O_7S_3$ (592·8) calculated: 50·65% C, 6·29% H, 3·21% F, 4·73% N, 16·23% S; found: 50·70% C, 6·56% H, 3·29% F, 4·70% N, 16·44% S.

Bis(hydrogen maleate) hemihydrate, m.p. 98–101°C (ethanol–ether). For $C_{31}H_{37}FN_2O_9S + 0{\cdot}5\ H_2O$ (641·7) calculated: 58·02% C, 5·97% H, 2·96% F, 4·37% N, 5·00% S; found: 58·04% C, 6·04% H, 3·21% F, 4·29% N, 5·33% S.

Basic (+)-tartrate (2 mol base *I* per 1 mol acid), m.p. 150·5–151·5°C (acetone or ethanol), $[\alpha]_D^{20}$ +7·2° (1% in methanol). This salt is a mixture of both diastereoisomers which were not separated by crystallization. For $C_{50}H_{64}F_2N_4O_8S_2$ (951·2) calculated: 63·13% C, 6·78% H, 3·99% F, 5·89% N, 6·74% S; found: 62·97% C, 6·40% H, 3·96% F, 5·73% N, 6·57% S.

Basic dibenzoyl-(−)-tartrate (2 mol base *I* per 1 mol acid), m.p. 177–178°C (acetone), $[\alpha]_D^{20}$ −35° (1% in methanol). This salt is probably one homogeneous diastereoisomer but the neutral salt was prefered for the resolution. For $C_{64}H_{72}F_2N_4O_{10}S_2$ (1158·4) calculated: 66·30% C, 6·26% H, 3·28% F, 4·83% N, 5·53% S; found: 66·71% C, 6·39% H, 3·02% F, 4·74% N, 5·60% S.

The benzene solution, which remained after the extraction of *I* with aqueous methanesulfonic acid, was washed with water, dried and evaporated; 40 g oily residue considered to be a mixture of neutral by-products. It was dissolved in 40 ml benzene and after the addition of 120 ml hexane, a solid crystallized; 8·6 g (3·5%) 7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl 2-[4-(7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)piperazino]ethyl ether (*II*) monomethanesulfonate, m.p. 182–183°C (benzene–hexane). IR spectrum (KBr): 820, 860, 900 (2 adjacent and solitary Ar—H), 1 035, 1 175 (R—O—R), 1 472, 1 590, 3 000, 3 025, 3 040 (Ar), 2 600 (NH^+), infl. 2 820 cm^{-1} (NCH_2). ^1H NMR spectrum: δ 6·70–7·40 (m, 12 H, ArH), 5·12 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 2·75 (s, 3 H, $CH_3SO_3^-$), 1·18 (d, J = 7·0 Hz, 12 H, 4 CH_3 of isopropyl groups), 2·70–4·20 (m, remaining CH_2 and CH groups). For $C_{41}H_{48}F_2N_2O_4S_3$ (767·0) calculated: 64·20% C, 6·31% H, 4·95% F, 3·65% N, 12·54% S; found: 64·15% C, 6·28% H, 4·93% F, 3·24% N, 12·26% S.

A sample of the salt (2·20 g) was decomposed with NH_4OH and the base *II* was isolated by extraction with benzene; 1·80 g glassy substance (mixture of two racemates). It was used for recording the spectra. Mass spectrum, *m/z* (%): 670 (M^+ corresponding to $C_{40}H_{44}F_2N_2OS_2$, <1%), 399, 384, 369, 356, 299, 286, 285, 271 (100), 229 (26), 196 (18), 99 (18), 56 (18). IR spectrum (KBr): 805, 821, 865 (2 adjacent and solitary Ar—H), 1 100 (R—O—R′), 1 485, 1 599 (Ar), 2 710 cm^{-1} (N—CH_2). ^1H NMR spectrum: δ 6·70–7·50 (m, 12 H, ArH), 5·32 (dd, J = 4·0; 9·0 Hz, 1 H, Ar—CH—O), 3·69 (bt, 2 H, OCH_2), 1·22 and 1·20 (2 d, J = 7·0 Hz, 12 H, 4 CH_3 of the isopropyl groups).

Neutralization of the base *II* with maleic acid in ethanol–benzene gave the maleate monohydrate, m.p. 150–152°C (ethanol). For $C_{44}H_{48}F_2N_2O_5S_2 + H_2O$ (805·0) calculated: 65·65% C, 6·26% H, 4·72% F, 3·48% N, 7·97% S; found: 65·87% C, 6·01% H, 4·96% F, 3·42% N, 8·39% S.

The mother liquor after *II* methanesulfonate was evaporated and the residue was chromatographed on 400 g neutral Al_2O_3 (activity II) using elution with benzene. The least polar fraction (16 g) was distilled; 12·0 g (7%) substance boiling at 163–170°C/70 Pa. The analysis corresponds to $C_{17}H_{15}FS$ and the compound is evidently 7-fluoro-2-isopropyldibenzo[*b,f*]thiepin. UV spectrum: λ_{max} 263·5 nm (log ε 4·33), infl. 293 nm (3·58). IR spectrum (film): 825, 834, 869 (2 adjacent and solitary Ar—H), 1 484, 1 569, 1 590, 3 010, 3 050 cm^{-1} (Ar). Ref.[1], b.p. 140°C/1·3 Pa.

B) (±)-*I* (10·5 g) and 9·80 g dibenzoyl-(+)-tartaric acid were dissolved in 100 ml boiling acetone and the solution was allowed to crystallize for 12 h at room temperature. There were obtained 4·95 g homogeneous neutral (−)-*I* dibenzoyl-(+)-tartrate, m.p. 174–175°C (methanol),

$[\alpha]_D^{20}$ +53·1° (1% in methanol). For $C_{41}H_{43}FN_2O_9S$ (758·9) calculated: 64·89% C, 5·71% H, 2·50% F, 3·69% N, 4·22% S; found: 64·61% C, 5·75% H, 2·44% F, 3·81% N, 4·60% S.

Decomposition of 4·1 g of this salt with NH_4OH and extraction with benzene afforded 2·36 g glassy base (−)-*I* which crystallized from a mixture of benzene and light petroleum, and melted at 93−94°C, $[\alpha]_D^{20}$ −14·4° (1% in methanol). For $C_{23}H_{29}FN_2OS$ (400·6) calculated: 68·97% C 7·30% H, 4·74% F, 7·00% N, 8·00% S; found: 69·34% C, 7·30% H, 4·51% F, 6·90% N, 8·34% S.

(−)-*I monomethanesulfonate*, m.p. 175−176°C (acetone), $[\alpha]_D^{20}$ −14·0° (1% in methanol). For $C_{24}H_{33}FN_2O_4S_2$ (496·7) calculated: 58·04% C, 6·70% H, 3·83% F, 5·64% N, 12·91% S; found: 57·97% C, 6·76% H, 3·67% F, 5·65% N, 12·72% S.

C) A solution of 20·0 g (±)-*I* in 50 ml methanol was neutralized with a solution of 18·8 g dibenzoyl-(−)-tartaric acid in 60 ml methanol. Crystallization by 15 h standing at room temperature gave 12·9 g homogeneous neutral (+)-*I* dibenzoyl-(−)-tartrate, m.p. 178−179°C (methanol), $[\alpha]_D^{20}$ −53·3° (1% in methanol).

Decomposition of 7·4 g of this salt with NH_4OH and extraction with benzene gave 4·0 g glassy base (+)-*I* which crystallized from a mixture of benzene and light petroleum and melted at 93−94°C, $[\alpha]_D^{20}$ +15·2° (1% in methanol).

(+)-*I monomethanesulfonate*, m.p. 174·5−175·5°C (acetone–ethanol), $[\alpha]_D^{20}$ +13·5° (1% in methanol).

11-(4-Ethoxycarbonylpiperazino)-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IV*)

A stirred mixture of 16·3 g 11-chloro-7-fluoro-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] and 33 g 1-(ethoxycarbonyl)piperazine was heated for 5 h to 110°C. After standing overnight the mixture was distributed between 120 ml benzene and 120 ml water, the benzene layer was washed with water and evaporated. The residue (22·5 g) was dissolved in 50 ml hexane and the solution was acidified with a solution of HCl in ether. After 1 h standing the precipitated hydrochloride (16·4 g, m.p. 120−121°C) was filtered and washed with benzene. It was suspended in 150 ml water, the suspension was made alkaline with NH_4OH and the product was isolated by extraction with benzene; 14·6 g (64%) oily *IV*. A solution of 1·3 g crude *IV* in 10 ml hexane was treated with a solution of 0·35 g maleic acid in 2 ml ethanol; 1·5 g (91%) hydrogen maleate, m.p. 167−169°C (ethanol). For $C_{28}H_{33}FN_2O_6S$ (544·6) calculated: 61·75% C, 6·11% H, 3·49% F, 5·14% N, 5·88% S; found: 61·69% C, 6·18% H, 3·71% F, 5·00% N, 5·94% S.

7-Fluoro-2-isopropyl-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*III*)

A solution of 13·3 g *IV* and 7·0 g 85% KOH in 15 ml ethanol was stirred and refluxed for 3 h (bath of 120°C), ethanol was evaporated and the residue was distributed between 120 ml benzene and 120 ml water. The residue was crystallized from 18 ml cyclohexane; 8·1 g (73%), m.p. 121 to 123°C. Analytical sample, m.p. 122−124°C (cyclohexane). ^{1}H 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, $ArCH_2CHAr$), 2·80 (m, 5 H, $CH_2N^4CH_2$ of piperazine and ArCH of isopropyl), 2·58 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 1·52 (bs, 1 H, NH), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). ^{19}F NMR spectrum: δ −117·2 (dt, $J_{F-(o-H)}$ = 8·0 Hz; $J_{F-(m-H)}$ = 5·5 Hz). For $C_{21}H_{25}FN_2S$ (356·5) calculated: 70·75% C, 7·07% H, 5·33% F, 7·86% N, 8·99% S; found: 70·92% C, 7·33% H, 5·24% F, 7·86% N, 8·90% S.

Maleate hemihydrate, m.p. 162°C with first changes at 84°C (ethanol–ether). For $C_{25}H_{29}FN_2O_4S$ + 0·5 H_2O (481·6) calculated: 62·35% C, 6·28% H, 3·95% F, 5·82% N, 6·66% S; found: 62·79% C, 6·49% H, 3·89% F, 5·96% N, 6·78% S.

7-Fluoro-11-[4-(2-hydroxyethyl)piperazino]-2-isopropyl-
-10,11-dihydrodibenzo[*b,f*]thiepin 5-Oxide (*XIX*)

A solution of 6·0 g *I* monomethanesulfonate in 35 ml water was treated with 35 ml 27% H_2O_2 and the mixture was allowed to stand for 72 h at room temperature. The solution was then decanted from the oily substance on the walls, made alkaline with 15 ml NH_4OH and extracted with benzene. Processing of the extract gave 3·77 g (75%) glassy base *XIX* which is seemingly homogeneous (TLC) but probably consists of both possible racemates. Neutralization with maleic acid in a small volume of acetone, evaporation, addition of 40 ml ether and slow addition of 10 ml ethanol with stirring induced crystallization of the maleate, m.p. 164–165°C (ethanol). IR spectrum: 848, 858, 875, 895 (2 adjacent and solitary Ar–H), 1 075 (CH_2OH), 1 090 (Ar_2SO), 1 362, 1 388 (CH_3 of isopropyl), 1 490, 1 580, 3 010, 3 063 (Ar), 3 300 cm^{-1} (OH). Polarographic reduction in 0·5M-HCl (towards a saturated calomel electrode), $E_{1/2} = -0{\cdot}49$ V (sulfoxide). For $C_{27}H_{33}FN_2O_6S$ (532·6) calculated: 60·88% C, 6·24% H, 3·57% F, 5·26% N, 6·02% S; found: 60·99% C, 6·27% H, 3·41% F, 5·16% N, 6·10% S.

7-Fluoro-2-isopropyl-11-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin 5-Oxide (*XX*)

III (4·5 g) was dissolved in a solution of 1·34 g methanesulfonic acid in 60 ml water, the solution was filtered and treated with 32 ml 30% H_2O_2. The mixture was allowed to stand at room temperature for 48 h. The cloudy solution formed was filtered with 3 g active carbon, the filtrate made alkaline with NH_4OH and the base was isolated by extraction with benzene. Processing of the extract gave 3·8 g (81%) *XX*, m.p. 147–152°C. Analytical sample, m.p. 161–162°C (acetone). UV spectrum: λ_{max} 226 nm (log ε 4·13), 273 nm (3·40), 280 nm (3·32). IR spectrum (KBr): 806, 825, 848, 859, 874, 884, 893 (2 adjacent and solitary Ar–H), 1 060 (Ar_2SO), 1 483, 1 587, 3 048 (Ar), 2 780, 2 800, 2 820 (N–CH_2), 3 230, 3 310 cm^{-1} (NH). ^1H NMR spectrum: δ 6·70–7·70 (m, 6 H, ArH), 4·18 (dd, J = 9·0; 4·0 Hz, 1 H, Ar–CH–N), c. 3·30 (m, 2 H, $ArCH_2$), 2·60 to 2·90 (m, 9 H, 4 CH_2N and ArCH of isopropyl), 1·85 (bs, 1 H, NH), 1·25 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). Polarographic reduction in 0·25M-H_2SO_4, $E_{1/2} = -0{\cdot}71$ V. For $C_{21}H_{25}FN_2OS$ (372·5) calculated: 67·71% C, 6·76% H, 5·10% F, 7·52% N, 8·61% S; found: 67·42% C, 6·88% H, 4·98% F, 7·30% N, 8·64% S.

Dimethanesulfonate, solvate with ethanol, m.p. 133–135°C (ethanol). Mass spectrum, *m/z*: 372 (M^+ corresponding to $C_{21}H_{25}FN_2OS$), 355·1636 ($C_{21}H_{24}FN_2S$, calculated 355 . 1644, typical cleavage of OH in the S-oxide), 316, 287, 271, 257, 238, 223, 197, 196, 85, 56. IR spectrum: 840, 895 (2 adjacent and solitary Ar–H), 1 040 (Ar_2SO), 1 145, 1 220 (C–N), 1 600 (Ar), 2 533, 2 590, 2 685, 2 750 (NH^+), 3 420 cm^{-1} (OH of ethanol). For $C_{23}H_{33}FN_2O_7S_3 + C_2H_5OH$ (610·8) calculated: 49·16% C, 6·44% H, 3·11% F, 4·58% N, 15·75% S; found: 49·26% C, 6·56% H, 3·37% F, 4·69% N, 15·36% S.

7-Fluoro-11-[4-(2-hydroxyethyl)piperazino]-2-isopropyl-
-10,11-dihydrodibenzo[*b,f*]thiepin N^4-Oxide (*XXI*)

A solution of 6·0 g *I* in 40 ml 95% ethanol was treated with 2·85 ml 27·5% H_2O_2 and the mixture was allowed to stand overnight at room temperature. Then it was heated for 3 h under reflux on the boiling water bath. The excess of peroxide was removed by refluxing for 1 h with a small tin of Pt, the mixture was diluted with water, ethanol was evaporated *in vacuo* and the product was isolated by extraction with chloroform. Processing of the extract gave the crude product which crystallized after trituration with 30 ml light petroleum; 5·25 g (84%). Crystallization from a mixture of acetone and light petroleum afforded the hemihydrate, m.p. 104–105°C. IR spectrum (KBr): 815, 822, 870 (2 adjacent and solitary Ar–H), 911 (N–O), 1 088 (CH_2OH),

1 490, 1 585, 1 599 (Ar), 3 200 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70—7·40 (m, 6 H, ArH), 4·60 (bs, 1·5 H, OH and 0·5 H_2O), 2·00—4·20 (m, 7 CH_2 and 2 CH), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). Polarographic reduction in 0·5M-HCl, $E_{1/2}$ = −0·30 V. For $C_{23}H_{29}FN_2O_2S$ + 0·5 H_2O (425·5) calculated: 64·90% C, 7·10% H, 4·47% F, 6·58% N, 7·53% S; found: 64·57% C, 7·30% H, 4·11% F, 6·45% N, 7·37% S.

Dihydrochloride monohydrate, m.p. 147—148°C (ethanol–ether). For $C_{23}H_{31}Cl_2FN_2O_2S$ + + H_2O (276·2) calculated: 54·44% C, 6·55% H, 13·97% Cl, 3·74% F, 5·51% N, 6·32% S; found: 54·96% C, 6·04% H, 13·84% Cl, 3·89% F, 5·42% N, 6·38% S.

7-Fluoro-11-[4-(2-hydroxyethyl)piperazino]-2-isopropyl--10,11-dihydrodibenzo[*b*,*f*]thiepin S,N^4-Dioxide (*XXII*)

A) A solution of 6·7 g *XXI* . 2 HCl . H_2O in 70 ml water was treated with 50 ml 30% H_2O_2 and the mixture was allowed to stand overnight at room temperature. The solution was separated by decantation from the insoluble substance, filtered with active carbon, the filtrate was made alkaline with NH_4OH, and extracted with chloroform. Processing of the extract gave 1·5 g (26%) crude product which crystallized from acetone and melted at 205°C. Mass spectrum, *m/z*: 432 (M^+ corresponding to $C_{23}H_{29}FN_2O_3S$), 430, 414, 399, 388, 329, 316, 287, 271, 129, 127, 100. IR spectrum: 811, 842, 883 (2 adjacent and solitary Ar—H), 982 (N—O), 1 089 (CH_2OH, SO), 1 490, 1 603, 3 028 (Ar), infl. 2 700 cm^{-1} (N···HO). ^1H NMR spectrum: δ 7·70 (d, J = 8·0 Hz, 1 H, 4-H), 6·80—7·60 (m, 5 H, remaining ArH), *c.* 6·50 (bs, 1 H, OH), 2·40—4·50 (m, 7 CH_2 and 2 CH), 1·20 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). Polarographic reduction in 0·5M-HCl, $E_{1/2}$ = −0·18 V (N—O) and −0·45 V (SO). For $C_{23}H_{29}FN_2O_3S$ (432·5) calculated: 63·86% C, 6·76% H, 4·39% F, 6·48% N, 7·41% S; found: 63·98% C, 6·96% H, 4·49% F, 6·27% N, 7·46% S.

B) *XIX* (3·77 g glassy base) was dissolved in 25 ml 95% ethanol, the solution was treated with 1·7 ml 27·5% H_2O_2, the mixture was allowed to stand overnight at room temperature, and refluxed for 3 h. Excess of H_2O_2 was removed by 1 h heating with a piece of Pt tin, the mixture was diluted with 25 ml water and evaporated *in vacuo*. The residue was dissolved in 100 ml chloroform, the solution was dried with K_2CO_3, filtered and evaporated. The residue crystallized after having been dissolved in 6 ml acetone; 2·7 g (69%), m.p. 203—204°C. The product is identical with that obtained under *A*.

11-(3-Chloropropoxy)-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXV*)

XXIV (13·7 g) (ref.[47]) and 7·5 g 3-chloropropanol were dissolved in 100 ml dichloromethane by warming, the solution was cooled to 20°C and treated dropwise under stirring with 7·0 ml BF_3 . $O(C_2H_5)_2$ over 20 min. The mixture was stirred for 3 h at room temperature, decomposed with 100 ml water, the organic layer was washed with water, dried with K_2CO_3 and evaporated. The residue was dissolved in a mixture of 40 ml benzene and 20 ml light petroleum and chromatographed on a column of 250 g silica gel. Elution with the mixture of 1 : 1 benzene and light petroleum gave first 3·85 g (30%) less polar product which crystallized from ethanol and melted in completely pure state at 70—72°C. It was identified as 2-methylthiodibenzo[*b*,*f*]thiepin (*XXIX*). ^1H NMR spectrum: δ 7·00—7·50 (m, 7 H, ArH), 7·11 and 6·88 (ABq, J = 13·0 Hz, 1 + 1 H, ArCH=CHAr), 2·40 (s, 3 H, SCH_3). For $C_{15}H_{12}S_2$ (256·4) calculated: 70·26% C, 4·72% H, 25·02% S; found: 70·50% C, 4·76% H, 24·88% S. Ref.[47], m.p. 89—91°C (apparently a crystal modification).

Continued elution gave 7·71 g (44%) oily *XXV* which did not crystallize. A sample of the homogeneous middle fraction was analyzed. For $C_{18}H_{19}ClOS_2$ (350·9) calculated: 61·60% C, 5·46% H, 10·10% Cl, 18·27% S; found: 62·50% C, 5·59% H, 9·68% Cl, 18·30% S.

11-(3-Bromopropoxy)-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVI*)

A similar reaction of 14·8 g *XXIV* (ref.[47]) and 11·4 g 3-bromopropanol in 150 ml benzene with 8·0 ml $BF_3 . O(C_2H_5)_2$ and similar processing gave 19·2 g mixture which was dissolved in 50 ml 1 : 1 benzene–light petroleum, and chromatographed on 300 g silica gel. Elution with 1 : 1 benzene–light petroleum gave first 4·32 g (31%) 2-methylthiodibenzo[*b*,*f*]thiepin (*XXIX*), m.p. 70—72°C (ethanol). It was followed by 7·35 g (35%) oily *XXVI* which was analyzed without further purification. For $C_{18}H_{19}BrOS_2$ (395·4) calculated: 54·68% C, 4·84% H; found: 54·58% C, 4·98% H.

11-(3-Iodopropoxy)-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVII*)

A solution of 3·0 g NaI in 30 ml 2-butanone was treated with 4·6 g crude *XXV* and the mixture was stirred and refluxed for 15 h. After cooling NaCl was filtered off, washed with 2-butanone and the filtrate was evaporated *in vacuo*. The residue was distributed between 80 ml water and 80 ml benzene, the organic layer was washed with a 10% solution of $Na_2S_2O_3$ and with 5% $NaHCO_3$, it was dried with $MgSO_4$ and evaporated; 5·24 g (90%) oil which was used in the following reaction. For $C_{18}H_{19}IOS_2$ (442·4) calculated: 14·50% S; found: 14·97% S.

2-Methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yl
3-[4-(2-Methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yl)piperazino]propyl Ether (*XXIII*)

A mixture of 3·4 g 2-methylthio-11-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[45,49], 4·8 g crude *XXVII*, 1·7 g K_2CO_3 and 7 ml chloroform was stirred for 9 h under reflux in a bath of 90°C. After cooling the mixture was treated with 3 ml NH_4OH and distributed between 80 ml chloroform and 80 ml water. The organic layer was washed with 10% $Na_2S_2O_3$ and water, dried with K_2CO_3, and evaporated *in vacuo*. The residue was dissolved in 20 ml benzene and chromatographed on a column of 200 g silica gel. Benzene and chloroform eluted small amount of less polar impurities. Chloroform containing 5% ethanol eluted 6·31 g (97%) glassy *XXIII* which did not crystallize. Its neutralization with maleic acid in a mixture of benzene and ethanol gave the maleate, m.p. 96—100°C (benzene–ether). For $C_{41}H_{44}N_2O_5S_4$ (773·0) calculated: 63·70% C, 5·74% H, 3·62% N, 16·59% S; found: 63·43% C, 5·82% H, 3·41% N, 16·29% S.

A sample of the maleate was decomposed with NH_4OH and the glassy base *XXIII*, which was isolated by extraction with benzene, was used for recording the spectra. IR spectrum: 750, 805, 885 (4 and 2 adjacent and solitary Ar—H), 1 100 (R—O—R'), 1 575 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60—7·60 (m, 14 H, ArH), 5·29 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 2·32 and 2·28 (2 s, 6 H, 2 SCH_3), 1·50—4·00 (m, remaining CH_2 and CH groups).

11-Decanoyloxy-2-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXVIII*)

A mixture of 5·5 g *XXIV* (ref.[47]), 60 ml benzene, 5·5 g K_2CO_3 and 5·7 g decanoyl chloride was stirred and refluxed for 5 h. After cooling it was diluted with 50 ml benzene and washed several times with water. The benzene solution was dried with K_2CO_3 and evaporated. The residue (6·6 g) was dissolved in 30 ml light petroleum and the solution was allowed for 2 h to crystallize; 1·7 g starting *XXIV*, m.p. 113—115°C, were recovered. The filtrate was evaporated, the residue was dissolved in 15 ml light petroleum and chromatographed on a column of 150 g silica gel. The product was eluted with a mixture 4 : 3 of light petroleum and benzene; 3·0 g (50% per conversion) homogeneous oil. A sample was distilled in vacuo of 26 Pa; the distillation proceeded at a bath temperature of 260°C under partial decomposition. The oily product from the chromatography was used for analysis and recording the ^1H NMR spectrum: δ 6·90—7·60 (m, 7 H, ArH),

6·45 (dd, $J = 4·0$; 8·0 Hz, 1 H, Ar—CH—O), c. 3·60 (m, 2 H, $ArCH_2$), 2·40 (s, 3 H, SCH_3), 2·30 (t, $J = 7·0$ Hz, 2 H, CH_2CO), 1·65 (m, 2 H, CH_2 adjacent to methyl), 1·30 (bs, 12 H, 6 CH_2 in the middle of nonyl), 0·90 (def. t, 3 H, CH_3 of nonyl). For $C_{25}H_{32}O_2S_2$ (428·6) calculated: 70·05% C, 7·53% H, 14·96% S; found: 70·05% C, 7·66% H, 14·82% S.

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