TRICYCLIC PSYCHOTROPIC AGENTS CONTAINING TWO CHALCOGEN ATOMS IN THE CENTRAL RING: SYNTHESIS OF 6-(AMINOALKYL) DERIVATIVES OF 6*H*-DIBENZ[*b,e*]-1,4-OXATHIEPIN*

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Heating of 2-(2-hydroxyphenylthio)benzoic acid (*XX*) with acetic anhydride gave dibenz[*b,e*]-1,4-oxathiepin-6-one (*XXII*). Demethylation of 2-(2-methoxyphenylthio)benzyl bromide (*XI*) with boron tribromide and the following treatment with aqueous sodium hydroxide in dimethyl sulfoxide afforded 6*H*-dibenz[*b,e*]-1,4-oxathiepin (*I*) which was halogenated with chlorine or N-bromosuccinimide only to the undesirable 2-halogeno derivatves *II* and *III*. A reaction of 2-(2-methoxyphenylthio)benzaldehyde (*XII*) with chloroform and 50% aqueous sodium hydroxide in the presence of triethylbenzylammonium chloride led to the α-chloro acid *XIX* whose demethylation with boron tribromide and the following cyclization with sodium hydroxide in dimethyl sulfoxide gave a mixture with prevailing 6*H*-dibenz[*b,e*]-1,4-oxathiepin-6-carboxylic acid (*IV*). Amino alcohols *XXV*—*XXVIII* were obtained by reactions of 2-(2-fluorophenylthio)-benzaldehyde (*XXIV*) with the corresponding Grignard reagents and the products were cyclized with sodium hydride in dimethylformamide to the title compounds *V*—*VIII*. While compounds *V* and *VI* showed antireserpine effects and can be considered as potential antidepresents, compound *VIII* has a strong central depressant activity, brings about ataxia, hypothermia and potentiates the cataleptic action of neuroleptics (properties of a tranquillizer).

In two preceding communications of this series we have described the synthesis of psychotropic derivatives of 11*H*-dibenzo[*b,e*]-1,4-dioxepin[1], 11*H*-dibenzo[*b,e*]-1,4-dithiepin[1] and 11*H*-dibenz[*b,f*]-1,4-oxathiepin[2] with basic substituents in position 11; the present paper reports on various approaches to the 6*H*-dibenz[*b,e*]-1,4-oxathiepin system (*I*) and on the synthesis of the title aminoalkyl derivatives *V*—*VIII*. In addition to our own preliminary communication[3] we have found in the literature[4] a single mentioning of this system relating to the synthesis of 2-methyl-8-nitro-dibenz[*b,e*]-1,4-oxathiepin-6-one, *i.e.* the 5-thio analogue of the corrresponding depsidone[1].

The aim of the present work was the preparation of 6*H*-dibenz[*b,e*]-1,4-oxathiepin (*I*) derivatives with basic substituents in position 6, for which psychotropic

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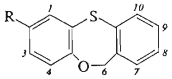
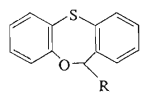
activity could be expected. Two approaches were considered to this purpose: *a*) synthesis of compounds with the skeleton *I* and the additional introduction of the basic side chain to position 6, *b*) synthetic elaboration of derivatives of *I* with a pre-

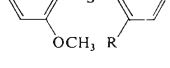


I, R = H
II, R = Cl
III, R = Br



IV, R = COOH
V, R = $(CH_2)_3N(CH_3)_2$
VI, R = $(CH_2)_3$N
VII, R = CH_2
VIII, R = N—CH_3

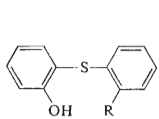
formed basic side chain. The first approach included the synthesis of the lactone *XXII* which can be designated as 5-thiodepsidone. A reaction of 2-iodobenzoic acid[5] with 2-methoxythiophenol[6] in a boiling aqueous solution of potassium hydroxide in the presence of copper gave the acid *IX* which was demethylated by heating with hydrogen bromide in acetic acid. The resulting hydroxy-acid *XX* was cyclized to the lactone *XXII* by heating with acetic anhydride. An attempt at a selective reduction of the oxo group with diborane in tetrahydrofuran was not successful: a mixture was obtained containing in addition to the starting compound *XXII* a further highly polar substance, evidently the corresponding diol.

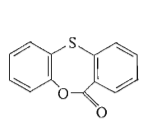


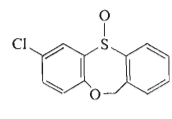
IX, R = COOH
X, R = CH_2OH
XI, R = CH_2Br
XII, R = CHO
XIII, R = $CONH_2$
XIV, R = CN

XV, R = $CO(CH_2)_3N(CH_3)_2$
VI, R = $CH(CH_2)_3N(CH_3)_2$ (OH)
XVII, R = $CON(CH_3)_2$
XVIII, R = $COOC_2H_5$
XIX, R = CHClCOOH

A further synthetic attempt belonging to approaches of type (*a*) aimed directly at 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*I*). 2-(2-Methoxyphenylthio)benzyl alcohol (*X*) was prepared by reduction of the acid *IX* with sodium dihydridobis(2-methoxyethoxy)-aluminate in benzene; its reactions with hydrogen bromide in benzene, as well as a reaction with a boiling mixture of hydrobromic and acetic acid, led only to the substitution of the hydroxyl group with bromine under preserving the methoxyl group and under the formation of 2-(2-methoxyphenylthio)benzyl bromide (*XI*).







XX, R = COOH
XXI, R = CH=CH-

XXII

XXIII

The treatment of compound *XI* with boron tribromide in dichloromethane led to demethylation; the product obtained was cyclized in crude state with sodium hydroxide in dimethyl sulfoxide at 70°C. The resulting mixture afforded by chromatography on aluminium oxide the oily 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*I*) as the least polar product whose identity was corroborated by means of the ^{1}H NMR spectrum. The chromathography afforded further as more polar products 2-(2-methoxyphenylthio)benzaldehyde (*XII*) in a small quantity (evidently the product of oxidation of compound *XI* by dimethyl sulfoxide; *cf*.[7,8]) and the alcohol *X* in a considerable amount (product of the alkaline hydrolysis of compound *XI* which escaped to the demethylation reaction). The hope that it will be possible to achieve functionalization at the carbon in position 6 proved erroneous. A reaction of compound *I* with chlorine in tetrachloromethane gave a monochloro derivative (does not react with 3-dimethylaminopropylmagnesium chloride) whose ^{1}H NMR spectrum indicates the presence of unchanged bridge —CH_2O— and localizes the atom of chlorine at the aromatic position 2. The IR spectrum is in agreement with this finding and the product is thus formulated as 2-chloro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*II*). Neither the continued chlorination did lead to substitution at $C_{(6)}$; in a low yield the sulfoxide *XXIII* was isolated as the result of the addition of molecule of chlorine to the sulfide sulfur atom and of the following hydrolysis with the air humidity[9]. The bromination of compound *I* with N-bromosuccinimide in benzene gave an unreactive monobromo derivative formulated on the basis of the IR spectrum and analogy with the preceding case as the 2-bromo derivative *III*.

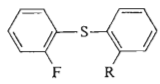
The ketone *XV* with an already preformed aminoalkyl side chain was chosen as

an intermediate. For its synthesis, the acid *IX* was transformed by reaction with ammonia and titanium tetrachloride (method, *cf.*[10]) in dichloromethane under very mild conditions to the amide *XIII* which was dehydrated by heating with phosphoryl chloride to the nitrile *XIV*. The following reaction with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gave the amino ketone *XV*. An attempt at its reduction with sodium borohydride in aqueous dioxane gave an oily product which could not be distilled without decomposition. The ^{1}H NMR spectrum identified this product as the desired secondary alcohol *XVI*. Attempts at its further processing by treatment with hydrogen bromide in dichloromethane, by the following demethylation with boron tribromide and final reaction with potassium carbonate did not lead to characterized products; instead of the presumed substitution of the hydroxyl group with an atom of bromine, the dehydration probably takes place making the whole reaction sequence useless.

The literature[11–13] described the synthesis of α-hydroxy acids and α-chloro acids by reactions of aldehydes or ketones with chloroform and a 50% solution of sodium hydroxide in the presence of triethylbenzylammonium chloride. We tried to use this reaction to our purpose. The crude acid chloride, obtained by treatment of the acid *IX* with thionyl chloride, was transformed by a reaction with dimethylamine in chloroform to the dimethylamide *XVII* (chromatography separated a small quantity of the ethyl ester *XVIII* as the product of a reaction of the acid chloride with ethanol contained in the chloroform used). The dimethylamide *XVII* was reduced with lithium triethoxyaluminium hydride prepared *in situ* by a partial decomposition of lithium aluminium hydride with ethyl acetate[14]; 2-(2-methoxyphenylthio)benzaldehyde (*XII*) was obtained, identical with the compound already mentioned in this paper. The following reaction with chloroform and 50% solution of sodium hydroxide in the presence of triethylbenzylammonium chloride afforded in a moderate yield the chloro-acid *XIX*. It was demethylated with boron tribromide and the product cyclized with aqueous sodium hydroxide in dimethyl sulfoxide to give a substance of acid character, identified by the mass spectrum as a mixture of the acid *IV* (C_{14}.$H_{10}O_3S$) and its monobromo derivative ($C_{14}H_9BrO_3S$). The attempt to separate this mixture was unsuccessful but the characterization of the acid *IV* by means of the ^{1}H NMR and IR spectra confirmed its identity. The localization of the atom of bromine in the accompanying monobromo acid could not be proven unequivocally; according to the spectra, position 6 seems more likely than any position on the aromatic nuclei. The inhomogeneous acid *IV* was not used in further syntheses.

The aminoalkyl derivatives *V*–*VIII* were finally obtained by a method, the analogy of which was used in the synthesis of 11-(3-dimethylaminopropyl)-11*H*-dibenzo-[*b*,*e*]-1,4-dioxepin[1]. A reaction of 2-fluorothiophenol[15] with 2-chlorobenzaldehyde in hexamethylphosphoramide in the presence of aqueous sodium hydroxide at 100°C gave 2-(2-fluorophenylthio)benzaldehyde (*XXIV*) which was subjected to treatment with basic Grignard reagents prepared from 3-dimethylaminopropyl chloride,

3-piperidinopropyl chloride[16], 3-chloromethyl-1-methylpiperidine[17] and 4-chloro--1-methylpiperidine[18] in tetrahydrofuran. Out of the resulting amino alcohols *XXV*–*XXVIII*, compounds *XXV*, *XXVI* and *XXVIII* were characterized and *XXVII* (mixture of two racemates) was further used in crude state without characterization. These amino alcohols were cyclized in the final step by treatment with sodium hydride in dimethylformamide at 70°C to *V*–*VIII*. It is assumed that these cyclization reactions represent rather nucleophilic substitutions of the fluorine atom, activated by the sulfidic *ortho*-substituent, by the corresponding alkoxide anion, than a sequence of elimination to the aryne intermediates with the following intramolecular addition of the corresponding alcohols. With the exception of the piperidine derivative *VI*, these reactions resulted in mixtures from which the desired bases had to be separated by chromatography on aluminium oxide as the least polar components; more polar components are mostly the starting amino alcohols. A more complex situation was noted only in the case of *VII* whose molecule contains two centres of chirality. In agreement with this situation, chromatography afforded as the least polar component a mixture of two bases *VII* and fractional crystallization of the oxalates resulted in separating the isomers *VII-A* and *VII-B*. The ^{1}H NMR spectra of the isomeric bases are almost identical. As a much more polar component, a further isomeric base with a high melting point was isolated by chromatography, for which the structure of the aminophenol *XXI* is suggested; the mass and IR spectra are in agreement with this formulation. A substance of this structure could be formed by dehydration of the secondary alcohol *XXVII* and by the following nucleophilic substitution of the fluorine atom by reaction with sodium hydroxide, formed by interaction of sodium hydride with the molecule of water, cleaved from compound *XXVII*.



XXIV, R = CHO

XXV, R = CH(OH)(CH$_2$)$_3$N(CH$_3$)$_2$

XXVI, R = CH(OH)(CH$_2$)$_3$N

XXVII, R = CH(OH)CH$_2$N–CH$_3$

XXVIII, R = CH(OH)–N–CH$_3$

Compounds *V*–*VIII* 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. Similar tests like in the

preceding communications[1,2] were used. Compounds *V* and *VI* underwent also a general screening (Dr M. Bartošová, affiliated unit of this institute at Rosice n/L) in which they were administered parenterally.

Compound V: Acute toxicity in mice, LD_{50} between 200 (a nontoxic dose) and 500 mg/kg (lethal for 80% animals) orally; 40 mg/kg *i.v.* Rotarod test in mice, ED_{50} = 46·8 mg/kg. Inhibition of motility in mice in the test of Ther, D_{50} = 4·0 mg/kg. Oral doses of 50 mg/kg are inactive in the test of catalepsy and do not influence the apomorphine effect in rats. Antireserpine effects: a dose of 10 mg/kg elevates the body temperature of mice by 2·42°C as compared with the reserpine control group (same doses of imipramine and amitriptyline elevate by 2·97°C, and 2·51°C, respectively). An oral dose of 50 mg/kg was inactive in the test of gastric ulcers in rats (the same dose of imipramine was significantly active). The blood pressure of normotensive rats was significantly decreased by a dose of 0·5 mg/kg *i.v.*. A dose of 2 mg/kg *i.v.* antagonized the adrenaline pressor reaction in rats by 50%. Contractions of the isolated rat duodenum, elicited with acetylcholine and barium chloride, were inhibited by 50% by concentrations of 1 – 10 μg/ml. Antihistamine effect: doses of 0·5 – 1·0 mg/kg *s.c.* protected 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly. A dose of 5 mg/kg *i.v.* prolonged the duration of the thiopental sleeping time in mice by 200% (for chlorpromazine, ED = 0·5 mg/kg *i.v.*). Summary of the effects found: mild central depressant, antihistamine, spasmolytic and α-adrenolytic; strong antireserpine effect in the test of hypothermia.

Compound VI: LD_{50} = 320 mg/kg orally, 22·5 mg/kg *i.v.* Rotarod test in mice, ED_{50} 25 mg/kg. Inhibition of motility of mice in the photo-cell method of Dews, ED = 10 mg/kg (D_{50} < 30 mg/kg). Antireserpine activity: a dose of 100 mg/kg antagonized significantly the reserpine ptosis in mice but did not influence the reserpine gastric ulcers in rats.

Compound VII-A: LD_{50} > 500 mg/kg orally (this dose was lethal for 30% animals). Rotarod test in mice: ED_{50} = 32 mg/kg. Doses of 50 mg/kg had not the antiapomorphine activity and did not antagonize the perphenazine catalepsy in rats. An oral dose of 100 mg/kg had only a slight inhibitory effect towards the reserpine gastric ulcers in rats.

Compound VIII: LD_{50} between 200 (nontoxic dose) and 500 mg/kg orally (lethal for 100% animals). Rotarod test in mice, ED_{50} = 4·2 mg/kg. Inhibition of motility in mice (Ther), D_{50} = 3·5 mg/kg. Hypothermic effect in mice: doses of 5 and 10 mg/kg decreased the body tempeature by 2·31°C, and 3·75°C, respectively (comparable with the effect of similar doses of chlorpromazine and perphenazine). Cataleptic activity: doses of 50 and 100 mg/kg appeared to be cataleptic for 15, and 60% of rats, respectively (we are dealing here with a pseudo-cataleptic effect resulting from a strong

sedation); a dose of 50 mg/kg significantly potentiated the cataleptic effect of perphenazine. The compound has the character of a strong tranquillizer with hypothermic and procataleptogenic effects.

The compounds were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *V* 25, *VI* 25, *VII-A* 50, *VIII* 25; *Streptococcus faecalis*, *V* 100, *VI* 100, *VII-A* 100, *VIII* 100; *Staphylococcus pyogenes aureus*, *V* 50, *VI* 50, *VII-A* 50, *VIII* 50; *Escherichia coli*, *V* 50, *VI* 50, *VII-A* 50, *VIII* 100; *Proteus vulgaris*, *VIII* 100; *Mycobacterium tuberculosis* H37Rv, *V* 12·5, *VI* 12·5, *VII-A* 25, *VIII* 12·5; *Trichophyton mentagrophytes*, *V* 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 KBr) with the Unicam SP 200G spectrophotometer, the ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument and the mass spectra with an MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol) and the preparative chromatographic separations were carried out on columns of neutral Al_2O_3 (activity II).

2-(2-Methoxyphenylthio)benzoic Acid (*IX*)

2-Iodobenzoic acid[5] (165 g), 103 g 2-methoxythiophenol[6] and 6·0 g Cu were added to a solution of 111 g KOH in 1 200 ml water and the mixture was stirred and refluxed for 7 h. It was filtered while hot and the filtrate was acidified with hydrochloric acid. The precipitated product was filtered after cooling and crystallized from a mixture of ethanol and benzene; 146 g (85%), m.p. 200–201°C. IR spectrum: 750 (4 adjacent Ar—H), 919, 1 250, **1 682**, 2 600 (COOH), 1 023, 1 044, 1 250 ($ArOCH_3$), 1 565, 1 586 cm^{-1} (Ar). For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·61% C, 4·65% H, 12·30% S; found: 64·97% C, 4·67% H, 12·04% S.

2-(2-Hydroxyphenylthio)benzoic Acid (*XX*)

A solution of 20·0 g *IX* in a warm mixture of 120 ml acetic acid and 30 ml acetic anhydride was treated with 40 ml hydrobromic acid and saturated for 2 h with HBr. The mixture was diluted with 200 ml water, allowed to stand overnight and the product was filtered; 16·3 g (86%), m.p. 184–187°C. Analytical sample, m.p. 185·5–187·5°C (benzene). UV spectrum: λ_{max} 250 nm (log ε 3·93), 286 nm (3·75), 310 nm (3·65). IR spectrum: 739 (4 adjacent Ar—H), 905 (COOH), 1 204, 1 237, 1 258 (ArOH, ArCOOH), 1 561, 1 573, 1 586, 1 596, 3 010, 3 060 (Ar), **1 677**, 2 510, 2 550, 2 650 (ArCOOH...HO), 3 390, 3 435 cm^{-1} (OH). For $C_{13}H_{10}O_3S$ (246·3) calculated: 63·40% C, 4·09% H, 13·02% S; found: 63·38% C, 4·29% H, 12·99% S.

Dibenz[*b*,*e*]-1,4-oxathiepin-6-one (*XXII*)

A mixture of 16·1 g *XX* and 50 ml acetic anhydride was heated for 2 h to 100°C and the volatile components were evaporated *in vacuo*. The residue was distilled (b.p. about 180°C/30 Pa),

the distillate dissolved in benzene, the solution washed with 10% Na_2CO_3, dried ($MgSO_4$) and evaporated. The residue was crystallized from aqueous acetone; 9·8 g (66%), m.p. 131 to 133°C. Analytical sample, m.p. 132·5—133·5°C (benzene–light petroleum). UV spectrum: inflexes at 230 nm (log ε 3·99), 249 nm (3·81) and 292 nm (3·06). IR spectrum: 721, 748, 766 (4 adjacent Ar—H), 1 089, 1 213, 1 237, 1 259, 1 279 (C—O—C of the lactone), 1 574, 1 589 (Ar), **1 745** cm^{-1} (lactone ArCOOAr). ^1H NMR spectrum: δ 7·75 (m, 1 H, 7-H), 6·90—7·10 (m, 7 H, remaining Ar—H). For $C_{13}H_8O_2S$ (228·3) calculated: 68·40% C, 3·54% H, 14·05% S; found: 68·60% C, 3·76% H, 14·18% S.

2-(2-Methoxyphenylthio)benzyl Alcohol (*X*)

IX (83 g) in 250 ml benzene was stirred and treated over 1 h with 236 g 55% solution of sodium dihydrobis(2-methoxyethoxy)aluminate in benzene. The mixture was stirred for 1·5 h, allowed to stand overnight, decomposed by a slow addition of 10% NaOH, the benzene layer separated, washed with water, dried ($MgSO_4$) and evaporated; 76·7 g (98%). A sample for analysis was distilled, b.p. 178—180°C/0·1 kPa. IR spectrum (film): 750 (4 adjacent Ar—H), 1 024, 1 069 (CH_2OH), 1 240, 1 274 ($ArOCH_3$), 1 479, 1 580 (Ar), 3 410 cm^{-1} (OH). For $C_{14}H_{14}O_2S$ (246·3) calculated: 68·26% C, 5·73% H, 13·02% S; found: 68·14% C, 5·64% H, 12·77% S.

2-(2-Methoxyphenylthio)benzyl Bromide (*XI*)

A) A solution of 48 g *X* in 250 benzene was treated with 50 g $MgSO_4$ and saturated for 1 h with HBr under stirring. The mixture was allowed to stand overnight, filtered, the filtrate was washed with water, dried and evaporated; 59·6 g (98%), m.p. 66—67°C (ether–light petroleum). IR spectrum (Nujol): 750, 769 (4 adjacent Ar—H), 1 020, 1 223, 1 242, 1 274 ($ArOCH_3$), 1 474, 1 579, 3 018, 3 068 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60—7·50 (m, 8 H, Ar—H), 4·65 (s, 2 H, $ArCH_2Br$), 3·79 (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: 54·70% C, 4·32% H, 25·86% Br, 10·13% S.

B) A solution of 9·1 g *X* in 20 ml acetic acid was treated with 20 ml hydrobromic acid and refluxed for 6 h. The mixture was diluted with water and extracted with ether, the extract was dried and evaporated. The residue was dissolved in 80 ml dichloromethane, 4·0 g $MgSO_4$ were added and the suspension was saturated for 30 min with HBr. After standing overnight it was filtered and the filtrate distilled; 4·6 g (40%), b.p. 180°C/0·16 kPa, m.p. 66—67°C.

6*H*-Dibenz[*b*,*e*]-1,4-oxathiepin (*I*)

A solution of 43·8 g *XI* in 300 ml dichloromethane was stirred and treated dropwise over 1 h with a solution of 36 g BBr_3 in 70 ml dichloromethane. The mixture was stirred for 5 h, allowed to stand overnight, washed with water and evaporated. The residue was dissolved in 450 ml dimethyl sulfoxide and the solution was added dropwise over 30 h to a stirred mixture of 105 ml 20% NaOH and 900 ml dimethyl sulfoxide. The mixture was stirred for 1 h at 70°C, diluted with 4 l water and extracted with light petroleum and benzene. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue (21·8 g oil) was chromatographed on 500 g Al_2O_3. A mixture of benzene and light petroleum eluted 10·4 g (34%) homogeneous oil boiling at 141—143°C/70 Pa which proved to be *I*. ^1H NMR spectrum: δ 6·50—7·60 (m, 8 H, Ar—H), 5·45 (s, 2 H, $ArOCH_2Ar$). For $C_{13}H_{10}OS$ (214·3) calculated: 72·86% C, 4·70% H, 14·96% S; found: 72·78% C, 4·72% H, 14·68% S.

Continued chromatography with elution with chloroform gave first 3·3 g inhomogeneous oil (mixture of two substances) and then 0·32 g homogeneous crystalline substance, m.p. 105 to 107°C (cyclohexane), which was identified as 2-(2-methoxyphenylthio)benzaldehyde (*XII*).

As the most polar component which was eluted with chloroform were 8·2 g homogeneous oil boiling at 170°C/50 Pa, identified as the alcohol *X*, already described in this communication (analysis, direct comparison with the authentic sample by TLC).

2-Chloro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*II*)

A solution of 6·3 g *I* in 40 ml tetrachloromethane was treated over 1·5 h with a solution of 2·2 g Cl_2 in 40 ml tetrachloromethane at −15°C. The mixture was stirred for 30 min, filtered and the filtrate was evaporated. The residue was crystallized from ethanol; 4·5 g (62%), m.p. 68−72°C. Analytical sample, m.p. 82−84°C (ethanol). Mass spectrum, *m/z*: 248 (M^+ corresponding to $C_{13}H_9ClOS$), 139. IR spectrum: 748, 820, 867 (4 and 2 adjacent and solitary Ar—H), 1 262 cm^{-1} (ArOR). ^1H NMR spectrum: δ *c.* 7·30 (m, 4 H, 7,8,9,10-H_4), 7·18 (d, $J = 2·5$ Hz, 1 H, 1-H), 6·98 (q, $J = 8·5$; 2·5 Hz, 1 H, 3-H), 6·68 (d, $J = 8·0$ Hz, 1 H, 4-H), 5·45 (s, 2 H, $ArCH_2O$). For $C_{13}H_9ClOS$ (248·7) calculated: 62·77% C, 3·65% H, 14·25% Cl, 12·89% S; found: 62·83% C, 3·78% H, 14·94% Cl, 12·63% S.

2-Chloro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin S-Oxide (*XXIII*)

A solution of 2·68 g *II* in 30 ml tetrachloromethane was treated over 30 min with a solution of 0·85 g Cl_2 in 15 ml tetrachloromethane at −15°C. The mixture was stirred for 30 min, the formed yellow precipitate was filtered but decomposed in contact with moist air under formation of HCl and a colourless product; 2·3 g (81%), m.p. approx. 140°C. Recrystallization from a mixture of benzene and light petroleum and then from benzene gave the pure substance, m.p. 168 to 170°C. UV spectrum: λ_{max} 269 nm (log ε 3·31), 278 nm (3·34), 285·5 nm (3·37), 293 nm (3·40), 302 nm (3·37) and infl. at 302·5 nm (3·37). IR spectrum: 763, 823, 880 (4 and 2 adjacent and solitary Ar—H), 1 035 (S—O), 1 087, 1 196, 1 236, 1 283 ($ArOCH_2$), 1 442, 1 466 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·80 (m, 1 H, 10-H). 7·68 (d, $J = 2·5$ Hz, 1 H, 1-H), 7·30−7·60 (m, 3 H, 7,8,9-H_3), 7·24 (q, $J = 8·5$; 2·5 Hz, 1 H, 3-H), 6·83 (d, $J = 8·5$ Hz, 1 H, 4-H), 5·58 and 5·15 (ABq, $J = 14·0$ Hz, 2 H, $ArCH_2O$). For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·98% C, 3·43% H, 13·39% Cl, 12·11% S; found: 58·89% C, 3·66% H, 13·56% Cl, 12·14% S.

2-Bromo-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*III*)

A solution of 5·0 g *I* in 20 ml benzene was treated with 4·2 g N-bromosuccinimide and stirred at 50°C for 6 h under irradiation with a 150 W bulb. The mixture was allowed to stand overnight in a refrigerator, the separated succinimide was filtered off and the filtrate evaporated under reduced pressure. The residue was crystallized from ethanol; m.p. 66−68°C. IR spectrum: 755, 808, 817, 863 (4 and 2 adjacent and solitary Ar—H), 1 214, 1 216 cm^{-1} ($ArOCH_2$). For $C_{13}H_9$. .BrOS (293·2) calculated: 53·25% C, 3·09% H, 27·26% Br, 10·94% S; found: 53·34% C, 3·40% H, 27·33% Br, 10·83% S.

2-(2-Methoxyphenylthio)benzamide (*XIII*)

A) *IX* (26 g) was added to a saturated solution of NH_3 in 300 ml dichloromethane at 0°C and the mixture was treated dropwise at 0°C with a solution of 10 g $TiCl_4$ in 200 ml dichloromethane. It was stirred for 4 h, allowed to stand overnight, decomposed with water, the solid was filtered off and washed with water and then with dichloromethane. The combined aqueous layers were acidified to obtain 11·4 g recovered *IX*. The organic layer was evaporated and gave 14·0 g (96% per conversion) crude *XIII*, m.p. 120−128°C. Analytical sample, m.p. 132·5−133·5°C (benzene). IR spectrum: 755 (4 adjacent Ar—H), 1 029, 1 042, 1 250, 1 274 ($ArOCH_3$), 1 479,

1 585, 1 619 (Ar), 1 645 ($ArCONH_2$), 3 200 and 3 400 cm^{-1} (NH_2). For $C_{14}H_{13}NO_2S$ (259·3) calculated: 64·84% C, 5·05% H, 5·40% N, 12·37% S; found: 64·81% C, 4·99% H, 5·18% N, 12·05% S.

B) A mixture of 13·0 g *IX* and 20 ml $SOCl_2$ was refluxed for 3 h and the excess of $SOCl_2$ was evaporated *in vacuo*. The residue was poured under vigorous stirring into 130 ml NH_4OH. It was stirred for 30 min and the product was filtered and crystallized from benzene; 11·0 g (85%) not completely pure *XIII*, m.p. 120–126°C.

2-(2-Methoxyphenylthio)benzonitrile (*XIV*)

A mixture of 26·2 g *XIII* and 20 g $POCl_3$ was stirred and heated for 2 h to 100°C. It was then poured into cold water, the mixture stirred for 30 min, neutralized with 20% NaOH, the separated product was filtered, dried and crystallized from a mixture of benzene and light petroleum; 15·6 g (64%) pure *XIV*, m.p. 82–83·5°C. IR spectrum: 762, 772 (4 adjacent Ar—H), 1 024, 1 253, 1 278 ($ArOCH_3$), 1 585 (Ar), 2 233 cm^{-1} (Ar—CN). For $C_{14}H_{11}NOS$ (241·3) calculated: 69·68% C, 4·59% H, 5·81% N, 13·29% S; found: 69·60% C, 4·63% H, 5·69% N, 12·96% S.

1-[2-(2-Methoxyphenylthio)phenyl]-4-dimethylaminobutan-1-one (*XV*)

The Grignard reagent was prepared from 2·5 g Mg and 13·0 g 3-dimethylaminopropyl chloride in 40 ml tetrahydrofuran (with the help of a crystal of iodine and 0·2 ml 1,2-dibromoethane) and treated under stirring over 5 min with a solution of 12·0 g *XIV* in 25 ml tetrahydrofuran. The mixture was refluxed for 30 min, allowed to stand for 1 h and decomposed with 30 ml 20% NH_4Cl. The solid was filtered off, washed with 200 ml ether, and the organic layer of the filtrate was extracted with 100 ml 1 : 1 diluted hydrochloric acid. The aqueous extract was made alkaline with NH_4OH and the base isolated by extraction with benzene. It crystallized from a small quantity of a mixture of ether and light petroleum; 13·8 g (84%), m.p. 60–63°C. Analytical sample of *XV*, m.p. 63·5–64·5°C (ether–light petroleum). UV spectrum: λ_{max} 229·5 nm ($\log \varepsilon$ 4·38), 260 nm (3·88), 281 nm (3·76), 334 nm (3·62). IR spectrum: 745, 769 (4 adjacent Ar—H), 1 017, 1 270 ($ArOCH_3$), 1 550, 1 577 (Ar), 1 656 (ArCOR), 2 755 cm^{-1} (NCH_3). ^1H NMR spectrum: δ 7·85 (m, 1 H, 6-H of benzoyl), 6·75–7·60 (m, 7 H, remaining Ar—H), 3·78 (s, 3 H, OCH_3), 3·05 (t, J = 7·0 Hz, 2 H, $COCH_2$), 2·30 (t, J = 7·0 Hz, 2 H, CH_2N), 2·23 (s, 6 H, CH_3NCH_3), 2·00 (m, 2 H, remaining CH_2 in the side chain). For $C_{19}H_{23}NO_2S$ (329·5) calculated: 69·27% C, 7·04% H, 4·25% N; found: 69·30% C, 7·43% H, 4·40% N.

Picrate, m.p. 150–152°C (ethanol). For $C_{25}H_{26}N_4O_9S$ (558·6) calculated: 53·76% C, 4·69% H, 10·03% N, 5·74% S; found: 53·94% C, 4·59% H, 10·42% N, 5·83% S.

A solution of 15·3 g *XV* in 70 ml dioxane was treated with a solution of 1·9 g $NaBH_4$ in 5 ml water containing 3 drops 20% NaOH, the mixture was allowed to stand for 1 day at room temperature and evaporated *in vacuo*. The residue was diluted with water and extracted with benzene. Processing of the extract gave 15·6 g oil which was chromatographed on 500 g Al_2O_3; there were obtained 14·0 g homogeneous oil which did not crystallize and did not afford crystalline salts. The ^1H NMR spectrum characterized the product as the expected 1-[2-(2-methoxyphenylthio)phenyl]-4-dimethylaminobutan-1-ol (*XVI*): δ 6·80–7·60 (m, 8 H, Ar—H), 5·18 (m, 1H, Ar—CH—O), 3·82 (s, 3 H, OCH_3), 2·70 (m, 2 H, CH_2N), 2·50 (s, 6 H, CH_3NCH_3), 1·62 (m, 4 H, remaining CH_2CH_2).

N,N-Dimethyl-2-(2-methoxyphenylthio)benzamide (*XVII*)

A mixture of 45 g *IX* and 90 ml $SOCl_2$ was refluxed for 3 h and evaporated *in vacuo*. The residue was dissolved in 100 ml chloroform and the stirred solution was saturated over 2 h with 39 g

dimethylamine under cooling with water. The mixture was allowed to stand overnight at room temperature, washed with water and 5% NaOH, dried with $MgSO_4$ and evaporated. The residue was chromatographed on a column of 1·5 kg Al_2O_3. Elution with benzene gave 4·7 g ethyl 2-(2-methoxyphenylthio)benzoate (*XVIII*), m.p. 98—100°C (ethanol). UV spectrum: λ_{max} 255nm (log ε 3·98), 280·5 nm (3·75), 288·5 nm (3·74), 319 nm (3·71). IR spectrum: 753 (4 adjacent Ar—H), 1 064, 1 100, 1 258, 1 274 ($ArOCH_3$, ArCOOR), 1 481, 1 576, 1 588, 3 075 (Ar), **1 714** (ArCOOR), 2 836 cm^{-1} ($ArOCH_3$). For $C_{16}H_{16}O_3S$ (288·4) calculated: 66·64% C, 5·59% H, 11·12% S; found: 66·71% C, 5·65% H, 11·12% S.

The elution was continued with chloroform and gave 31·3 g (63%) *XVII*, m.p. 94—96°C (aqueous ethanol). UV spectrum: λ_{max} 252 nm (log ε 3·97), 286 nm (3·83). IR spectrum (Nujol): 745, 772 (4 adjacent Ar—H), 1 072, 1 251, 1 281 ($ArOCH_3$), 1 480, 1 586, 3 010, 3 055, 3 078 (Ar), **1 631** cm^{-1} ($ArCONR_2$). ^1H NMR spectrum: δ 6·60—7·30 (m, 8 H, Ar—H), 3·70 (s, 3 H, OCH_3), 3·03 and 2·80 (2 s, 6 H, CH_3NCH_3). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·87% C, 5·96% H, 4·87% N, 11·16% S; found: 66·27% C, 6·03% H, 4·75% N, 11·10% S.

2-(2-Methoxyphenylthio)benzaldehyde (*XII*)

A suspension of 6·0 g $LiAlH_4$ in 100 ml ether was stirred under nitrogen and treated over 30 min at 0—7°C with 3·9 g ethyl acetate, added dropwise. The solution was stirred for 30 min and over 5 min a solution of 30·2 g *XVII* in a mixture of 150 ml tetrahydrofuran and 100 ml ether was added at −10—0°C. The mixture was stirred for 6 h, allowed to stand overnight and decomposed with 100 ml 30% H_2SO_4. It was filtered, the organic layer of the filtrate dried with $MgSO_4$ and evaporated; 22·8 g (89%) crude *XII*, melting approx. at 100°C. Analytical sample, m.p. 107·5—109·5°C (ethanol). UV spectrum: λ_{max} 233 nm (log ε 4·23), 340 nm (3·49); infl. 271 nm (3·85) and 284 nm (3·74). IR spectrum (Nujol): 762 (4 adjacent Ar—H), 1 028, 1 253, 1 280 ($ArOCH_3$), 1 469, 1 480, 1 561, 1 590, 3 020, 3 065 (Ar), 1 681, **1 700**, 2 765 cm^{-1} (ArCHO). ^1H NMR spectrum: δ 10·35 (s, 1 H, CHO), 7·80 (m, 1 H, 6-H of benzaldehyde), 6·80—7·50 (m, 7 H, remaining Ar—H), 3·76 (s, 3 H, OCH_3). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·83% C, 4·95% H, 13·12% S; found: 68·64% C, 5·10% H, 13·00% S.

2-Chloro-2-[2-(2-methoxyphenylthio)phenyl]acetic Acid (*XIX*)

A stirred solution of 6·1 g *XII* in 9 ml chloroform was treated with 0·3 g triethylbenzylammonium chloride and then at 54—60°C over 75 min with 6 ml 50% NaOH. The mixture was stirred for 1 h, diluted with water and extracted with ether. Evaporation of the extract recovered 1·7 g starting *XII*. The alkaline layer was acidified with hydrochloric acid and the separated oil was extracted with chloroform. The solution was chromatographed on a column of 200 g silica gel. Elution with chloroform gave 2·92 g (53% per conversion) *XIX*, m.p. 166—168°C (benzene). Mass spectrum, *m/z* (%): 308·0291 (M^+ corresponding to $C_{15}H_{13}ClO_3S$, 74), 290 ($M-H_2O$), 227 (100), 212 (43), 197 (65). IR spectrum (Nujol): 760 (4 adjacent Ar—H), 925, **1 728**, 2 582, 2 700 (COOH), 1 032, 1 218, 1 385 ($ArOCH_3$, COOH), 1 475, 1 588 cm^{-1} (Ar). ^1H NMR spectrum (C^2H_3·SOC^2H_3): δ 6·70—7·70 (m, 8 H, Ar—H), 6·03 (s, 1 H, Ar—CHCl—CO), 3·70 (s, 3H,OCH_3). For $C_{15}H_{13}ClO_3S$ (308·8) calculated: 58·34% C, 4·24% H, 10·38% S; found: 58·68% C, 4·40% H, 10·15% S.

A suspension of 3·0 g *XIX* in 40 ml dichloromethane was stirred and treated over 15 min with a solution of 5·0 g BBr_3 in 10 ml dichloromethane. The mixture was stirred for 6 h, allowed to stand overnight, decomposed with 600 ml ethanol and evaporated. The residue was dissolved in 30 ml dimethyl sulfoxide and the solution was added over 5 h to a mixture of 60 ml dimethyl sulfoxide and 10 ml 20% NaOH at 70°C. The mixture was stirred for 1 h at 70°C, diluted with

water and washed with benzene. The aqueous solution was acidified with hydrochloric acid and the product was extracted with chloroform. Evaporation gave 3·0 g oil giving by crystallization 0·80 g fraction A, m.p. 97·5—99°C (benzene–light petroleum), and by chromatography of the mother liquors 1·35 g fraction B (elution with chloroform), m.p. 156—159°C (benzene). Both fractions represent 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin-6-carboxylic acid (*IV*) contaminated with its monobromo derivative of unclear structure. Mass spectrum, *m*/*z*: 258·034 (M^+ corresponding to $C_{14}H_{10}O_3S$), 336·338 (M^+ corresponding to $C_{14}H_9BrO_3S$). IR spectrum of fraction B (Nujol): 749, 763 (4 adjacent Ar—H), 910, 1 279, 1 290, **1 709**, **1 729**, 2 573, 2 650, 2 745 (COOH), 1 020, 1 051 (ArOR), 1 471, 1 480, 1 570 cm^{-1} (Ar). ^1H NMR spectrum of fraction A: δ 11·40 (bs, 1 H, COOH), 6·80—7·50 (m, 8 H, Ar—H), 6·48 (s, 1 H, Ar—CH—O). Analysis of fraction B: For $C_{14}H_{10}O_3S$ (258·3) calculated: 65·10% C, 3·90% H, 12·42% S; found: 62·43% C, 3·65% H, 11·40% S.

2-(2-Fluorophenylthio)benzaldehyde (*XXIV*)

A solution of 43·8 g 2-fluorothiophenol[15] in 85 ml hexamethylphosphoramide was treated with a solution of 13·6 g NaOH in 26 ml water and then with 45·0 g 2-chlorobenzaldehyde. The mixture was stirred under nitrogen at 100°C for 3·5 h, poured into 500 ml water and the product extracted with benzene. The extract was dried ($MgSO_4$) and evaporated. The residue crystallized from light petroleum; 57·1 g (77%), m.p. 53—57°C. Analytical sample, m.p. 56—57°C (benzene–light petroleum). UV spectrum: λ_{max} 235 nm (log ε 4·25), 332 nm (3·52), inflexes at 230 nm (4·22), 259·5 nm (3·89) and 268 nm (3·87). IR spectrum (Nujol): 760 (4 adjacent Ar—H), 1 559, 1 589, 3 030 (Ar), 1 675, 1 695 cm^{-1} (ArCHO). ^1H NMR spectrum: δ 10·40 (s, 1 H, ArCHO), 7·90 (m, 1 H, 6 H of benzaldehyde), 6·90—7·60 (m, 7 H, remaining Ar—H). ^{19}F NMR spectrum: δ —107·6 (m). For $C_{13}H_9FOS$ (232·3) calculated: 67·22% C, 3·91% H, 8·18% F, 13·80% S; found: 67·41% C, 3·86% H, 8·11% F, 14·00% S.

1-[2-(2-Fluorophenylthio)phenyl]-4-dimethylaminobutan-1-ol (*XXV*)

The Grignard reagent was prepared by a reaction of 1·7 g Mg with 8·5 g 3-dimethylaminopropyl chloride in 30 ml tetrahydrofuran (the reaction was started with a crystal of iodine and several drops of 1,2-dibromoethane), the mixture was refluxed for 3 h and then treated dropwise over 30 min with a solution of 11·6 g *XXIV* in 20 ml tetrahydrofuran. The mixture was refluxed for 3 h, allowed to stand overnight, diluted with ether and decomposed with a 20% solution of NH_4Cl. The organic layer was dried with K_2CO_3 and evaporated; 16·0 g (100%) crude oily *XXV* which was used without further purification. For characterization, the 2,4,6-trinitrobenzoate was prepared, m.p. 103—103·5°C with decomposition (ethanol–ether). For $C_{25}H_{25}FN_4O_9S$ (576·6) calculated: 52·08% C, 4·37% H, 3·30% F, 9·72% N, 5·56% S; found: 52·50% C, 4·42% H, 3·55% F, 9·74% N, 5·82% S. The pure oily base was released from this salt and used for recording the spectra. IR spectrum (film): 755 (4 adjacent Ar—H), 1 071 (CHOH), 1 471, 1 574, 1 590 (Ar), 2 775, 2 815 $N(CH_3)_2$, 3 055, 3 140, 3 341 cm^{-1} (OH, OH...N). ^1H NMR spectrum: δ 7·70 (bd, 1 H, 6-H in the benzyl alcohol fragment), 6·80—7·40 (m, 7 H, remaining Ar—H), 5·10 (bm, 1 H, Ar—CH—O), 2·20 (s, 6 H, CH_3NCH_3), 1·50—2·40 (m, 7 H, 3 CH_2 in the side chain and OH).

1-[2-(2-Fluorophenylthio)phenyl]-4-piperidinobutan-1-ol (*XXVI*)

The Grignard reagent was prepared from 1·46 g Mg and 9·70 g 3-piperidinopropyl chloride[16] in 25 ml tetrahydrofuran and processed by treatment with 9·30 g *XXIV* in 15 ml tetrahydrofuran similarly like in the preceding case. The crude oily *XXVI* was obtained in a theoretical yield

(14·4 g) and further used without purification. By standing it slowly crystallized; m.p. 93—94°C (cyclohexane). IR spectrum (Nujol): 760, 770 (4 adjacent Ar—H), 1 075, 1 125 (CHOH), 1 475, 1 570, 1 580, 1 596, 3 035, 3 060 (Ar), infl. 3 150 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·90—7·80 (m, 8 H, Ar—H), 5·05 (bm, 1 H, Ar—CH—O), 2·20—2·70 (m, 6 H, 3 NCH_2), 1·20—2·00 (m, 11H, remaining 5 CH_2 and OH). For $C_{21}H_{26}FNOS$ (359·5) calculated: 70·16% C, 7·29% H, 5·28% F, 3·90% N, 8·92% S; found: 70·57% C, 7·46% H, 5·03% F, 3·69% N, 8·78% S.

α-(1-Methyl-4-piperidyl)-2-(2-fluorophenylthio)benzyl Alcohol (*XXVIII*)

The Grignard reagent was prepared from 1·46 g Mg and 8·0 g 4-chloro-1-methylpiperidine[18] in 25 ml tetrahydrofuran and was treated with a solution of 9·3 g *XXIV* in 15 ml tetrahydrofuran like in the preceding cases. There were obtained 13·2 g (100%) crude oily *XXVIII* which was used for the cyclization step without purification. On standing, it crystallized, m.p. 111—114°C (cyclohexane). IR spectrum (Nujol): 758, 766 (4 adjacent Ar—H), 1 034, 1 073 (CHOH), 1 473, 1 574, 1 579, 3 035 (Ar), 3 280 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·80—7·60 (m, 8 H, Ar—H), 5·00 (bs, 1 H, Ar—CH—O), 3·60 (bs, 1 H, OH), 2·15 (s, 3 H, NCH_3), 1·10—3·00 (m, 9 H, 4 CH_2 and CH of piperidine). ^{19}F NMR spectrum: δ —109·8 (m). For $C_{19}H_{22}FNOS$ (331·5) calculated: 68·85% C, 6·69% H, 5·73% F, 4·23% N, 9·67% S; found: 69·49% C, 6·99% H, 5·46% F, 4·21% N, 9·42% S.

6-(3-Dimethylaminopropyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*V*)

A solution of 15·75 g crude *XXV* in 80 ml dimethylformamide was added dropwise over 6 h to a stirred suspension of 2·0 g NaH in 120 ml dimethylformamide at 70°C under nitrogen and this temperature was maintained for further 8 h. The mixture was then poured into 2·5 l water and cooled in a refrigerator. The oil was separated from the aqueous supernatant, dissolved in ether, the solution was dried with K_2CO_3 and evaporated. The residue was dissolved in benzene and the solution was chromatographed on a column of 500 g Al_2O_3. Elution with benzene and a mixture of benzene and chloroform gave 10·94 g (97% per conversion) homogeneous oily *V* which was transformed by neutralization with maleic acid in a mixture of acetone and ether to the hydrogen maleate, m.p. 117—118°C (acetone–ether). For $C_{22}H_{25}NO_5S$ (415·5) calculated: 63·59% C, 6·06% H, 3·37% N, 7·72% S; found: 64·09% C, 6·18% H, 3·39% N, 8·00% S. A sample of the maleate was decomposed with NH_4OH and the pure base was isolated by extraction with ether. It was used for recording the ^{1}H NMR spectrum: δ 6·60—7·60 (m, 8 H, Ar—H), 6·15 (dd, 1 H, Ar—CH—O), 2·35 (t, 2 H, CH_2N), 2·19 (s, 6 H, CH_3NCH_3), 1·50—2·10 (m, 4 H, remaining 2 CH_2).

Continuation of the chromatography and elution with a mixture of chloroform and ethanol led to the recovery of 3·70 g starting *XXV* (2,4,6-trinitrobenzoate, m.p. 103—103·5°C).

6-(3-Piperidinopropyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*VI*)

XXVI (14·0 g) was similarly cyclized by 3·0 g NaH in 180 ml dimethylformamide at 70°C. Similar processing gave 12·25 g (93%) homogeneous oily *VI* which was transformed to the hydrogen maleate, m.p. 145—147°C (ethanol–ether). Mass spectrum, *m/z*: 339 (M^+ corresponding to $C_{21}H_{25}NOS$), 213, 194, 184, 126, 99, 98 (base peak, $CH_2{=}\overset{+}{N}$⟨⟩). For $C_{25}H_{29}NO_5S$ (455·6) calculated: 65·91% C, 6·42% H, 3·07% N, 7·04% S; found: 65·75% C, 6·52% H, 2·99% N, 6·73% S.

6-(1-Methyl-3-piperidylmethyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*VII*)

The Grignard reagent was prepared from 1·46 g Mg and 8·86 g 3-chloromethyl-1-methylpiperidine[17] in 25 ml tetrahydrofuran. It was treated under stirring with a solution of 9·30 g *XXIV* in 15 ml tetrahydrofuran and the mixture was refluxed for 3 h. After standing overnight it was decomposed by a slow addition of 50 ml 20% NH_4Cl and the mixture was extracted with ether. The extract was dried with K_2CO_3 and evaporated; 13·8 g (100%) oily mixture of stereoisomeric α-(1-methyl-3-piperidylmethyl)-2-(2-fluorophenylthio)benzyl alcohols (*XXVII*) which was used for the cyclization step without separation.

Crude *XXVII* (13·8 g) was cyclized by 3·0 g NaH in 180 ml dimethylformamide at 70°C like in the preceding cases. Similar processing gave 12·0 g oily mixture which was chromatographed on 500 g Al_2O_3. Elution with benzene and then with chloroform gave 11·01 g (85%) mixture of stereoisomeric bases *VII*. Neutralization with oxalic acid in ethanol gave a mixture of hydrogen oxalates which was crystallized from ethanol. In this way the homogeneous hydrogen oxalate of the base *VII-A* was obtained, m.p. 192—193°C. For $C_{22}H_{25}NO_5S$ (415·5) calculated: 63·59% C, 6·06% H, 3·37% N, 7·72% S; found: 63·60% C, 6·05% H, 3·43% N, 8·03% S. Treatment with NH_4OH and extraction with ether afforded *VII-A*, m.p. 102—103·5°C (cyclohexane–light petroleum). ^{1}H-NMR spectrum: δ 6·60—7·60 (m, 8 H, Ar—H), 6·30 (m, 1 H, Ar—CH—O), 2·21 (s, 3 H, NCH_3), 1·30—3·00 (m, 11 H, remaining 5 CH_2 and CH). For $C_{20}H_{23}NOS$ (325·5) calculated: 73·81% C, 7·12% H, 4·30% N, 9·85% S; found: 73·49% C, 7·30% H, 4·09% N, 9·88% S.

The mother liquor after the hydrogen oxalate of *VII-A* was evaporated and the residue was crystallized from a mixture of acetone and ethanol; there was obtained the homogeneous hydrogen oxalate of the stereoisomeric base *VII-B* crystallizing in needles, m.p. 174—175·5°C. For $C_{22}H_{25}$. NO_5S (415·5) calculated: 63·59% C, 6·06% H, 3·37% N, 7·72% S; found: 63·79% C, 6·34% H, 3·26% N, 7·94% S. Treatment with NH_4OH and extraction with ether gave the oily base *VII-B* which was used for recording the ^{1}H NMR spectrum: δ 6·50—7·60 (m, 8 H, Ar—H), 6·28 (m, 1 H, Ar—CH—O), 2·18 (s, 3 H, NCH_3), 1·30—3·00 (m, 11 H, remaining 5 CH_2 and CH).

Continuation of the chromatography with the use of ethanol as eluent gave 0·61 g amphoteric substance characterized as 1-[2-(2-hydroxyphenylthio)phenyl]-2-(1-methyl-3-piperidyl)ethene (*XXI*), m.p. 203—207°C (benzene). Mass spectrum, *m*/*z* (%): 325 (M^+ corresponding to $C_{20}H_{23}$. NOS, 4%), 324 (4), 215 (3·4), 214 (7·8), 213 (47·2), 184 (11·5), 113 (100), 97 (15·2), 58 (50·1), 44 (18). IR spectrum (Nujol): 744, 757, 769 (4 adjacent Ar—H), 1 040, 1 056, 1 093, 1 140, 1 156 (ArOH), 2 650 (NH^+ of the inner salt), 3 140 cm^{-1} (ArOH...N). For $C_{20}H_{23}NOS$ (325·5) calculated: 73·81% C, 7·12% H, 4·30% N, 9·85% S; found: 73·49% C, 7·30% H, 4·09% N, 9·88% S.

6-(1-Methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*VIII*)

Crude *XXVIII* (13·2 g) was cyclized like in the preceding cases by treatment with 2·5 g NaH in 180 ml dimethylformamide at 70°C. The oily product (12·1 g) was chromatographed on 500 g Al_2O_3. Benzene and a mixture of benzene and chloroform eluted 7·33 g (74% per conversion) base *VIII* which crystallized from a mixture of cyclohexane and light petroleum, m.p. 77—79°C. ^{1}H NMR spectrum: δ 6·50—7·60 (m, 8 H, Ar—H), 5·80 (d, J = 9·0 Hz, 1 H, Ar—CH—O), 2·25 (s, 3 H, NCH_3), 1·20—3·0 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{19}H_{21}NOS$ (311·5) calculated: 73·27% C, 6·80% H, 4·50% N, 10·29% S; found: 73·49% C, 6·98% H, 4·53% N, 10·15% S.

Hydrogen maleate, m.p. 152—153°C (acetone–ether). For $C_{23}H_{25}NO_5S$ (427·5) calculated: 64·62% C, 5·89% H, 3·28% N, 7·50% S; found: 64·53% C, 5·77% H, 3·28% N, 7·63% S.

The chromatography was continued using ethanol as the eluent and recovered 2·65 g starting *XXVIII*, m.p. 111–114°C (cyclohexane).

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