TRICYCLIC PSYCHOTROPIC AGENTS CONTAINING TWO CHALCOGEN ATOMS IN THE CENTRAL RING: DERIVATIVES OF 11H-DIBENZ[*b*,*f*]-1,4-OXATHIEPIN*

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Reactions of 2-bromobenzyl bromide and its analogues *XVII* and *XXV* with 2-hydroxythiophenol resulted in 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*Ia*) and its 2-chloro (*Ib*) and 2-trifluoromethyl derivative (*Ic*). Treatment of the lithium compounds derived from *Ia* and *Ib* with carbon dioxide and dimethylaminoalkyl chlorides gave compounds *IIa*, *Va* and *VIab*; modification of the side chains led to amines *IVa*, *VIIa* and *VIIIa*. 11-(1-Methyl-4-piperidyl) derivatives *Xbc* were obtained by chlorination of compounds *Ibc* with sulfuryl chloride or N-chlorosuccinimide and the following treatment with 1-methyl-4-piperidylmagnesium chloride. Compound *Ib* was transformed by oxidation to the sulfone *XX* affording by treatment with sodium hydride and tert-aminoalkyl chlorides the basic sulfones *XXI* and *XXII*. While the nuclearly unsubstituted amines with the aliphatic side chains (*IVa* and *VIIa*) have intensive antireserpine activity and are potential antidepressants, the 11-(1-methyl-4-piperidyl) derivatives with a substituent in position 2 of the skeleton (*Xbc*) are potential neuroleptics; the trifluoromethyl derivative *Xc* especially has outstanding cataleptic and antiapomorphine efficacy.

In a recent communication[1] we outlined the project of searching after psychotropic agents among derivatives of the linearly condensed tricyclic systems with two chalcogen atoms in the central seven-membered ring and described the synthesis and pharmacology of several 11-(dimethylaminoalkyl) derivatives of 11*H*-dibenzo[*b*,*e*]-1,4-dioxepin and 11*H*-dibenzo[*b*, *e*]-1,4-dithiepin. The presently described synthesis of 11-(aminoalkyl) derivatives of 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*Ia*) and its 2-chloro (*Ib*) and 2-trifluoromethyl derivative (*Ic*) is a continuation of this work. With the exception of our own preliminary communication[2], dealing only with the synthesis of the basic compound *Ia*, the 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin system was not described in the literature.

Compound *Ia* was obtained by two methods. The first one started from a reaction of 2-methoxythiophenol[3] with 2-bromobenzyl bromide[4] in an ethanolic solution of sodium hydroxide leading to 2-(2-bromobenzylthio)anisole (*XII*) which was de-

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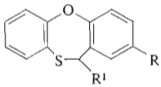
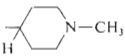
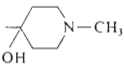


a, R = H
b, R = Cl
c, R = CF_3

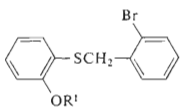
I, R^1 = H
II, R^1 = COOH
III, R^1 = $CON(CH_3)_2$
IV, R^1 = $CH_2N(CH_3)_2$
V, R^1 = $(CH_2)_2N(CH_3)_2$
VI, R^1 = $(CH_2)_3N(CH_3)_2$
VII, R^1 = $(CH_2)_2NHCH_3$

VIII, R^1 = $(CH_2)_3NHCH_3$
IX, R^1 = Cl

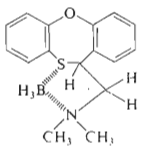
X, R^1 = 

XI, R^1 = 

methylated by boiling with a mixture of hydrobromic acid and acetic anhydride to 2-(2-bromobenzylthio)phenol (*XIII*). This compound was cyclized with potassium carbonate in boiling dimethylformamide in the presence of copper; compound *Ia* was obtained and characterized by analyses and spectra. The same substance was obtained in a single step by a reaction of 2-hydroxythiophenol[5] and 2-bromobenzyl bromide[4] in the presence of potassium carbonate in dimethylformamide first at room temperature (reaction of the benzyl bromide with the thiol) and after the addition of copper as a catalyst by boiling the mixture (Ullmann reaction[6]).



XII, R^1 = CH_3
XIII, R^1 = H



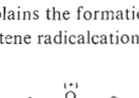
XIV

A reaction of compound *Ia* with n-butyllithium in a mixture of ether and hexane leads successively to the formation of the C(11) carbanion (a dark red coloration) and then to separation of a solid precipitate; the following treatment with an excess of solid carbon dioxide results in 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxylic acid (*IIa*). This acid was reacted with thionyl chloride in boiling benzene and the crude acid chloride was subjected to treatment with an excess of dimethylamine in benzene; the dimethylamide *IIIa* was obtained in an almost theoretical yield. Its reduction with diborane *in situ*, generated by a reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran, gave only partly the basic product, affording a hydrogen oxalate of the desired 11-(dimethylaminomethyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*IVa*). The main product is an oily little polar substance containing boron

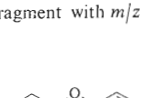
which was characterized with the help of the ^{1}H NMR spectrum as the aminothioborane with the tentatively suggested structure *XIV*: the signals of protons of the CH_2 group prove their nonequivalency on the basis of hindered rotation which is explained by the location of this CH_2 group in a five-membered ring of the chelate *XIV*. Alkaline hydrolysis of this borane complex gave a further amount of the amine *IVa*.

A similarly prepared organolithium compound afforded by reactions with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride the amines *Va* and *VIa* which were characterized by means of the ^{1}H NMR spectra and analyzed in the form of hydrogen oxalates. Reactions of the tertiary amines *Va* and *VIa* with ethyl chloroformate in boiling benzene effected partial N-demethylations and the obtained neutral products (carbamates) were hydrolyzed in crude state with potassium hydroxide in a small volume of ethanol. The secondary amines *VIIa* and *VIIIa* were obtained and their identity corroborated by ^{1}H NMR spectra and by analyses of the hydrogen oxalates.

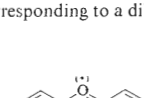
The mass spectrum of compound *VIIa* shows an interesting fragmentation which can be followed in two ways. In the first one, there comes first to the cleavage of the sulfur atom and the spectrum shows a little abundant fragment with m/z 239. Further fragmentation of this species proceeds under cleavage of the ammonium ion $CH_2{=}\overset{(+)}{=}NHCH_3$ with m/z 44 (base peak) typical for fragmentations of methylaminoalkyl derivatives[7]. Simultaneously a rather abundant fragment with m/z 195 is formed, formulated as the cation *A*. The other way of fragmentation seems to participate in a lesser extent. Cleavage of the whole side chain (being apparently again the source of the mentioned ammonium ion leads to a fragment with m/z 213 for which a formulation as cation *B* seems probable. Further clevage of sulfur results in a cation with m/z 181, formulated tentatively as *C*. This second fragmentation route is common with the fragmentation of the basic compoud *Ia* which cleaves in the first step a hydrogen radical under the formation of the already mentioned cation *B*. Compound *Ia* is likewise fragmented by a further way starting with cleavage of oxygen and a hydrogen radical and the formation of a fragment with m/z 197 formulated as the 6*H*-dibenzo [*b*,*d*] thiopyran cation *D*. A further fragment (m/z 185) is apparently formed by cleavage of CO from the cation *B*. Finally, a cleavage of SH· explains the formation of a fragment with m/z 152, corresponding to a dibenzocyclobutene radicalcation *E*.



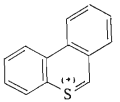
A



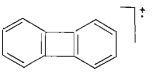
B



C

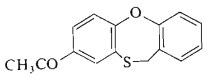


D

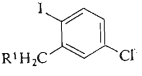


E

A reaction of compound *Ia* with acetyl chloride and aluminium chloride in carbon disulfide gave a mixture which was separated by fractional distillation and crystallization resulting in a low yield of a conjugated ketone formulated on the basis of the ^{1}H NMR spectrum as 8-acetyl-11*H*-dibenz[*b*, *f*]-1,4-oxathiepin (*XV*).



XV



XVI, R^1 = OH
XVII, R^1 = Br
XVIII, R^1 = S

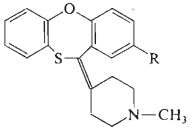
2-Chloro-11*H*-dibenz[*b*, *e*]-1,4-oxathiepin (*Ib*) was likewise synthesized by two ways. Reduction of 5-chloro-2-iodobenzoic acid[8] with diborane *in situ*, generated by a reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran, gave the alcohol *XVI* which afforded by treatment with phosphorus tribromide the benzyl bromide derivative *XVII*. Reaction of this compound with 2-hydroxythiophenol[5] in the ethanolic solution of sodium hydroxide resulted in 2-(5-chloro-2-iodobenzylthio)phenol (*XVIII*). This compound was cyclized by the Ullmann reaction[6], *i.e.* by treatment with potassium carbonate in boiling dimethylformamide in the presence of copper; the compound *Ib* was obtained in a moderate yield. The same substance was prepared directly by a reaction of 5-chloro-2-iodobenzyl bromide (*XVII*) with 2-hydroxythiophenol[5] and potassium carbonate in dimethylformamide first at room temperature and after the addition of copper at the boiling point of the mixture. This direct method afforded the desired compound *Ib* in a better yield than the preceding procedure.

Reaction of compound *Ib* with n-butyllithium and the following treatment with 3-dimethylaminopropyl chloride had not such a smooth course like in the case of the unsubstituted compound *Ia*. A mixture was formed from which the desired base *VIb* was isolated by chromatography on alumina. It was analyzed as the hydrogen oxalate and characterized by spectra. The mass spectrum shows fragments corresponding to a cleavage of the side chain and cleavage of the side chain and sulfur; the

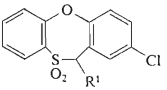
base peak with m/z of 58 represents evidently the ammonium ion $CH_2{=}\overset{(+)}{N}(CH_3)_2$. Since an attempt at reacting the crude organolithium compound with 4-chloro-1-methylpiperidine[9] gave a totally negative result (compound *Ib* was partly recovered and neutralization of the basic fraction with maleic acid and crystallization led to 4-chloro-1-methylpiperidine hydrogen maleate as the only product), an alternative route for the introduction of the 1-methyl-4-piperidyl residue to position 11 was elaborated. Compound *Ib* was first chlorinated with sulfuryl chloride in tetrachloromethane at 60°C and the 11-chloro derivative *IXb* formed was subjected – without isolation of the pure substance and without characterization – to treatment with 1-methyl-4-piperidylmagnesium chloride[10] in a mixture of benzene and tetrahydrofuran. The mixture formed was separated by chromatography on alumina. The more polar main product was identified as *Xb*; it afforded a crystalline hydrogen maleate and the identity of the oily base was confirmed by spectra. The mass spectrum shows fragments corresponding to 2-chloro derivatives of fragments *B* and *C* encountered in the spectra of compounds *Ia* and *VIIa*. The less polar base gave also a crystalline hydrogen maleate and the mass spectrum indicates the composition $C_{19}H_{18}ClNOS$; in comparison with compound *Xb* it shows a deficit of 2 hydrogen atoms. This compound was prepared by another and unequivocal way which enabled to ascribe to it the structure of the unsaturated base *XIXb*. In the present case, it is necessary to explain the formation of compound *XIXb* by chlorination of a part of compound *Ib* until the stage of 11,11-dichloro derivative reacting then with 1-methyl-4-piperidylmagnesium chloride in the first line by the substitution reaction and eliminating hydrogen chloride in the next step. Chlorination of compound *Ib* was carried out also with N-chlorosuccinimide in benzene; the following reaction of the crude chloro derivative *IXb* with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran led again to a inhomogeneous product from which the base *Xb* was isolated by chromatography in an better yield than in the preceding case. The reaction was not complicated by the formation of the unsaturated base *XIXb*. Reaction of the lithium derivative of compound *Ib* with 1-methyl-4-piperidone in ether gave the amino alcohol *XIb* which was dehydrated by treatment with thionyl chloride in pyridine at 100°C. The product obtained is identical with the olefinic amine, formed as a by-product of the preparation of compound *Xb*. Both routes of formation of the substance mutually confirm its structure *XIXb*.

Oxidation of compound *Ib* with an excess of hydrogen peroxide in boiling acetic acid gave the sulfone *XX*. In the case of this compound, sodium hydride in dimethylformamide at 70°C is sufficient for the formation of the 11-carbanion as the intermediate for the introduction of the aminoalkyl. The following treatment with 2-dimethylaminoethyl chloride and 3-piperidinopropyl chloride[11] afforded the amines *XXI* and *XXII* which were isolated as hydrochlorides and characterized by spectra.

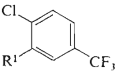
2-Trifluoromethyl-11*H*-dibenz[*b*, *f*]-1,4-oxathiepin (*Ic*) was obtained similarly



XIXa, R = H
XIXb, R = Cl
XIXc, R = CF_3



XX, R^1 = H
XXI, R^1 = $(CH_2)_2N(CH_3)_2$
XXII, R^1 = $(CH_2)_3N$ 



XXIII, R^1 = CHO
XXIV, R^1 = CH_2OH
XXV, R^1 = CH_2Cl

like *Ia* and *Ib* by a direct reaction of 2-chloro-5-trifluoromethylbenzyl chloride (*XXV*) with 2-hydroxythiophenol[5] and potassium carbonate in dimethylformamide – in the first stage at room temperature and in the second one in the presence of copper at the boiling point of the mixture. The starting compound *XXV* was obtained on the one hand using the literature procedure[12] by chloromethylation of 4-chlorobenzotrifluoride and by a new method from 3-amino-4-chlorobenzotrifluoride[13] on the other. This aniline derivative was first transformed by application of the Beech method[14] in a more recent modification[15] to 2-chloro-5-trifluoromethylbenzaldehyde (*XXIII*): 3-amino-4-chlorobenzotrifluoride was diazotized, the diazonium salt solution was subjected to treatment with formaldoxime[15] in the presence of copper sulfate and sodium sulfite and the product was hydrolyzed with boiling dilute hydrochloric acid. The aldehyde *XXIII* was obtained in this way in a moderate yield and gave by reduction with sodium borohydride in aqueous dioxane 2-chloro-5-trifluoromethylbenzyl alcohol (*XXIV*). Reaction of this alcohol with thionyl chloride in chloroform in the presence of pyridine led in a high yield to the chloromethyl derivative *XXV*. The regressive conversion of compound *XXV* to the aldehyde *XXIII* was also carried out: reaction with potassium acetate in dimethyl sulfoxide in the presence of triethylbenzylammonium chloride at 60°C and the following hydrolysis with boiling dilute hydrochloric acid in ethanol resulted in an almost theoretical yield of alcohol *XXIV* which was oxidized with potassium dichromate in the presence of triethylbenzylammonium chloride in the two-phase-system of dichloromethane and dilute sulfuric acid at room temperature to the aldehyde *XXIII* (method, *cf.*[16]). The direct conversion of the chloro derivative *XXV* to the aldehyde *XXIII* was carried out by reaction with hexamethylenetetramine in boiling aqueous acetic acid and by the following hydrolysis with boiling dilute hydrochloric acid (Sommelet reaction[17,18]).

Reaction of compound *Ic* with n-butyllithium and the following treatment of the crude lithium derivative with carbon dioxide or with various halogeno derivatives resulted only in polymeric products which could not be caracterized; an interaction of butyllithium with the trifluoromethyl group of compound *Ic* takes probably place already in the first step of the sequence. For this reason, the mentioned alternative

method was used again consisting first in the chlorination of compound *Ic* with sulfuryl chloride in tetrachloromethane to the chloro derivative *IXc* which underwent, in crude state, a reaction with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran[10]. Chromatography of the product separated again two bases, both affording crystalline oxalates. The more polar base was identified by means of the ^{1}H NMR spectrum as the desired compound *Xc*. The less polar base was shown by the mass spectrum to have the elemental composition $C_{20}H_{18}F_3NOS$, *i.e.* 2 hydrogen atoms less than compound *Xc*; in analogy with the preceding series, the structure of the olefinic amine *XIXC* is suggested. The explanation of its formation is the same like in the case of the 2-chloro analogue *XIXb*.

The compounds prepared were pharmacologically evaluated as potential psychotropic agents in the form of salts described in the Experimental; the substances were administered orally and the doses were calculated on the base. For pharmacological methods, *cf.*[1].

Acute toxicity in mice; LD_{50}, mg/kg: *Va* 227, *VIa* 373, *VIb* between 200 (a non-toxic dose) and 500 (lethal for 80% animals), *VIIa* 248, *VIIIa* 284 (30 *i.v.*), *Xb* 299, *Xc* 384 (for imipramine 370, for chlorpromazine 198). Incoordinating effect in the rotarod test in mice, ED_{50} in mg/kg (medium effective dose bringing about ataxia at the time of maximum activity): *IVa* 23·8, *Va* 57·5, *VIa* 61·9, *VIb* 84·9, *VIIa* 60·2, *VIIIa* 79·5, *Xb* 14·0 (24 h after the administration ataxia in 30% animals after a dose of 25 mg/kg), *Xc* 12.0, *XIb* 56, *XIXb* 25, *XXI* 100 (ataxia in 60% mice), *XXII* 75 (for chlorpromazine 8·2). Inhibition of motility in mice in the test of Ther, D_{50} in mg/kg (dose bringing about an effect corresponding to 50% of the control value): *VIb* 10, *VIIa* 50 (for chlorpromazine 4·8). Inhibition of motility in the photo-cell method of Dews, D_{50} in mg/kg: *VIa* 50, *VIIa* 50, *Xc* 5·7. Antireserpine activity in the test of ptosis in mice (dose having significant effect): *IVa* 10, *Va* and *VIa* inactive at 150, *VIIa* 10, *VIIIa* 150 (6 mg/kg on *i.p.* administration) (for imipramine 100 orally and 10 *i.p.*). Antireserpine effect in the test of hypothermia in mice (elevation of the body temperature in °C elicited by a dose of 10 mg/kg as compared with the reserpine control group): *VIb* 1·42°, *VIIa* significant effect (for imipramine 2·97). Antireserpine effect in the test of gastric ulcers in rats (dose in mg/kg bringing about significant inhibition of reserpine ulcers): Compounds *IVa*, *Va*, *VIa*, *VIb* and *VIIIa* inactive at 50 mg/kg, *VIIa* 50 (for imipramine 25). Cataleptic effect in rats, ED_{50} in mg/kg: *VIb* inactive at 50, *Xb* 41, *Xc* 4·7, *XIb* inactive at 100, *XIXb* 22, *XXI* inactive at 100 (for chlorpromazine 16). Antiapomorphine activity in rats, D_{50} in mg/kg for the inhibition of apomorphine stereotypies (chewing) and agitation: *VIb* inactive at 50 *Xc* 1·7/1·4 (for chlorpromazine 69/38).

The results show that compound *VIIa* is a potential antidepressant (antireserpine activity in all the three tests used) and compound *Xc* is a very active neuroleptic agent (outstanding cataleptic and antiapomorphine activity with relatively low central depressant effect and low toxicity).

Some of the products 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 (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus, VIa* 100, *VIb* 25, *VIIa* 100, *VIIIa* 100, *Xb* 50; *Streptococcus faecalis, VIb* 50, *Xb* 50; *Staphylococcus pyogenes aureus, Va* 100, *VIa* 100, *VIb* 25, *VIIa* 100, *VIIIa* 100, *Xb* 12·5; *Escherichia coli, VIa* 100, *VIb* 50, *VIIa* 100, *VIIIa* 100, *Xb* 12·5; *Proteus vulgaris, VIb* 100, *VIIa* 100, *Xb 100*; *Mycobacterium tuberculosis* H37Rv, *VIb* 12·5, *Xb* 100, *XIb* 100; *Trichophyton mentagrophytes, Va* 50, *VIb* 50, *XIb* 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 mass spectra with Varian MAT-311 and MS 902 (AEI) spectrometers. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

2-Chloro-5-trifluoromethylbenzaldehyde (*XXIII*)

A) 3-Amino-4-chlorobenzotrifluoride[13] (222 g) was slowly added to a stirred warm solution of 260 ml hydrochloric acid in 230 ml water. The suspension of hydrochloride formed was cooled, 450 g ice were added, and the mixture was diazotized at 0—5°C with a solution of 80 g $NaNO_2$ in 110 ml water added dropwise. After 1 h stirring at 0—5°C the mixture was treated with a solution of 100 g sodium acetate trihydrate in 150 ml water. The unreacted hydrochloride of the starting amine was quickly filtered off (decomposition with Na_2CO_3, extraction with benzene and distillation recovered 70·8 g 3-amino-4-chlorobenzotrifluoride) and the filtrate was added to a solution of formaldoxime (prepared by mixing 57·5 g paraformaldehyde, 131·5 g hydroxylamine hydrochloride and 850 ml water, heating until a clear solution was formed, addition of 255 g sodium acetate trihydrate and refluxing for 15 min). The mixture was treated at 10—20°C with 32·5 g $CuSO_4.5\,H_20$, 5·0 g Na_2SO_3, a solution of 800 g sodium acetate trihydrate in 300 ml water, and with 300 ml toluene, it was stirred for 2 h, treated with 1 100 ml hydrochloric acid and distilled with steam. The distillate was extracted with benzene, the extract washed with 5% $NaHCO_3$, and evaporated. The residue was dissolved in 200 ml ether and the solution stirred for 2 h with 450 ml 40% $NaHSO_3$, the mixture allowed to stand overnight, the addition product filtered, washed with ether, decomposed by 2 h refluxing with a solution of 200 ml hydrochloric acid in 1 l water, cooled and extracted with benzene. The extract was dried with $MgSO_4$, evaporated and the residue was distilled; 49·1 g (31% per conversion), b.p. 93—96°C/2.1 kPa. For $C_8H_4ClF_3O$ (208·6) calculated: 46·07% C, 1·93% H, 17·00% Cl, 27·33% F; found: 45·74% C, 2·01% H, 16·78% Cl, 26·72% F.

B) A solution of 12·2 g *XXIV* in 150 ml dichloromethane was shaken for 2 min with a solution of 7·0 g $K_2Cr_2O_7$ and 50 ml H_2SO_4 in 100 ml water in the presence of 1·2 g triethylbenzylammonium chloride. The mixture was allowed to stand for 1 h at room temperature, the organic layer was washed with water, dilute NaOH, filtered, dried with $MgSO_4$ and distilled; 7·4 g (61%), b.p. 80—85°C/1·7 kPa. The product was identical with that prepared under *A*.

C) A mixture of 34·4 g *XXV* (ref.[12]), 60 ml acetic acid, 60 ml water and 42 g hexamethylenetetramine was refluxed for 2 h, 50 ml hydrochloric acid were added and the refluxing continued

for 15 min. The mixture was distilled with steam, the distillate (1·5 l) was extracted with benzene, the extract dried with $MgSO_4$ and distilled; 9·5 g (30%), b.p. 93—97°C/2·1 kPa.

5-Chloro-2-iodobenzyl Alcohol (*XVI*)

A solution of 120 g 5-chloro-2-iodobenzoic acid[8] in 145 ml tetrahydrofuran was stirred and treated over 45 min at 10—20°C with 16·1 g $NaBH_4$. The mixture was stirred for 30 min at 10—20°C and slowly treated with a solution of 80·3 g (71·4 ml) boron trifluoride etherate in 40 ml tetrahydrofuran. After 3 h stirring, the mixture was cooled below 8°C, decomposed by a slow addition of 50 ml 5% hydrochloric acid, diluted with water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated; 110 g (96%), m.p. 115 to 117°C. Analytical sample, m.p. 116—117°C (ethanol). IR spectrum: 814, 884 (2 adjacent and solitary Ar-H), 1 063 (CH_2OH), 1 500, 1 581, 1 621, 3 060 (Ar), 3 200, 3 280 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·82 (d, J = 8·0 Hz, 1 H, 3-H), 7·49 (d, J = 2·0 Hz, 1 H, 6-H), 7·12 (q, J = 8·0; 2·0 Hz, 1 H, 4-H), 5·64 (t, J = 6·0 Hz, 1 H, OH), 4·41 (d, J = 6·0 Hz, 2 H, $ArCH_2O$). For C_7H_6ClIO (268·5) calculated: 31·31% C, 2·25% H, 13·21% Cl, 47·27% I; found: 31·23% C, 2·05% H, 13·02% Cl, 47·42% I.

2-Chloro-5-trifluoromethylbenzyl Alcohol (*XXIV*)

A) A solution of 48·7 g *XXIII* in 100 ml dioxane was stirred and treated over 30 min at 30 to 40°C with a solution of 7·4 g $NaBH_4$ in 25 ml water. The mixture was stirred for 3 h and allowed to stand overnight. Dioxane was evaporated under reduced pressure, the residue diluted with water and extracted with benzene. Processing of the extract gave 48·7 g (99%) product melting at 57 to 58°C (light petroleum). IR spectrum: 832, 900 (2 adjacent and solitary Ar—H), 1 084 (CH_2OH), 1 130, 1 180, 1 334 ($ArCF_3$), 1 500, 1 590, 1 610 (Ar), 3 195, 3 260 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·78 (bs, 1 H, 6-H), 7·50 and 7·38 (ABq, J = 8·5 Hz, 2 H, 3,4-H_2), 4·78 (s, 2 H, $ArCH_2O$), 2·31 (s, 1 H, OH). For $C_8H_6ClF_3O$ (210·6) calculated: 45·63% C, 2·87% H, 16·84% Cl, 27·07% F; found: 45·36% C, 2·94% H, 16·33% Cl, 27·08% F.

B) A mixture of 13·9 g *XXV* (ref.[12]), 6·54 g potassium acetate, 2·76 g triethylbenzylammonium chloride and 40 ml dimethyl sulfoxide was stirred for 4 h at 60°C. It was then diluted with water and extracted with benzene. The extract was evaporated under reduced pressure, the residue treated with 50 ml ethanol, 40 ml water and 5 ml hydrochloric acid and the mixture refluxed for 7 h. Ethanol was evaporated, the residue diluted with water and extracted with benzene. Processing of the extract gave 12·6 g (98%) *XXIV*, m.p. 54—57°C.

5-Chloro-2-iodobenzyl Bromide (*XVII*)

A solution of 41·6 g PBr_3 in 25 ml benzene was slowly treated at 0°C with 8·2 ml pyridine and under stirring and cooling 108 g *XVI* were added over 1·5 h. The mixture was diluted with 40 ml benzene, stirred for 4 h at room temperature, heated for 1 h to 50°C and cooled. It was diluted with 120 ml chloroform, washed with 25 ml 5% hydrochloric acid, 5% NaOH and water, dried with $MgSO_4$ and evaporated under reduced pressure; 126 g (95%), m.p. 75—79°C. Analytical sample, m.p. 77—79°C (benzene–light petroleum). ^{1}H NMR spectrum: δ 7·80 (d, J = 8·0 Hz, 1 H, 3-H), 7·49 (d, J = 3·0 Hz, 1 H, 6-H), 7·00 (q, J = 8·0; 3·0 Hz, 1 H, 4-H), 4·52 (s, 2 H, $ArCH_2Br$). For C_7H_5BrClI (331·4) calculated: 25·37% C, 1·52% H, 24·11% Br, 10·70% Cl, 38·30% I; found: 25·65% C, 1·59% H, 24·34% Br, 10·73% Cl, 37·97% I.

2-Chloro-5-(trifluoromethyl)benzyl Chloride (*XXV*)

A) A reaction of 181 g 4-chlorobenzotrifluoride with 40 g paraformaldehyde and 117 g chlorosulfonic acid at 0—2°C according to the literature[12] gave 65·4 g (29%) product, b.p. 89—93°C/1·2 kPa. Lit.[12], b.p. 98—100°C/2·8 kPa.

B) A mixture of 48·5 g *XXIV*, 24 ml pyridine and 70 ml chloroform was stirred and treated at 10—20°C with 32 g $SOCl_2$, added dropwise. The mixture was stirred for 5 h, allowed to stand for 2 days, decomposed with water and extracted with chloroform. The extract was washed with 5% hydrochloric acid, 5% NaOH and water, dried with $MgSO_4$ and distilled; 45·5 g (86%), b.p. 93°C/2 kPa.

2-(2-Bromobenzylthio)anisole (*XII*)

2-Methoxythiophenol[3] (60·1 g) was added to a stirred solution of 17·2 g NaOH in 640 ml ethanol, the solution obtained was heated to 50—56°C and treated over 20 min under nitrogen with 107 g 2-bromobenzyl bromide[4]. The mixture was refluxed for 10 h, ethanol was distilled off, the residue was diluted with water and extracted with benzene. The extract was dried with Na_2SO_4 and distilled; 112 g (85%), b.p. 156—158°C/13 Pa. ^{1}H NMR spectrum: δ 6·70—7·70 (m, 8 H, Ar—H), 4·19 (s, 2 H, $ArCH_2S$), 3·85 (s, 3 H, OCH_3). For $C_{14}H_{13}BrOS$ (309·2) calculated: 54·38% C, 4·24% H, 25·84% Br, 10·37% S; found: 54·38% C, 4·20% H, 25·55% Br, 11·01% S.

2-(2-Bromobenzylthio)phenol (*XIII*)

A mixture of 96·4 g *XII*, 200 ml acetic anhydride and 4·0 g $NaH_2PO_2.H_2O$ was stirred and slowly treated under nitrogen with 200 ml 50% HBr, the mixture was refluxed for 4 h, poured into 2·5 l water and extracted with benzene. The extract was washed with 1 l 5% NaOH, dried with Na_2SO_4 and evaporated; 46·7 g recovered starting *XII*. The aqueous alkaline washings were acidified with 700 ml 3M-HCl and extracted with benzene. Drying and distillation of the extract gave 11·1 g (23% per conversion) *XIII*, b.p. 153°C/0·1 kPa. ^{1}H NMR spectrum: δ 6·70—7·60 (m, 8 H, Ar—H), 6·60 (s, disappears after ^2H_2O, 1 H, OH), 3·92 (s, 2 H, $ArCH_2S$). For $C_{13}H_{11}BrOS$ (295·2) calculated: 52·89% C, 3·76% H, 27·07% Br, 10·86% S; found: 53·25% C, 3·85% H, 26·64% Br, 11·30% S.

2-(5-Chloro-2-iodobenzylthio)phenol (*XVIII*)

A solution of 19·8 g 2-hydroxythiophenol[5] and 6·3 g NaOH in 150 ml ethanol was treated with 52 g *XVIII* and the mixture was refluxed for 3 h. Ethanol was distilled off, the residue was diluted with water and extracted with benzene. The extract was dried with $MgSO_4$ and distilled; 38·0 g (64%), b.p. 158°C/52 Pa, m.p. 45—47°C (light petroleum). IR spectrum: 756, 761, 818, 879, 900 (4 and 2 adjacent and solitary Ar—H), 1190, 1196 (ArOH), 1 471, 1 568, 1 573, 3 035 (Ar), 3 380 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·78 (d, J = 8·0 Hz, 1 H, 3′-H), 6·70—7·40 (m, 6 H remaining Ar—H), 6·58 (bs, 1 H, OH), 3·95 (s, 2 H, $ArCH_2S$). For $C_{13}H_{10}ClIOS$ (376·7) calculated: 41·45% C, 2·68% H, 9·41% Cl, 33·70% I, 8·51% S; found: 41·23% C, 2·74% H, 10·09% Cl, 33·83% I, 8·85% S.

11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin (*Ia*)

A) A mixture of 10·0 g *XIII*, 200 ml dimethylformamide, 1·0 g Cu and 4·6 g K_2CO_3 was refluxed under nitrogen (bath of 160°C) for 6 h. Dimethylformamide was evaporated *in vacuo*, the residue

was diluted with water and extracted with benzene. After filtration the benzene layer was separated, dried with Na_2SO_4 and distilled; 3·45 g (48%), b.p. 123°C/27 Pa. The distillate crystallized from methanol, m.p. 49–50°C. Mass spectrum, *m/z* (%): 214 (M^+ corresponding to $C_{13}H_{10}OS$, 100%), 213 (M – 1, 40), 197 ($C_{13}H_9S$, 6·4), 185 (213 – CO, 36), 181 (213 – 32, 16·8), 152 (185 – SH, 9·6), 134 (C_8H_6S, 18·4). UV spectrum: λ_{max} 257 nm (log ε 3·88), infl. 285 nm (3·27), infl. 294 nm (3·25). IR spectrum: 740 (4 adjacent Ar—H), 1 202, 1 238, 1 263 (Ar—O—Ar), 1 470, 1 490, 1 568, 1 590, 1 605 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80–7·30 (m, 8 H, Ar—H), 4·22 (s, 2 H, $ArCH_2S$). For $C_{13}H_{10}OS$ (214·3) calculated: 72·87% C, 4·70% H, 14·96% S; found: 72·97% C, 4·74% H, 15·22% S.

B) A mixture of 600 ml dimethylformamide, 25·2 g 2-hydroxythiophenol[5], 27·6 g K_2CO_3 and 50 g 2-bromobenzyl bromide[4] was stirred for 1 h at room temperature. K_2CO_3 (30 g) and 2·5 g Cu were added and the mixture was refluxed for 6 h. Dimethylformamide was distilled off *in vacuo*, the residue diluted with water and extracted with benzene. Processing of the extract gave 24·4 g (57%) *Ia*, b.p. 152–155°C/0·13 kPa, m.p. 44–49°C.

2-Chloro-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*Ib*)

A) A solution of 51·7 g *XVIII* in 200 ml dimethylformamide was added over 6 h to a refluxing mixture of 500 ml dimethylformamide, 19·1 g K_2CO_3 and 5·0 g Cu. The mixture was refluxed for 7 h, dimethylformamide was distilled off, the residue was shaken with 500 ml water and 500 ml benzene, the mixture was filtered and extracted with benzene. The extract was dried with $MgSO_4$ and distilled; 12·4 g (36%), b.p. 168—175°C/0·2 kPa. The distillate crystallized, m.p. 78–79°C (methanol). IR spectrum: 750, 834, 900 (4 and 2 adjacent and solitary Ar—H), 1 182, 1 240 (Ar—O—Ar), 1 472, 1 487, 1 570, 1 591, 3 028, 3 043 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90–7·30 (m, 7 H, Ar—H), 4·24 (s, 2 H, $ArCH_2S$). For $C_{13}H_9ClOS$ (248·7) calculated: 62·77% C, 3·65% H, 14·26% Cl, 12·89% S; found: 62·81% C, 3·72% H, 14·35% Cl, 12·98% S.

B) A mixture of 47·8 g 2-hydroxythiophenol[5], 1 150 ml dimethylformamide, 52·4 g K_2CO_3 and 126 g *XVII* was stirred for 1 h at room temperature. K_2CO_3 (57 g) and 4·3 g Cu were added and the mixture was refluxed for 6 h. Processing like under *A* gave 42·5 g (45%) *Ib*, b.p. 155–165°C/67 Pa, m.p. 76°C.

2-Trifluoromethyl-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*Ic*)

A mixture of 30·4 g *XXV*, 540 ml dimethylformamide, 18·6 g 2-hydroxythiophenol[5] and 18·4 g K_2CO_3 was stirred under nitrogen for 3 h at room temperature. K_2CO_3 (20 g) and 2·0 g Cu were added and the mixture was refluxed for 12 h. Similar processing like in the preceding cases gave 27·9 g (75%) *Ic*, b.p. 125–128°C/50 Pa, m.p. 70–71°C (light petroleum). UV spectrum: λ_{max} 257 nm (log ε 3·89), infl. 285 nm (3·28), 294 nm (3·16). IR spectrum: 745, 755, 860, 890, 910 (4 and 2 adjacent and solitary Ar—H), 1 120, 1 170, 1 180, 1 335 ($ArCF_3$), 1 245, 1 265, 1 282 (Ar—O—Ar), 1 475, 1 505, 1 600, 1 620, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80–7·60 (m, 7 H, Ar—H), 4·21 (s, 2 H, $ArCH_2S$). For $C_{14}H_9F_3OS$ (282·3) calculated: 59·57% C, 3·21% H, 20·19% F, 11·36% S; found: 59·84% C, 3·20% H, 20·00% F, 11·67% S.

11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxylic Acid (*IIa*)

A solution of 3·2 g *Ia* in 40 ml ether was stirred and treated over 30 min with 10 ml 15% n-butyllithium in hexane at room temperature (a dark red coloration and then precipitation of a solid). The mixture was stirred for 30 min, treated with an excess of solid CO_2, stirred for 1 h, decomposed

with 50 ml water and extracted with ether. The extract was shaken with 5% NaOH, the alkaline layer was separated, acidified with hydrochloric acid and the mixture allowed to stand for 2 days in the presence of a small quantity of light petroleum. The solid product was filtered; 3·22 g (84%), m.p. 150·5–151·5°C (benzene–light petroleum). IR spectrum: 722, 758 (4 adjacent Ar—H), 920, 1 210, *1 717*, 2 632, 2 780, 2 880 (COOH), 1 240, 1 270 (Ar—O—Ar, COOH), 1 493, 1 570 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90–7·50 (m, 8 H, Ar—H), 5·35 (s, 1 H, Ar—CH—S). For $C_{14}H_{10}O_3S$ (258·3) calculated: 65·10% C, 3·90% H, 12·42% S; found: 65·26% C, 3·98% H, 12·42% S.

N,N-Dimethyl-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxamide (*IIIa*)

A mixture of 2·50 g *IIa*, 10 ml benzene and 5 ml $SOCl_2$ was refluxed for 2·5 h and evaporated *in vacuo*. The residue was dissolved in 20 ml benzene and the solution treated under cooling over 5 min with a solution of 15 g dimethylamine in 50 ml benzene. The mixture was stirred for 4 h, allowed to stand overnight, washed with water, dried with $MgSO_4$ and evaporated; 2·65 g (96%), m.p. 144·5–146°C (benzene–light petroleum). IR spectrum (KBr): 727, 750 (4 adjacent Ar—H), 1 189, 1 221 (Ar—O—Ar), 1 484, 1 584, 3 028 (Ar), 1 655 cm^{-1} ($RCONR'_2$). ^1H NMR spectrum: δ 6·80–7·25 (m, 8 H, Ar—H), 6·40 (s, 1 H, Ar—CH—S), 3·01 and 2·82 (2 s, 6 H, CH_3—N—CH_3). For $C_{16}H_{15}NO_2S$ (285·4) calculated: 67·34% C, 5·30% H, 4·91% N, 11·24% S; found: 67·61% C, 5·48% H, 5·08% N, 11·17% S.

11-(Dimethylaminomethyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*IVa*)

A solution of 2·60 g *IIIa* in 40 ml tetrahydrofuran was treated under nitrogen with 1·9 g $NaBH_4$, the mixture was cooled with ice and 6 ml boron trifluoride etherate were added. The mixture was refluxed for 3 h and evaporated under reduced pressure. The residue (3·0 g) was dissolved in ether and treated with 1·3 g oxalic acid; 0·93 g hydrogen oxalate of *IVa*, m.p. 178–180°C (acetone–ethanol-ether). Mass spectrum, *m/z* (%): 271 (M^+ corresponding to $C_{16}H_{17}NOS$, 1), 181 (3), 58 ($CH_2{=}\overset{+}{N}(CH_3)_2$, 100). For $C_{18}H_{19}NO_5S$ (361·4) calculated: 59·82% C, 5·30% H, 3·88% N, 8·87% S; found: 60·28% C, 5·42% H, 3·89% N, 8·79% S. The released base was used for recording the ^1H NMR spectrum: δ 6·90–7·30 (m, 8 H, Ar—H), 4·90 (t, J = 8·0 Hz, 1 H, Ar—CH—S), 3·10 (d, J = 8·0 Hz, 2 H, CH_2N), 2·40 (s, 6 H, CH_3—N—CH_3).

The ethereal mother liquor after the precipitation of the crude oxalate was washed wtih a solution of Na_2CO_3 and evaporated; 2·1 g little polar substance identified as the aminothioborane *XIV*. IR spectrum (film): 754 (4 adjacent Ar—H, 1 170, 1 220, 1 231, 1 261 (Ar—O—Ar), 1 470 1 569, 1 591, 1 608, 3 030 (Ar), 2 260, 2 300, 2 335, 2 365 (B—H), 2 748, 2 798 cm^{-1} [$N(CH_3)_2$]. ^1H NMR spectrum: δ 6·80–7·50 (m, Ar—H), 4·71 (dd, J = 7·5; 4·0 Hz, 1 H, Ar—CH—S), 3·98 and 3·55 (2 dd, J = 12·0 Hz, 2 H, CH_2N), 2·55 and 2·28 (2 s, 6 H, CH_3NCH_3).

XIV (2·1 g) was refluxed for 6 h with 40 m ethanol and 20 ml 20% NaOH, the mixture was evaporated under reduced pressure, the residue was diluted with water and extracted with benzene. Processing of the extract gave 1·8 g oily *IV* which was transformed to the hydrogen oxalate (2·0 g, m.p. 179·5–180·5°C); total yield of this salt of *IVa* was thus 2·93 g (89%).

11-(2-Dimethylaminoethyl)-11*H*-dibenzo[*b*,*f*]-1,4-oxathiepin (*Va*)

A solution of 10·1 g *Ia* in 120 ml ether was stirred and treated under nitrogen at 5–10°C over 30 min with 30 ml 15% n-butyllithium in hexane. The mixutre was stirred for 30 min, treated with 30 g 2-dimethylaminoethyl chloride, stirred for 5 h at room temperature and allowed to stand

overnight. It was then washed with water and the basic product was extracted with dilute hydrochloric acid. The separated aqueous layer was made alkaline with NH_4OH and the base isolated by extraction with benzene; 11·5 g (86%). Neutralization with oxalic acid in acetone gave 15·2 g hydrogen oxalate, m.p. 187·5—189·5°C (95% ethanol–ether). For $C_{19}H_{21}NO_5S$ (375·5) calculated: 60·78% C, 5·64% H, 3·73% N, 8·54% S; found: 60·23% C, 5·58% H, 3·81% N, 8·04% S. A sample of the pure base, released from the oxalate, was used for recording the ^1H NMR spectrum: δ 6·80—7·70 (m, 8 H, Ar—H), 4·65 (t, 1 H, Ar—CH—S), c. 2·35 (m, 4 H, CH_2CH_2N), 2·15 (s, 6 H, CH_3NCH_3).

11-(3-Dimethylaminopropyl)-*11H*-dibenz[*b,f*]-1,4-oxathiepin (*VIa*)

A similar reaction of 10·1 g *Ia*, 30 ml 15% n-butyllithium in hexane and 30 g 3-dimethylaminopropyl chloride in 120 ml ether gave 12·6 g (89%) oily base *VIa* which was neutralized with oxalic acid in acetone to give 16·1 g hydrogen oxalate hemihydrate, m.p. 118—121°C (acetone–ethanol–ether). For $C_{20}H_{23}.NO_5S + 0{\cdot}5\,H_2O$ (398·5) calculated: 60·28% C, 6·07% H, 3·52% N, 8·05% S; found: 60·38% C, 5·81% H, 3·96% N, 7·72% S. The released base was used for recording the ^1H NMR spectrum: δ 6·80—7·30 (m, 8 H, Ar—H), 4·65 (t, J = 7·0 Hz, 1 H, Ar—CH—S), 2·22 (t, J = 7·0 Hz, 2 H, CH_2N), 2·12 (s, 6 H, CH_3NCH_3), 1·40—2·20 (m, 4 H, remaining 2 CH_2 of the propane chain).

2-Chloro-11-(3-dimethylaminopropyl)-11*H*-dibenz[*b,f*]-1,4 oxathiepin (*VIb*)

A similar reaction of 6·0 g *Ib*, 18 ml 15% n-butyllithium in hexane and 20 g 3-dimethylaminopropyl chloride in 100 ml ether gave 6·4 g inhomogeneous oily product which was chromatographed on a column of 450 g neutral Al_2O_3 (activity II). Elution with benzene and chloroform gave 4·8 g (60%) homogeneous oily *VIb* which was neutralized with oxalic acid in acetone to give 4·3 g hydrogen oxalate, m.p. 167—168°C (acetone–ethanol). For $C_{20}H_{22}ClNO_5S$ (423·9) calculated: 56·67% C, 5·23% H, 8·36% Cl, 3·30% N, 7·56% S; found: 56·84% C, 5·39% H, 8·41% Cl, 3·26% N, 7·72% S. A sample of the pure base, released from the oxalate, was used for recording the spectra. Mass spectrum, m/z: 333 (M^+ corresponding to $C_{18}H_{20}ClNOS$), 301 (M — 32), 215 ($C_{13}H_8ClO$), 58 ($CH_2{=}\overset{+}{N}(CH_3)_2$, base peak). ^1H NMR spectrum: δ 6·80—7·30 (m, 7 H, Ar—H), 4·68 (t, 1 H, ArCHS), 2·28 (t, 2 H, CH_2N), 2·16 (s, 6 H, CH_3NCH_3), 1·50—2·20 (m, 4 H, remaining 2 CH_2 of the propane chain).

11-(2-Methylaminoethyl)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*VIIa*)

A refluxing solution of 7·65 g *Va* in 30 ml benzene was treated over 1 h with a solution of 3·9 g ethyl chloroformate in 15 ml benzene, the mixture was refluxed for 1·5 h, cooled, washed with water, 10% H_2SO_4 and water, dried with $MgSO_4$ and evaporated. The neutral oily residue (8·6 g) was dissolved in 10 ml ethanol and refluxed with 9 g KOH for 2 h in a bath of 130 °C. It was diluted with water and extracted with benzene. The benzene layer was shaken with 10% hydrochloric acid, the oily hydrochloride and the aqueous layer were combined, made alkaline with NH_4OH and the base isolated by extraction with benzene; 4·0 g (55%) oil. Neutralization with oxalic acid in acetone gave 5·15 g hydrogen oxalate, m.p. 209—210°C (aqueous ethanol). Mass spectrum, m/z (%): 271 (M^+ corresponding to $C_{16}H_{17}NOS$, 6%), 239 (M — 32, 6), 213 (11), 195 (40), 181, (213 — 32, 17), 152 (4), 146 (48), 115 (20), 44 (100). For $C_{18}H_{19}NO_5S$ (361·4) calculated: 59·82% C, 5·30% H, 3·88% N, 8·87% S; found: 59·86% C, 5·48% H, 3·75% N, 8·87% S. A sample of the oxalate was decomposed with NH_4OH and the oily base was iso-

lated by extraction with ether. ^{1}H NMR spectrum: δ 6·80—7·40 (m, 8 H, Ar—H), 4·72 (t, 1 H, ArCHS), 2·61 (t, 2 H, CH_2N), 2·35 (s, 3 H, NCH_3), c. 2·25 (m, 2 H, remaining CH_2 in the chain), 1·10 (s, disappears after ^2H_2O, 1 H, NH).

11-(3-Methylaminopropyl)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*VIIIa*)

A similar reaction of 8·2 g *VIa* with 3·86 g ethyl chloroformate in 45 ml benzene gave 8·5 g neutral product which was hydrolyzed with 9·0 g KOH in 10 ml boiling ethanol; 6·1 g (79%) oily *VIIIa*. Neutralization with 2·8 g oxalic acid in acetone gave 7·7 g hydrogen oxalate, m.p. 161—162°C (ethanol). For $C_{19}H_{21}NO_5S$ (375·5) calculated: 60·78% C, 5·64% H, 3·73% N, 8·54% S; found: 60·73% C, 5·76% H, 3·56% N, 8·41% S. Treatment of a sample of the oxalate with NH_4OH and extraction with ether gave the oily base, used for recording the ^{1}H NMR spectrum: δ 6·80—7·30 (m, 8 H, Ar—H), 4·63 (t, J = 7·0 Hz, 1 H, ArCHS), 2·59 (t, J = 7·0 Hz, 2 H, CH_2N), 2·35 (s, 3 H, NCH_3), 1·40—2·20 (m, 4 H, remaining 2 CH_2 in the propane chain), 1·31 (s, 1 H, NH).

8-Acetyl-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*XV*)

A mixture of 12·2 g *Ia* and 5·3 g acetyl chloride was slowly added to a stirred mixture of 20 ml CS_2 and 8·28 g $AlCl_3$ at a temperature below —5°C. The mixture was stirred without cooling for 3 h, poured into 100 g ice and 20 ml hydrochloric acid and extracted with ether. Processing of the extract gave 4·14 g (28%) product boiling unsharply at 185—215°C/0·2 kPa which crystallized from benzene and was recrystallized from ethanol, m.p. 118—122°C. UV spectrum: λ_{max} 240 nm (log ε 3·99), 316 nm (4·13), infl. 300 nm (4·06). IR spectrum: 758, 818, 880 (4 and 2 adjacent and solitary Ar-H), 1 482, 1 550, 1 590 (Ar), 1 665 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·74 (d, J = 2·0 Hz, 1 H, 9-H), 7·46 (q, J = 8·5; 2·0 Hz, 1 H, 7-H), c. 7·20 (m, 4·H, 1,2,3,4-H_4), 7·00 (d, J = 8·5 Hz, 1 H, 6-H), 4·30 (s, 2 H, $ArCH_2S$), 2·50 (s, 3 H, $COCH_3$). The calculated values of δ corresponding to signals of 7-H and 9-H are in agreement with those found experimentally. For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·29% C, 4·72% H, 12·51% S; found: 70·67% C, 4·89% H, 12·37% S.

2-Chloro-11-(4-hydroxy-1-methyl-4-piperidyl)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*XIb*)

A solution of 9·9 g *Ib* in 130 ml ether was treated under nitrogen over 10 min with 30 ml 15% n-butyllithium in hexane at 10°C. The mixture was stirred for 1 h and treated over 10 min with a solution of 7·2 g 1-methyl-4-piperidone in 20 ml ether. It was allowed to stand overnight at room temperature, washed with water, dried with K_2CO_3 and evaporated. The residue (14·6 g oil) was dissolved in ether and the solution neutralized with 4·5 g maleic acid in ethanol; 10·8 g (57%) hydrogen maleate, m.p. 195·5—197°C (ethanol). For $C_{23}H_{24}ClNO_6S$ (478·0) calculated: 57·80% C, 5·06% H, 7·42% Cl, 2·93% N, 6·71% S; found: 58·24% C, 5·18% H, 7·62% Cl, 2·97% N, 6·50% S. A sample was decomposed with NH_4OH and the oily base was isolated by extraction with ether. ^{1}H NMR spectrum: δ 6·90—7·30 (m, 7 H, Ar—H), 4·05 (s, 1 H, Ar—CH—S), 2·28 (s, 3 H, NCH_3), remaining 4 CH_2 and OH in an unresolvable multiplet.

2-Chloro-11-(1-methyl-4-piperidylidene)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*XIXb*)

A solution of 3·9 g *XIb* in 15 ml pyridine was treated with 1 ml $SOCl_2$ and heated for 5 h to 100°C. After cooling it was diluted with benzene, washed with water, dried with K_2CO_3 and evaporated; 2·2 g (59%) oily base which was chromatographed on a column of 180 g neutral Al_2O_3 (activity II). Benzene eluted 1·31 g homogeneous base *XIXb*, m.p. 125—127°C (benzene–cyclohexane). UV

spectrum: λ_{max} 253 nm (log ε 3·84), infl. 225 nm (4·28), 280 nm (3·55). IR spectrum: 770, 840, 880 (4 and 2 adjacent and solitary Ar—H), 1 100, 1 200, 1 228, 1 255 (ArOAr), 1 460, 1 561, 3 035 (Ar), 2 710, 2 745, 2 770 cm^{-1} (NCH_3). For $C_{19}H_{18}ClNOS$ (343·9) calculated: 66·36% C, 5·28% H, 10·31% Cl, 4·07% N, 9·32% S; found: 66·65% C, 5·30% H, 10·09% Cl, 3·92% N, 9·42% S.

The hydrogen maleate crystallizes from a mixture of acetone and ether in the form of two modifications: A. needles, m.p. 196—197·5°C. For $C_{23}H_{22}ClNO_5S$ (460·0) calculated: 60·06% C, 4·82% H, 7·71% Cl, 3·05% N, 6·97% S; found: 60·00% C, 4·65% H, 7·94% Cl, 3·07% N, 6·86% S. B. leaflets, m.p. 190·5—193·5°C. For $C_{23}H_{22}ClNO_5S$ (460·0) calculated: 60·06% C, 4·82% H, 7·71% Cl, 3·05% N, 6·97% S; found: 60·00% C, 4·93% H, 7·81% Cl, 2·91% N, 7·00% S.

2-Chloro-11-(1-methyl-4-piperidyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*Xb*)

A) A solution of 6·45 g *Ib* in 100 ml CCl_4 was treated over 4·5 h at 60°C with a solution of 3·54 g SO_2Cl_2 in 100 ml CCl_4, the mixture was stirred for 1 h and evaporated. The residue was dissolved in 20 ml benzene and the solution was slowly added to a refluxing solution of the Grignard reagent, prepared from 7·0 g 4-chloro-1-methylpiperidine[9,10] and 1·3 g Mg in 45 ml tetrahydrofuran. The mixture was refluxed for 3·5 h, after cooling decomposed with a solution of NH_4Cl and extracted with benzene. The organic layer was washed with water and then shaken with dilute hydrochloric acid. The aqueous acid solution was separated, made alkaline with NH_4OH and the mixture of bases isolated by extraction with benzene. Chromatography on a column of 400 g neutral Al_2O_3 (activity II) gave first 0·41 g less polar component (elution with benzene) which was transformed to a hydrogen maleate, needles melting at 196—197·5°C. It proved identical with modification A of *XIXb* hydrogen maleate. To confirm it, the mass spectrum was recorded, *m*/*z* (%): 343 (M^+ corresponding to $C_{19}H_{18}ClNOS$, 30%), 96 (100).

Continued elution with a mixture of benzene and chloroform afforded 1·47 g (16%) oily base *Xb* which was transformed to the hydrogen maleate, m.p. 184—186·5°C (acetone–ether). Mass spectrum, *m*/*z* (%): 345 (M^+ corresponding to $C_{19}H_{20}ClNOS$, 11%), 317 (2), 247 (4), 215 (6), 98 (1-methyl-2,3,4,5-tetrahydropyridinium, 100). 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: 59·58% C, 5·15% H, 7·80% Cl, 3·03% N, 6·66% S. A sample of the maleate was decomposed with NH_4OH, the pure base isolated by extraction with ether and used for recording the ^1H NMR spectrum: δ 6·80—7·40 (m, 7 H, Ar-H), 3·52 (d, $J \simeq 10·0$ Hz, 1 H, ArCH-S), 2·20 (s, 3 H, NCH_3), remaining 4 CH_2 and CH appear as an unresolvable multiplet.

B) A solution of 7·05 g *Ib* in 30 ml benzene was treated with 3·85 g N-chlorosuccinimide and the mixture was stirred for 5 h (the temperature at the beginning maintained at 20—25°C by cooling). After standing overnight, the solution was slowly added to a Grignard reagent, prepared from 7·0 g 4-chloro-1-methylpiperidine[9,10] and 1·3 g Mg in 40 ml tetrahydrofuran at 20—25°C. The mixture was stirred for 5 h, allowed to stand for 2 days, decomposed with a solution of NH_4Cl, extracted with benzene and processed similarly like in the preceding case. Chromatography of the crude product (6·4 g) on 400 g Al_2O_3 gave 4·16 g (42%) homogeneous base *Xb* (elution with a mixture of benzene and chloroform) as the sole product to be isolated; hydrogen maleate, m.p. 184—186·5°C (acetone–ether).

C) An attempt to prepare *Xb* from *Ib* by treatment with n-butyllithium, followed by 4-chloro--1-methylpiperidine, gave by the usual processing the hydrogen maleate of 4-chloro-1-methylpiperidine as the sole product to be isolated; m.p. 138—142°C (acetone–ether). For $C_{10}H_{16}ClNO_4$ (249·7) calculated: 48·10% C, 6·46% H, 14·20% Cl, 5·61% N; found: 48·65% C, 6·13% H, 13·82% Cl, 5·46% N.

2-Trifluoromethyl-11-(1-methyl-4-piperidyl)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*Xc*)

A solution of 7·4 g *Ic* in 100 ml CCl_4 was stirred and treated over 4 h at 60°C with a solution of 3·54 g SO_2Cl_2 in 100 ml CCl_4. The mixture was stirred for 1·5 h at 60°C, allowed to stand overnight at room temperature and evaporated. The residue was dissolved in 20 ml tetrahydrofuran and the solution slowly added to a Grignard reagent, prepared from 7·0 g 4-chloro-1-methylpiperidine[9,10] and 1·3 g Mg in 30 ml tetrahydrofuran. The mixture was refluxed for 3 h, allowed to stand overnight at room temperature, diluted with ether and decomposed with a solution of NH_4Cl. The organic layer was extracted with dilute hydrochloric acid, the aqueous acid layer was separated, made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 5·0 g mixture of bases which was chromatographed on 200 g Al_2O_3. Benzene eluted 0·60 g less polar component which was identified as 2-trifluoromethyl-11-(1-methyl-4-piperidylidene)-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*XIXc*). The hydrogen oxalate crystallized from a mixture of aqueous ethanol and acetone as the hemihydrate, m.p. 222—224°C with decomposition. Mass spectrum, *m/z* (%): 377 (M^+ corresponding to $C_{20}H_{18}F_3NOS$, 25%), 96 (1-methyl-2,3-dihydropyridinium, 100). For $C_{22}H_{20}F_3NO_5S + 0{\cdot}5\ H_2O$ (476·5) calculated: 55·46% C, 4·44% H, 11·96% F, 2·94% N, 6·73% S; found: 55·45% C, 4·36% H, 11·86% F, 2·78% N, 6·85% S.

Continued chromatography with elution with a mixture of benzene and chloroform gave 1·8 g (18%) oily base *Xc*. Hydrogen oxalate monohydrate, m.p. 193—197°C with decomposition (acetone). For $C_{22}H_{22}F_3NO_5S + H_2O$ (487·5) calculated: 54·20% C, 4·96% H, 11·69% F, 2·87% N, 6·58% S; found: 54·25% C, 4·96% H, 11·42% F, 2·84% N, 6·42% S. A sample was decomposed, with NH_4OH and the pure based isolated by extraction with ether. ^1H NMR spectrum: δ 6·90—7·60 (m, 7 H, Ar—H), 3·60 (d, $J = 10{\cdot}0$ Hz, 1 H, Ar—CH—S), 2·21 (s, 3 H, NCH_3), 1·70—3·00 (m, 4 CH_2 and CH of piperidine).

2-Chloro-11*H*-dibenz[*b,f*]-1,4-oxathiepin 10,10-Dioxide (*XX*)

A solution of 10·0 g *Ib* in 100 ml acetic acid was treated with 12 ml 30% H_2O_2, the mixture was refluxed for 30 min, poured to 500 ml water and the product was extracted with chloroform. The extract was dried with $MgSO_4$, evaporated and the residue was crystallized from a mixture of ethanol and benzene; 9·29 g (82%), m.p. 163—166°C. Analytical sample, m.p. 166·5—167·5°C (ethanol). IR spectrum: 756, 828, 848, 891 (4 and 2 adjacent and solitary Ar—H), 1 135, 1 302 (SO_2), 1 470, 1 580, 1 600, 3 000, 3 020, 3 045 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·80 (m, 1 H, 9-H), 7·00—7·50 (m, 6 H, remaining Ar—H), 4·62 (s, 2 H, $ArCH_2SO_2$). For $C_{13}H_9ClO_3S$ (280·7) calculated: 55·62% C, 3·23% H, 12·63% Cl, 11·42% S; found: 56·11% C, 3·10% H, 12·41% Cl, 10·93% S.

2-Chloro-11-(2-dimethylaminoethyl)-11*H*-dibenz[*b,f*]-1,4-oxathiepin 10,10-Dioxide (*XXI*)

A mixture of 4·0 g *XX*, 40 ml dimethylformamide and 0·63 g NaH was stirred for 30 min at 70°C. 2-Dimethylaminoethyl chloride (11 g) was added and the heating to 70°C was continued for 3·5 h. It was then decomposed with 4 ml ethanol, diluted with 500 ml water and extracted with benzene. The extract was washed with water and shaken with 100 ml 3M-HCl. The obtained solution of the hydrochloride was made alkaline with NH_4OH and the base was isolated by extraction with chloroform; 2·65 g (53%) oil. Hydrochloride, m.p. 235—237°C (ethanol). IR spectrum: 770, 835, 850, 860, 895 (4 and 2 adjacent and solitary Ar—H), 1130, 1295 (SO_2), 1 480, 1 509, 1 520, 1 540, 1 568, 1 591, 1 600, 3 000, 3 015, 3 055 (Ar), 2 300, 2 365 cm^{-1} (NH^+). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 11·40 (bs, 1 H, NH^+), 7·30—8·00 (m, 7 H, Ar—H), 5·50 (bt, 1 H, $ArCHSO_2$), 2·60—3·50 (m, 4 H, CH_2CH_2N), 2·75 (s, 6 H, CH_3NCH_3). For

$C_{17}H_{19}Cl_2NO_3S$ (388·3) calculated: 52·58% C, 4·93% H, 18·26% Cl, 3·61% N, 8·26% S; found: 52·82% C, 4·91% H, 18·50% Cl, 3·48% N, 8·21% S.

2-Chloro-11-(3-piperidinopropyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin 10,10-Dioxide (*XXII*)

A similar reaction of 4·18 g *XX*, 0·65 g NaH and 10 g 3-piperidinopropyl chloride[11] in 40 ml dimethylformamide followed by chromatography of the crude product on 400 g Al_2O_3 gave 3·12 g (52%) oily base (elution with chloroform) which was transformed to the hydrochloride, m.p. 177—179°C (ethanol–ether). IR spectrum: 754, 772, 839, 850, 860, 877 (4 and 2 adjacent and solitary Ar—H), 1 134, 1 309 (SO_2), 1 569, 1 589 (Ar), 2 520, 2 600 cm^{-1} (NH^+). ^1H NMR spectrum: δ 7·00—8·00 (m, 7 H, Ar—H), 4·90 (bt, 1 H, $ArCHSO_2$), 1·40—3·00 (remaining CH_2 groups of the chain and of piperidine). For $C_{21}H_{25}Cl_2NO_3S$ (442·4) calculated: 57·01% C, 5·70% H, 16·03% Cl, 3·17% N, 7·24% S; found: 56·64% C, 5·91% H, 15·86% Cl, 3·04% N, 7·45% S.

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REFERENCES

1. Šindelář K., Holubek J., Ryska M., Svátek E., Dlabač A., Hrubantová M., Protiva M.: This Journal *47*, 72 (1982).
2. Šindelář K., Holubek J., Protiva M.: 6th Symp. Heterocycl. Compounds, Brno, July 1978; Abstr. p. 95; Heterocycles *9*, 1498 (1978).
3. Mauthner F.: Ber. Deut. Chem. Ges. *39*, 1348 (1906).
4. Letsinger R. L., Skoog I. H.: J. Amer. Chem. Soc. *77*, 5176 (1955).
5. Lange J., Urbański T.: Diss. Pharm. Pharmacol. *20*, 599 (1968).
6. Ungnade H. E.: Chem. Rev. *38*, 407 (1946).
7. Šindelář K., Holubek J., Metyš J., Bartošová M., Protiva M.: This Journal *46*, 597 (1981).
8. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
9. McElvain S. M., Rorig K.: J. Amer. Chem. Soc. *70*, 1826 (1948).
10. Adlerová E., Seidlová V., Protiva M.: Česk. Farm. *12*, 122 (1963).
11. Ofner P., Walton W.: J. Chem. Soc. *1950*, 2158.
12. Pecherer B. (Hoffmann-La Roche Inc.): U.S. 3,465.051 (Appl. 28.12.66); Chem. Abstr. *71*, 123 885 (1969).
13. Porai-Koshits A. E., Porai-Koshits B. A., Efros L. S., Krylova M. I., Livshits D. A., Maryanovskaya K. Yu., Aleksandrov I. P., Ulman K. E.: Zh. Prikl. Khim. (Leningrad) *28*, 969 (1955); Chem. Abstr. *50*, 4880 (1956).
14. Beech W. F.: J. Chem. Soc. *1954*, 1297.
15. Jolad S. D., Rajagopal S.: Org. Syn., Coll. Vol. *5*, 139 (1973).
16. Pletcher D., Tait S. J. D.: Tetrahedron Lett. *1978*, 1601.
17. Angyal S. J.: Org. Reactions *8*, 197 (1954).
18. Angyal S. J., Tetaz J. R., Wilson J. G.: Org. Syn., Coll. Vol. *4*, 690 (1963).

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