TRICYCLIC PSYCHOTROPIC AGENTS CONTAINING TWO CHALCOGEN ATOMS IN THE CENTRAL RING: 2-FLUORO-8-SUBSTITUTED 6-(4-PIPERIDYL)-6*H*-DIBENZ[*b*,*e*]-1,4-OXATHIEPINS*

Karel Šindelář, Jiří Holubek, Emil Svátek, Miroslav Ryska, Antonín Dlabač, Jiřina Metyšová and Miroslav Protiva

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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The aldehydes *VIa* and *VIb* were transformed by treatment with chloroform and sodium hydroxide in the presence of triethylbenzylammonium chloride to the α-chloro acids *VIIa* and *VIIb* which were demethylated with boron tribromide and the products were cyclized with sodium hydroxide in dimethyl sulfoxide to 2-fluoro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin-6-carboxylic acids *Ia* and *Ib*. Syntheses of the aldehydes *XVIIbcd* were carried out and the products treated with 1-methyl--4-piperidylmagnesium chloride to give the amino alcohols *XVIbcd*. Cyclizations with sodium hydride in dimethylformamide afforded the title compounds *XIIbcd*; compounds *XVIIIbc* and *XIX* were isolated as by-products and characterized. Compound *XIIb* was transformed *via* the secondary amine *XIIIb* to the amino alcohol *XIVb* which was esterified to the decanoate *XVb*. Substances *XIIbcd* are highly active neuroleptic agents with an important prolongation of the central depressant effect. The decanoate *XVb* revealed the properties of a medium long acting depot neuroleptic.

In one of the previous communications of this series[1] we described an attempt at preparing 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin-6-carboxylic acid by demethylation of 2-chloro-2-[2-(2-methoxyphenylthio)phenyl]acetic acid with boron tribromide and by the following cyclization with sodium hydroxide in dimethyl sulfoxide. The reaction was complicated by a simultaneously proceeding bromination which made impossible the preparation of the desired acid in pure state. Within the same study we could establish that in the molecule of 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin the position 2 of the skeleton is the most accessible for halogenation. In the first part of the present paper we describe the synthesis of the acids *Ia* and *Ib* with the position 2 blocked by fluorination by making use of the just mentioned method. By substitution of the position 2 with an atom of fluorine two purposes were followed: *a*) to prevent the mentioned simultaneous bromination in the reaction with boron tribromide and *2*) to prepare fluorinated precursors suitable for the synthesis of neuroleptic agents with a prolonged effectiveness after the oral administration (analogy in the series of 10-piperazinodibenzo[*b*,*f*]thiepin derivatives, *cf.*[2]).

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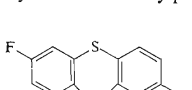
The known 5-fluoro-2-methoxyaniline[3] was the fluorinated starting material of our investigation; it was transformed *via* the corresponding aryldiazonium xanthate and aryl xanthate (method[4,5]) to 5-fluoro-2-methoxythiophenol (*IV*). By a reaction with 2-chlorobenzaldehyde in hexamethylphosphoramide in the presence of aque-

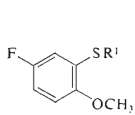


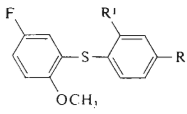
I, $R^1 = OH$
II, $R^1 = NH_2$
III, $R^1 = OC_2H_5$

a, R = H
b, R = Cl
c, $R = OCH_3$
d, $R = SCF_3$
e, $R = NO_2$
f, R = OH

ous sodium hydroxide at 100°C the aldehyde *VIa* was obtained which was subjected to treatment with chloroform and 50% aqueous sodium hydroxide in the presence of triethylbenzylammonium chloride (reaction, *cf.*[6–8]). The α-chloro acid *VIIa* resulted in a satisfactory yield and its identity was corroborated by spectra. The treatment with boron tribromide in dichloromethane at room temperature effected the demethylation and the crude product was subjected to the action of aqueous sodium hydroxide in dimethyl sulfoxide at 70°C in order to achieve the cyclization. In a yield of 53% the homogeneous acid *Ia* was obtained with characteristic IR and ^{1}H NMR spectra. In order to prepare the amide *IIa* a reaction of the acid *Ia* with ethyl chloroformate in tetrahydrofuran in the presence of triethylamine was carried out and the mixed anhydride obtained was treated *in situ* with concentrated aqueous ammonia. Chromatography of the product on silica gel gave the amide *IIa* in a moderate yield and a similar quantity of a nitrogen-free substance which was identified as the ethyl ester *IIIa*. The formation of ethyl esters in reactions of acids of the phenylacetic type with ethyl chloroformate in the presence of triethylamine has already been observed[9,10] and their formation is probably due to the instability of the mixed anhydrides formed which cleave carbon dioxide under mild conditions already. We consider now this explanation as a more likely one than the basic catalyzed re-esterification of ethyl chloroformate with the acid used, which was a hypothesis expressed previously[10].

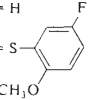
A further goal of our work was the synthesis of the 2-fluoro-8-chloro acid *Ib*. The starting 5-fluoro-2-methoxythiophenol (*IV*) was treated with 2-chloro-5-nitrobenzaldehyde[11] in ethanol in the presence of sodium hydroxide. The conditions used were evidently not much favourable because a mixture was formed from which the desired product *VIe* was isolated in a yield of only some 30%. By crystallization there were separated as by-products the disulfide *V*, formed by the oxidation of the thiol *IV* with air oxygen, and further the diethyl acetal *VIIIe* whose identity was con-





IV, $R^1 = H$

V, $R^1 = S$



VI, $R^1 = CHO$

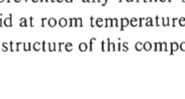
VII, $R^1 = CHClCOOH$

VIII, $R^1 = CH(OC_2H_5)_2$

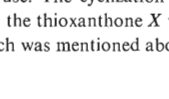
IX, $R^1 = COOH$

firmed by spectra. The acetal formation in an alkaline medium is hardly to be expected even though the acetalization of all the three isomeric nitrobenzaldehydes was described by treatment with dimethyl sulfate in the presence of sodium hydroxide[12]. In our case it is necessary to presume that the acetalization takes place under the catalytic action of the thiophenol *IV* prior to the addition of sodium hydroxide to the mixture. In the next step the nitroaldehyde *VIe* was reduced with stannous chloride in a mixture of acetic and hydrochloric acids and the aminoaldehyde formed was not isolated but immediately diazotized and subjected to the Sandmeyer reaction by treatment with cuprous chloride. Chromatography of the mixture formed on silica gel gave the chloroaldehyde *VIb* in a low yield. As a more polar component there was eluted from the column a highly melting substance $C_{14}H_8ClFO_2S$ (mass spectrum and analysis) whose UV spectrum indicated a high degree of conjugation and the IR spectrum the presence of a keto group between two aromatic nuclei. All this material represents a sufficient evidence for assigning the structure of 7-chloro--1-fluoro-4-methoxythioxanthone (*X*) to our product. Its formation has to be explained by oxidation of a small part of the aldehyde *VIb* to the acid *IXb* and its cyclization (acetic, hydrochloric and nitrous acids involved). The correctness of this hypothesis could experimentally be confirmed as explained at the end of this paragraph. In a further experiment the reduction of the nitroaldehyde *VIe* with stannous chloride was carried out in a mixture of dioxane and hydrochloric acid and the following procedure was similar like in the preceding case. From the mixture formed chromatography on silica gel separated first the disulfide *V* as the least polar product. This was followed by the chloroaldehyde *VIb* in a somewhat better yield than in the preceding case, and further by a little more polar isomeric product to which on the basis of IR and especially ^1H NMR spectra the structure of the chloroaldehyde *XI* was attributed. While the signal of the proton in *ortho*-position to the aldehyde group in compound *VIb* is shifted under the influence of strong shielding to 7·89 ppm, in the spectrum of the isomer this signal is absent which indicates that the *ortho*-position to the aldehyde group is occupied by another substituent, in our case by the chlorine atom. We are dealing here with a rather rarely observed shift of the substi-

tuent during the Sandmeyer reaction into a neighbouring position which is a phenomenon which was described[13,14] and explained for example by a transitive formation of an aryne intermediate and by the following addition reaction. As the most polar product there was obtained from the chromatography the unsubstituted aldehyde *VIa*, *i.e.* the product of the amino group elimination. The chloroaldehyde *VIb* was treated similarly like in the preceding case with chloroform and 50% sodium hydroxide in the presence of triethylbenzylammonium chloride. In a small amount the acid *IXb* was obtained, evidently as the product of oxidation of the aldehyde *VIb*. The mother liquor after this compounds yielded a further homogeneous, though non crystallizing acid which was assumed to be the desired α-chloro acid *VIIb*. It was subjected to demethylation with boron tribromide in dichloromethane and the crude product was treated with aqueous sodium hydroxide in dimethyl sulfoxide. The wanted reaction sequence took evidently place because the acid *Ib* was isolated in a low yield; its identity was confirmed by analyses and spectra. The low yield prevented any further synthetic use. The cyclization of the acid *IXb* with sulfuric acid at room temperature afforded the thioxanthone *X* which represents a final proof of structure of this compound which was mentioned above.



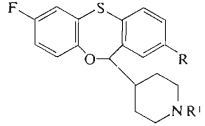
X

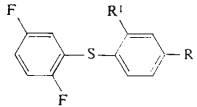


XI

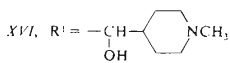
Similarly like in the preceding communications of this series[1,15,16] we chose for the synthesis of the pharmacologically most promising 6-(1-methyl-4-piperidyl) derivatives *XIIbcd* the cyclization of the corresponding carbinols *XVI* with sodium hydride in dimethylformamide. The starting material was 2,5-difluorothiophenol whose preparation from 2,5-difluoroaniline by diazotization and the xanthate method has recently been described[17]. Under the conditions described, however, 2,5-difluorothiophenol was obtained in a yield of only 25% and the main product was 1,3-bis(2,5-difluorophenyl)triazene, resulting already in the stage of diazotization. This inconvenience was now solved by making use of the Claus method[18] consisting in diazotization with nitrosylsulfuric acid, prepared from sulfuric acid and sodium nitrite (analogy, *cf.*[19,20]); in this way it was possible to obtain 2,5-difluorothiophenol in a yield of 70%.

In series *b* (chloro derivatives) 2,5-difluorothiophenol was condensed with 2,5-dichlorobenzaldehyde[16] by means of aqueous sodium hydroxide in hexamethylphosphoramide. The aldehyde *XVIIb* was obtained which was subjected to the action





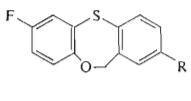
XII, $R^1 = CH_3$
XIII, $R^1 = H$
XIV, $R^1 = CH_2CH_2OH$
XV, $R^1 = (CH_2)_2OCO(CH_2)_8CH_3$



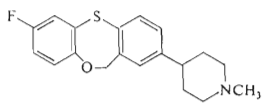
XVII, $R^1 = CHO$

of the Grignard reagent[21] prepared from 4-chloro-1-methylpiperidine[22] in tetrahydrofuran. The resulting amino alcohol *XVIb* was cyclized in crude state and without characterization by treatment with sodium hydride in dimethylformamide at 70°C. There was obtained an oily mixture of products which was separated by chromatography on aluminium oxide. As the least polar product there was eluted a nitrogen-free substance whose analysis and ^{1}H NMR spectrum enable its identification as 2-fluoro-8-chloro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XVIIIb*). Its formation has to be explained in that way that during the reaction of the aldehyde *XVIIb* with the Grignard reagent there comes in the extent of some 10% to the reduction of the aldehyde to the corresponding primary alcohol which is then cyclized by the action of sodium hydride. As a further component there was eluted a base which is the main product and was identified as the desired compound *XIIb*. The single proton at $C_{(6)}$ corresponds in the ^{1}H NMR spectrum to a doublet at 5·60 ppm. The compound affords a crystalline hydrogen maleate. The rechromatography of the most polar fractions on silica gel resulted in the isolation of the third product which is isomeric with compound *XIIb* but the ^{1}H NMR spectrum exhibits a singlet at 5·70 ppm corresponding to a CH_2 group in position 6. The base peak of the mass spectrum (*m*/*z* 70) is an ammonium ion consisting only in a fragment of the piperidine ring. We have encountered with a similar product in the previous work[16] already and formulate similarly the present product as a compound *XIX*. The explanation of its formation supposes the sequence of three reactions: *1*) reduction of the aldehyde *XVIIb* by the Grignard reagent to the alcohol, *2*) nucleophilic substitution of the atom of chlorine by reaction with 1-methyl-4-piperidylmagnesium chloride and *3*) cyclization of the fluorinated primary alcohol with sodium hydride. A reaction of compound *XIIb* with ethyl chloroformate in benzene effected the N-demethylation and the primary product obtained (the carbamate) was hydrolyzed with potassium hydride in ethanol. The secondary amine *XIIIb* was obtained and alkylated with 2-bromoethanol in acetone in the presence of potassium carbonate to give the amino alcohol *XIVb*. This was esterified with decanoic acid in boiling xylene under the conditions

of azeotropic distillation. The ester *XVb* formed was purified by crystallization of the hydrogen maleate and by its cautious decomposition with dilute sodium hydroxide; the ^{1}H NMR spectrum confirmed its identity and homogeneity.



XVIII

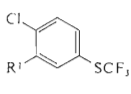


XIX

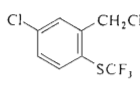
In the series *c* (methoxy derivatives) the work started from a reaction of 2,5-difluorothiophenol with 2-bromo-5-methoxybenzaldehyde[23], carried out in dimethylformamide in the presence of potassium carbonate and copper at 150°C. Methoxybenzaldehyde *XVIIc* was obtained as the main product which was distilled and crystallized. In a smaller amount there was isolated a further product as the higher boiling fraction. It contains a free phenolic hydroxyl (IR and ^{1}H NMR spectra) and was identified as the hydroxyaldehyde *XVIIf*. The demethylation was evidently effected by the potassium salt of 2,5-difluorothiophenol; potassium thiophenoxide was described as a reagent for the cleavage of the aryl methyl ethers[24]. Reaction of the aldehyde *XVIIc* with 1-methyl-4-piperidylmagnesium chloride gave the amino alcohol *XVIc* which was characterized as the oxalate and by the mass spectrum; the fragment with m/z 362 (M − 17) is typical for benzyl alcohols and the base peak with m/z 98 corresponds to the ammonium ion with preserved piperidine nucleus. The cyclization of compound *XVIc* with sodium hydride was carried out similarly like in the preceding case and the separation of the inhomogeneous product by chromatography on aluminium oxide yielded 2-fluoro-8-methoxy-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XVIIIc*) as a minor product and the base *XIIc* as the main product. The identity of both compounds has been confirmed by spectra and for the formation of the compound *XVIIIc* there is the same explanation as for the formation of compound *XVIIIb*.

In compound *XIId* the trifluoromethylthio group appears as the neuroleptic substituent with which we did not yet experiment in this connection but which showed to be in some series of tricyclic neuroleptics a substituent with positive influence on the activity[25,26]. For the introduction of this substituent we used the known 4-chlorophenyl trifluoromethyl sulfide[27] as the starting compound. It was chloromethylated with paraformaldehyde and chlorosulfonic acid; distillation of the product gave as the main fraction a mixture of monochloromethyl derivatives and a higher boiling fraction consisting in a mixture of bis(chloromethyl) derivatives. The monochloromethyl derivatives *XX* and *XXIII* can be differentiated by the ^{1}H NMR spectrum and using this method there could be established that our product consisted in some

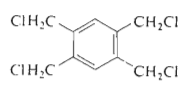
80% of the compound *XX* and the rest is the position isomer *XXIII*; the gas chromatography gave a similar result. From the higher boiling fraction there crystallized from hexane a small amount of the substance $C_{10}H_{10}Cl_4$ (mass spectrum, analysis) whose ^{1}H NMR spectrum indicates that we are dealing here with one of the tetra(chloromethyl)benzenes[28,29]. With regard to the fact that all of the eight protons of the four CH_2Cl groups appear in the spectrum as a singlet, there seems to be a complete equivalence of these four CH_2Cl groups which is fulfilled only in the structure of 1,2,4,5-tetra(chloromethyl)benzene (*XXIV*). The literature[29] reports for this compound a melting point value which is in a complete agreement with the melting point of our product. For these reasons we ascribe structure *XXIV* to our compound but we do not try to explain its formation in the reaction described.



XX, $R^1 = CH_2Cl$
XXI, $R^1 = CH_2OH$
XXII, $R^1 = CHO$



XXIII



XXIV

Reaction of the crude chloromethyl derivative *XX* with potassium acetate in dimethyl sulfoxide in the presence of triethylbenzylammonium chloride at 60°C and the following hydrolysis with boiling hydrochloric acid in a mixture of water and ethanol gave the crude 2-chloro-5-(trifluoromethylthio)benzyl alcohol (*XXI*) which was characterized by means of the ^{1}H NMR spectrum as to contain again approximately 80% of the desired substance in addition to the corresponding position isomer. Without an attempt at purification the oxidation with potassium dichromate in a two-phase system of dichloromethane–aqueous sulfuric acid in the presence of triethylbenzylammonium chloride at room temperature was carried out. The aldehyde *XXII* was obtained whose ^{1}H NMR spectrum indicates again the presence of some 20% of the undesired isomer. In the following reaction with 2,5-difluorothiophenol in hexamethylphosphoramide in the presence of aqueous sodium hydroxide at 100°C only compound *XXII* does react and affords the crystalline product *XVIId*; the less reactive position isomer of compound *XXII* remains unchanged in the mother liquor. The aldehyde *XVIId* was then treated with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran and gave the amino alcohol *XVId* which was cyclized in crude state with sodium hydride similarly like in the preceding cases. Chromatography of the mixture formed on aluminium oxide resulted in isolation of *XIId* as the single characterized product (spectra and the crystalline hydrogen maleate).

Compounds *XIIbcd* were pharmacologically evaluated in the form of maleates as potential oral neuroleptic agents with the possibility of a prolonged action; the

doses (in mg/kg) given were calculated for the bases. Similar pharmacological methods like in one of the preceding communications of this series[30] were used (oral administration throughout).

XIIb: LD_{50} = 184 mg/kg. The effect on motor coordination of mice in the rotarod test is strongly protracted; ED_{50} in 1 h after the administration = 0·9 mg/kg; in 3 h 0·3 mg/kg (maximum activity), in 24 h 1·4 mg/kg, in 48 h 3·2 mg/kg; after 72 h a dose of 5 mg/kg brought about ataxia in 50% mice, after 96 h in 20% mice. Cataleptic effect in rats, ED_{50} = 1·7 mg/kg (after 24 h the effect disappeared). Antiapomorphine effect in rats in 4 h after the administration, D_{50} = 1·14 mg/kg (for the inhibition of the apomorphine chewing) and 1·06 mg/kg (apomorphine agitation).

XIIc: LD_{50} = 164 mg/kg. Rotarod, ED_{50} = 0·77 (1 h), 0·46 (4 h), 2·3 (24 h), 3·6 mg/kg (48 h); inactive after 72 h. Catalepsy, ED_{50} = 3·0 mg/kg (inactive after 24 h). Antiapomorphine effects (4 h), D_{50} = 2·9 (chewing) and 3·5 mg/kg (agitation). This compound was also tested with intravenous administration in further tests (effective doses or effective concentrations given) (Dr M. Bartošová, affiliated unit of this institute at Rosice n/L): LD_{50} 60 mg/kg; analgetic effect (Haffner's test) 1—5 mg/kg; corneal anaesthesia (rabbits'eye), 0·1—0·5%; α-adrenolytic effect (rat), 0·01 mg/kg; spasmolytic anti-acetylcholine effect (isolated rat duodenum),1 μg/ml; spasmolytic anti-$BaCl_2$ effect, 1—10 μg/ml; hypothermic effect (mice), 1—5 mg/kg; antihistamine effect (detoxication of histamine in guinea-pigs), 0·1—1·0 mg/kg *s.c.*; thiopental potentiation (mice), 0·1—1·0 mg/kg; antiamphetamine effect (mice), 0·01—0·1 mg/kg.

XIId: LD_{50} = 338 mg/kg. Rotarod, ED_{50} = 3·0 (2 h), 1·8 (5 h), 6·0 mg/kg (24 h); in 48 h a dose of 10 mg/kg brings about ataxia in 30% mice, in 72 h in 10%. Catalepsy, ED_{50} = 3·3 mg/kg (after 24 h the effect disappeared). Antiapomorphine effects in 4 h, D_{50} = 1·6 (chewing) and 1·6 mg/kg (agitation), ineffective after 24 h. A dose of 5 mg/kg influenced in a typical manner the dopamine metabolism in striatum of the rat brain (Dr M. Valchář, Pharmacological department of this institute): in 3 h after the administration the concentration of homovanillic acid (metabolite of dopamine) was significantly increased. After 24 h the increase of this metabolite is only insignificant. The compound did not influence the metabolism of serotonin in the rat striatum (the level of 5-hydroxyindoleacetic acid unchanged).

XVb was tested as a potential depot neuroleptic agent. Doses of 25 and 50 mg/kg intramuscularly (a 2·5% solution of the base in Miglyol) had antiapomorphine effects in rats lasting 3, and 8 days, respectively. A dose of 5 mg/kg *i.m.* inhibited the apomorphine emesis in dogs for 2 weeks and the effect disappeared in the 3rd week after the administration. The oral acute toxicity of the hydrogen maleate was tested and the dose was calculated for the base, LD_{50} = 425 mg/kg.

IIa was nontoxic until the dose of 500 mg/kg orally. Rotarod, ED_{50} = 108 mg/kg. The compound was ineffective in a dose of 50 mg/kg (orally) towards the electroshock convulsions in mice.

In conclusion, compounds *XIIbcd* are extremely potent neuroleptic agents with clear prolongation of the central depressant effect.

Three of the compounds were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, Bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml given: *Streptococcus* β-*haemolyticus*, *XIIb* 12·5, *XIIc* 50; *Streptococcus faecalis*, *XIIb* 25, *XIIc* 100; *Staphylococcus pyogenes aureus*, *XIIb* 6·2, *XIIc* 50; *Escherichia coli*, *IIa* 100, *XIIb* 25, *XIIc* 12·5; *Proteus vulgaris*, *XIIb* 50; *Mycobacterium tuberculosis* H37Rv, *IIa* 50; *Trichophyton mentagrophytes*, *IIa* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder. The samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, the ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the ^{19}F NMR spectra (in $CHCl_3$, $\delta_{CFCl3} = 0$) with the same instrument. The mass spectra were recorded with the spectrometers MS 902 (AEI) and Varian MAT-311. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatographic separations were carried out either on neutral Al_2O_3 (activity II) or on silica gel (Silpearl).

5-Fluoro-2-methoxythiophenol (*IV*)

5-Fluoro-2-methoxyaniline[3] (106 g) was slowly added to a stirred mixture of 150 ml hydrochloric acid and 150 ml water, the mixture was cooled to 0°C and diazotized at 0—4°C with a solution of 55·2 g $NaNO_2$ in 120 ml water. It was stirred for 30 min and the cooled diazonium salt solution was added dropwise over 1 h to a stirred solution of 140 g potassium ethyl xanthate in 180 ml water containing 0·3 g $NiSO_4.7\,H_2O$ at 40—45°C. The mixture was stirred for 1 h, cooled and extracted with ether. The extract was washed with 10% NaOH and water and ether was evaporated. The residue was dissolved in a mixture of 500 ml ethanol and 20 ml water and the refluxing solution was slowly treated with 180 g KOH. It was refluxed for 8 h, ethanol was evaporated, the residue diluted with 400 ml water and the solution washed with ether. The aqueous layer was acidified with a mixture of 110 ml H_2SO_4 and 500 ml water, 10 g Zn were added and the product was distilled with steam. The distillate was extracted with ether, the extract dried with Na_2SO_4 and distilled; 73·3 g (62%), b.p. 92—96°C/1·1 kPa. ^1H NMR spectrum: δ 6·60—7·10 (m, 3 H, Ar—H), 3·90 (s, 1 H, SH), 3.80 (s, 3 H, OCH_3). For C_7H_7FOS (158·2) calculated: 53·15% C, 4·46% H, 12·01% F, 20·27% S; found: 52·89% C, 4·44% H, 12·28% F, 20·03% S.

2-(5-Fluoro-2-methoxyphenylthio)benzaldehyde (*VIa*)

A solution of 31·6 g *IV* in 50 ml hexamethylphosphoramide was treated with a solution of 8·0 g NaOH in 15 ml water and then 28·2 g 2-chlorobenzaldehyde were added. The mixture was stirred and heated for 3·5 h to 100°C, poured into 300 ml water and extracted with benzene. Processing of the extract gave 55 g oily residue which crystallized from light petroleum; 37·4 g (71%), m.p. 78—82·5°C. Analytical sample, m.p. 83—84°C (benzene–light petroleum). UV spectrum: λ_{max} 210 nm (log ε 4·39), 236 nm (4·21), 295 nm (3·84), infl. 335 nm (3·49). IR spectrum: 739, 752, 810, 880 (4 and 2 adjacent and solitary Ar—H), 1 190, 1 200, 1 255 ($ArOCH_3$), 1 485, 1 560, 1 588, 3 000, 3 035, 3 054 (Ar), **1 680**, 1 700, 2 745 cm^{-1} (CHO). ^1H NMR spectrum: δ 10·45 (s 1 H, CHO), 7·95 (m, 1 H, 6-H), 6·80—7·60 (m, 6 H, remaining Ar—H), 3·81 (s, 3 H, $ArOCH_3$). ^{19}F NMR spectrum: δ −122·8 (dt, $J_{F(o-H)} = 7·5$ Hz, $J_{F(m-H)} = 6·0$ Hz). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·11% C, 4·23% H, 7·24% F, 12·22% S; found: 64·36% C, 4·28% H, 7·38% F, 12·18% S.

2-(5-Fluoro-2-methoxyphenylthio)-5-nitrobenzaldehyde (*VIe*)

A solution of 31·2 g *IV* and 36·6 g 2-chloro-5-nitrobenzaldehyde[11] in 200 ml ethanol was stirred and treated over 20 min at 40°C with a solution of 7·9 g NaOH in 150 ml ethanol, added dropwise.

The mixture was stirred at 60–70°C for 3 h, ethanol was distilled off at normal pressure, the residue was diluted with water and extracted with benzene. The undissolved substance was filtered off and dried *in vacuo*; 19·7 g (33%) *VIe*, m.p. 180–187°C. Analytical sample, m.p. 186–187°C (dioxane). UV spectrum: λ_{max} 297 nm (log ε 3·92), 337 nm (4·08). IR spectrum: 816, 880, 900 (2 adjacent and solitary Ar—H), 1 020, 1 192, 1 270 ($ArOCH_3$), 1 344, 1 490 ($ArNO_2$), 1 571, 1 596, 3 053, 3 082 (Ar), 1 689 cm^{-1} (ArCHO). For $C_{14}H_{10}FNO_4S$ (307·3) calculated: 54·72% C, 3·28% H, 6·18% F, 4·56% N, 10·43% S; found: 54·74% C, 3·33% H, 6·32% F, 4·47% N, 10·13% S.

The filtrate was separated, the benzene layer was dried and evaporated. The oily residue is a mixture of at least three components, one of them being a further quantity of *VIe* which, however, could not be separated in a preparative way. It was crystallized from a mixture of benzene and light petroleum and gave 39·7 g mixture of crystals. The mother liquor deposited on standing 7·5g crystals which were recrystallized from light petroleum and melted at 98–100°C.The substance was identified as 2-(5-fluoro-2-methoxyphenylthio)-5-nitrobenzaldehyde diethyl acetal (*VIIIe*). Mass spectrum, *m/z* (%): 381 (M^+ corresponding to $C_{18}H_{20}FNO_5S$, 20), 306 (81), 276 (31), 260 (25), 182 (100), 150 (28), 136 (25), 126 (41). IR spectrum: 809, 830, 872, 903 (2 adjacent and solitary Ar—H), 1 058, 1 064, 1 195 ($ArOCH_3$, ROR'), 1 349, 1 489, 1 527 ($ArNO_2$), 1582 1 603, 3 010, 3 085 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·51 (d, J = 2·5 Hz, 1 H, 6-H), 7·96 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 6·90–7·30 (m, 4 H, remaining Ar-H), 5·80 (s, 1 H, ArCH(O)(O)), 3·75 (s, 3 H, OCH_3), 3·68 (q, J = 7·0 Hz, 4 H, 2 OCH_2), 1·31 (t, J = 7·0 Hz, 6 H, 2 C—CH_3). ^{19}F NMR spectrum: δ −122·8 (dt, $J_{F(o-H)}$ = 7·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{18}H_{20}$. .FNO_5S (381·4) calculated: 56·68% C, 5·28% H, 4·98% F, 3·67% N, 8·41% S; found: 56·37% C, 5·32% H, 4·83% F, 3·65% N, 8·19% S.

The above mixture of crystals was recrystallized first from a mixture of benzene and light petroleum and then from acetic acid without obtaining a homogeneous product. The acetic acid mother liquor deposited on standing 0·8 g bis(5-fluoro-2-methoxyphenyl) disulfide (*V*), m.p. 119–122°C (cyclohexane). Mass spectrum, *m/z* (%): 314 (M^+ corresponding to $C_{14}H_{12}$. .$F_2O_2S_2$, 91), 158 (20), 157 (26), 156 (34), 155 (21), 111 (100), 92 (26), 91 (41), 83 (62). IR spectrum: 798, 861, 892 (2 adjacent and solitary Ar—H), 1 174, 1 191 ($ArOCH_3$), 1 480, 1 590, 1 598, 3 025, 3 040, 3 080 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·21 (q, J_{H-F} = 9·0 Hz, 2 H, 6,6'-H_2), 6·80 (m, 4 H, remaining Ar—H), 3·88 (s, 6 H, 2 OCH_3). ^{19}F NMR spectrum: δ −122·5 (dt, $J_{F(o-H)}$ = 7·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{14}H_{12}F_2O_2S_2$ (314·4) calculated: 53·49% C, 3·85% H, 12·09% F, 20·40% S; found: 54·08% C, 3·94% H, 12·08% F, 19·97% S.

5-Chloro-2-(5-fluoro-2-methoxyphenylthio)benzaldehyde (*VIb*)

A) A solution of 6·15 g *VIe* in 90 ml acetic acid was treated with a solution of 13·54 g $SnCl_2$. .2 H_2O in 90 ml hydrochloric acid and the mixture was heated for 2 h gradually to 80°C. The solution was cooled to 0°C and diazotized with a solution of 1·5 g $NaNO_2$ in 5 ml water. After 20 min stirring at 0–4°C, 3 g CuCl in 15 ml hydrochloric acid were added, the mixture was stirred for 1 h at room temperature and then heated on a boiling water bath for 2 h. After cooling it was extracted with benzene, the extract was washed with water and 15% Na_2CO_3, dried with $MgSO_4$ and evaporated. The oily residue was chromatographed on a column of 200 g silica gel. Elution with benzene removed in the first fractions the least polar impurities and afforded then 1·40 g (27% per conversion) *VIb*, m.p. 89–91°C (cyclohexane). UV spectrum: λ_{max} 295 nm (log ε 3·91), 347 nm (3·10), inflexes at 232 nm (4·18), 253 nm (4·00), 277 nm (3·84). IR spectrum: 800, 830, 865, 882, 890 (2 adjacent and solitary Ar—H), 1 190, 1 205 ($ArOCH_3$), 1 492, 1 549,

1 578·, 1 599, 1 605, 3 045, 3 065, 3 090 (Ar), 1 690, 1 702 cm^{-1} (ArCHO). ^1H NMR-spectrum δ 10·40 (s, 1 H, CHO), 7·89 (d, J = 2·5 Hz, 1 H, 6-H), 7·41 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 7·18 (d, J = 8·0 Hz, 1 H, 3-H), *c.* 6·85 (m, 3 H, remaining Ar—H), 3·80 (s, 3 H, OCH_3). For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·66% C, 3·40% H, 11·95% Cl, 6·40% F, 10·81% S; found: 57·40% C, 3·51% H, 12·15% Cl, 6·64% F, 10·87% S.

Continued elution with benzene led to recovery of 0·81 g starting *VIe*, m.p. 182—185°C (benzene). Elution with chloroform gave 0·52 g compound crystallizing from benzene and melting at 231—233°C which was identified as 7-chloro-1-fluoro-4-methoxythioxanthone (*X*). Mass spectrum, *m/z*: 294 (M^+ corresponding to $C_{14}H_8ClFO_2S$), 279, 251, 223. UV spectrum: λ_{max} 255·5 nm (log ε 4·55), 318·5 nm (4·06), 391 nm (3·72), inflexes at 263 nm (4·52), 309 nm (3·91). IR spectrum (KBr): 816, 828, 868 (2 adjacent and solitary Ar—H), 1 065, 1 251, 1 277, 2 829 ($ArOCH_3$), 1 575, 1 604, 3 045, 3 071 (Ar), 1 642 cm^{-1} (ArCOAr'). For $C_{14}H_8ClFO_2S$ (294·7) calculated: 57·05% C, 2·74% H, 12·03% Cl, 6·45% F, 10·88% S; found: 57·12% C, 2·75% H, 11·25% Cl, 6·22% F, 10·20% S. The same compound was obtained by standing of a solution of 0·1 g *IXb* in 2 ml H_2SO_4 at room temperature for 2 days; the mixture was decomposed with water, the solid filtered, washed with water and dried, m.p. 232·5—233·5°C.

B) A solution of 26·2 g *VIe* in 300 ml dioxane was treated with a solution of 69·2 g $SnCl_2 . 2\,H_2O$ in 300 ml hydrochloric acid and the mixture was stirred at 70°C for 2·5 h. The solution was cooled to 0°C and diazotized with a solution of 6·4 g $NaNO_2$ in 20 ml water. It was stirred for 15 min at 0°C, treated with a solution of 13 g CuCl in 60 ml hydrochloric acid, stirred for 30 min at room temperature and for 30 min on the boiling water bath. After cooling it was extracted with benzene, the extract was washed with water, 10% Na_2CO_3 and water, dried with $MgSO_4$ and evaporated. The oily residue was chromatographed on 400 g silica gel. The first to be eluted with benzene was 0·63 g disulfide *V*, m.p. 121—123°C (cyclohexane), identical with the product described above. It was followed by 7·51 g (30%) aldehyde *VIb*, m.p. 88—92°C (cyclohexane).

This was immediately followed by 0·44 g compound crystallizing also from cyclohexane but melting at 113—116·5°C which was identified as 2-chloro-6-(5-fluoro-2-methoxyphenylthio)-benzaldehyde (*XI*). Mass spectrum, *m/z*: 296 (M^+ corresponding to $C_{14}H_{10}ClFO_2S$), 265, 218, 189, 170, 126. UV spectrum: λ_{max} 278 nm (log ε 4·03), 292 nm (4·02), 349 nm (3·85), inflexes at 226 nm (4·46), 240 nm (4·39) and 300 nm (3·99). IR spectrum (KBr): 743, 780, 809, 862 (3 and 2 adjacent and solitary Ar—H), 1 190, 1 209, 1 263, 2 820 ($ArOCH_3$), 1 486, 1 543, 1 576, 3 030, 3 045, 3 070 (Ar), 1 693, 2 740 cm^{-1} (ArCHO). ^1H NMR spectrum: δ 10·65 (s, 1 H, CHO), 6·50—7·40 (m, 6 H, Ar—H), 3·71 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ −122·8 (dt, $J_{F(o-H)}$ = = 7·5 Hz. $J_{F(m-H)}$ = 6·0 Hz). For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·66 % C, 3·40% H, 11·95% Cl, 6·40% F, 10·81% S; found: 57·10% C, 3·41% H, 11·69% Cl, 6·50% F, 10·95% S.

As the last compound eluted with benzene was *VIa*, a product of the amino group elimination, identical with the compound described above; 2·71 g, m.p. 82—83°C (cyclohexane).

2-Chloro-2-[2-(5-fluoro-2-methoxyphenylthio)phenyl]acetic Acid (*VIIa*)

A mixture of 37·2 g *VIa*, 200 ml chloroform and 1·5 g triethylbenzylammonium chloride was stirred and treated dropwise over 7 h at 30°C with a solution of 80 g NaOH in 80 ml water. It was allowed to stand for 2 days, stirred for 4 h and diluted with water. The aqueous layer was separated and acidified with hydrochloric acid, the product was extracted with ether, the extract was dried with Na_2SO_4 and evaporated. The residue was dissolved in benzene and chromatographed on 1·1 kg silica gel. Benzene and chloroform eluted small fractions of less polar impurities. The acid *VIIa* was eluted with a mixture of chloroform and ethanol; 30·2 g

(65%), m.p. 107—111°C. Analytical sample, m.p. 109—111°C (benzene–light petroleum). Mass spectrum, m/z (%): 326 (M^+ corresponding to $C_{15}H_{12}ClFO_3S$, 33), 249 (20), 245 (100), 231 (37) 230 (48), 215 (37), 202 (48). IR spectrum: 738, 750, 809, 877 (4 and 2 adjacent and solitary Ar—H) 902, **1 734** (RCOOH), 1 179, 1 184, 1 193, 1 204, 1 256 ($ArOCH_3$, COOH), 1 486, 1 594, 3 040 cm^{-1} (Ar). ^1H NMR spectrum: δ 10·80 (bs, 1 H, COOH), 6·30—7·80 (m, 7 H, Ar—H), 6·21 (s, 1 H, Ar—CHCl—COO), 3·82 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ —122·8 (dt, $J_{F(o-H)}$ = = 7·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{15}H_{12}ClFO_3S$ (326·8) calculated: 55·13% C, 3·70% H, 10·85% Cl; found: 55·65% C, 3·77% H, 10·20% Cl.

2-Fluoro-6*H*-dibenz[*b,e*]-1,4-oxathiepin-6-carboxylic Acid (*Ia*)

A solution of 16·1 g *VIIa* in 200 ml dichloromethane was treated dropwise over 10 min with 25·1 g BBr_3, the mixture was stirred for 5 h at room temperature, allowed to stand overnight, treated with 100 ml ethanol and the solvents evaporated *in vacuo*. The residue was dissolved in 150 ml dimethyl sulfoxide and the solution was added dropwise over 5·5 h to a stirred mixture of 50 ml 20% NaOH and 300 ml dimethyl sulfoxide at 70°C. The heating was continued for 1 h, the mixture was diluted with water and the solution washed with benzene. The aqueous layer was then acidified with hydrochloric acid and the product was extracted with benzene. Evaporation of the extract gave 7·2 g (63%) *Ia*, m.p. 199—202°C (benzene–ethanol). IR spectrum: 726, 776, 811, 868 (4 and 2 adjacent and solitary Ar—H), 935, **1 729**, 2 630, 3 150 (R—COOH), 1 100, 1 182, 1 254 (ArOR, COOH), 1 580, 1 590, 1 609 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 13·40 (bs, 1 H, COOH), 6·80—7·70 (m, 7 H, Ar—H), 6·12 (s, 1 H, ArCH—O—). For $C_{14}H_9$. FO_3S (276·3) calculated: 60·86% C, 3·28% H, 6·88% F, 11·61% S; found: 60·69% C, 3·30% H, 6·82% F, 11·82% S.

8-Chloro-2-fluoro-6*H*-dibenz[*b,e*]-1,4-oxathiepin-6-carboxylic Acid (*Ib*)

A mixture of 5·63 g *VIb*, 40 ml chloroform and 0·3 g triethylbenzylammonium chloride was treated dropwise over 2 h with a solution of 15 g NaOH in 15 ml water. The solution was stirred for 5 h at 30°C, diluted with water and the organic layer was separated. The aqueous layer was acidified with hydrochloric acid and the product extracted with benzene. The benzene solution was chromatographed on a column of 120 g silica gel. Benzene eluted only small amounts of the least polar impurities. The main acid fraction was eluted with chloroform; 2·63 g oil. It was dissolved in a small volume of cyclohexane and 0·40 g compound was obtained, m.p. 208—209°C (benzene–light petroleum). It was identified as 5-chloro-2-(5-fluoro-2-methoxyphenylthio)benzoic acid (*IXb*). UV spectrum: λ_{max} 221 nm (log ε 4·40), 258·5 nm (4·04), 297 nm (3·92), infl. 325 nm (3·76). IR spectrum: 784, 811, 824, 780 (2 adjacent and solitary Ar—H), 925, **1 695**, 2 535, 2 600, 2 640, 2 705 (ArCOOH), 1 259 ($ArOCH_3$, COOH), 1 490, 1 550, 1 588, 1 600 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·90 (d, J = 2·5 Hz, 1 H, 6-H), 7·00—7·50 (m, 4 H, 4-H and 3 ArH of the fluorophenyl), 6·70 (d, J = 8·0 Hz, 1 H, 3-H), 3·70 (s, 3 H, OCH_3).For $C_{14}H_{10}ClFO_3S$ (312·8) calculated: 53·77% C, 3·22% H, 11·34% Cl, 6·08% F, 10·25% S; found: 53·56% C, 3·29% H, 11·13% Cl, 6·13% F, 10·62% S.

The cyclohexane mother liquor was evaporated. The oily residue (2·23 g) represents the crude acid *VIIb*. It was dissolved in 25 ml dichloromethane and the solution was treated with 3·1 g BBr_3. The mixture was stirred for 7 h at room temperature, treated with 20 ml ethanol and the solvents were evaporated. The residue was dissolved in 20 ml dimethyl sulfoxide and the solution was added dropwise over 90 min to a stirred mixture of 8 ml 20% NaOH and 40 ml dimethyl sulfoxide at 70°C. It was stirred for 4 h at 70°C, diluted with water and washed with benzene.

The aqueous solution was acidified with hydrochloric acid and the product extracted with chloroform. The extract was washed with water, dried with $MgSO_4$ and evaporated. The oily residue crystallized partly from benzene; 0·90 g (15% calculated per starting *VIb*) crude *Ib*, m.p. 180 to 185°C. Analytical sample, m.p. 197—198°C (benzene). UV spectrum: λ_{max} 277 nm (log ε 3·89), 284 nm (3·95), inflexes at 252 nm (4·03) and 300 nm (3·86). IR spectrum: 814, 860, 876 (2 adjacent and solitary Ar—H), 907, **1 714**, **1 740**, 2 660, 3 140 (R—COOH), 1 193, 1 250 (ArOR, COOH), 1 564, 1 584, 1 610 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·30—7·70 (m, 3 H, 7,9,10-H_3), 6·80—7·20 (m, 3 H, 1,3,4-H_3), 6·18 (s, 1 H, ArCH—O—). For $C_{14}H_8ClFO_3S$ (310·7) calculated: 54·11% C, 2·60% H, 11·41% Cl, 6·11% F, 10·32% S; found: 54·14% C, 2·64% H, 11·31% Cl, 6·23% F, 10·28% S.

2-Fluoro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin-6-carboxamide (*IIa*)

A solution of 7·25 g *Ia* and 7·0 g triethylamine in 100 ml tetrahydrofuran was stirred and treated at −5°C with 6·0 ml ethyl chloroformate, added dropwise. The mixture was stirred for 90 min, 200 ml 20% NH_4OH were added and the stirring at room temperature continued for 4 h. The mixture was extracted with ether, the extract washed with water, dried with K_2CO_3 and evaporated. The residue was dissolved in ethanol and a small amount of an insoluble substance was filtered off. The filtrate was evaporated again and the residue (6·9 g) was dissolved in benzene and the solution was chromatographed on 200 g silica gel. Benzene eluted 2·82 g (35%) of a less polar component which was identified as ethyl 2-fluoro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin-6-carboxylate (*IIIa*), m.p. 86·5—87·5°C (cyclohexane). IR spectrum: 727, 750, 770, 810, 864 (4 and 2 adjacent and solitary Ar—H), 1 050, 1 063, 1 079, 1 180 (ArOR), 1 240, 1 253, **1 750** (R—COOR′), 1 480, 1 607, 3 020, 3 035, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·15—7·70 (m, 4 H, 7,8,9,10-H_4), 6·60—7·00 (m, 3 H, 1,3,4-H_3), 6·31 (s, 1 H, Ar—CH—O), 4·34 (q, J = 7·0 Hz, 2 H, CH_2O), 1·29 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{16}H_{13}FO_3S$ (304·3) calculated: 63·14% C, 4·31% H, 6·24% F, 10·54% S; found: 63·18% C, 4·53% H, 6·15% F, 10·50% S.

The chromatography was continued using chloroform as the eluent. There were obtained 2·85 g (40%) amide *IIa*, m.p. 175·5—176·5°C (benzene). IR spectrum (KBr): 774, 797, 816, 854 (4 adjacent and solitary Ar—H), 1 192, 1 250 (ArOR), 1 483, 1 592, 1 609 (Ar), **1 673**, **1 704** ($CONH_2$), 3 110, 3 180, 3 220, 3 448 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·88 (bd, 2 H, $CONH_2$), 6·80—7·60 (m, 7 H, Ar—H), 6·38 (s, 1 H, Ar—CH—O). For $C_{14}H_{10}FNO_2S$ (275·3) calculated: 61·08% C, 3·66% H, 6·90% F, 5·09% N, 11·65% S; found: 60·50% C, 3·84% H, 6·98% F, 5·17% N, 11·34% S.

2,5-Difluorothiophenol

$NaNO_2$ (24·0 g) was slowly added with stirring to 152 ml H_2SO_4 at 5—10°C, the mixture was heated to 70°C, the clear solution formed was cooled and treated dropwise at 15—20°C over 1 h with a solution of 35·8 g 2,5-difluoroaniline[31] in 270 ml acetic acid. The mixture was stirred for 3 h at 20°C, allowed to stand overnight at 0°C and added dropwise over 75 min to a stirred solution of 80 g potassium ethyl xanthate and 545 g Na_2CO_3 in 1 500 ml water at 50°C. The mixture was stirred for 2 h at room temperature and extracted with ether. The extract was washed with water and evaporated. The residue was dissolved in 190 ml ethanol and the refluxing solution was slowly treated with a solution of 87 g KOH in 65 ml water. The mixture was refluxed for 12 h under nitrogen. Ethanol was distilled off *in vacuo*, the residue dissolved in 200 ml water, 7 g Zn were added and the mixture treated dropwise at 5—10°C with 165 ml hydrochloric acid. The product was extracted with ether, the extract dried with $MgSO_4$ and distilled; 28·3 g (70%), b.p. 58—60°C/2 kPa. Lit.[17], b.p. 60—62°C/2 kPa.

2-Chloro-5-(trifluoromethylthio)benzyl Chloride (*XX*)

A stirred mixture of 116·8 g 4-chlorophenyl trifluoromethyl sulfide[27] and 20 g paraformaldehyde was treated dropwise at −5°C with 60 g chlorosulfonic acid, the mixture was stirred for 3 h at −5°C and allowed to stand for 3 days at this temperature. It was then decomposed by pouring on ice and extracted with chloroform. The extract was filtered, dried with $MgSO_4$ and distilled. First of all there were recovered 54·1 g starting 4-chlorophenyl trifluoromethyl sulfide, b.p. 70–80°C/1·6–2 kPa. The fraction boiling at 115–140°C/2 kPa is a mixture of monochloromethyl derivatives consisting mainly in *XX*; 33·7 g (44% per conversion). IR spectrum (film): 824, 888 (2 adjacent and solitary Ar—H), 1 091, 1 113, 1 135, 1 162 ($ArSCF_3$), 1 469, 1 580, 3 030, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·20–8·00 (m, 3 H, Ar—H), 4·63 (s, 1·6 H, $ArCH_2Cl$ in *XX*), 4·75 (s, 0·4 H, $ArCH_2Cl$ in *XXIII*); this spectrum indicates that the product contains 80% *XX* and 20% *XXIII*. The analysis by gas chromatography gave the same result. For $C_8H_5Cl_2F_3S$ (261·1) calculated: 36·80% C, 1·93% H, 27·16% Cl, 21·83% F, 12·28% S; found: 37·25% C, 2·00% H, 26·81% Cl, 20·79% F, 12·80% S.

There were further obtained 5·2 g fraction boiling at 140–180°C/2 kPa consisting mainly in a mixture of isomeric bis(chloromethyl) derivatives. The fraction was dissolved in a small volume of hexane. By standing the solution deposited 0·2 g crystals melting at 152·5–153°C (benzene–light petroleum). On the basis of the evidence available this product is formulated as 1,2,4,5-tetra(chloromethyl)benzene (*XXIV*). Mass spectrum, *m/z*: 270 (M^+ corresponding to $C_{10}H_{10}{}^{35}Cl_4$), 235 ($C_{10}H_{10}{}^{35}Cl_3$). ^1H NMR spectrum: δ 7·39 (s, 2 H, Ar—H), 4·65 (s, 8 H, 4 $ArCH_2Cl$). For $C_{10}H_{10}Cl_4$ (272·0) calculated: 44·16% C, 3·71% H, 52·14% Cl; found: 44·25% C, 3·65% H, 51·24% Cl. Lit.[29], m.p. 151–153°C.

2-Chloro-5-(trifluoromethylthio)benzyl Alcohol (*XXI*)

A mixture of 55·6 g crude *XX*, 23 g potassium acetate, 150 ml dimethyl sulfoxide and 10 g triethylbenzylammonium chloride was stirred for 5 h at 60°C, poured into water, extracted with benzene and the extract was evaporated. The residue (55 g oil) was dissolved in 200 ml ethanol, the solution was treated with 100 ml water and 20 ml hydrochloric acid and the mixture was stirred and refluxed for 7 h. Ethanol was distilled off, the residue was diluted with water and extracted with benzene. The extract was dried and distilled; 40·2 g (78%), b.p. 140–150°C/2 kPa. According to the ^1H NMR spectrum the product contains 80% *XXI* and 20% of the position isomer: δ 7·18–7·90 (m, 3 H, Ar—H), 4·71 (s, 1·6H, $ArCH_2O$ in *XXI*), 4·83 (s, 0·4 H, $ArCH_2O$ in the isomer), 2·39 (s, 1 H, OH). IR spectrum (film): 821, 876, 894 (2 adjacent and solitary Ar—H), 1 090, 1 114, 1 143, 1 164 ($ArSCF_3$), 1 040, 1 055, 3 290 (CH_2OH), 1 460, 1 560, 1 580 cm^{-1} (Ar). For $C_8H_6ClF_3OS$ (242·7) calculated: 39·60% C, 2·49% H, 14·61% Cl, 23·49% F, 13·21% S; found: 40·45% C, 2·55% H, 15·21% Cl, 23·17% F, 13·47% S.

2-Chloro-5-(trifluoromethylthio)benzaldehyde (*XXII*)

Triethylbenzylammonium chloride (3·6 g) was added to a solution of 39·9 g crude *XXI* in 400 ml dichloromethane, the mixture was cooled to 15–20°C and treated dropwise under stirring with a solution of 20·6 g $K_2Cr_2O_7$ and 135 ml H_2SO_4 in 270 ml water with maintaining the temperature mentioned. The mixture was stirred for 4 h, allowed to stand overnight, the organic layer was separated, washed with water and 5% NaOH, dried with $MgSO_4$ and distilled; 34·1 g (37%), b.p. 120–130°C/2 kPa. IR spectrum (film): 744, 756 (C—Cl), 831, 900 (2 adjacent and solitary Ar—H), 1 091, 1 113, 1 135, 1 163 ($ArSCF_3$), 1 462, 1 578, 3 030, 3 055 (Ar), 1 700 cm^{-1} (ArCHO). ^1H NMR spectrum indicates again the presence of some 80% *XXII* and 20% of its

position isomer: δ 10·53 (s, 0·2 H, ArCHO in the isomer), 10·45 (s, 0·8 H, ArCHO in *XXII*), 7·30—8·30 (m, 3 H, Ar—H), For $C_8H_4ClF_3OS$ (240·6) calculated: 39·93% C, 1·68% H, 14·73% Cl, 23·69% F, 13·32% S; found: 40·51% C, 1·75% H, 15·13% Cl, 23·66% F, 13·47% S.

5-Chloro-2-(2,5-difluorophenylthio)benzaldehyde (*XVIIb*)

A solution of 3·60 g NaOH in 6 ml water was added to a solution of 13·1 g 2,5-difluorothiophenol in 20 ml hexamethylphosphoramide, the mixture was treated with 13·65 g 2,5-dichlorobenzaldehyde[16] and heated for 5·5 h to 100°C. After cooling it was diluted with 150 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated under reduced pressure. Crystallization of the residue from a mixture of benzene and light petroleum and processing of the mother liquors gave 16·4 g (74%) product melting at 84—89°C. Analytical sample, m.p. 88—90°C (benzene–light petroleum). UV spectrum: λ_{max} 235 nm (log ε 4·17), 280 nm (3·90), infl. 245 nm (4·10). IR spectrum (KBr): 760 (C—Cl), 825, 880 (2 adjacent and solitary Ar—H), 1 480, 1 548, 3 025, 3 062 (Ar), 1 688 cm^{-1} (ArCHO). For $C_{13}H_7ClF_2OS$ (284·7) calculated: 54·84% C, 2·48% H, 12·46% Cl, 13·34% F, 11·26% S; found: 55·31% C, 2·40% H, 12·15% Cl, 13·82% F, 11·08% S.

2-(2,5-Difluorophenylthio)-5-methoxybenzaldehyde (*XVIIc*)

A mixture of 19·7 g 2-bromo-5-methoxybenzaldehyde[23], 14·1 g 2,5-difluorothiophenol, 14·0 g K_2CO_3, 75 ml dimethylformamide and 2·1 g Cu was stirred and heated for 6 h to 150°C. After cooling it was diluted with 150 ml water and 150 ml benzene, filtered and the filtrate was extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and distilled. The lower boiling fraction is the crude product *XVIIc*; 13·3 g (52%), b.p. 163—165°C/40 Pa. This crude product was chromatographed on a column of 500 g Al_2O_3; first fractions of benzene eluted 9·97 g (39%) *XVIIc*, m.p. 67—68°C (cyclohexane). UV spectrum: λ_{max} 228 nm (log ε 4·32), 241 nm (4·28), 281 nm (3·86), inflexes at 322 nm (3·09), 335 nm (3·00), 350 nm (2·92), 366 nm (2·88). IR spectrum: 817, 830, 869, 877 (2 adjacent and solitary Ar—H), 1 166, 1 183, 1 230, 1 275, 1 304 ($ArOCH_3$), 1 475, 1 582, 1 610, 3 030 (Ar), 1 689 cm^{-1} (ArCHO). ^1H NMR spectrum δ 10·40 (s, 1 H, CHO), 7·41 (d, J = 3·0 Hz, 1 H, 6-H), 7·35 (d, J = 8·5 Hz, 1 H, 3-H), 7·02 (q, J = 8·5; 3·0 Hz, 1 H, 4-H), 6·30—6·95 (m, 3 H, Ar—H in difluorophenyl), 3·80 (s, 3 H, OCH_3). ^{19}F NMR spectrum: δ −117·78 (m, 2 F). For $C_{14}H_{10}F_2O_2S$ (280·3) calculated: 59·99% C, 3·60% H, 13·56% F, 11·43% S; found: 60·22% C, 3·52% H, 13·76% F, 11·51% S.

There were further obtained 2·8 g of a higher boiling fraction, b.p. 170—190°C/60—100 Pa, which crystallized from a mixture of benzene and light petroleum and was recrystallized from benzene, m.p. 161—162°C. It was identified as 2-(2,5-difluorophenylthio)-5-hydroxybenzaldehyde (*XVIIf*). UV spectrum: λ_{max} 222 nm (log ε 4·28), 280 nm (3·79), 325 nm (3·16), inflexes at 240 nm (4·23), 350 nm (2·93), 364 nm (2·87). IR spectrum: 791, 811, 823, 880 (2 adjacent and solitary Ar—H), 1 250, 1 300 (ArOH), 1 480, 1 563 (Ar), 1 669 (ArCHO...HOAr), 3 170 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·36 (s, disappears after ^2H_2O, 1 H, OH), 1025 (s, 1 H, CHO), 6·60—7·40 (m, 6 H, Ar—H). For $C_{13}H_8F_2O_2S$ (266·3) calculated: 58·64% C, 3·03% H, 14·27% F, 12·04% S; found: 59·12% C, 2·84% H, 14·37% F, 12·05% S.

5-(Trifluoromethylthio)-2-(2,5-difluorophenylthio)benzaldehyde (*XVIId*)

A solution of 27·6 g crude *XXII* (containing 22·1 g pure *XXII*) in 30 ml hexamethylphosphoramide was treated with 13·4 g 2,5-difluorothiophenol and then with a solution of 4·0 g NaOH in 7 ml water. The mixture was stirred for 5·5 h at 100°C, poured into water, the precipitated product

was filtered, washed with water, dried and crystallized from cyclohexane; 24·0 g (75%), m.p. 92—102°C. Analytical sample, m.p. 103—104·5°C (cyclohexane). UV spectrum: λ_{max} 238 nm (log ε 4·04), 279 nm (4·00), infl. 230 nm (4·06). IR spectrum: 820, 876 (2 adjacent and solitary Ar—H), 1 110, 1 125 ($ArSCF_3$), 1 481, 1 534, 1 578, 3 013, 3 040, 3 073 (Ar), 1 689 cm^{-1} (ArCHO). ^1H NMR spectrum: δ 10·22 (s, 1 H, CHO), 8·09 (s, J = 2·0 Hz, 1 H, 6-H), 7·59 (q, J = 9·0; 2·0 Hz, 1 H, 4-H), *c.* 7·15 (m, 3 H, Ar—H of difluorophenyl), 6·95 (d, J = 9·0 Hz, 1 H, 3-H). For $C_{14}H_7F_5OS_2$ (350·3) calculated: 48·00% C, 2·01% H, 27·12% F, 18·30% S; found: 48·29% C, 2·01% H, 27·07% F, 18·68% S.

2-(2,5-Difluorophenylthio)-5-methoxy-α-(1-methyl-4-piperidyl)benzyl Alcohol (*XVIc*)

The Grignard reagent was prepared by reacting 1·25 g Mg and 6·7 g 4-chloro-1-methylpiperidine[22] in 40 ml tetrahydrofuran and refluxing for 1·5 h. It was stirred and treated over 10 min with a solution of 9·35 g *XVIIc* in 20 ml tetrahydrofuran, added dropwise. The mixture was refluxed for 3 h, cooled, decomposed with a solution of NH_4Cl and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated *in vacuo*; 12·6 g (100%) oily product which was used without purification for the next step. A sample was neutralized with oxalic acid giving the hydrogen oxalate, m.p. 160—163°C (acetone). Mass spectrum, *m/z* (%): 379 (M^+ corresponding to $C_{20}H_{23}FNO_2S$, 10%), 362 (M—17, 1·5), 361 (1), 360 (2), 99(100), 98 (100). For $C_{22}H_{25}F_2NO_6S$ (469·5) calculated: 56·28% C, 5·37% H, 8·09% F, 2·98% N, 6·83% S; found: 56·43% C, 5·53% H, 7·98% F, 3·34% N, 7·10% S.

8-Chloro-2-fluoro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIIb*)

The Grignard reagent was prepared from 4·5 g Mg and 22·3 g 4-chloro-1-methylpiperidine[22] in 140 ml tetrahydrofuran and was treated over 10 min with a solution of 31·6 g *XVIIb* in 80 ml tetrahydrofuran, added dropwise. The mixture was refluxed for 2 h, allowed to stand overnight, decomposed with 150 ml 20% NH_4Cl solution and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated *in vacuo* giving 42·6 g crude *XVIb*. It was dissolved in 200 ml dimethylformamide and the solution was added to a mixture of 7·8 g NaH and 300 ml dimethylformamide. It was stirred under nitrogen for 2 h at room temperature and for 14 h at 50°C. Afterwards it was poured into water and extracted with ether. The extract was washed with water, dried with K_2CO_3 and evaporated. The oil obtained was chromatographed on a column of 1 kg Al_2O_3. Elution with benzene gave first 1·75 g 8-chloro-2-fluoro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XVIIIb*), m.p. 121·5—123·5°C (cyclohexane). IR spectrum: 815, 870 (2 adjacent and solitary Ar—H), 1 260 (ArOR), 1 490, 1 588, 1 606, 3 005, 3 025 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·70—7·50 (m, 6 H, Ar—H), 5·35 (s, 2 H, $ArCH_2O$). ^{19}F NMR spectrum: δ —122·09 (dt, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·0 Hz). For $C_{13}H_8ClFOS$ (266·7) calculated: 58·54% C, 3·02% H, 13·29% Cl, 7·12% F, 12·02% S; found: 58·66% C, 3·13% H, 13·25% Cl, 7·15% F, 11·92% S.

Continued elution with benzene gave 12·39 g *XIIb* which was recrystallized from cyclohexane and melted at 127—129°C. ^1H NMR spectrum: δ 6·70—7·50 (m, 6 H, Ar—H), 5·60 (d, J = = 9·0 Hz, 1 H, Ar—CH—O), 2·28 (s, 3 H, NCH_3), 1·40—3·00 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{19}H_{19}ClFNOS$ (363·9) calculated: 62·71% C, 5·26% H, 9·74% Cl, 5·22% F, 3·85% N, 8·81% S; found: 62·67% C, 5·30% H, 9·50% Cl, 5·33% F, 3·79% N, 8·62% S.

Neutralization of the base *XIIb* with maleic acid in a mixture of acetone and ether gave the hydrogen maleate, m.p. 190—192°C (ethanol). For $C_{23}H_{23}ClFNO_5S$ (480·0) calculated: 57·56% C, 4·83% H, 7·39% Cl, 3·96% F, 2·92% N, 6·68% S; found: 57·55% C, 5·11% H, 7·64% Cl, 3·60% F, 2·71% N, 6·65% S.

Hydrochloride monohydrate, m.p. 168–170°C (95% ethanol–ether). For $C_{19}H_{20}Cl_2FNOS + H_2O$ (418·4) calculated: 54·55% C, 5·30% H, 16·95% Cl, 4·54% F, 3·35% N, 7·66% S; found: 54·75% C, 5·29% H, 16·31% Cl, 4·33% F, 3·18% N, 7·47% S.

Chromatography was continued using a mixture of benzene and chloroform as the eluent. There were obtained 3·08 g mixture which was rechromatographed on 200 g silica gel. Elution with a mixture of chloroform and ethanol gave first 2·24 g *XIIb*, m.p. 126–128·5°C, The total yield is thus 14·63 g (36%). Continued elution with the same mixture yielded 0·52 g 2-fluoro-8-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIX*) m.p. 111–112°C (hexane). Mass spectrum, *m*/*z* (%): 329 (M^+ corresponding to $C_{19}H_{20}FNOS$, 6·8%), 328 (17·6), 311 (23·6), 300 (6·4), 267 (9·6), 253 (6·4), 128 (11·6), 115 (16·8), 98 (12·0), 70 (100), 58 (36), 57 (40). IR spectrum: 812, 872, 898 (2 adjacent and solitary Ar—H), 1 188, 1 255 (ArOR, Ar—F), 1 484, 1 567, 1 585, 1 605 (Ar), 2 720, 2 760, 2 780 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·60–7·50 (m, 6 H, Ar—H), 5·70 (s, 2 H, $ArCH_2O$), 2·30 (s, 3 H, NCH_3), 1·70–3·10 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{19}H_{20}FNOS$ (329·4) calculated: 69·27% C, 6·12% H, 5·77% F, 4·25% N, 9·73% S; found: 68·93% C, 6·30% H, 5·82% F, 4·00% N, 9·90% S.

2-Fluoro-8-methoxy-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIIc*)

A solution of 12·5 g *XVIc* in 60 ml dimethylformamide was added to a suspension of 2·5 g NaH in 80 ml tetrahydrofuran and the mixture was stirred under nitrogen for 11 h at 70°C. It was then poured into water and extracted with ether. Processing of the extract gave 10·0 g oil which was chromatographed on 500 g Al_2O_3. Benzene eluted as the least polar fraction 1·06 g 2-fluoro-8-methoxy-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XVIIIc*), m.p. 119–120°C (cyclohexane). UV spectrum: λ_{max} 230 nm (log ε 4·42), 279 nm (3·94), inflexes at 295 cm (3·83), 302 nm (3·76). IR spectrum: 820, 829, 856, 873, 895 (2 adjacent and solitary Ar—H), 1 182, 1 240, 1 250 (ArOR, C—F), 1 478, 1 570, 1 600, 3 038 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·39 (d, J = 8·5 Hz, 1 H, 10-H), 6·60–7·00 (m, 5 H, remaining Ar—H), 5·40 (s, 2 H, $ArCH_2O$), 3·80 (s, 3 H, OCH_3). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·11% C, 4·23% H, 7·24% F, 12·23% S; found: 64·88% C, 4·29% H, 7·45% F, 12·03% S.

Continued elution with benzene, a mixture of benzene and chloroform and finally with chloroform resulted in 7·17 g (61%) homogeneous oily *XIIc* which was neutralized with maleic acid in a mixture of acetone and ether and gave the hydrogen maleate, m.p. 180–181·5°C (acetone–ether). For $C_{24}H_{26}FNO_6S$ (475·5) calculated: 60·62% C, 5·51% H, 4·00% F, 2·95% N, 6·74% S; found: 61·25% C, 5·68% H, 3·82% F, 2·91% N, 6·75% S.

Decomposition of the maleate with NH_4OH and extraction with ether gave the pure oily base *XIIc* which was used for recording the spectra. ^1H NMR spectrum: δ 7·48 (d, J = 8·5 Hz, 1 H, 10-H), 6·60–7·00 (m, 5 H, remaining Ar—H), 5·70 (d, J = 9·0 Hz, 1 H, Ar—CH—O), 3·80 (s, 3 H, OCH_3), 2·28 (s, 3 H, NCH_3), 1·40–3·00 (m, 9 H, 4 CH_2 and CH of piperidine). ^{19}F NMR spectrum: δ −122·59 (dt, $J_{F(o-H)}$ = 8·5 Hz, $J_{F(m-H)}$ = 6·0 H).

2-Fluoro-8-(trifluoromethylthio)-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIId*)

The Grignard reagent was prepared from 2·4 g Mg and 12·0 g 4-chloro-1-methylpiperidine[22] in 70 ml tetrahydrofuran and was treated similarly like in the preceding cases with a solution of 21·2 g *XVIId* in 40 ml tetrahydrofuran. Similar processing gave the crude oily *XVId* which was dissolved in 100 ml dimethylformamide and the solution was added to a suspension of 4·3 g NaH in 150 ml dimethylformamide. The mixture was stirred under nitrogen for 15 h at 70°C. Processing gave 16·35 g oily mixture which was chromatographed on 1 kg Al_2O_3. Elution with

benzene separated first 0·81 g less polar impurities. Continued elution with benzene and then with chloroform resulted in 5·34 g (21%) *XIId* which crystallized from light petroleum and melted at 77–81°C. IR spectrum: 810, 830, 860 (2 adjacent and solitary Ar—H), 1 100, 1 120, 1 165 ($ArSCF_3$ and ArOR), 1 480, 1 580, 1 605 (Ar), 2 700, 2 745 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·50 (s, 3 H, 7,9,10-H_3), 6·60–7·00 (m, 3 H, 1,3,4-H_3), 5·50 (d, J = 8·0 Hz, 1 H, Ar—CH—O), 2·25 (s, 3 H, NCH_3), 1·40–3·00 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{20}H_{19}F_4NOS_2$ (429·5) calculated: 55·93% C, 4·46% H, 17·69% F, 3·26% N, 14·93% S; found: 56·05% C, 4·37% H, 17·93% F, 3·09% N, 15·09% S.

Hydrogen maleate, m.p. 151–153°C (acetone–ether). For $C_{24}H_{23}F_4NO_5S_2$ (545·6) calculated: 52·84% C, 4·25% H, 13·93% F, 2·57% N, 11·75% S; found: 53·09% C, 4·29% H, 14·13% F, 2·29% N, 11·83% S.

8-Chloro-2-fluoro-6-(4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIIIb*)

A refluxing solution of 11·0 g *XIIb* in 50 ml benzene was treated over 30 min dropwise with a solution of 5·7 ml ethyl chloroformate in 30 ml benzene. The mixture was refluxed for 1·5 h and after cooling, 0·35 g substance was filtered off which proved to be the hydrochloride of the starting *XIIb*, m.p. 232·5–235°C, and after recrystallization from a mixture of 95% ethanol and ether, m.p. 168–170°C (monohydrate described above). The filtrate was washed with water, 10% H_2SO_4 and 5% $NaHCO_3$, dried with $MgSO_4$ and evaporated under reduced pressure. The residue (the carbamate) was dissolved in 15 ml ethanol, 13 g KOH were added and the mixture was refluxed for 2 h (bath temperature of 125°C). It was then diluted with water and extracted with benzene. The extract was shaken with an excess of 10% hydrochloric acid. The precipitated hydrochloride was filtered, added to the aqueous layer of the filtrate, the suspension was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with K_2CO_3 and evaporated under reduced pressure; 8·96 g (85%), m.p. 120–122°C (cyclohexane). IR spectrum: 782, 821, 857, 882, 900 (2 adjacent and solitary Ar—H), 1 193, 1 250 (ArOR), 1 480, 1 608 (Ar), 3 323 cm^{-1} (NH). ^1H NMR spectrum: δ 6·60–7·50 (m, 6 H, Ar—H), 5·52 (d, J = 8·0 Hz, 1 H, Ar—CH—O), 1·49 (s, disappears after ^2H_2O, 1 H, NH), 1·40–3·00 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{18}H_{17}ClFNOS$ (349·9) calculated: 61·79% C, 4·90% H, 10·13% Cl, 5·43% F, 4·00% N, 9·17% S; found: 62·27% C, 5·00% H, 10·22% Cl, 5·21% F, 3·99% N, 9·30% S.

Hydrochloride, m.p. 313–317°C with decomposition (aqueous ethanol). For $C_{18}H_{18}Cl_2FNOS$ (386·3) calculated: 55·96% C, 4·70% H, 18·35% Cl, 4·92% F, 3·63% N, 8·30% S; found: 56·12% C, 4·60% H, 17·88% Cl, 4·72% F, 3·68% N, 8·26% S.

8-Chloro-2-fluoro-6-[1-(2-hydroxyethyl)-4-piperidyl]-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIb*)

A mixture of 7·0 g *XIIIb*, 3·75 g 2-bromoethanol, 5·0 g K_2CO_3 and 100 ml acetone was stirred and refluxed for 6 h, filtered, the solid washed with acetone and the filtrate evaporated *in vacuo*. The residue was dissolved in ether and the undissolved solid was filtered off. The filtrate was evaporated again; 5·45 g (69%) homogeneous oily *XIVb* which was neutralized with oxalic acid in acetone. Hydrogen oxalate, m.p. 141–143°C (acetone). For $C_{22}H_{23}ClFNO_6S$ (484·0) calculated: 54·60% C, 4·79% H, 7·33% Cl, 3·93% F, 2·89% N, 6·63% S; found: 54·32% C, 4·68% H, 7·52% Cl, 3·88% F, 2·65% N, 6·50% S.

8-Chloro-6-[1-(2-decanoyloxyethyl)-4-piperidyl]-2-fluoro-6*H*-dibenz[*b*,*e*]-1,4 -oxathiepin (*XVb*)

A mixture of 4·35 g *XIVb*, 6·0 g decanoic acid and 50 ml xylene was distilled through a column and the evaporated xylene was substituted in the course of 6 h by a slow addition of 350 ml dry

xylene. The residue was diluted with benzene, the solution washed with 5% NaOH and water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in benzene and the solution was filtered through a column of 150 g Al_2O_3. The elution with benzene gave first 0·32 g neutral impurity and then 3·35 g (55%) homogeneous oily base *XVb*. ^{1}H NMR spectrum: δ 6·60 to 7·50 (m, 6 H, ArH), 5·60 (d, J = 9·0 Hz, 1 H, Ar—CH—O), 4·20 (t, 2 H, CH_2O), 2·65 (t, 2 H, NCH_2 in the chain), 0·86 (def. t, 3 H, terminal CH_3), 1·00—3·00 (m, 25 H, remaining 12 CH_2 and 1 CH groups).

Hydrogen maleate, m.p. 135—136·5°C (acetone–ether). For $C_{34}H_{43}ClFNO_7S$ (664·2) calculated: 61·48% C, 6·53% H, 5·34% Cl, 2·86% F, 2·11% N, 4·83% S; found: 61·11% C, 6·40% H, 5·54% Cl, 3·21% F, 1·94% N, 5·07% S.

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