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

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2-(2-Fluorophenylthio)benzaldehydes *IXa—c* and 5-chloro-2-(2-fluorophenylthio)acetophenone were treated with 1-methyl-4-piperidylmagnesium chloride and 3-dimethylaminopropylmagnesium chloride, respectively, and the resulting amino alcohols *VIa—c*, *XVII* and *XVIII* were cyclized with sodium hydride in dimethylformamide. In addition to the title compounds *Ia—c*, *XIX* and *XX*, several types of by-products were obtained. Demethylation of compound *Ib* by the chloroformate method afforded the secondary amine *IIb* which was transformed to the amino alcohols *IIIb* and *Vb*. Compounds *Ia—c* are very potent neuroleptics with a high degree of central depressant and cataleptic activity. The amino alcohol *Vb* exhibits a very strong antiapomorphine effect in rats.

In a previous communication[1] dealing with the 6-(aminoalkyl) derivatives of 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin, we described the finding of tranquillizing properties of the corresponding 6-(1-methyl-4-piperidyl) derivative (central depressant, hypothermic and procataleptogenic activity) which were in contrast with the properties of the analogues with an aliphatic connecting chain between the nitrogen atom and the central ring (potential antidepressants with a mild sedative effect). One could expect that the introduction of a suitable "neuroleptic" substituent into the usual position of the aromatic nucleus will result in a further increasing the intensity of effects and attaining the pharmacological profile of neuroleptic agents. The object of the present communication is the synthesis of 8-chloro, 8-methoxy and 8-trifluoromethyl derivatives of 6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ia—c*) and some N-substituted analogues. The presence of a saturated six-membered nitrogen heterocycle (piperazine, piperidine), which is directly connected to the central seven-

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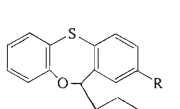
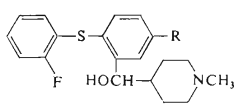
-membered ring, is typical for a large group of tricyclic neuroleptic agents and in combination with a suitable neuroleptic substituent, it leads usually to highly potent substances[2,3].



a, R = Cl
b, R = OCH_3
c, R = CF_3
d, R = H

I, $R^1 = CH_3$
II, $R^1 = H$
III, $R^1 = CH_2CH_2OH$
IV, $R^1 = (CH_2)_3COCH_3$
V, $R^1 = (CH_2)_2CH(OH)CH_3$

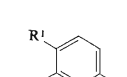
The synthesis of compounds *Ia–c* was carried out by making use of a method described in two communications of this series[1,4], consisting in cyclization of 2-(2-fluorophenylthio)benzyl alcohols *VI* by treatment with sodium hydride in dimethylformamide at 70°C.



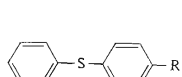
VI

2,5-Dichlorobenzyl chloride, obtained by chloromethylation of 1,4-dichlorobenzene[5], was the starting compound in series *a*. For transforming this substance to 2,5-dichlorobenzyl alcohol[6,7] a two-step sequence was used starting with a reaction with potassium acetate in dimethyl sulfoxide in the presence of triethylbenzylammonium chloride at 60°C which was followed by hydrolysis with hydrochloric acid in aqueous ethanol (analogy, *cf.*[8]). A little soluble alcohol was separated as a by-product and identified as the known 2,5-dichlorobenzene-1,4-dimethanol[9]. Its origin consists in a small amount of the product of double chloromethylation in the first reaction step. Oxidation of 2,5-dichlorobenzyl alcohol with potassium dichromate in the presence of triethylbenzylammonium chloride in a two-phase system of dichloromethane–dilute sulfuric acid at room temperature afforded 2,5-dichlorobenzaldehyde (*VIIa*) (method, *cf.*[10]) whose preparation by a different method has already been described[11]. The following reaction with 2-fluorothiophenol[12] in hexamethylphosphoramide in the presence of aqueous sodium hydroxide at 100°C resulted

in 5-chloro-2-(2-fluorophenylthio)benzaldehyde (*IXa*) which was treated with the Grignard reagent[13], prepared from 4-chloro-1-methylpiperidine[14]. The amino alcohol *VIa* was obtained which was characterized as the crystalline 2,4,6-trinitrobenzoate and used for further work in the crude state.



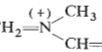
VII, $R^1 = Cl$
VIII, $R^1 = Br$



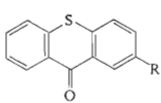
IX

The cyclization of the amino alcohol *VIa* was carried out under the already mentioned conditions (sodium hydride, dimethylformamide, 70°C) and gave a mixture which was separated by chromatography. As the least polar component of the mixture there was eluted in a small amount a nitrogen-free substance which was identified on the basis of elemental analysis, UV and IR spectra and a direct comparison with an authentic compound[15,16] as thioxanthone (*Xd*). With thioxanthones as products of similar reactions we meet quite commonly and we shall discuss this point in one of the following paragraphs; in the present case, an additional removal of the atom of chlorine from the nucleus took place which is explained by a nucleophilic substitution reaction (the atom of chlorine is activated by the atom of sulfur in *para*-position) with the hydride anion. As the main product (35%) there was then eluted the base *Ia* which is oily but afforded a crystalline maleate and its ^{1}H NMR spectrum corroborated the structure. As the most polar component of the mixture there was eluted in a small quantity a further oily base, giving likewise a crystalline hydrogen maleate. Its analyses and mass spectrum showed the absence of chlorine in the molecule and proved the elemental composition $C_{19}H_{21}NOS$. Structure *XI* is suggested for this compound after the elimination of the alternatives *Id* and *XIId*. Preparation of compound *Id* has been described in a previous communication[1]; the base was crystalline, less polar than the present substance and the hydrogen maleates differ greatly by their melting points. A structure analogous to *XIId* was suggested for one of the products described in a previous paper[1]; it was a highly polar product with excellent ability to crystallize and with a high melting point. The compound which has now been isolated is also rather polar but the base could not be induced to crystallize. The most important difference was found in the mass spectra of both compounds and for this purpose it is necessary to compare with a substance described in one of the following paragraphs of this paper and for which the structure *XIIc* is suggested. Fragmentations of compounds, for which we assume the structures of unsaturated phenolic bases, exhibit as the main fragment an ammonium ion with 6 (*cf.* compound *XIIc*), and 7 carbon atoms[1] respectively, formed under the shift

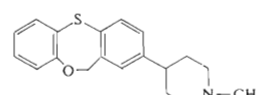
of hydrogens from the rest of the molecule which cyclizes and yields as further typical fragments the oxonium ions *XIII* with m/z 281 (*XIIIc*), and 213 (*XIIId*, *cf.*[1]), respectively, occurring very often in the mass spectra of 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin derivatives. Ammonium ions as fragments with preserved piperidine ring are typical for compounds in which this piperidine ring is attached to an aliphatic carbon atom. On the other hand, the presently isolated substance, to which structure *XI* is assigned, exhibits in the mass spectrum a base peak with m/z 70 which may be interpreted as corresponding to the ion



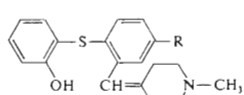
i.e. to a product of cleavage of the piperidine ring; fragments with m/z 96 and 98 appear in much lower abundance. This fragmentation pattern is considered to correspond more likely to a compound in which the piperidine ring is attached to an aromatic carbon atom. The second most important fragment is that of m/z 294, *i.e.* M − 17. A cleavage of oxygen and one hydrogen from the central ring takes thus place, the product of which could be the thioxanthylium ion *XIV* (R = 1-methyl-4-piperidyl). The facts mentioned are considered an evidence of correctness of formula *XI*. The compound of this formula could be formed from the aldehyde *IX* by the following sequence of reactions: *a*) reduction of the aldehyde function to the primary alcoholic one by the action of the Grignard reagent or of sodium hydride[17],



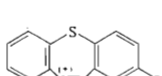
X



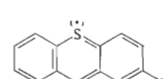
XI



XII



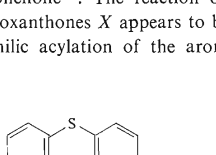
XIII



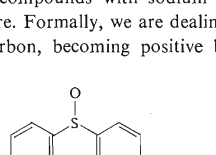
XIV

b) nucleophilic substitution of the chlorine atom by reaction with the Grignard reagent, *c*) cyclization of the fluorinated benzyl alcohol by treatment with sodium hydride.

Oxidation of the base *Ia* with hydrogen peroxide in ethanol at room temperature yielded a compound containing one oxygen atom more, whose IR spectrum together with the course of polarographic reduction allow its formulation as the N-oxide *XV*. Oxidation of the methanesulfonate of *Ia* with hydrogen peroxide in aqueous solution at room temperature resulted in an oily base affording a crystalline oxalate. The IR spectrum and polarography indicate the structure of the sulfoxide *XVI*. Reactions of 5-chloro-2-(2-fluorophenylthio)acetophenone[12] with 3-dimethylaminopropylmagnesium chloride and 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran gave the amino alcohols *XVII* and *XVIII*, the former having been characterized as the crystalline oxalate, and the latter processed without characterization in crude state. Both were cyclized by a reaction with sodium hydride in dimethylformamide at 70°C; resulting mixtures were separated by chromatography. In both cases 2-chlorothioxanthone[18] (*Xa*) was isolated in small amounts as the least polar product, which was followed by the bases *XIX* and *XX*, eluted in moderate yields. The identity of the base *XIX*, affording a crystalline oxalate, was corroborated by the ^{1}H NMR spectrum. The base *XX* gave also an oxalate and for characterization its mass spectrum was recorded which confirmed the assumed elemental composition. The base peak corresponds to m/z 96 and we are dealing here with the 1-methyl-2,3-dihydropyridinium ion. At this occasion the origin of thioxanthones in reactions of the type just discussed was examined more closely; we proved by experiment that 2-chlorothioxanthone (*Xa*) is formed in a yield of about 12% by heating 5-chloro-2-(2-fluorophenylthio)acetophenone[12] with sodium hydride in dimethylformamide to 70°C. In agreement with our expectation, the thioxanthones are not formed from the amino alcohols *VI*, *XVII* and *XVIII*, but from the corresponding carbonyl precursors, *i.e.* the aldehydes *IX* and the used ketone, *i.e.* 5-chloro-2-(2-fluorophenylthio)acetophenone[12]. The reaction of these compounds with sodium hydride affording thioxanthones *X* appears to be obscure. Formally, we are dealing here with a nucleophilic acylation of the aromatic carbon, becoming positive by cleavage



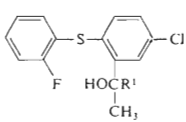
XV

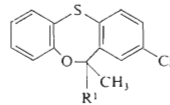


XVI

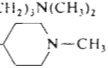
of the fluoride anion; the acylating agent would be the acyl anions generated by interaction of the aldehyde or ketone function with the hydride anion under the simultaneous formation of molecules of hydrogen or methane. Even though acyl anions or their equivalents are really supposed as intermediates in some reactions[19], we were not able to find in the literature an analogy to the reaction just described.

In series *b* we started from 2-bromo-5-methoxybenzaldehyde[20] (*VIIIb*) which produced by a reaction with 2-fluorothiophenol[12] in dimethylformamide in the presence of potassium carbonate and copper at 150°C the aldehyde *IXb*. A reaction with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran gave the crude amino alcohol *VIb* which was not characterized and cyclized in the crude state by treatment with sodium hydride similarly like in the preceding cases. The crude product afforded by crystallization from a mixture of cyclohexane and light petroleum and by chromatography the base *Ib* in a rather high yield. Its identity was corroborated by spectra and it gave a crystalline maleate. The mother liquors were chromatographed and as the least polar component there was isolated a nitrogen-free substance which was identified as 2-methoxythioxanthone[21] (*Xb*). A reaction of compound *Ib* with ethyl chloroformate in boiling benzene effected the N-demethylation and the neutral product obtained (the carbamate) was transformed

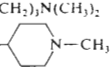




XVII, $R^1 = (CH_2)_3N(CH_3)_2$

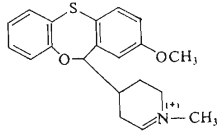
XVIII, $R^1 =$ 

XIX, $R^1 = (CH_2)_3N(CH_3)_2$

XX, $R^1 =$ 

by hydrolysis with potassium hydroxide in a small volume of boiling ethanol to the secondary amine *IIb*. The mass spectrum of this compound shows important fragments with m/z 243 and 227 corresponding to the ions *XIIIb* and *XIVb*; the nitrogen-containing fragment C_5H_8N (m/z 82) is evidently the 2,3-dihydropyridinium ion. Alkylation of compound *IIb* with 2-bromoethanol in acetone in the presence of potassium carbonate gave the amino alcohol *IIIb* whose mass spectrum shows as the main fragment $M-CH_2OH$ (m/z 340) with the probable structure *XXI*. The less abundant fragments are with m/z 243 (*XIIIb*) and 98 (the 1-methyl-1-piperideinium ion). A similar alkylation of compound *IIb* with 5-bromopentan-2-one[22] resulted in the amino ketone *IVb*, the mass spectrum of which shows again fragments with m/z 340 and 243 (*XXI*, *XIIIb*). Reduction with sodium borohydride in aqueous

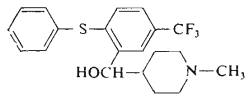
ethanol gave the amino alcohol *Vb*; its mass spectrum likewise exhibits as the base peak the fragment with *m/z* 340 (*XXI*). This amino alcohol was prepared for examination of the potential dissociation of the antiapomorphine and cataleptic activity, described for the structurally similar N-(4-hydroxypentyl) analogue of the neuroleptic agent loxapine[23].



XXI

The synthesis in series *c* was started by a reaction of 2-chloro-5-trifluoromethylbenzaldehyde[8] (*VIIc*) with 2-fluorothiophenol[12] in hexamethylphosphoramide in the presence of the aqueous sodium hydroxide at 100°C. The obtained 2-(2-fluorophenylthio)-5-trifluoromethylbenzaldehyde (*IXc*) was treated with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran and the crude amino alcohol *VIc* formed was processed without characterization by cyclization with sodium hydride similarly like in the preceding cases. From the mixture obtained four substances were separated by chromatography in addition to the starting compound *VIc*. The least polar one was identified as 2-trifluoromethylthioxanthone[24] (*Xc*). In a low yield there was further isolated a somewhat more polar desired base *Ic*; its identity was confirmed by the ^{1}H NMR spectrum and by the analysis of its oxalate. Its mass spectrum shows moderately abundant fragments with *m/z* 281 and 265 (*XIIIc*, *XIVc*). The nitrogen-containing fragments with *m/z* 98 (base peak), 96 and 70 (the relatively weakest one) are the already mentioned ammonium ions. As a further component there was eluted an isomeric substance ($C_{20}H_{20}F_3NOS$) having – according to the IR spectrum – the character of an inner salt and formulated as *XIIc*. Its mass spectrum has been discussed previously in this communication and its formation is explained similarly like the formation of an analogous product in a previous paper[1]: dehydration of the amino alcohol *VIc*, formation of sodium hydroxide by decomposition of sodium hydride with the molecule of water cleaved and nucleophilic substitution of the fluorine atom with the hydroxyl anion. Finally, there was eluted a little more polar base, which gave a crystalline oxalate. According to the mass spectrum it contains two hydrogen atoms more than the preceding two compounds and has the formula $C_{20}H_{22}F_3NOS$. The IR spectrum indicates a secondary alcohol function which is confirmed in the mass spectrum by the fragment M – 17, typical for benzylic alcohols. The structure *XXII* is suggested for the product and its formation is explained from the fluorinated amino alcohol *VIc* by a nucleophilic substitution of the fluorine

atom with the hydride anion. As the most polar component, the starting compound *VIc* was eluted; it was contaminated by polymeric products and did not crystallize.



XXII

The compounds prepared were pharmacologically tested with a view to the expected central depressant and cataleptic activity (the neuroleptic profile). The compounds were administered orally in the form of salts described in the Experimental; the doses given (in mg/kg) were calculated for the bases. The results are summarized in Table I. The first column shows the acute toxicity for mice expressed by the usual LD_{50}. In the rotarod test in mice, the effect of the compounds on motor coordination was examined. The medium effective doses (ED_{50}) were estimated at the time of optimum effect; in 24 h after the administration the effect mostly disappeared. The cataleptic effect was evaluated in rats and the medium effective doses (ED_{50}) are given. For comparison, data on chlorpromazine and clorothepin[25] were included.

Compounds *Iabc* are strong neuroleptic agents comparable with clorothepin or even more active. The amino alcohol *IIIb* is less cataleptic and its incoordinating effect shows some protraction (after 24 h ED_{50} = 10 mg/kg). For compound *Vb* the antiapomorphine effect in rats was evaluated and the D_{50} estimated (doses

TABLE I

Pharmacological properties of the compounds prepared (Administered orally, doses in mg/kg)

Compound	Acute toxicity LD_{50}	Rotarod test ED_{50}	Catalepsy ED_{50}
Ia	108	2·0	4·2
Ib	98	0·92	3·6
Ic	115	2·6	1·8
IIIb	[a]	2·8	8·0
Vb	[a]	10·0	5·6
XIX	556	39	[a]
XX	[a]	75	>100[b]
Chlorpromazine	198	8·2	16·0
Clorothepin	78	2·2	4·3

[a] Was not estimated. [b] The dose is cataleptic for 20% animals.

decreasing the medium control values of the apomorphine chewing and agitation to 50%): 3·1, and 2·5 mg/kg, respectively (for clorothepin 4·1 and 4·5 mg/kg). In comparison with clorothepin, compound *Vb* shows a certain degree of dissociation of cataleptic and antiapomorphine effects but not so important as given for the mentioned loxapine analogue[23]. Compound *XIX* was tested also for the potential antidepressant activity: an oral dose of 50 mg/kg does not inhibit the perphenazine catalepsy in rats and has no antiapomorphine effect in rats; a dose of 100 mg/kg is inactive in the test of reserpine ptosis in mice and does not inhibit the reserpine gastric ulcers in rats. The simultaneous presence of a methyl group and the basic side chain in position 6 has a negative effect on the activity (compounds *XIX* and *XX*).

Some of the compounds were also tested for the antimicrobial activity *in vitro* (Dr J. Turinová, Bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Ia* 50, *Vb* 100, *XIX* 50; *Streptococcus faecalis*, *Ia* 100, *Vb* 100, *XIX* 50; *Staphylococcus pyogenes aureus*, *Ia* 25, *Ib* 100, *Vb* 50, *XIX* 50; *Pseudomonas aeruginosa*, *XIX* 100; *Escherichia coli*, *Ia* 50, *Ib* 100, *Vb* 100, *XIX* 25; *Proteus vulgaris*, *Ia* 100; *Mycobacterium tuberculosis* H37Rv, *Ia* 100, *XIX* 12·5; *Trichophyton mentagrophytes*, *Ia* 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, the ^{19}F NMR spectrum (in $CHCl_3$, $\delta(CFCl_3) = 0$) with the same instrument and the mass spectra with a Varian MAT-311 spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatographic separations were carried out mostly on neutral Al_2O_3 (activity II).

2,5-Dichlorobenzyl Alcohol

A mixture of 81·6 g crude 2,5-dichlorobenzyl chloride[5] (b.p. 135—140°C/2·7 kPa), 45 g potassium acetate, 18·8 g triethylbenzylammonium chloride and 275 ml dimethyl sulfoxide was stirred and heated for 4 h to 60°C, then diluted with 1 l water and extracted with benzene. The extract was evaporated, the residue was treated with 340 ml ethanol, 270 ml water and 34 ml hydrochloric acid and the mixture was refluxed for 7 h. Ethanol was distilled off, the residue was diluted with 1 l water and extracted with benzene. The undissolved solid (4·7 g) was filtered off, the extract was dried with $MgSO_4$ and evaporated; 68·8 g (94%) product, m.p. 76—78°C. Literature[6,7] reported the values of 78°C, and 80°C. respectively.

The undissolved substance was crystallized from ethanol, m.p. 198·5—199·5°C. The analysis (corresponding to $C_8H_8Cl_2O_2$) and the spectra enabled to identify the product as 2,5-dichlorobenzene-1,4-dimethanol. IR spectrum: 882 (solitary Ar—H), 1 045 (CH_2OH), 1 480, 3 070 (Ar), 3 210, 3 280 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·41 (s, 2 H, 3,6-H_2), 5·40 (bs, 2 H, 2 OH), 4·45 (s, 4 H, 2 $ArCH_2O$). Lit.[9], m.p. 201—202°C.

2,5-Dichlorobenzaldehyde (*VIIa*)

A solution of 33·3 g 2,5-dichlorobenzyl alcohol in 450 ml dichloromethane was stirred with a solution of 23·0 g $K_2Cr_2O_7$, 150 ml H_2SO_4 and 3·6 g triethylbenzylammonium chloride in 300 ml water for 4 h at room temperature. The organic layer was separated, washed with water and 5% NaOH, dried with $MgSO_4$ and evaporated; 32·3 g (98%), m.p. 53–55·5°C. Lit.[11], m.p. 57–58°C.

5-Chloro-2-(2-fluorophenylthio)benzaldehyde (*IXa*)

A solution of 10·8 g 2-fluorothiophenol[12] in 20 ml hexamethylphosphoramide was treated with a solution of 3·4 g NaOH in 6 ml water and then with 14·0 g *VIIa*. The mixture was stirred and heated to 100°C for 5·5 h, diluted with 150 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated. The residue was crystallized from 20 ml ethanol; 16·0 g (75%) *IXa*, m.p. 85·5–88°C. Analytical sample, m.p. 87–88°C (ethanol). UV spectrum: λ_{max} 236 nm (log ε 4·16), 271 nm (3·92), 343 nm (3·11), infl. 247 nm (4·09). IR spectrum: 735, 751, 825, 870, 880 (4 and 2 adjacent and solitary Ar–H), 1 545, 1 560, 1 594, 3 020, 3 055 (Ar), 1 686 cm^{-1} (ArCHO). ^{1}H NMR spectrum: δ 10·40 (s, 1 H, CHO), 7·88 (d, J = 2·5 Hz, 1 H, 6-H), 7·38 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 7·02 (d, J = 8·0 Hz, 1 H, 3-H), 7·10–7·60 (m, 4 H, 4 Ar–H of fluorophenyl). ^{19}F NMR spectrum: δ −107·54 (m). For $C_{13}H_8ClFOS$ (266·7) calculated: 58·54% C, 3·02% H, 13·30% Cl, 7·12% F, 12·02% S; found: 58·43% C, 2·92% H, 13·49% Cl, 7·07% F, 12·05% S.

2-(2-Fluorphenylthio)-5-methoxybenzaldehyde (*IXb*)

A mixture of 27·1 g 2-bromo-5-methoxybenzaldehyde[20] (m.p. 72–75°C), 17·0 g 2-fluorothiophenol[12], 19·3 g K_2CO_3, 100 ml dimethylformamide and 3·0 g Cu catalyst was stirred and heated for 6 h in a bath to 150°C. After cooling the mixture was diluted with water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The oily residue (33·6 g) was chromatographed on a column of 500 g Al_2O_3. Elution with benzene gave 24·4 g oil which was distilled; 18·9 g (57%), b.p. 153°C/40 Pa. The distillate crystallized on standing, m.p. 55–58·5°C. Analytical sample, m.p. 58–59°C (cyclohexane–light petroleum). UV spectrum: λ_{max} 227 nm (log ε 4·30), 238 nm (4·27), 329 nm (3·18), 352 nm (3·12), infl. 338 nm (3·16) and 366 nm (3·10). IR spectrum: 767, 840, 883 (4 and 2 adjacent and solitary Ar–H), 1 173, 1 226, 1 240, 1 315 ($ArOCH_3$), 1 474, 1 575, 1 591, 3 045, 3 060 (Ar), 1 690, 2 740 cm^{-1} (ArCHO). ^{1}H NMR spectrum: δ 10·60 (s, 1 H, CHO), 7·48 (d, J = 3·0 Hz, 1 H, 6-H), 7·39 (d, J = 8·5 Hz, 1 H, 3-H), 6·90–7·30 (m, 5 H, 4-H and 4 Ar–H of fluorophenyl), 3·85 (s, 3 H, OCH_3). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·11% C, 4·23% H, 7·24% F, 12·22% S; found: 64·56% C, 4·08% H, 7·24% F, 11·99% S.

2-(2-Fluorophenylthio)-5-trifluoromethylbenzaldehyde (*IXc*)

A mixture of 12·2 g 2-fluorothiophenol[12] in 25 ml hexamethylphosphoramide, 4·0 g NaOH in 7 ml water and 16·8 g 2-chloro-5-trifluoromethylbenzaldehyde was reacted for 6 h at 100°C and the mixture was processed similarly like in the preparation of *IXa*; 25·5 g (97%), m.p. 130 to 132°C. Analytical sample, m.p. 130–131·5°C (benzene–light petroleum). UV spectrum: λ_{max} 236 nm (log ε 4·04), 251 nm (3·98), 274 nm (3·96), 327 nm (3·20). IR spectrum (KBr): 760, 823, 843, 895 (4 and 2 adjacent and solitary Ar–H), 1 123, 1 173, 1 340 ($ArCF_3$), 1 476, 1 560, 1 600, 1 616, 3 028, 3 045 (Ar), 1 697, 2 740 cm^{-1} (ArCHO). ^{1}H NMR spectrum: δ 10·40 (s, 1 H,

CHO), 8·10 (bs, 1 H, 6-H), 6·90—7·80 (m, 6 H, remaining Ar—H). For $C_{14}H_8F_4OS$ (300·3) calculated: 56·00% C, 2·69% H, 25·31% F, 10·68% S; found: 56·41% C, 2·49% H, 25·29% F, 10·47% S.

5-Chloro-2-(2-fluorophenylthio)-α-(1-methyl-4-piperidyl)benzyl Alcohol (*VIa*)

Mg (2·7 g) in 80 ml tetrahydrofuran was treated dropwise with 13·7 g 4-chloro-1-methylpiperidine[14] and the mixture was stirred and refluxed for 1 h giving a solution of the Grignard reagent[13]. This was treated over 10 min with a solution of 20·0 g *IXa* in 40 ml tetrahydrofuran and the mixture was refluxed for 4·5 h. After standing overnight the mixture was decomposed with a 20% NH_4Cl solution and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated; 27·4 g (100%) crude oily *VIa*. A sample was neutralized with 2,4,6-trinitrobenzoic acid giving the 2,4,6-trinitrobenzoate, m.p. 100—101·5°C with decomposition (ethanol–ether). For $C_{26}H_{24}ClFN_4O_9S$ (623·0) calculated: 50·12% C, 3·88% H, 3·05% F, 8·99% N, 5·15% S; found: 50·60% C, 4·16% H, 2·84% F, 9·30% N, 5·16% S.

2-[5-Chloro-2-(2-fluorophenylthio)phenyl]-5-dimethylaminopentan-2-ol (*XVII*)

The Grignard reagent was prepared from 1·46 g Mg and 7·3 g 3-dimethylaminopropyl chloride in 25 ml tetrahydrofuran and by refluxing for 2 h. It was treated with a solution of 11·2 g 5-chloro-2-(2-fluorophenylthio)acetophenone[12] in 20 ml tetrahydrofuran and the mixture was refluxed for 4 h. After cooling it was decomposed with 50 ml 20% NH_4Cl solution and the product was isolated by extraction with ether; 13·2 g (90%) inhomogeneous oil. A sample was neutralized with oxalic acid in a mixture of acetone and ether and gave the hydrogen oxalate, m.p. 127 to 131°C (acetone–ether). For $C_{21}H_{25}ClFNO_5S$ (458·0) calculated: 55·08% C, 5·50% H, 7·74% Cl, 4·15% F, 3·06% N, 7·00% S; found: 54·66% C, 5·64% H, 7·51% Cl, 3·99% F, 3·34% N, 7·22% S.

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

A solution of 26·8 g crude *VIa* in 130 ml dimethylformamide was added to a suspension of 5·7 g NaH in 180 ml dimethylformamide under nitrogen, the mixture was stirred for 14 h at 70°C, poured into water and extracted with ether. The extract was washed with water, dried with K_2CO_3 and evaporated. The oily residue (20·0 g) was chromatographed on a column of 1 kg Al_2O_3. Benzene eluted first 0·62 g of a solid which crystallized from cyclohexane and melted at 211—214°C. It was identified as thioxanthone (*Xd*). UV spectrum: λ_{max} 254 nm ($\log \varepsilon$ 4·68), 375 nm (3·90), inflexes at 285 nm (3·70) and 296 nm (3·56). IR spectrum: 730 (4 adjacent Ar—H), 1 589 (Ar), 1 642 cm^{-1} (ArCOAr). Lit.[16], m.p. 212—214°C.

Continued elution with benzene yielded 6·57 g homogeneous oily base *Ia*. The following 3·52 g oily substance represent a mixture which was rechromatographed on a column of 220 g silica gel (Silpearl). Chloroform eluted further 2·18 g base *Ia*, the total yield of which is thus 8·75 g (35%). ^1H NMR spectrum: δ 7·48 (d, J = 8·5 Hz, 1 H, 10-H), 6·60—7·30 (m, 6 H, remaining 6 Ar—H). 5·72 (d, J = 9·0 Hz, 1 H, 6-H), 2·20 (s, 3 H, NCH_3), 1·30—3·10 (m, 9 H, 4 CH_2 and CH of piperidine). Neutralization with maleic acid in a mixture of acetone and ether gave the hydrogen maleate, m.p. 188·5—190°C (acetone–ethanol–ether). For $C_{23}H_{24}ClNO_5S$ (462·0) calculated: 59·80% C, 5·24% H, 7·68% Cl, 3·03% N, 6·94% S; found: 59·97% C, 5·35% H, 7·90% Cl, 2·89% N, 6·73% S.

Continued rechromatography on silica gel and elution with a mixture of chloroform and ethanol gave 0·48 g of the most polar homogeneous oily base to which the structure of 8-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XI*) was assigned. Its neutralization with maleic acid in ether gave the hydrogen maleate, m.p. 183·5—185°C (acetone). Mass spectrum, m/z (%):

311 (M^+ corresponding to $C_{19}H_{21}NOS$, 32%), 310 (3), 294 (43), 283 (10), 250 (17), 236 (13), 70 (100). For $C_{23}H_{25}NO_5S$ (427·5) calculated: 64·62% C, 5·89% H, 3·28% N, 7·50% S; found: 64·59% C, 5·82% H, 3·24% N, 7·70% S.

8-Chloro-6-methyl-6-(3-dimethylaminopropyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*XIX*)

A solution of 13·0 g crude *XVII* in 80 ml dimethylformamide was added dropwise over 5·5 h at 70°C to a stirred suspension of 3·0 g NaH in 100 ml dimethylformamide under nitrogen. The mixture was stirred for 8 h at 70°C, poured into water and the product was extracted with benzene. The extract was dried (K_2CO_3) and evaporated. The inhomogeneous oily residue (12·1 g) was chromatographed on 450 g Al_2O_3. Benzene eluted first 0·17 g solid which was crystallized from a mixture of benzene and light petroleum and was identified as 2-chlorothioxanthone (*Xa*). Its analysis corresponds to $C_{13}H_7ClOS$. UV spectrum: λ_{max} 250 nm (log ε 4·61), 292 nm (3·65), 304 nm (3·60), 386 nm (3·80), IR spectrum: 740, 812, 866 (4 and 2 adjacent and solitary Ar—H), 1 598, 3 035 (Ar), 1 640 cm^{-1} (ArCOAr). Lit.[18], m.p. 147—153°C. Direct comparison with the authentic sample[18] proved identity.

Continued washing with benzene gave then 1·5 g mixture and afterwards 4·34 g (35%) oily *XIX*. ^1H NMR spectrum: δ 6·90—7·50 (m, 7 H, Ar—H), 2·15 (s, 6 H, CH_3NCH_3), 1·40—2·20 (m, 6 H, 3 CH_2 in the side chain), 1·60 (s, 3 H, C—CH_3). Neutralization with 1·5 g oxalic acid in a mixture of acetone and ether gave 4·8 g hydrogen maleate, m.p. 78—80°C (acetone–ether). For $C_{21}H_{24}ClNO_5S$ (438·0) calculated: 57·59% C, 5·52% H, 8·10% Cl, 3·20% N, 7·32% S; found: 57·72% C, 5·90% H, 8·04% Cl, 3·00% N, 7·43% S.

Reaction of 5-Chloro-2-(2-fluorophenylthio)acetophenone with Sodium Hydride

A solution of 4·0 g 5-chloro-2-(2-fluorophenylthio)acetophenone[12] in 25 ml dimethylformamide was added to a suspension of 1·0 g NaH in 30 ml dimethylformamide and the mixture was stirred for 8 h at 70°C under nitrogen. The mixture was poured into 500 ml water and extracted with benzene. The extract was dried and evaporated and the residue was chromatographed on 200 g Al_2O_3. The only product which was eluted with benzene was 2-chlorothioxanthone (*Xa*), 0·41 g (12%), m.p. 146—150°C (cyclohexane). Lit.[18], m.p. 147—153°C.

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

The Grignard reagent was prepared by treatment of 2·92 g Mg with 16·03 g 4-chloro-1-methylpiperidine[14] in 50 ml tetrahydrofuran (refluxing for 3 h) and under stirring it was treated dropwise with a solution of 22·46 g 5-chloro-2-(2-fluorophenylthio)acetophenone[12] in 40 ml tetrahydrofuran. The mixture was refluxed for 3 h and allowed to stand overnight at room temperature. It was then diluted with ether and decomposed with 100 ml 20% NH_4Cl solution, added dropwise. The organic layer was dried with K_2CO_3 and evaporated to give 24·8 g (82%) crude *XVIII*.

A solution of 20·0 g crude *XVIII* in 120 ml dimethylformamide was added dropwise over 6 h at 70° to a stirred suspension of 4·5 g NaH in 150 ml dimethylformamide under nitrogen. The mixture was stirred for 8 h at 70°C, after cooling its was decomposed with water and extracted with benzene. The extract was dried and evaporated to give 20 g oily mixture which was chromatographed on 500 g Al_2O_3. Elution with benzene gave first 0·4 g oily less polar fractions and then 1·88 g 2-chlorothioxanthone (*Xa*), m.p. 150—151·5°C (cyclohexane). Comparison with the authentic product[18] and with the products from the last two experiments proved the identity. Continued elution with benzene gave only 4·45 g mixture which was rechromatographed on 90 g silica gel (Silpearl). Here, benzene eluted 1·4 g nonbasic oils, chloroform eluted 1·0 g

basic amorphous products and finally the mixture of chloroform and ethanol eluted 1·56 g (8%) homogeneous oily *XX*. Neutralization with oxalic acid in a mixture of acetone and ether gave the hydrogen oxalate, m.p. 167–169°C (acetone–ether). Mass spectrum, *m/z* (%): 359 (M^+ corresponding to $C_{20}H_{22}ClNOS$, 13%), 344 ($M-CH_3$, 1), 96 (100), 70 (40). For $C_{22}H_{24}ClNO_5S$ (450·0) calculated: 58·72% C, 5·38% H, 7·88% Cl, 3·11% N, 7·13% S; found: 58·15% C, 5·39% H, 8·03% Cl, 3·01% N, 7·03% S.

8-Methoxy-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ib*)

Similarly like in the preceding cases, the Grignard reagent was prepared from 2·5 g Mg and 13·35 g 4-chloro-1-methylpiperidine[14] in 80 ml tetrahydrofuran and was treated with a solution of 18·2 g *IXb* in 40 ml tetrahydrofuran. After refluxing for 4 h the mixture gave 23·7 g (100%) crude *VIb* which was further used without purification and characterization. It was dissolved in 120 ml dimethylformamide and the solution was added dropwise over 4 h at 70°C to a stirred suspension of 5·4 g NaH in 170 dimethylformamide under nitrogen. The mixture was stirred for 11 h at 70°C and processed like in the preceding cases. The crude oily product (22·3 g) crystallized from a mixture of cyclohexane and light petroleum giving 8·4 g crude *Ib*, m.p. 91–104°C. Two recrystallizations from the same mixture and then from aqueous methanol gave 5·7 g pure *Ib*, m.p. 103–105°C. The mother liquors were combined, evaporated and chromatographed on 500 g Al_2O_3. Elution with benzene gave first 1·22 g of 2-methoxythioxanthone (*Xb*), m.p. 131·5–132°C (benzene–light petroleum). The analysis confirmed the elemental composition $C_{14}H_{10}O_2S$. UV spectrum: λ_{max} 250 nm (log ε 4·59), 269 nm (4·53), 296 nm (3·49), 394 nm (3·83). IR spectrum: 745, 815, 880 (4 and 2 adjacent and solitary Ar—H), 1 030, 1 345 ($ArOCH_3$), 1 478, 1 593, 1 603 (Ar), 1 638 cm^{-1} (ArCOAr). Lit.[21], m.p. 129°C.

Continued elution with benzene and then with a mixture of benzene and chloroform yielded further 11·4 g pure *Ib* raising thus the total yield to 17·1 g (76%), m.p. 103–105°C (aqueous methanol). IR spectrum (KBr): 749, 809, 879, 899 (4 and 2 adjacent and solitary Ar—H), 1 230, 1 293, 1 300 ($ArOCH_3$, ArOR), 1 472, 1 576, 1 601, 3 035 (Ar), 2 727, 2 770 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·60–7·60 (m, 7 H, Ar—H), 5·89 (d, J = 9·0 Hz, 1 H, 6-H), 3·78 (s, 3 H, OCH_3), 3·23 (s, 3 H, NCH_3), 1·20–3·00 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{20}H_{23}NO_2S$ (341·5) calculated: 70·35% C, 6·79% H, 4·10% N, 9·39% S; found: 70·14% C, 6·87% H, 4·06% N, 9·14% S.

Hydrogen maleate, m.p. 182·5–183·5°C (acetone–ethanol). For $C_{24}H_{27}NO_6S$ (457·6) calculated: 63·00% C, 5·95% H, 3·06% N, 7·01% S; found: 63·41% C, 6·13% H, 2·91% N, 7·17% S.

8-Trifluoromethyl-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ic*)

The Grignard reagent was prepared similarly like in the preceding cases from 2·3 g Mg and 12·0 g 4-chloro-1-methylpiperidine[14] in 70 ml tetrahydrofuran and was processed by treatment with a solution of 17·4 g *IXc* in 40 ml tetrahydrofuran. After 4 h of refluxing it was decomposed with a 20% NH_4Cl solution and the crude *VIc* was isolated by extraction with benzene, 23·2 g (100%) inhomogeneous oil. It was dissolved in 100 ml dimethylformamide and the solution was added over 6 h at 70°C to a stirred suspension of 4·5 g NaH in 140 ml dimethylformamide under nitrogen. The mixture was stirred for 16 h at 70°C and processed similarly like in the preceding cases. There were obtained 17·3 g inhomogeneous oil which was chromatographed on 500 g Al_2O_3. The first fraction (0·23 g) was obtained by elution with benzene and was identified as 2-trifluoromethylthioxanthone (*Xc*), m.p. 147–148°C (cyclohexane). Its analysis corresponds to $C_{14}H_7F_3OS$. UV spectrum: λ_{max} 253 nm (log ε 4·57), 291 nm (3·83), 301 nm (3·92),

374 nm (3·78). IR spectrum: 742, 844, 868 (4 and 2 adjacent and solitary Ar—H), 1 100, 1 118, 1 155, 1 260, 1 298, 1 315, 1 345 ($ArCF_3$), 1462, 1 593, 1 608, 3 018 (Ar), 1 645 cm^{-1} (ArCOAr). Lit[24], m.p. 143—144·5°C.

The chromatography was continued by elution with a mixture of benzene and chloroform which led to isolation of 1·48 g (7%) homogeneous oily *Ic*. Mass spectrum, *m/z* (%): 379 (M^+ corresponding to $C_{20}H_{20}F_3NOS$, 30%), 360 (M—F, 5), 351 (M—28, 12), 320 (3), 281 (10), 265 (3), 283 (6), 215 (7), 184 (7), 99 (85), 98 (100), 96 (75), 70 (60). ^1H NMR spectrum: δ 6·70 to 7·80 (m, 7 H, Ar—H), 5·72 (d, J = 9·0 Hz, 1 H, 6-H), 2·22 (s, 3 H, NCH_3), 1·30—3·10 (m, 9 H, 4 CH_2 and CH of piperidine). Neutralization with oxalic acid in a mixture of acetone and ethanol gave the hydrogen oxalate, m.p. 215·5—216·5°C with decomposition (acetone–ethanol). For $C_{22}H_{22}F_3NO_5S$ (469·5) calculated: 56·28% C, 4·72% H, 12·14% F, 2·98% N, 6·83% S; found: 56·97% C, 4·77% H, 12·40% F, 3·05% N, 7·10% S.

A further product was obtained by elution with chloroform: 0·95 g, m.p. 247·5—248°C (benzene). The data available suggest its identity as 4-[2-(2-hydroxyphenylthio)-5-trifluoromethylbenzylidene]-1-methylpiperidine (*XIIc*). Mass spectrum, *m/z* (%): 379 (M^+ corresponding to $C_{20}H_{20}F_3NOS$, 0·5%), 360 (M—F, 1), 281 (47), 233 (5), 184 (5), 99 (75), 98 (100). UV spectrum: λ_{max} 277 nm (log ε 4·11), 252 nm (3·84), 280 nm (4·04). IR spectrum: 745, 825, 860 (4 and 2 adjacent and solitary Ar—H), 1 087, 1 115 (ArOH?), 1 147, 1 165, 1 333 ($ArCF_3$), 1 566, 1 580, 1 589, 3 040 (Ar), 1 610 (C=C), 2 670, 2 725 (NH^+), 2 780 (N—CH_3), 3 130 cm^{-1} (O—H...N). For $C_{20}H_{20}F_3NOS$ (379·5) calculated: 63·31% C, 5·31% H, 15·02% F, 3·69% N, 8·45% S; found: 63·43% C, 5·32% H, 15·22% F, 3·60% N, 8·73% S.

The last product was obtained by continued elution with chlorofom; 5·1 g basic oil having the R_F very close to that of the starting *VIc* and suggested to be 5-trifluoromethyl-2-phenylthio-α-(1-methyl-4-piperidyl)benzyl alcohol (*XXII*). Mass spectrum, *m/z* (%): 381 (M^+ corresponding to $C_{20}H_{22}F_3NOS$, 55%), 364 (M—17, 7), 288 (6), 256 (17), 190 (7), 98 (100), 96 (75), 70 (50). IR spectrum: 759 (C_6H_5), 830, 894 (2 adjacent and solitary Ar—H), 1 090 (CHOH), 1 132, 1 174, 1 333 ($ArCF_3$). 1 580, 1 610 (Ar), 3 330 cm^{-1} (OH). ^1H NMR spectrum: δ 6·40—7·40 (m, 8 H, Ar—H and Ar—CH—O), 5·85 (bs, disappears with ^2H_2O, 1 H, OH), 2·15 (s, 3 H, NCH_3), 1·00—3·00 (m, 9 H, 4 CH_2 and CH of piperidine). Neutralization with oxalic acid in a mixture of acetone and ether gave the hydrogen oxalate, m.p. 187·5—188·5°C with decomposition (acetone–ether). For $C_{22}H_{24}F_3NO_5S$ (471·5) calculated: 56·04% C, 5·13% H, 12·09% F, 2·97% N, 6·80% S; found: 56·26% C, 5·26% H, 12·02% F, 2·90% N, 6·81% S.

The starting *VIc* (4·1 g) was eluted with a mixture of chloroform and ethanol as the most polar component and because of contamination with polymeric material it did not crystallize.

8-Chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin N-Oxide (*XV*)

A solution of 2·24 g *Ia* in 15 ml ethanol was treated with 1·5 ml 28% H_2O_2 and the mixture was stirred for 4 h at 0°C. It was allowed to stand for 3 days at room temperature, cooled and the solid product was filtered; 1·50 g (64%), m.p. 122—128°C. Analytical sample, m.p. 126—129°C (ethanol). IR spectrum: 752, 832, 882 (4 and 2 adjacent and solitary Ar—H), 982, 990 (N—O), 1 218, 1 289 (ArOR), 1 561, 1 579, 1 586, 3 020 (Ar), 2 715, 2 755 cm^{-1} (N—CH_3). It is polarographically reduced in 0·5M-HCl at $E_{1/2}$ −0·1 V (against a saturated calomel electrode). ^1H NMR spectrum: δ 7·48 (d, 1 H, 10-H), 6·60—7·30 (m, 6 H, remaining Ar—H), 5·75 (d, J = 9·0 Hz, 1 H, 6-H), 2·25 (s, 3 H, NCH_3), 1·30—3·10 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{19}H_{20}ClNO_2S$ (361·9) calculated: 63·06% C, 5·57% H, 9·80% Cl, 3·87% N, 8·86% S; found: 62·76% C, 5·92% H, 9·77% Cl, 3·63% N, 9·04% S.

8-Chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin 11-Oxide (*XVI*)

XIa (2·18 g) was dissolved in a solution of 0·8 g methanesulfonic acid in 25 ml water and treated with 36 ml 30% H_2O_2. The mixture was allowed to stand for 24 h at room temperature, made alkaline with NH_4OH and extracted with benzene, the extract was dried with K_2CO_3 and evaporated. The residue (2·23 g) was neutralized with oxalic acid in a mixture of acetone and ether and gave 2·6 g (91%) hemioxalate solvated with C_2H_5OH, m.p. 150–154°C (95% ethanol–ether). IR spectrum: 732, 775, 835, 872 (4 and 2 adjacent and solitary Ar–H, S–O), 1 048, 1 075 (ArOR), 1 512, 1 583, 3 010 (Ar), 1 620 (COO^-), 2 640 (NH^+), 3 160 cm^{-1} (OH of ethanol). It is polarographically reduced in 0·5M-HCl at $E_{1/2}$ −0·626 V (against a saturated calomel electrode) which corresponds to the behaviour of the S-oxide. For $C_{20}H_{21}ClNO_4S + C_2H_6O$ (453·0) calculated: 58·33% C, 6·01% H, 7·83% Cl, 3·09% N, 7·08% S; found: 58·34% C, 6·19% H, 7·87% Cl, 3·01% N, 7·06% S.

8-Methoxy-6-(4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*IIb*)

A solution of 13·1 g *Ib* in 50 ml benzene was stirred and treated over 1·5 h with a solution of 6·5 g ethyl chloroformate in 30 ml benzene. The mixture was then stirred and refluxed for 1·5 h, cooled, washed with water, 10% H_2SO_4 and 5% $NaHCO_3$, dried with $MgSO_4$ and evaporated. The oily carbamate (15·2 g) obtained was dissolved in 17 ml ethanol and the solution was treated with 15 g KOH. The mixture was refluxed for 2 h, diluted with water and extracted with benzene. The extract was washed with an excess of 10% hydrochloric acid and water, the acid aqueous layer was separated, made alkaline with NH_4OH and the base was extracted with benzene. Processing of the extract gave 11·1 g (88%) oily base *IIb* which was neutralized with oxalic acid in acetone. Crystallization of the salt from ethanol gave the hemioxalate hemihydrate, m.p. 234–235·5°C with decomposition. For $C_{20}H_{22}NO_4S + 0{\cdot}5\ H_2O$ (381·5) calculated: 62·97% C, 6·08% H, 3·67% N, 8·41% S; found: 63·06% C, 5·72% H, 3·47% N, 8·24% S.

A sample of the salt was decomposed with NH_4OH and the pure oily base was isolated by extraction with ether and used for recording the spectra. Mass spectrum, *m/z* (%): 327·1196 (M^+ corresponding to $C_{19}H_{21}NO_2S$, 100%), 312·1068 ($M-CH_3$, 6), 299·0973 ($M-C_2H_4$, 23), 286·0893 ($C_{16}H_{16}NO_2S$, 12), 270·0721 ($C_{16}H_{14}O_2S$, 17), 257 (5), 243·0488 ($C_{14}H_{11}O_2S$, 33), 227·0540 ($C_{14}H_{11}OS$, 23), 202 (26), 82·0654 (C_5H_8N, 100). ^1H NMR spectrum: δ 7·40 (d, J = 8·5 Hz, 1 H, 10-H), 6·60–7·20 (m, 6 H, remaining Ar–H), 5·79 (d, J 9·0 Hz, 1 H, 6-H), 3·75 (s, 3 H, OCH_3), 1·80 (s, 1 H, NH), 1·30–3·10 (m, 9 H, 4 CH_2 and CH of piperidine).

6-[1-(2-Hydroxyethyl)-4-piperidyl]-8-methoxy-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*IIIb*)

A mixture of 5·05 g *IIb*, 5·8 g 2-bromoethanol, 5·0 g K_2CO_3 and 100 ml acetone was refluxed for 8 h. After cooling the mixture was filtered and the filtrate was evaporated *in vacuo*. The inhomogeneous oily residue was chromatographed on 400 g Al_2O_3. The mixture of benzene and chloroform eluted some less polar impurities and chloroform eluted then 2·16 g (38%) homogeneous oily base which was neutralized with fumaric acid in ether giving the hydrogen fumarate, m.p. 101–104°C. Mass spectrum, *m/z* (%): 371 (M^+ corresponding to $C_{21}H_{25}NO_3S$, 10%), 340 ($M-CH_2OH$, 100), 243 (5), 98 (15). For $C_{25}H_{29}NO_7S$ (487·6) calculated: 61·58% C, 6·00% H, 2·87% N, 6·58% S; found: 61·62% C, 6·20%H, 2·90% N, 6·44% S.

8-Methoxy-6-[1-(4-oxopentyl)-4-piperidyl]-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*IVb*)

A mixture of 5·65 g *IIb*, 3·9 g 5-bromopentan-2-one[22], 5·0 g K_2CO_3 and 100 ml acetone was stirred and refluxed for 7 h. After cooling it was filtered and the filtrate was evaporated under

reduced pressure. The oily residue was neutralized with oxalic acid in a mixture of acetone and ether yielding 7·9 g (91%) hydrogen oxalate, m.p. 87—89°C (acetone–ethanol). Mass spectrum, *m/z* (%): 411 (M^+ corresponding to $C_{24}H_{29}NO_3S$, 14%), 340 (100), 243 (10). For $C_{26}H_{31}NO_7S$ (501·6) calculated: 62·26% C, 6·23% H, 2·79% N, 6·39% S; found: 61·65% C, 6·18% H, 2·82% N, 6·38% S.

6-[1-(4-Hydroxypentyl)-4-piperidyl]-8-methoxy-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Vb*)

A solution of 5·90 g *IVb* in 100 ml ethanol was treated with a solution of 1·0 g $NaBH_4$ in 5 ml water containing 1 drop 20% NaOH. The mixture was stirred and refluxed for 3 h, diluted with 10 ml acetone and stirred for 30 min. The volatile components were evaporated, the residue diluted with dilute NaOH and extracted with benzene. Evaporation of the extract gave the crude oily base which was neutralized with fumaric acid in ether yielding 5·35 g (71%) hydrogen fumarate. m.p. 95—99°C. Mass spectrum, *m/z* (%): 413 (M^+ corresponding to $C_{24}H_{31}NO_3S$, 15%), 398 ($M-CH_3$, 6), 385 (M—28, 1), 368 (1), 366 (1), 354 (1), 340 (100), 243 (15), 211 (5), 171 (50), 98 (75). For $C_{28}H_{35}NO_7S$ (529·7) calculated: 63·49% C, 6·66% H, 2·65% N, 6·05% S; found: 63·77% C, 6·63% H, 2·68% N, 6·15% S.

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