FLUORINATED TRICYCLIC NEUROLEPTICS WITH PROLONGED ACTION: 3-FLUORO-8-TRIFLUOROMETHYL DERIVATIVES OF 10-(4-METHYLPIPERAZINO)- AND 10-[4-(2-HYDROXYETHYL)PIPERAZINO]-10,11-DIHYDRODIBENZO-[*b*,*f*]THIEPIN*

Karel Šindelář,[a] Miroslav Ryska,[a] Jiří Holubek,[a] Emil Svátek,[a] Jiřina Metyšová,[a] Jiří Protiva[b] and Miroslav Protiva[a]

[a] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3 and*
[b] *Institute of Organic Chemistry, Charles University, 128 40 Prague 2.*

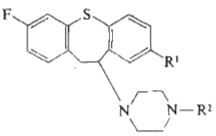
Received May 26th, 1980

A reaction of (4-fluoro-2-iodophenyl)acetic acid with 4-(trifluoromethyl)thiophenol gave the acid *VIII* which was cyclized with the reagent consisting from methanesulfonic acid and phosphorus pentoxide and afforded the methanesulfonic enol ester *XIX*. The alkaline hydrolysis resulted in 3-fluoro-8-trifluoromethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVI*) which was transformed *via* the alcohol *XXIV* to the chloro derivative *XXV*. Substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine resulted in the title compounds *IV* and *V*. These products are very potent cataleptic neuroleptic agents with a prolongation of duration of the effects comparable to that of isofloxythepin and tefluthixol. A series of further synthetic experiments aimed at alternative syntheses of the acid *VIII* and the ketone *XVI*; their results were mostly not of use for preparative purpose but they led to isolation and characterization of a series of interesting heterocyclic products (*XVII*, *XVIII*, *XXII*, *XXIII*, *XXIX*—*XXXI*, *XXXVI*—*XXXIX*).

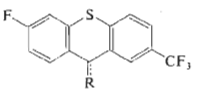
In the group of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin derivatives having central depressant and neuroleptic activity, the introduction of the fluorine atom to position 3 led to compound *I*, representing a very potent tranquilizer with clear prolongation of the effect. At the same time, this compound failed to reveal the neuroleptic character[1]. For attaining the neuroleptic effect, the presence of a "neuroleptic substituent" in position 8 of the skeleton is indispensable; molecules of compounds *II* (ref.[2]) and *III* (ref.[3]) are examples showing the correctness of this conclusion. The 3-fluoro-8-R^1 substitution is simultaneously a precondition of a long-lasting neuroleptic effect after the oral administration which is explained by the blockade of the metabolic hydroxylation by the fluorine atom in position 3 of the skeleton[4–6]. A similar substitution pattern in structures of the neuroleptic agents in the thioxanthene series forms the precondition of similar properties: maximum intensity of the neuroleptic effect and its long duration[2,7]. In this series, a combination of the fluorine

* Part CXLV in the series Neurotropic and Psychotropic Agents; Part CXLIV: This Journal *45*, 3182 (1980).

atom with trifluoromethyl as substituents seems to be optimum; it is demonstrated by the outstanding properties of the experimental agents tefluthixol (*VI*) (ref.[8,9]) and pifluthixol (*VII*) (ref.[10,11]). In our series, an information about this combination of substituents has been lacking until now; we are describing in the present communication the synthesis and pharmacology of the title compounds *IV* and *V* (a part of the synthesis was mentioned in a preliminary communication[12]).



I, $R^1 = H$, $R^2 = CH_3$
II, $R^1 = Cl$, $R^2 = CH_3$
III, $R^1 = SCH_3$, $R^2 = CH_3$
IV, $R^1 = CF_3$, $R^2 = CH_3$
V, $R^1 = CF_3$, $R^2 = CH_2CH_2OH$



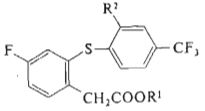
VI, $R = (CH_2)_3N$ NCH$_2$CH$_2$OH

VII, $R = =CH(CH_2)_2N$ (H, CH$_2$CH$_2$OH)

In the synthesis of compounds *IV* and *V* we used the acid *VIII* as the key intermediate; it was obtained by reaction of (4-fluoro-2-iodophenyl)acetic acid[1] with 4-(trifluoromethyl)thiophenol[13-16] in dimethylformamide in the presence of potassium carbonate and copper at 140°C; the disadvantage of this method is the relatively uneasy accessibility of both of the starting compounds. This fact led to a series of further synthetic attempts described in the second part of this paper. For continuing the synthesis, it was necessary to carry out the cyclization of the acid *VIII* to 3-fluoro--8-trifluoromethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVI*). In this line, we had to expect at least some of the complications encountered during cyclizations of analogous acids containing the trifluoromethyl group as substituent[17,20]. In agreement with this expectation, a reaction of the acid *VIII* with polyphosphoric acid in 1,2-dichlorobenzene at 160°C gave only 8% of the ketone *XVI* in addition to some 40% of the keto acid *XVII*. An attempt to cyclize the acid *VIII* by means of hydrogen fluoride led to the ketone *XVI* in a yield of about 10%; most of the acid *VIII* was recovered

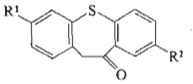
unchanged. Similar results were obtained in cyclization experiments with polyphosphoric acid at lower temperature (140°C) or with polyphosphoric ester at 120°C. These unfavourable results induced us to try a reagent which is obtained by dissolving one part of phosphorus pentoxide in ten parts of methanesulfonic acid and which was characterized as a convenient alternative to polyphosphoric acid[21]. The first attempt to cyclize the acid *VIII* with this reagent was carried out in chlorobenzene at 125°C. There was obtained a heterogeneous neutral product which was first distilled and the fractions obtained were then purified by crystallization, and chromatography, respectively. The main product was 4-chlorophenyl methyl sulfone, formed by interaction of the reagent with the medium used. The melting point found is in agreement with the value given in the literature[22]. The smooth formation of aryl methyl sulfones by reactions of aromatics with methanesulfonic anhydride is known[23] and the presence of this anhydride in the reagent used has to be considered almost sure. From a higher boiling fraction a crystalline compound $C_{16}H_{10}F_4O_3S_2$ was obtained, the UV spectrum of which indicated the presence of the dibenzo[*b*,*f*]thiepin chromophore. The substance was identified by means of the ^{1}H-NMR spectrum as the methanesulfonic ester of the enol form of the ketone *XVI*, *i.e.* as compound *XIX*. This structure was confirmed by the easy transformation by alkaline hydrolysis to the ketone *XVI*. Chromatography of the mother liquors after the crystalline products led to the isolation of a small amount of a further crystalline substance having a composition $C_{13}H_9ClF_4OS$. The presence of chlorine indicates the participation of chlorobenzene in the construction of its molecule. The tentative structure *XXII* is suggested which is not at variance with the spectra recorded. It is presumed that a small part of chlorobenzene is oxidized during the reaction with air oxygen (the oxidation could be catalyzed by traces of copper contained in the greenish starting acid *VIII*, the preparation of which was catalyzed by copper) to chlorophenols with predominating 4-chlorophenol (for oxidation of aromatics by air oxygen to phenols, *cf.*[24]). Reaction of 4-chlorophenol with the methanesulfonic ester *XIX* could then result in the corresponding 4-chlorophenyl enol ether which was stabilized by spontaneous dehydrogenation (influence of air oxygen again) to the furan derivative *XXII*. We suppose thus a similar mechanism like in the formation of furo[2,3-*m*; 4,5-*m'*]-bis(dibenzo[*b*,*f*]thiepin) derivatives from dibenzo[*b*,*f*]thiepin-10(11*H*)-ones observed repeatedly[25]; similar reactions are evidently the formation of 2,3,4,5-tetraphenylfuran from deoxybenzoin[26] and formation of diphenanthro[9,10-*b*; 9',10'-*d*]furan from phenanthrene derivatives[27,28]. The complicated course of the cyclization reaction could be simplified by elimination of chlorobenzene and use of 1,1,2,2-tetrachloroethane as the reaction medium; the crude primary product was immediately hydrolyzed with ethanolic sodium hydroxide and the ketone *XVI* was obtained in a yield of 42%. In one case, the alkaline reaction mixture was allowed to stand for a longer time without protection against the contact with air and the ketone *XVI* was not obtained at all. A different crystal-

line compound was isolated instead as the main reaction product, having the composition $C_{16}H_{11}F_3O_2S$. Its IR spectrum indicated the character of a diaryl ketone and the presence of an aromatic ether fragment. These facts are compatible with formulating the compound as 2-trifluoromethyl-6-ethoxythioxanthone (*XXIII*). Its origin is to be explained by the following sequence of reactions: the primarily formed ketone *XVI* was oxidized with air oxygen to the corresponding 10,11-diketone, this underwent a benzilic rearrangement, the α-hydroxy acid formed was decomposed to the ketone (for a similar formation of thioxanthone, *cf.*[29]) and the final step was the nucleophilic substitution of the already activated fluorine atom by the action of the ethoxide anion.

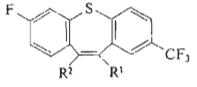


VIII, $R^1 = R^2 = H$
IX, $R^1 = H$, $R^2 = NO_2$
X, $R^1 = H$, $R^2 = NH_2$
XI, $R^1 = H$, $R^2 = CN$

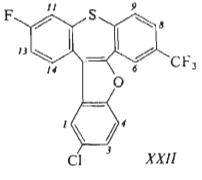
XII, $R^1 = H$, $R^2 = CONH_2$
XIII, $R^1 = H$, $R^2 = COOH$
XIV, $R^1 = CH_3$, $R^2 = COOCH_3$
XV, $R^1 = CH_3$, $R^2 = COOH$



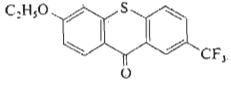
XVI, $R^1 = F$, $R^2 = CF_3$
XVII, $R^1 = F$, $R^2 = COOH$
XVIII, $R^1 = OCH_3$, $R^2 = CF_3$



XIX, $R^1 = OSO_2CH_3$, $R^2 = H$
XX, $R^1 = R^2 = H$
XXI, $R^1 = OH$, $R^2 = COOCH_3$

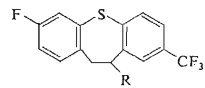


XXII



XXIII

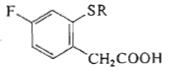
Reduction of the ketone *XVI* with sodium borohydride in aqueous dioxane afforded the alcohol *XXIV* which was treated by boiling thionyl chloride and gave the chloro derivative *XXV*. Substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in boiling chloroform resulted in the piperazine derivatives *IV* and *V*. 7-Fluoro-2-trifluoromethyldibenzo[*b*,*f*]thiepin (*XX*) was obtained in a rather important amount as the neutral by-product of the simultaneously proceeding elimination reaction.



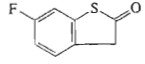
XXIV, R = OH
XXV, R = Cl

The just described synthesis of compounds *IV* and *V* was preceded by several synthetic attempts at the possibility of avoiding the use of 4-(trifluoromethyl)thiophenol as the intermediate; these attempts were directed to an alternative synthesis of the acid *VIII*. It was the intention to start from 4-chlorobenzotrifluoride and proceed *via* 4-chloro-3-nitrobenzotrifluoride[30], further the nitro acid *IX* and the amino acid *X*. Elimination of the amino group should lead to the desired acid *VIII*. To this end we needed in the first line as the thiophenol component the unknown (4-fluoro-2-mercaptophenyl)acetic acid (*XXVI*). It was obtained from the sodium salt of (2-amino-4-fluorophenyl)acetic acid[1] by diazotization, the following reaction of the diazonium salt solution with a solution of sodium disulfide and by reduction of the formed disulfide diacid with zinc in acetic acid. The acid *XXVI* was obtained in this way in a rather low yield; the majority of the product did not crystallize and was subjected to steam distillation from dilute sulfuric acid which resulted in obtaining the thiolactone *XXVIII* from the distillate. This thiolactone has the same synthetic utility as the free acid *XXVI*. From the distillation residue there was obtained a small amount of the acid $C_{16}H_{12}F_2O_4S$ which was identified as 5,5'-difluorodiphenyl sulfide-2,2'-diacetic acid (*XXVII*). It was probably formed already in the step of reaction of the diazonium salt with sodium disulfide solution which evidently contained some sulfide. The literature[31,32] described procedures of preparation of the analogous (2-mercaptophenyl)acetic acid from (2-aminophenyl)acetic acid by diazotization, the following reaction with potassium ethyl xanthate and by the final alkaline hydrolysis. The nitro acid *IX* was obtained in a high yield by a reaction of the thiolactone *XXVIII* with 4-chloro-3-nitrobenzotrifluoride[30] in boiling aqueous ethanol in the presence of potassium carbonate and a small amount of potassium iodide. A by-product $C_{23}H_{12}F_5NO_4S_2$ was separated in a very small quantity; the composition

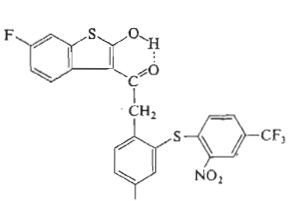
indicates that two fragments of the thiolactone *XXVIII* and one fragment of 4-chloro--3-nitrobenzotrifluoride participate on the construction of the molecule. The ^{1}H-NMR spectrum shows the presence of one very acid hydrogen atom which, however, does not belong to a carboxyl group (IR spectrum). The bands in the IR spectrum at 1600 and 1621 cm^{-1} indicate the presence of a chelate formed by the hydrogen bond between an enol hydroxyl and the oxygen of a keto group; the chelate character was confirmed by the blue coloration obtained by the reaction of the substance with ferric chloride in ethanol. The product is formulated as *XXIX*, *i.e.* the enol form of the starting thiolactone *XXVIII* acylated to position 3 by the whole residue of the nitro acid *IX*. For explaining the unusual acylation we suppose that the nitro acid *IX* reacted with a small quantity of 4-chloro-3-nitrobenzotrifluoride under the formation of an activated ester which was then responsible for the acylation under unusual conditions.



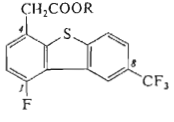
XXVI, R = H
XXVII, R =



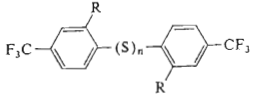
XXVIII



XXIX



XXX, R = H
XXXI, R = C_2H_5

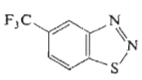


XXXII, R = NO_2, $n = 2$
XXXIII, R = NO_2, $n = 1$
XXXIV, R = NH_2, $n = 2$
XXXV, R = NH_2, $n = 1$

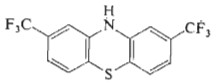
The reduction of the nitro acid *IX* to the amino acid *X* proceeded smoothly with the use of hydrazine hydrate in ethanol in the presence of ferric chloride. The elimination of the amino group, carried out by diazotization of the amino acid *X* in a mixture of ethanol and hydrochloric acid and by reduction of the diazonium salt with hypophosphorous acid, was also successful and the acid *VIII* was obtained in a yield of 70%. Two different by-products were isolated. The first one was a carboxylic acid which was separated from the acid *VIII* on the basis of a low solubility of the sodium salt. The second has the character of an ester (ν(COOR) 1729 cm^{-1}) and was thus easily isolated as a substance insoluble in the sodium hydroxide solution. The mass spectra and analyses determined the composition $C_{15}H_8F_4O_2S$, and $C_{17}H_{12}F_4O_2S$, respectively. We are evidently dealing here with an acid and the corresponding ethyl ester. The UV spectrum indicates a strong conjugation and the presence of an aromatic polycycle. The only polycycle which can be considered is dibenzothiophene and the products have then the structures *XXX* and *XXXI*. Diazotization of a 2-aminodiphenyl sulfide derivative as the source of formation of a dibenzothiophene derivative was already observed by us earlier[33].

We attempted further to use bis(2-amino-4-trifluoromethylphenyl) disulfide (*XXXIV*) which was mentioned in a patent[34]. The compound is accessible *via* the dinitro disulfide *XXXII* (ref.[35]) obtained by a reaction of 4-chloro-3-nitrobenzotrifluoride[30] with a sodium disulfide solution. We could establish that the crude product obtained in this way is not homogeneous and is contaminated by the sulfide *XXXIII* whose preparation by different methods was described in the literature[36]. We carried out the reduction of the dinitro disulfide *XXXII* to the diamino disulfide *XXXIV* with hydrazine hydrate in ethanol in the presence of ferric chloride. From the product so obtained, we tried to eliminate the amino group by diazotization in a mixture of ethanol and hydrochloric acid and by the following reduction with hypophosphorous acid. A heterogeneous product was formed which was separated on a column of alumina. Two products were isolated, both of them containing nitrogen, which were in the first line characterized by spectra and analyses. The main product is a little polar and low-melting substance $C_7H_3F_3N_2S$ and the minor product is a more polar compound $C_{14}H_7F_6NS$. The product with the small molecule was identified as the new 5-trifluoromethyl-1,2,3-benzothiadiazole (*XXXVI*). Its formation is not surprising since it is known that 1,2,3-benzothiadiazoles are generally formed by reactions of 2-aminothiophenols or the corresponding disulfides with nitrous acid[37]. For the more polar product, the structure of 2,8-bis(trifluoromethyl)phenothiazine (*XXXVII*) has been suggested and confirmed by the ^{1}H-NMR spectrum. Roe and coworkers[38] attempted without success to prepare this compound by heating bis(2-amino-4-trifluoromethylphenyl) sulfide (*XXXV*) with zinc chloride. In our case, the sulfide *XXXV* must have been the precursor of the obtained phenothiazine derivative *XXXVII*; the formation of *XXXVII* is explained by a nucleophilic intramolecular reaction of the partially deaminated diamino sulfide *XXXV*. This com-

pound formed a contamination of the used diamino disulfide *XXXIV* which was proven in the next experiment.



XXXVI

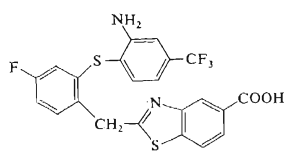


XXXVII

The crude dinitro disulfide *XXXII* was reduced according to the literature[35] with zinc and hydrochloric acid to the crude zinc salt of 2-amino-4-trifluoromethylthiophenol and an attempt was carried out to react this compound with (4-fluoro-2-iodophenyl)acetic acid[1] in a boiling aqueous potassium hydroxide solution in the presence of copper. An inhomogeneous product was formed which was chromatographed on a column of silica gel. The diamino sulfide *XXXV*, identical with the compound described in the literature[38], was isolated as the least polar product. Its isolation proves that it must have been present also in the crude diamino disulfide *XXXIV*, used in the preceding experiment. The desired amino acid *X* was isolated as the more polar product in a yield of about 20%; the procedure used is not suitable for preparing the acid *X*. In a similar amount, a more polar compound with a high melting point was finally isolated, for which the mass spectrum and the analyses established the formula $C_{22}H_{14}F_4N_2O_2S_2$. For proposing a plausible structure it was necessary to suppose that the interaction of the *o*-aminothiol fragment with carboxyl or one trifluoromethyl led to the formation of the benzothiazole system (a general synthesis of benzothiazole derivatives, *cf.*[39,40]); simultaneously, one trifluoromethyl was destroyed by the just mentioned reaction or by hydrolysis to carboxyl. Three isomeric structures were suggested, all of them rather compatible with the IR spectrum recorded. On the basis of the ^{1}H-NMR spectrum, however, it is necessary to prefer the structure *XXXVIII* with regard to the chemical shifts corresponding to the hydrogen atoms in the vicinity of carboxyl on the nucleus with the simultaneous absence of the free amino group on the same nucleus. This formula implies the presumption that one trifluoromethyl was hydrolyzed to carboxyl. It would be very unusual if this hydrolysis would have taken place in the last step, *i.e.* in an alkaline medium; it is, however, impossible to exclude that the hydrolysis took place already during the reduction of the nitro group in an acid medium and that the zinc salt of the corresponding carboxylic acid formed a contamination of the crude zinc salt of 2-amino-4-trifluoromethylthiophenol[35].

The last synthetic experiment carried out had the purpose to construct a suitable dibenzo[*b*,*f*]thiepin intermediate by the Dieckmann cyclization. The starting point was the reaction of the thiolactone *XXVIII* with 2-chloro-5-trifluoromethylbenzonitrile[41] (prepared *via* 3-amino-4-chlorobenzotrifluoride[30]) in boiling aqueous

ethanol in the presence of potassium carbonate and a small amount of potassium iodide. An inhomogeneous product was obtained from which crystallization separated some 15% of a less soluble and high-melting compound $C_{16}H_{11}F_4NO_3S$. The cyano acid *XI* was obtained in a yield of 63% from the mother liquor. The less soluble compound was identified by spectra as the aminocarbonyl acid *XII*; the reaction is thus accompanied with a partial hydration of the nitrile group. Compound *XI* was then hydrolyzed with aqueous potassium hydroxide to the di-acid *XIII* which was esterified with methanol in the presence of boron trifluoride etherate to the dimethyl ester *XIV*. A monomethyl ester resulted simultaneously in a yield of 23% and was identified as compound *XV* (the band of ArCOOH in the IR spectrum

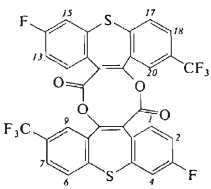


XXXVIII

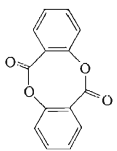
at 1696 cm^{-1} shows that the esterification was not complete on the carboxyl which is in conjugation with the benzene nucleus). Attempts to cyclize the dimethyl ester *XIV* with sodium hydride in toluene did not lead to the desired reaction; the starting compound was recovered. For this reason the attempt was made to cyclize with potassium tert-butoxide in boiling xylene and with the use of the high dilution technique[42,43]. A mixture was obtained in which the starting dimethyl ester *XIV* predominated again. Chromatography on a column of silica gel separated first 7% of a little polar substance melting at 275–278°C, and then a very small quantity of a somewhat more polar compound melting at 141–143°C. For the first substance the mass spectrum indicated the composition $C_{16}H_6F_4O_2S$ which was in agreement with the analyses. The empirical formula $C_{16}H_{11}F_3O_2S$ was similarly determined for the second substance.

The IR spectrum characterized the first compound as an unsaturated lactone and its empirical formula agrees for a product of methanol cleavage from the expected keto ester *XXI* which was not isolated and which is formulated as the enol form. It cannot be expected that we did isolate the monomolecular product with the unsaturated four-membered lactone ring. We prefer the explanation that our product is the dimeric heptacyclic dilactone with an eight-membered ring having the structure *XXXIX*. We presume that this compound is not sufficiently stable and that

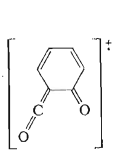
in the mass spectrum the peak of its molecular ion does not appear at all. It is cleaved to a fragment with *m/e* 338, *i.e.* the precise half of the molecule, which simulated the molecular ion; the correct formula, however, is $C_{32}H_{12}F_8O_4S_2$. For supporting this hypothesis, we prepared the known disalicylide *XL* (ref.[44]) and registered its mass spectrum. This compound, which is rather volatile in comparison with our substance, displays in the spectrum the molecular ion with *m/e* 240; the main fragment (base peak), however, is the precise half of the molecule with *m/e* 120. Only after the termination of our experimental work, the Indian authors[45] published the mass spectrum of disalicylide *XL* in perfect agreement with our result; the mentioned fragment is formulated as the radical cation *XLI*. This finding is considered a confirmation of correctness of the suggested formula *XXXIX*.



XXXIX



XL



XLI

The second product of the cyclization experiment was characterized by the IR spectrum to be a conjugated ketone and an aryl alkyl ether. The ^{1}H-NMR spectrum is in agreement with its formulation as a methoxy ketone of the dibenzo[*b*,*f*]thiepin series *XVIII*. It is again a proof of the fact that the desired cyclization took place in a small extent at least. The formation of compound *XVIII* has to be explained as the result of the following simultaneous or consecutive reactions: cyclization and elimination of hydrogen fluoride from the intermediate by the action of potassium tert-butoxide under the formation of the benzyne intermediate, addition of methanol which was formed during the transformation of the primary product *XXI* to the dilactone *XXXIX* (the only methanol available), cleavage of the β-keto ester to the ketone during decomposition of the reaction mixture with acetic acid. With regard to the fact that methoxyl evidently did not enter the molecule by a substitution reaction but by a sequence of elimination and addition, the position of methoxyl as suggested in formula *XVIII* is not completely sure. In conclusion, the attempt to use the Dieckmann cyclization in connection with the purpose of this work did not lead to preparatively useful results.

Compounds *IV* and *V* were pharmacologically investigated for central depressant and neuroleptic activity with regard to the duration of the effects. In this line they

were compared with isofloxythepin (ISOF), *i.e.* 7-fluoro-11-[4-(2-hydroxyethyl)-piperazino]-2-isopropyl-10,11-dihydrodibenzo[*b*,*f*]thiepin[4–6,46–48], and tefluthixol *VI* (ref.[8]). The results are summarized in the Table I; the compounds were administered orally in the form of salts but the results were calculated for bases. The acute toxicity of the new compounds in mice is higher than that of isofloxythepin. The influence on the motor coordination of mice was investigated by the rotatod method. The medium effective doses causing ataxia (ED_{50}) were estimated in the intervals of 1, 2, 24 and 48 h after the administration. The maximum activity was attained in the 2 h interval. The compounds *IV* and *V* were more active than the stan-

TABLE I

Pharmacological Properties of Compounds *IV* and *V* in Comparison with Isofloxythepin (ISOF) and Tefluthixol (*VI*) (oral administration, doses in mg/kg)

Test	Interval h	*IV*	*V*	ISOF	*VI*
Mice, acute toxicity, LD_{50}		52	100	230	—
Mice, ataxia (rotarod), ED_{50}	1	1·2	0·58	2·8	2·7
	2	0·47	0·58	1·3	2·4
	24	1·2	1·3	4·1	7·8
	48[a]	i	i	>10	i
Mice, locomotor activity, D_{50}	1	0·21	0·24	0·97	0·90
	24	0·19	0·23	0·51	<0·51
	48	i	>0·5	2·1	0·97
	72	i	i	4·0	3·3
Rats, catalepsy, ED_{50}	1—5[b]	0·93	1·1	2·0	1·4
	24	>5·0	i	4·0	i
	48	i	i	i	i
Rats, antiapomorphine activity, chewing, D_{50}	4	1·1	0·82	2·7	1·6
	24	>2·5	i	8·4	2·0
	48	i	i	i	i
Agitation, D_{50}	4	1·1	0·73		
Dogs, antiapomorphine activity	4[c]	75[+]	75[+]	—	100[+]
% of animals with complete	24	100[+]	88[+]	88[+]	100[+]
blockade of emesis after	48	50	62	38	88[+]
a dose of 1 mg/kg	96	i	i	i	i

[a] i Inactive. [b] ED_{50} as the most favourable value in the course of the first 5 h of the experiment. [c] + indicates statistical significance (0·05 level).

dards used and displayed the same protraction of the effect. The effect disappeared after 48 h (with some indication of persisting effect with isofloxythepin). The influence on the spontaneous locomotor activity of mice was tested by the photo-cell method. Doses decreasing the locomotor activity to 50% of the control values, D_{50}, are given for the intervals of 1, 24, 48 and 72 h after the administration. Compounds *IV* and *V* were more active in the first two intervals than the standards, which, however, showed longer duration of the effects. The cataleptic activity was investigated in rats and the medium effective doses (ED_{50}) estimated for the intervals of 1–5, 24 and 48 h after the administration. The acute activity of compounds *IV* and *V* was higher than that of the standards but the protraction of effects was not significantly apparent. The antiapomorphine activity was studied in rats, as well as in dogs. In rats, the influence on the apomorphine stereotypies (chewing, agitation) was determined and the activity is expressed as the medium effective dose (D_{50}) decreasing the appearance of stereotypies to 50% of the control values. The effects were observed in the intervals of 4, 24 and 48 h after the administration. The acute activity of compounds *IV* and *V* is again more pronounced than with the standards but the activity disappears more quickly. In the dogs, the blockade of the apomorphine-induced emesis was investigated after the dose of 1 mg/kg of the tested compounds. The results are expressed as percent of the animals with complete blockade of the emesis. In the important 24 h interval, the activity of all the four compounds was comparable. After 48 h, the effect is statistically significant only with tefluthixol; it disappears completely after 96 h. In conclusion, compounds *IV* and *V* are very potent neuroleptic agents with clear prolongation of the effects.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and 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 registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer and ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument. The mass spectra were recorded with MS 902 (AEI) and Varian MAT-311 spectrometers. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

6-Fluorobenzo[*b*]thiophen-2(3*H*)-one (*XXVIII*)

A) A solution of 33 g 90% sodium (2-amino-4-fluorophenyl)acetate[1] and 11·7 g $NaNO_2$ in 50 ml water was slowly added to a stirred mixture of 70 g ice and 70 ml hydrochloric acid at 0—5°C. The mixture was stirred for 1 h at 0°C and then slowly added over 15 min to a stirred solution of 58 g $Na_2S.9\,H_2O$, 6·4 g S and 8·0 g NaOH in 70 ml water at 5—10°C. It was made alkaline by addition of 20% NaOH, stirred for 2·5 h at room temperature and acidified with 40 ml hydrochloric acid. The separated solid was dissolved in a solution of 15 g Na_2CO_3 in 500 ml water at 80°C, sulfur was filtered off and the filtrate acidified with hydrochloric acid. The semi-

-solid product was dissolved in 100 ml acetic acid, 15 g Zn dust were added and the mixture stirred and refluxed for 4 h. After cooling, it was filtered, the filtrate was evaporated in *vacuo*, the residue dissolved in boiling 5% NaOH, the solution was filtered and the filtrate acidified with hydrochloric acid. The semi-solid product was filtered, suspended in 20% H_2SO_4, 5 g Zn were added and the mixture was subjected to steam distillation. The distillate deposited on cooling 4·7 g crystals; further 3·4 g were obtained by extraction of the mother liquor with ether. The total yield was 8·1 g (31%) *XXVIII*, m.p. 52—56°C. Analytical sample, m.p. 56—59°C (light petroleum). IR spectrum: 796, 851, 905 (2 adjacent and solitary Ar—H), 1020, 1182, 1208, 1244, 1268 (COS), 1480, 1582, 1600, 3095 (Ar), 1720 cm^{-1} (Ar—SCO—R). ^{1}H-NMR spectrum: δ 6·70—7·40 (m, 3 H, Ar—H), 3·90 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —113·1 (m). For C_8H_5FOS (168·2) calculated: 57·13% C, 3·00% H, 11·30% F, 19·06% S; found: 57·04% C, 3·13% H, 11·44% F, 18·89% S.

The mother liquor after the semi-solid crude product deposited on standing 3·3 g (11%) (4-fluoro-2-mercaptophenyl)acetic acid (*XXVI*), m.p. 110—116°C. Analytical sample, m.p. 113—117°C (benzene–cyclohexane). IR spectrum: 805, 841, 863, 901 (2 adjacent and solitary Ar—H), 1249, 1796, 2660, 2762, 3120 (COOH), 1493, 1580, 1590, 1609 (Ar), 2565 cm^{-1} (SH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·80—7·40 (m, 3 H, Ar—H), 3·60 (s, 2 H, $ArCH_2CO$). For $C_8H_7FO_2S$ (186·2) calculated: 51·60% C, 3·79% H, 10·20% F, 17·22% S; found: 52·25% C, 3·88% H, 10·15% F, 16·71% S.

The residue after the steam distillation deposited on standing 0·7 g 5,5′-difluorodiphenyl sulfide-2,2′-diacetic acid (*XXVII*), m.p. 176—190°C. Analytical sample, m.p. 196—200°C (aqueous ethanol). Mass spectrum, *m/e* (%): 338 (M^+ corresponding to $C_{16}H_{12}F_2O_4S$, 40), 247 (100), 233 (93), 214 (26), 139 (13). IR spectrum (KBr): 800, 853 (2 adjacent and solitary Ar—H), 908, 1250, 1712, 3110 (COOH), 1493, 1582, 1608 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 12·40 (bs, 2 H, 2 COOH), 6·60—7·50 (m, 6 H, Ar—H), 3·65 (s, 4 H, 2 $ArCH_2CO$). For $C_{16}H_{12}F_2O_4S$ (338·3) calculated: 56·80% C, 3·57% H, 11·23% F, 9·48% S; found: 56·65% C, 3·62% H, 11·11% F, 9·73% S.

B) A slightly modified procedure starting from 66 g 90% sodium (2-amino-4-fluorophenyl)-acetate[1], in which the crude product, obtained by evaporation of the solution in acetic acid, was directly subjected to steam distillation, gave 20·2 g (49%) *XXVIII*, m.p. 52—56°C.

[4-Fluoro-2-(4-trifluoromethyl-2-nitrophenylthio)phenyl]acetic Acid (*IX*)

XXVIII (17·8 g) was dissolved by heating in a solution of 32·6 g K_2CO_3 in 120 ml water, the solution was treated with 1·2 g KI and 30 g 4-chloro-3-nitrobenzotrifluoride[30] in 240 ml ethanol and the mixture was stirred and refluxed for 14 h. Ethanol was evaporated *in vacuo*, the residue diluted with water and washed with ether. The solution was acidified with hydrochloric acid. The precipitated solid was filtered, washed with water and dried *in vacuo*; 32·4 g (82%) *IX*, m.p. 144—153°C. Analytical sample, m.p. 154—158°C (aqueous ethanol). UV spectrum: λ_{max} 245·5 nm (log ε 4·17), infl. 271 nm (4·05), 355 nm (3·73). IR spectrum: 796, 849, 884 (2 adjacent and solitary Ar—H), 917, 1245, 1693, 2655, 2735 (COOH), 1123, 1148, 1154, 1333 ($ArCF_3$), 1333, 1532 ($ArNO_2$), 1491, 1566, 1580, 1593, 3070, 3100 cm^{-1} (Ar). For $C_{15}H_9F_4NO_4S$ (375·3) calculated: 48·00% C, 2·42% H, 20·25% F, 3·73% N, 8·55% S; found: 48·54% C, 2·60% H, 20·16% F, 3·53% N, 8·90% S.

Crystallization of the crude *IX* from aqueous ethanol led to separation of 0·5 g little soluble yellow needles, m.p. 170—177°C; analytical sample, m.p. 176—177°C (ethanol). The substance was characterized as 6-fluoro-2-hydroxy-3-[4-fluoro-2-(4-trifluoromethyl-2-nitrophenylthio)phenylacetyl]benzo[*b*]thiophene (*XXIX*). Mass spectrum, *m/e* (%): 525 (M^+ corresponding to $C_{23}H_{12}F_5NO_4S_2$, 18), 358 (5), 330 (7), 311 (7), 297 (24), 284 (29), 195 (100), 167 (11), 139 (49). UV spectrum: λ_{max} 240 nm (infl.) (log ε 4·45), infl. 270 nm (4·11), 328 nm (4·14). IR spectrum (KBr):

796, 820, 839, 847, 863, 881, 900 (2 adjacent and solitary Ar—H), 1146, 1165, 1330 ($ArCF_3$), 1343, 1565 ($ArNO_2$), 1480, 1529, 1580, 1596 (Ar), 1621 cm^{-1} (HO—C=C—CO with intramolecular H-bond); in $CHCl_3$: 1600, 1621 cm^{-1}. ^{1}H-NMR spectrum: δ 14·57 (bs, 1 H, OH in H-bond), 8·28 (mcs, 1 H, Ar—H between NO_2 and CF_3), 6·60—7·70 (m, 8 H, remaining Ar—H), 4·25 (s, 2 H, $ArCH_2CO$). For $C_{23}H_{12}F_5NO_4S_2$ (525·5) calculated: 52·57% C, 2·30% H, 18·08% F, 2·66% N, 12·20% S; found: 52·73% C, 2·38% H, 17·92% F, 2·48% N, 12·45% S.

Bis(4-trifluoromethyl-2-nitrophenyl) Disulfide (*XXXII*)

A solution was prepared by boiling 50·5 g $Na_2S.9\,H_2O$, 6·7 g S and 25 ml water and added over 30 min to a refluxing solution of 90·4 g 4-chloro-3-nitrobenzotrifluoride[30] in 250 ml ethanol. The mixture was refluxed for 1 h and cooled. Crystallization gave 87·2 g (98%) crude *XXXII*, m.p. 158—162°C. The literature[35] described a similar preparation using 2-propanol as the solvent and reported the m.p. of 160—162°C.

The mother liquor deposited on standing a small quantity of bis(4-trifluoromethyl-2-nitrophenyl) sulfide (*XXXIII*), m.p. 147—148°C (ethanol). IR spectrum (KBr): 771, 806, 847, 861, 905 (2 adjacent and solitary Ar—H), 1144, 1165, 1188, 1337 ($ArCF_3$), 1337, 1552 cm^{-1} ($ArNO_2$). The literature[36,38] reported the m.p. 146°C, and 142—143°C respectively.

Bis(2-amino-4-trifluoromethylphenyl) Disulfide (*XXXIV*)

A mixture of 71·7 g *XXXII*, 33 ml 80% $N_2H_4.H_2O$, 3 g charcoal, 1·5 g $FeCl_3$, 300 ml ethanol and 150 ml benzene was stirred and refluxed for 10 h. It was then filtered and the filtrate evaporated *in vacuo*; 62 g (100%) crude *XXXIV*, m.p. 65—77°C. It was used in this form for further work. The literature[34] mentioned the m.p. of 77—78° (hexane).

5-Trifluoromethyl-1,2,3-benzothiadiazole (*XXXVI*)

A solution of 62 g crude *XXXIV* in 500 ml ethanol was treated with 140 ml hydrochloric acid, the mixture was stirred and cooled to 0°C, and diazotized by a slow addition of a solution of 24·5 g $NaNO_2$ in 50 ml water at 0—5°C. The mixture was then treated with a solution of 140 g $NaH_2PO_2.H_2O$ in 300 ml water, it was stirred for 5 h with cooling, allowed to stand overnight at room temperature and extracted with light petroleum. Evaporation of the extract gave 60 g inhomogeneous oil which was chromatographed on a column of 600 g neutral alumina (activity II). Light petroleum eluted first 22·7 g (35%) *XXXVI* as the less polar component, m.p. 38—40°C; analytical sample, m.p. 41°C (light petroleum). Mass spectrum, *m/e*: 204 (M^+ corresponding to $C_7H_3F_3N_2S$), 185, 176, 157, 132, 126. UV spectrum: λ_{max} 256 nm (log ε 3·51), 262·5 nm (3·48), 303 nm (3·32). IR spectrum (KBr): 839, 896 (2 adjacent and solitary Ar—H), 1132, 1194, 1332 ($ArCF_3$), 1620 cm^{-1} (N=N). ^{1}H-NMR spectrum: δ 8·90 (mcs, J = 1·5 Hz, 1 H, 4-H), 8·24 (d, J = 8·0 Hz, 1 H, 7-H), 7·98 (mcd, J = 8·0; 1·5 Hz, 1 H, 6-H). For $C_7H_3F_3N_2S$ (204·2) calculated: 41·18% C, 1·48% H, 27·92% F, 13·72% N, 15·70% S; found: 40·87% C, 1·36% H, 28·31% F, 13·81% N, 15·71% S.

Continuation of the chromatography using a mixture of benzene and light petroleum as the eluent gave 1·9 g 2,8-bis(trifluoromethyl)phenothiazine (*XXXVII*), m.p. 148·5—149°C (benzene-light petroleum). Mass spectrum, *m/e*: 335 (M^+ corresponding to $C_{14}H_7F_6NS$). IR spectrum (KBr): 843, 885 (2 adjacent and solitary Ar—H), 1149, 1192, 1340 ($ArCF_3$), 1475, 1520, 1541 (Ar), 3350 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·06 and 6·91 (ABq, J = 8·0 Hz, 4 H, 3,4,6,7-H_4), 6·66 (s, 2 H, 1,9-H_2), 5·89 (bs, 1 H, NH). For $C_{14}H_7F_6NS$ (335·3) calculated: 50·15% C, 2·10% H, 34·00% F, 4·18% N, 9·56% S; found: 50·34% C, 2·11% H, 34·12% F, 4·15% N, 9·28% S.

[2-(2-Amino-4-trifluoromethylphenylthio)-4-fluorophenyl]acetic Acid (*X*)

A) A mixture of 31·9 g *IX*, 220 ml ethanol, 4·0 g charcoal, 15 ml 99% $N_2H_4.H_2O$ and 1·0 g $FeCl_3$ was stirred and refluxed for 10 h. It was then filtered, the filtrate evaporated *in vacuo*, the residue diluted with water and acidified with acetic acid. The precipitated solid was filtered, washed with water and dried *in vacuo*; 25·5 g (87%), m.p. of one crystal modification 127—130°C (aqueous ethanol), m.p. of the second modification 147—149°C (benzene–light petroleum). IR spectrum: 803, 813, 875 (2 adjacent and solitary Ar—H), 905, 1242, 1253, 1710, 2640, 2740, 3060 (COOH), 1134, 1160, 1340 ($ArCF_3$), 1490, 1603, 1614 (Ar), 3372, 3472 cm^{-1} (NH_2). For $C_{15}H_{11}F_4NO_2S$ (345·3) calculated: 52·17% C, 3·21% H, 22·00% F, 4·06% N, 9·29% S; found: 53·24% C, 3·51% H, 22·40% F, 3·96% N, 9·70% S.

B) A mixture of 33·4 g (4-fluoro-2-iodophenyl)acetic acid[1], 28·2 g crude Zn salt of 2-amino-4-trifluoromethylthiophenol[35], 16·5 g KOH, 5 g Cu catalyst and 300 ml water was stirred and refluxed under nitrogen for 8 h. After filtration, the filtrate was acidified with acetic acid and the mixture extracted with benzene. The extract was dried with $MgSO_4$, evaporated and the inhomogeneous residue was chromatographed on a column of 900 g silica gel (Silpearl). Benzene eluted first 1·2 g bis(2-amino-4-trifluoromethylphenyl) sulfide (*XXXV*), m.p. 89·5—90·5°C (light petroleum). Mass spectrum, *m/e* (%): 352 (M^+ corresponding to $C_{14}H_{10}F_6N_2S$, 100), 335 (80), 318 (40). UV spectrum: λ_{max} 248 nm (infl.) (log ε 4·20), 320 nm (3·96). IR spectrum: 816, 879 (2 adjacent and solitary Ar—H), 1119, 1180, 1345 ($ArCF_3$), 1494, 1580 (Ar), 1618 ($ArNH_2$), 3335, 3435 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·12 and 6·82 (2 d, J = 8·5 Hz, 4 H, 5,6,5′,6′-H_4), 6·75 (s, 2 H, 3,3′-H_2), 4·24 (bs, disappears after D_2O, 2 NH_2). The literature[38] reported the m.p. 89—90°C for a differently prepared product.

Continuation of the chromatography using chloroform as the eluent led to recovery of 16 g starting (4-fluoro-2-iodophenyl)acetic acid, m.p. 105—110°C. This compounds was followed (elution with a mixture of chloroform and ethanol) by 2·7 g (7%) of the amino acid *X*, m.p. 131—133°C (benzene–light petroleum), the lower melting crystal modification. An even more polar fraction (6·4 g) gave on crystallization from benzene 0·48 g product characterized as 2-[4-fluoro-2-(4-trifluoromethyl-2-aminophenylthio)benzyl]benzothiazole-5-carboxylic acid (*XXXVIII*), m.p. 216—218°C (benzene–ethanol). Mass spectrum, *m/e*: 478 (M^+ corresponding to $C_{22}H_{14}F_4N_2O_2S_2$), 401 (M — COOH—S). UV spectrum: λ_{max} 239 nm (log ε 4·51), 310 nm (4·28), 359 nm (3·95). IR spectrum: 821, 865, 891 (2 adjacent and solitary Ar—H), 1138, 1172, 1337 ($ArCF_3$), 1234, 1723, 2545, 2680 (COOH), 1486, 1599, 1605 (Ar), 1632 ($ArNH_2$, C=N) cm^{-1}. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 12·40 (bs, 1 H, COOH), 8·46 (bd, J = 8·5 Hz, 1 H, 6-H of benzothiazole), 8·40 (bs, 1 H, 4-H of benzothiazole), 7·80 (bd, J = 8·5 Hz, 1 H, 7-H of benzothiazole), 7·10—7·60 (m, 4 H, 6-H of fluorobenzyl and 3,5,6-H_3 of arylthio), 7·52 (mct, J_{H-F} = 8·5 Hz, J_{H-H} = 3·5 Hz, 1 H, 5-H of fluorobenzyl), 7·05 (mcd, J_{H-F} = 8·5 Hz, J_{H-H} = 3·5 Hz, 1 H, 3-H of fluorobenzyl), 3·75 (s, 2 H, $ArCH_2$). For $C_{22}H_{14}F_4N_2O_2S_2$ (478·5) calculated: 55·32% C, 2·95% H, 15·88% F, 5·85% N, 13·40% S; found: 56·32% C, 3·12% H, 15·23% F, 5·84% N, 13·24% S.

[4-Fluoro-2-(4-trifluoromethylphenylthio)phenyl]acetic Acid (*VIII*)

A) A mixture of 17·6 g 4-(trifluoromethyl)thiophenol[15], 26·3 g (4-fluoro-2-iodophenyl)-acetic acid[1], 40 g K_2CO_3, 2 g Cu and 100 ml dimethylformamide was stirred and heated under nitrogen to 140°C for 5 h. It was then filtered, the filtrate evaporated *in vacuo*, the residue diluted with water, filtered again and the filtrate acidified with hydrochloric acid. The product was extracted with benzene, the extract was dried with Na_2SO_4, evaporated and the residue was crystallized from a mixture of benzene and light petroleum; 22·6 g (73%), m.p. 97—104°C.

Analytical sample, m.p. 104—106°C (benzene–light petroleum). IR spectrum: 809, 840, 883 (2 adjacent and solitary Ar—H), 901, 1243, 1700, 2555, 2655, 2740 (COOH), 1128, 1165, 1328 ($ArCF_3$), 1490, 1576, 1602 cm^{-1} (Ar). For $C_{15}H_{10}F_4O_2S$ (330·3) calculated: 54·54% C, 3·05% H, 23·01% F, 9·71% S; found: 55·08% C, 3·14% H, 23·19% F, 10·08% S.

B) A solution of 25·3 g *X* in 240 ml ethanol and 80 ml hydrochloric acid was stirred and diazotized at 0—5°C with a solution of 6·9 g $NaNO_2$ in 20 ml water. The mixture was stirred for 2 h at 0°C, treated with a solution of 40 g $NaH_2PO_2.H_2O$ in 200 ml water and stirred for 3 h without cooling. It was allowed to stand overnight, diluted with 500 ml water and extracted with benzene. The extract was shaken with an excess of 5% NaOH, the alkaline layer, containing a small amount of a solid, was was filtered, the filtrate was acidified with hydrochloric acid and the product isolated by extraction with benzene; 16·9 g (70%) *VIII*, m.p. 103—106°C (benzene–light petroleum). The product was identical with that obtained under *A*.

The little soluble sodium salt, which was filtered off from the alkaline layer, was suspended in water, the suspension acidified with hydrochloric acid, the solid filtered, washed with water and dried *in vacuo*; 1·6 g (7%) 1-fluoro-8-(trifluoromethyl)dibenzothiophene-4-acetic acid (*XXX*), m.p. 207—210°C with decomposition. Analytical sample, m.p. 210—211·5°C (aqueous ethanol). Mass spectrum, *m/e*: 328·0108 (M^+ corresponding to $C_{15}H_8F_4O_2S$). IR spectrum: 827, 880 (2 adjacent and solitary Ar—H), 906, 1280, 1709, 2655, 2730 (COOH), 1125, 1180, 1340, ($ArCF_3$), 1502, 1606 cm^{-1} (Ar). For $C_{15}H_8F_4O_2S$ (328·3) calculated: 54·87% C, 2·45% H, 23·15% F, 9·76% S; found: 54·96% C, 2·80% H, 23·25% F, 9·55% S.

Evaporation of the benzene layer (after the extraction with 5% NaOH) gave 1·1 g (4%) ethyl 1-fluoro-8-(trifluoromethyl)dibenzothiophene-4-acetate (*XXXI*), m.p. 133—144°C. Analytical sample, m.p. 149—150°C (benzene–light petroleum). Mass spectrum, *m/e* (%): 356·0507 (M^+ corresponding to $C_{17}H_{12}F_4O_2S$, 85), 340 (10), 283 (100), 265 (6), 214 (12). UV spectrum: λ_{max} 241 nm (log ε 4·64), infl. 269 nm (4·06), 311·5 nm (3·34), 324·5 (3·47). IR spectrum: 826, 869 (2 adjacent and solitary Ar—H), 1126, 1182, 1343 ($ArCF_3$), 1278, 1729 (RCOOR'), 1502, 1605 cm^{-1} (Ar). For $C_{17}H_{12}F_4O_2S$ (356·3) calculated: 57·30% C, 3·39% H, 21·33% F, 9·00% S; found: 57·55% C, 3·53% H, 21·08% F, 9·29% S.

7-Fluoro-2-(trifluoromethyl)-11-(methanesulfonyloxy)dibenzo[*b,f*]thiepin (*XIX*)

A solution of 6·0 g *VIII* in 100 ml chlorobenzene was treated with the reagent prepared by dissolving 18 g P_2O_5 in 180 g methanesulfonic acid[21], the mixture was stirred for 2 h at 125°C, decomposed with ice and water, the organic layer was washed with 2% NaOH, dried with $CaCl_2$, evaporated and the residue distilled *in vacuo*. The first fraction (7·6 g), b.p. 125—130°C/0·2 kPa, was the almost pure 4-chlorophenyl methyl sulfone. Crystallization from light petroleum gave 6·2 g solid, m.p. 60—78°C; analytical sample, m.p. 95—98°C (benzene). ^{1}H-NMR spectrum: δ 7·75 (d, J = 8·0 Hz, 2 H, 2,6-H_2), 7·48 (d, J = 8·0 Hz, 3,5-H_2), 3·01 (s, 3 H, CH_3). The literature[22,23] reported for the m.p. the values of 96°C, and 97°C, respectively.

The broad second fraction (2·0 g, b.p. 130—190°C/0·2 kPa) crystallized from light petroleum and gave 1·7 g (24%) crude *XIX*, m.p. 160—173°C. Analytical sample, m.p. 175·5—176°C (benzene–light petroleum). Mass spectrum, *m/e* (%): 390·0032 (M^+ corresponding to $C_{16}H_{10}F_4O_3S_2$, 17), 283 (100), 223 (12), 190 (23), 175 (35), 111 (82), 75 (35). UV spectrum: λ_{max} 233 nm (log ε 4·26), 264 nm (4·23), 295 nm (3·69). IR spectrum (KBr): 800, 837, 899 (2 adjacent and solitary Ar—H), 1123, 1170, 1320, 1386 ($ArCF_3$ and RSO_2OR'), 1493, 1573, 1597, 3020, 3038, 3072, 3100 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·90—7·90 (m, 7 H, Ar—H and CH=C), 3·10 (s, 3 H, SO_2CH_3). ^{19}F-NMR spectrum: δ —63·6 (s, 3 F, CF_3), —111·4 (dt, 1 F, J_{o-H-F} = = 8·0 Hz, J_{m-H-F} = 5·5 Hz). For $C_{16}H_{10}F_4O_3S_2$ (390·4) calculated: 49·23% C, 2·58% H, 19·47% F, 16·43% S; found: 49·44% C, 2·75% H, 19·38% F, 16·94% S.

The mother liquors after the crystalline products from the first and second fraction were combined and chromatographed on a column of 30 g neutral alumina (activity II). Elution with a mixture 1 : 5 benzene and light petroleum gave 0·36 g solid, m.p. 168—170°C (light petroleum), believed to be 2-chloro-12-fluoro-7-trifluoromethyltribenzo[*b,e,h*]thiepino[4,5-*b*]furan (*XXII*). Mass spectrum, *m/e*: 420 (M^+ corresponding to $C_{21}H_9ClF_4OS$). UV spectrum: λ_{max} 247 nm (log ε 4·53), 281 nm (4·32), infl. 350 nm (3·72). IR spectrum (KBr): 812, 828, 839, 872, 907 (2 adjacent and solitary Ar—H), 1122, 1170, 1324 ($ArCF_3$), 1500, 1600, 3075 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·02 (s, 1 H, 6-H), 7·00—7·80 (m, 8 H, remaining Ar—H). ^{19}F-NMR spectrum: δ —63·5 (s, 3 F, CF_3), —113·0 (dt, 1 F, $J_{o-H-F} = 8·0$ Hz, $J_{m-H-F} = 5·5$ Hz). For $C_{21}H_9ClF_4OS$ (420·8) calculated: 59·93% C, 2·16% H, 8·42% Cl, 18·06% F, 7·62% S; found: 60·06% C, 2·15% H, 8·80% Cl, 18·53% F, 7·98% S.

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

A) A solution of 16·7 g *VIII* in 300 ml 1,2-dichlorobenzene was added to polyphosphoric acid (from 120 g P_2O_5 and 60 ml 85% H_3PO_4) and the mixture was stirred and heated for 6 h to 160°C. It was decomposed with 500 ml water, the precipitated solid was filtered off, the filtrate separated, the organic layer washed with 5% NaOH, dried with $MgSO_4$ and evaporated. The residue was diluted with light petroleum, the insoluble impurity filtered off, the filtrate evaporated and the residue distilled; 1·2 g (8%) *XVI*, b.p. 160°C/0·27 kPa, m.p. 97—98°C (light petroleum). UV spectrum: λ_{max} 241 nm (log ε 4·24), infl. 265 nm (4·00), 325 nm (3·66). IR spectrum: 810, 828, 871 (2 adjacent and solitary Ar—H), 1117, 1154, 1171, 1339 ($ArCF_3$), 1489, 1580, 1600, 1610 (Ar), 1689 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 8·40 (s, 1 H, 9-H), 6·90—7·70 (m, 5 H, 1,2,4,6,7-H$_5$), 4·30 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR spectrum: δ —63·6 (s, 3 F, CF_3), —114·3 (dt, 1 F, $J_{o-H-F} = 8·0$ Hz, $J_{m-H-F} = 5·5$ Hz). For $C_{15}H_8F_4OS$ (312·3) calculated: 57·69% C, 2·58% H, 24·34% F, 10·27% S; found: 57·38% C, 2·79% H, 24·64% F, 10·51% S.

Acidification of the alkaline washings with hydrochloric acid gave a semi-solid product which was combined with the solid filtered off from the reaction mixture after the decomposition with water; 5·4 g (37%) 7-fluoro-11-oxo-10*H*-dibenzo[*b,f*]thiepin-2-carboxylic acid (*XVII*), m.p. 268—273°C (ethanol). UV spectrum: λ_{max} 248 nm (log ε 4·33), infl. 280 nm (4·06), 326 nm (3·73). IR spectrum: 770, 809, 881 (2 adjacent and solitary Ar—H), 940, 1227, 1258, 1310, 1705, 2550, 2610, 2666, 2720 (COOH), 1487, 1551, 1594 (Ar), 1680 cm^{-1} (ArCO). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·65 (mcd, $J = 2·0$ Hz, 1 H, 1-H), 8·04 (mcd, $J = 8·5$; 2·0 Hz, 1 H, 3-H), 7·75 (d, $J = 8·5$ Hz, 1 H, 4-H), 7·00—7·70 (m, 3 H, remaining Ar—H), 4·28 (s, 2 H, $ArCH_2CO$). For $C_{15}H_9FO_3S$ (288·3) calculated: 62·49% C, 3·15% H, 6·59% F, 11·12% S; found: 62·83% C, 3·17% H, 6·35% F, 10·90% S.

B) A mixture of 16·0 g *VIII* and 170 ml anhydrous hydrogen fluoride was stirred for 5 h in a closed flask and then in an open one until the evaporation of H_2F_2. The residue was stirred with 10% Na_2CO_3 and extracted with light petrolcum. Evaporation of the extract and distillation of the residue gave 1·6 g (11%) ketone *XVI*, b.p. 160°C/0·27 kPa, m.p. 85—95°C, after crystallization from light petroleum 97—98°C. The acidification of the alkaline solution and extraction with benzene gave 1·55 g (11%) little soluble acid *XVII*, m.p. 260—268°C, after crystallization from ethanol 268—273°C. Evaporation of benzene recovered 12·5 g starting *VIII*.

C) A mixture of 400 mg *XIX*, 20 ml ethanol and 5 ml 20% NaOH was refluxed for 2 h, ethanol was evaporated, the residue diluted with water and extracted with light petroleum. Evaporation of the extract gave 220 mg (69%) ketone *XVI*, m.p. 88—96°C. Analytical sample, m.p. 97—98°C (light petroleum).

D) A solution of 36 g P_2O_5 in 350 g methanesulfonic acid was heated for 2 h to 125°C, a solution of 13·0 g *VIII* in 200 ml 1,1,2,2-tetrachloroethane was added and the mixture stirred for 2 h at 125°C. After cooling, it was decomposed with ice, the organic layer washed with 5% NaOH and the solvent evaporated *in vacuo*. The residue was dissolved in 200 ml ethanol, 40 ml 20% NaOH were added and the mixture was refluxed for 5 h. It was filtered, the filtrate evaporated under reduced pressure, the residue mixed with water and extracted with benzene. The extract was evaporated and the residue distilled; 5·1 g (42%) *XVI*, b.p. 160—170°C/130 Pa, m.p. 97—98°C (light petroleum).

6-Ethoxy-2-(trifluoromethyl)thioxanthone (*XXIII*)

A solution of 22·6 g *VIII* in 230 ml 1,1,2,2-tetrachloroethane was cyclized by heating with a solution of 36 g P_2O_5 in 350 g methanesulfonic acid to 125°C for 2 h. The mixture was decomposed with water, the organic layer washed with 5% NaOH and evaporated. The residue was refluxed with 300 ml ethanol and 40 ml 20% NaOH for 5 h, the alkaline mixture was allowed to stand for 48 h at room temperature without protection against the air, then filtered, the filtrate evaporated, the residue mixed with water and extracted with benzene. Evaporation of the extract and crystallization from a small volume of benzene gave 1·4 g of *XXIII*, m.p. 178—181°C. Analytical sample, m.p. 180—181·5°C (benzene). Mass spectrum, *m/e* (%): 324 (M^+ corresponding to $C_{16}H_{11}F_3O_2S$, 100), 305 (5), 296 (96), 279 (4), 268 (48), 251 (4), 239 (25), 220 (3), 207 (5), 189 (3), 171 (15). UV spectrum: λ_{max} 251 nm (log ε 4·50), 285 nm (4·51), 316 nm (3·86), 364 nm (3·80). IR spectrum: 775, 830, 858 (2 adjacent and solitary Ar—H), 1120, 1152, 1161, 1312 ($ArCF_3$), 1245, 1260, 1292 (ArOR), 1478, 1495, 1600, 3032, 3062 (Ar), 1640 cm^{-1} (ArCOAr). For $C_{16}H_{11}F_3O_2S$ (324·3) calculated: 59·25% C, 3·42% H, 17·57% F, 9·89% S; found: 59·24% C, 3·39% H, 18·01% F, 10·31% S.

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

A solution of 7·6 g *XVI* in 80 ml dioxane was treated with a solution of 1·0 g $NaBH_4$ in 3 ml water containing 1 drop of 20% NaOH. The mixture was stirred for 3 h at room temperature, allowed to stand overnight, evaporated *in vacuo*, the residue mixed with water and extracted with benzene. The extract was dried (Na_2SO_4) and evaporated. The residue crystallized after mixing with light petroleum; 6·4 g (84%), m.p. 111—114°C. Analytical sample, m.p. 114—116°C (benzene–light petroleum). IR spectrum: 810, 840, 850, 883, 890, 900 (2 adjacent and solitary Ar—H), 1067 (CHOH in the cycle), 1129, 1134, 1177, 1346 ($ArCF_3$), 1500, 1592, 1607, 3058 (Ar), 3305, 3375 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·82 (bs, 1 H, 9 H), 7·52 (d, 1 H, 6-H), 6·80—7·40 (m, 4 H, remaining Ar—H), 5·31 (dt, after D_2O dd, 1 H, Ar—CH—O), 3·72 and 3·31 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·20 (d, J = 8·0 Hz, disappears after D_2O, 1 H, OH). ^{19}F-NMR spectrum: δ —63·4 (s, 3 F, CF_3), —115·6 (dt, 1 F, J_{o-H-F} = 8·0 Hz, J_{m-H-F} = 5·5 Hz). For $C_{15}H_{10}F_4OS$ (314·3) calculated: 57·32% C, 3·21% H, 24·18% F, 10·20% S; found: 57·33% C, 3·13% H, 24·31% F, 10·29% S.

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

A mixture of 6·3 g *XXIV* and 25 ml $SOCl_2$ was refluxed for 30 min, evaporated *in vacuo* and crystallized from light petroleum; 6·6 g (100%), m.p. 92—94°C; analytical sample, m.p. 93—95°C. ^{1}H-NMR spectrum: δ 7·75 (bs, 1 H, 1-H), 7·52 (d, 1 H, 4-H), 6·80—7·40 (m, 4 H, remaining Ar—H), 5·71 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·99 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). ^{19}F-NMR spectrum: δ —63·6 (s, 3 F, CF_3), —114·9 (dt, 1 F, J_{o-H-F}

= 8·0 Hz, J_{m-H-F} = 5·5 Hz). For $C_{15}H_9ClF_4S$ (332·8) calculated: 54·14% C, 2·73% H, 10·66% Cl, 22·84% F, 9·64% S; found: 54·11% C, 2·78% H, 10·61% Cl, 22·98% F, 9·66% S.

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

A mixture of 3·9 g *XXV*, 15 ml 1-methylpiperazine and 15 ml chloroform was refluxed for 8 h, diluted with benzene, washed with water and extracted with excessive 5% hydrochloric acid. The precipitated hydrochloride was filtered, combined with the aqueous layer of the filtrate, the suspension was made alkaline with NH_4OH and extracted with benzene. The extract was dried (K_2CO_3) and evaporated; 3·1 g (66%) oily base *IV*. Neutralization with 2·0 g maleic acid in ethanol and addition of ether gave 4·4 g bis(hydrogen maleate), m.p. 123—125°C (acetone–ether). For $C_{28}H_{28}F_4N_2O_8S$ (628·6) calculated: 53·50% C, 4·49% H, 12·09% F, 4·46% N, 5·10% S; found: 53·19% C, 4·53% H, 11·83% F, 4·19% N, 5·10% S.

A sample of the maleate was decomposed with NH_4OH and the purified base extracted with ether. The oil obtained by careful evaporation of the solvent was used for measuring the ^{1}H-NMR spectrum: δ 6·70—8·00 (m, 6 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·58 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3).

The benzene layer, from which the basic product was removed by extraction with HCl, was evaporated; 1·18 g (34%) 7-fluoro-2-(trifluoromethyl)dibenzo[*b,f*]thiepin (*XX*), m.p. 72—73°C (methanol). UV spectrum: λ_{max} 265 nm (log ε 4·39), infl. 295 nm (3·65), infl. 338 nm (2·96). ^{1}H-NMR spectrum: δ 6·80—7·70 (m, Ar—H and CH=CH). ^{19}F-NMR spectrum: δ —63·6 (s, 3 F, CF_3), —113·0 (dt, 1 F, J_{o-H-F} = 8·0 Hz, J_{m-H-F} = 5·5 Hz). For $C_{15}H_8F_4S$ (296·3) calculated: 60·81% C, 2·72% H, 25·65% F, 10·82% S; found: 60·56% C, 2·78% H, 25·93% F, 10·84% S.

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

A mixture of 2·54 g *XXV*, 10 g 1-(2-hydroxyethyl)piperazine and 10 ml chloroform was refluxed for 8 h and processed like in the preceding case; 2·10 g (65%) oily base *V*. Neutralization with maleic acid gave bis(hydrogen maleate), m.p. 120—122°C (acetone–ether). For $C_{29}H_{30}F_4N_2O_9S$ (658·6) calculated: 52·88% C, 4·59% H, 11·54% F, 4·26% N, 4·87% S; found: 52·88% C, 4·57% H, 11·25% F, 4·18% N, 4·80% S.

Treatment of the maleate with NH_4OH and extraction with ether gave the purified oily base *V*. ^{1}H-NMR spectrum: δ 8·00 (bs, 1 H, 1-H), 7·49 (d, J = 8·5 Hz, 1 H, 4-H), 6·95 (mct, J = 8·0; 2·5 Hz, 1 H, 8-H), 7·10—7·30 (m, 3 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, 2 H, CH_2O), 2·85 (bs, 1 H, OH), 2·40—2·80 (m, 10 H, 5 NCH_2).

[2-(2-Cyano-4-trifluoromethylphenylthio)-4-fluorophenyl]acetic Acid (*XI*)

A solution of 7·4 g *XXVIII* in 60 ml water was treated with 12·4 g K_2CO_3, a solution of 10·4 g 2-chloro-5-(trifluoromethyl)benzonitrile[41] in 120 ml ethanol and 0·6 g KI and the mixture was stirred and refluxed for 13 h. The solvent was evaporated, the residue diluted with water, the solution washed with benzene and acidified with hydrochloric acid. The inhomogeneous solid (16·5 g, m.p. 120—130°C) was filtered, dried and crystallized from benzene; 2·3 g (14%) [2-(2-aminocarbonyl-4-trifluoromethylphenylthio)-4-fluorophenyl]acetic acid (*XII*), m.p. 217—221°C (benzene–ethanol). Mass spectrum, *m/e* (%): 373·0393 (M^+ corresponding to $C_{16}H_{11}F_4NO_3S$, 70), 356 (80), 328 (50), 284 (100), 220 (30). UV spectrum: λ_{max} 262 nm (log ε 4·01). IR spectrum: 837, 850, 888 (2 adjacent and solitary Ar—H), 920, 1 243, 1 720, 2 630, 2 702 (COOH), 1 143, 1 169, 1 330

($ArCF_3$), 1500, 1590, 1600 (Ar), 1659, 3215, 3315 cm^{-1} ($CONH_2$). For $C_{16}H_{11}F_4NO_3S$ (373·3) calculated: 51·48% C, 2·97% H, 20·36% F, 3·75% N, 8·58% S; found: 51·75% C, 3·06% H, 20·08% F, 3·98% N, 8·80% S.

The mother liquor was evaporated and the residue crystallized from a mixture of benzene and light petroleum; 9·8 g (63%) *XI*, m.p. 141—152°C; analytical sample, m.p. 151—153°C. UV spectrum: λ_{max} 267 nm (log ε 4·03), 313 nm (3·71). IR spectrum (KBr): 810, 844, 884 (2 adjacent and solitary Ar—H), 910, 918, 1092, 1250, 1720, 2665, 2755 (COOH), 1143, 1177, 1340 ($ArCF_3$), 1498, 1617 (Ar), 2243 cm^{-1} (ArCN). For $C_{16}H_9F_4NO_2S$ (355·3) calculated: 54·09% C, 2·55% H, 21·39% F, 3·94% N, 9·02% S; found: 54·04% C, 2·54% H, 21·79% F, 4·18% N, 8·78% S.

[2-(2-Carboxy-4-trifluoromethylphenylthio)-4-fluorophenyl]acetic Acid (*XIII*)

A solution of 13·4 g *XI* and 10 g KOH in 200 ml water was refluxed for 3·5 h, filtered and the filtrate acidified with hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 13·6 g (96%), m.p. 233—240°C. Analytical sample, m.p. 241—244°C (benzene–ethanol). UV spectrum: λ_{max} 262 nm (log ε 4·02), 305 nm (3·66). IR spectrum: 792, 810, 842, 870, 909 (2 adjacent and solitary Ar—H), 923, 936, 941, 1270, 2500, 2550, 2575, 3160 (COOH), 1138 ($ArCF_3$), 1500, 1570, 1586, 1610 (Ar), 1693 (ArCOOH), 1716 cm^{-1} (RCOOH). For $C_{16}H_{10}F_4O_4S$ (374·3) calculated: 51·34% C, 2·69% H, 20·30% F, 8·57% S; found: 51·54% C, 2·65% H, 20·23% F, 8·90% S.

Methyl [4-Fluoro-2-(4-trifluoromethyl-2-methoxycarbonylphenylthio)phenyl]acetate (*XIV*)

A solution of 14·2 g *XIII* in 200 ml methanol was treated with 18·5 g boron trifluoride etherate and the mixture stirred and refluxed for 20 h. Methanol was evaporated *in vacuo*, the residue diluted with water and the mixture extracted with ether. The extract was washed with 15% Na_2CO_3 and water, dried with $MgSO_4$ and evaporated; 11·1 g (73%) *XIV*, m.p. 98—103°C. Analytical sample, m.p. 102·5—103·5°C (methanol). UV spectrum: λ_{max} 223 nm (log ε 4·29), 263 nm (4·05), 315 nm (3·78). IR spectrum: 790, 830, 870 (2 adjacent and solitary Ar—H), 1123, 1181, 1346 ($ArCF_3$), 1249, 1254, 1729 (RCOOR', ArCOOR), 1491, 1569, 1580, 1610, 3090 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·30 (bs, 1 H, 3-H adjacent to methoxycarbonyl), 7·00 to 7·70 (m, 4 H, Ar—H in the fluorophenylacetate residue and 5-H adjacent to trifluoromethyl), 6·80 (d, J = 8·0 Hz, 1 H, 6-H in the benzotrifluoride residue), 4·02 (s, 3 H, $ArCOOCH_3$), 3·80 (s, 2 H, $ArCH_2$), 3·55 (s, 3 H, $RCOOCH_3$). For $C_{18}H_{14}F_4O_4S$ (402·4) calculated: 53·73% C, 3·51% H, 18·89% F, 7·97% S; found: 53·90% C, 3·57% H, 18·93% F, 8·23% S.

Acidification of the alkaline washings with hydrochloric acid gave 3·4 g (23%) methyl [2-(2-carboxy-4-trifluoromethylphenylthio)-4-fluorophenyl]acetate (*XV*), m.p. 180—185°C. Analytical sample, m.p. 185—190°C (aqueous methanol). UV spectrum: λ_{max} 222 nm (log ε 4·28), 261 nm (4·07), 305 nm (3·73). IR spectrum: 839, 880 (2 adjacent and solitary Ar—H), 910, 2645, 3160 (COOH), 1121, 1190, 1317 ($ArCF_3$), 1499, 1565, 1580, 1613 (Ar), 1696 (ArCOOH), 1732 cm^{-1} (RCOOR'). For $C_{17}H_{12}F_4O_4S$ (388·4) calculated: 52·58% C, 3·11% H, 19·57% F, 8·26% S; found: 52·26% C, 3·10% H, 19·43% F, 8·48% S.

Cyclization of Methyl [4-Fluoro-2-(4-trifluoromethyl-2-methoxycarbonylphenylthio)phenyl]-acetate (*XIV*)

Potassium (2·9 g) was dissolved in a solution of 16 g tert-butyl alcohol in 300 ml xylene and 50 ml xylene were distilled off. The reaction flask was connected with a high-dilution technique apparatus[42,43] containing 350 ml xylene; it was stirred, refluxed and treated under nitrogen with

a solution of 12·8 g *XIV* in 250 ml xylene over 20 h. The refluxing was continued for 4 h, the cooled mixture decomposed with a solution of 50 ml acetic acid in 50 ml xylene, 200 ml water were added and the organic layer was separated. It was washed with water, filtered and xylene was evaporated *in vacuo*. The residue (11·7 g inhomogeneous oil) was dissolved in benzene and chromatographed on a column of 200 g silica gel. Benzene eluted first 0·73 g fraction which crystallized from benzene m.p. 275—278°C. In agreement with the spectral and analytical finding, the substance is tentatively formulated as 3,14-difluoro-8,19-bis(trifluoromethyl)tetrabenzo-[*a,d,j,m*]dithiepino[4,5-*b*; 4′,5′-*f*]-1,5-dioxocin-11,22-dione (*XXXIX*). Mass spectrum, *m/e* (%): M^+ is missing, 338·0036 (base peak corresponding to $C_{16}H_6F_4O_2S$, *i.e.* precisely the half of the molecule), 319 (5), 310 (24), 291 (2), 282 (20), 269 (5), 241 (10), 238 (25), 219 (7), 213 (18). UV spectrum: λ_{max} 222·5 nm (log ε 4·76), 232·5 nm (4·76), 239 nm (4·76), 302 nm (4·20), 348 (3·96). IR spectrum (KBr): 832, 841, 869, 900 (2 adjacent and solitary Ar-H), 1133, 1180, 1321 ($ArCF_3$), 1262, 1340 (RCOOR′), 1477, 1513, 1532, 1560, 1590, 1610, 3095, 3130 (Ar), 1629, 1756 cm^{-1} (C—C—COO—C=C in the eight-membered ring). For $C_{32}H_{12}F_8O_4S_2$ (676·6) calculated: 56·81% C, 1·79% H, 22·47% F, 9·48% S; found: 56·62% C, 1·92% H, 22·82% F, 10·29% S.

Continued elution with benzene gave 0·20 g fraction crystallizing from light petroleum, m.p. 141—143°C. The substance was assigned to be 8-trifluoromethyl-3-methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*XVIII*). Mass spectrum, *m/e* (%): 324·0438 (M^+ corresponding to $C_{16}H_{11}F_3O_2S$, 100), 309 (60), 295 (100), 291 (72), 265 (56), 253 (94), 184 (56). UV spectrum: λ_{max} 235 nm (log ε 4·40), infl. 265 nm (4·00), 328 nm (3·65). IR spectrum (KBr): 843, 879 (2 adjacent and solitary Ar—H), 1033, 1126, 1261, 1291 (ArOR), 1126, 1161, 1340 ($ArCF_3$), 1496, 1600, 3030, 3088, 3097 (Ar), 1680 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 8·40 (bs, 1 H, 9-H), 7·60 (bs, 2 H, 6, 7-H_2), 7·30 (d, J = 8·0 Hz, 1 H, 1-H), 7·11 (mcs, J = 2·5 Hz, 1 H, 4-H), 6·87 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 4·22 (s, 2 H, $ArCH_2$), 3·71 (s, 3 H, OCH_3). For $C_{16}H_{11}F_3O_2S$ (324·3) calculated: 59·25% C, 3·42% H, 17·67% F, 9·89% S; found: 59·32% C, 3·60% H, 17·18% F, 10·24% S.

Elution with a mixture of benzene and chloroform led to recovery of 5·74 g starting *XIV*, m.p. 103—104°C.

Disalicylide (*XL*)

Was prepared from salicylic acid by refluxing with $SOCl_2$ (and $AlCl_3$) and by the following treatment with N,N-diethylaniline[44]; m.p. 233—237°C (literature[44], m.p. 234°C). Mass spectrum, *m/e* (%): 240 (M^+ corresponding to $C_{14}H_8O_4$, 52), 212 (3), 196 (2), 184 (1), 120 (base peak corresponding to $C_7H_4O_2$, *i.e.* the precise half of the molecule), 92 (52), 76 (2), 64 (24), 63 (19), *cf.*[45]. IR spectrum: 775, 782 (4 adjacent Ar—H), 1117, 1202, 1250, 1293 (ArCOOAr), 1482, 1580, 3045, 3080, 3113 (Ar), 1606, 1749, 1765 cm^{-1} (ArCOOAr in the eight-membered ring).

The authors are indebted to Mrs L. Machová for technical assistance with the synthetic part and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs J. Kropáčová (analytical department of this institute) for carrying out the analyses.

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Translated by the author (M. P.).