TRICYCLIC PSYCHOTROPIC AGENTS CONTAINING TWO CHALCOGEN ATOMS IN THE CENTRAL RING: SYNTHESIS OF 11-(DIMETHYLAMINOALKYL) DERIVATIVES OF 11H-DIBENZO[*b,e*]-1,4-DIOXEPIN AND 11H-DIBENZO[*b,e*]-1,4-DITHIEPIN*

Karel Šindelář, Jiří Holubek, Miroslav Ryska, Emil Svátek, Antonín Dlabač, Marta Hrubantová and Miroslav Protiva

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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1-[2-(2-Fluorophenoxy)phenyl]-4-dimethylaminobutanol (*XI*) was synthesized from 2-(2-fluorophenoxy)benzoic acid (*VIII*) in three steps and cyclized with sodium hydride in dimethylformamide to the title compound *V*. Reaction of 5-chloro-2-(methylthio)thiophenol (*XIV*) with sodium and liquid ammonia afforded benzene-1,2-dithiol (*XIII*) which was treated with 2-bromobenzyl bromide and gave 11*H*-dibenzo[*b,e*]-1,4-dithiepin (*II*). An alternative synthesis of compound *II* consisted in the cyclization of 2-(2-bromophenylthiomethyl)thiophenol (*XVIII*) and was accompanied by the simultaneous formation of 6*H*,12*H*-dibenzo[*b,f*]-1,5-dithiocin (*XIX*) and thianthrene (*XX*). Reaction of compound *II* with n-butyllithium and the following treatment with dimethylaminoalkyl chlorides or with carbon dioxide resulted on the one hand in two further title compounds *VI* and *VII*, and in the carboxylic acid *XXI* on the other. 2-Chloro-11*H*-dibenzo[*b,e*]-1,4-dithiepin (*XXII*) was obtained by a further synthesis alternative using in the first step the cyclization of 2-(4-chloro-2-chloromethylphenylthio)thiophenol (*XXV*). Compound *VI* and *VII* showed a high degree of activity in the test of antagonization of reserpine hypothermia in mice.

The area of structures of tricyclic psychotropic agents, the basis of which are the linearly condensed skeletons formed by a central seven-membered ring and two annelated aromatic or heteroaromatic nuclei, has been for many years the object of concentrated efforts of medicinal chemists and became a source of a number of potent psychotropic agents of various types (antidepressants, neuroleptics, tranquillizers) (*cf.*[1,2], a complete review of the whole area is lacking). Several times this topic has been claimed to be exhausted but every year new tricyclic compounds of this type are being added representing mostly new combinations of heteroatoms in the central ring and heteroaromatic nuclei in the exterior position[3-5]. In compiling the inventory of tricyclic and chemically related neuroleptic agents[6] it has been found that completely neglected was the area of tricyclic structures with two chalcogen atoms

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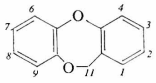
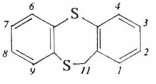
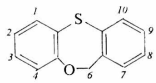
in the central seven-membered ring. Oxygen and sulfur were considered in the first line and the following tricyclic dibenzo systems were derived: 11*H*-dibenzo[*b*,*e*]-1,4-dioxepin (*I*), 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*II*), 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*III*) and 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*IV*). For some time we investigated systematically the chemistry of these four systems with the aim of developing new psychotropic agents on their basis. The present communication is limited to systems I and II; the synthesis of the title compounds *V*–*VII* is being described. In a preliminary way we indicated in a lecture[7] our orientation in this line.



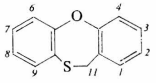
I



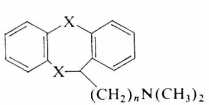
II



III



IV

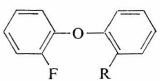


V, X = O, $n = 3$
VI, X = S, $n = 2$
VII, X = S, $n = 3$

A number of communications deals with the chemistry of 11*H*-dibenzo[*b*,*e*]-1,4-dioxepin (*I*) and especially its derivatives; compound *I* was called depsidan and its synthesis was described[8,9]. The corresponding 11-oxo derivative (*i.e.* the lactone "depsidone") has also been prepared by syntheses[10–12]. Depsidone is the parent compound of a large group of lichen metabolites, the "depsidones". The syntheses of several simpler substituted depsidones were described[13–15]; starting from 1975–1976, two Australian groups[16,17] are systematically engaged in the total synthesis of natural depsidones.

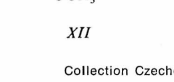
For our purpose, neither depsidan (*I*) nor depsidone were of use because they do not enable the introduction of a basic side chain into position 11, *i.e.* on the single carbon atom of the central ring capable of carrying substituents. For this reason we had to use a completely different synthetic approach than all of the mentioned

communications. 2-Fluoroanisole[18,19] was demethylated with pyridine hydrochloride at 200°C to 2-fluorophenol (the demethylation was described by heating with aluminium chloride in benzene[20,21]). Its reaction with 2-iodobenzoic acid[22] in boiling dimethylformamide in the presence of potassium carbonate and copper afforded 2-(2-fluorophenoxy)benzoic acid (*VIII*), the preparation of which has likewise been described differently[23]. Reduction of the acid *VIII* to 2-(2-fluorophenoxy)benzyl alcohol (*IX*) was carried out with diborane generated by a reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran. For the following oxidation to 2-(2-fluorophenoxy)benzaldehyde (*X*), ceric ammonium nitrate in aqueous acetic acid was used which was described as a specific agent for the oxidation of benzyl alcohols to benzaldehydes[24]. A reaction of the aldehyde *X* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gave the secondary alcohol *XI*, characterized by means of the crystalline 2,4,6-trinitrobenzoate. The cyclization to the desired depsidan derivative *V* proceeded by treatment with sodium hydride in dimethylformamide at 70°C. We are dealing here with an intramolecular nucleophilic substitution which has already been used to the construction of some tricycles with a benzyl ether bridge in the central ring[25,26] being difficult to obtain differently



VIII, R = COOH *X*, R = CHO
IX, R = CH_2OH *XI*, R = $CH(CH_2)_3N(CH_3)_2$ (OH)

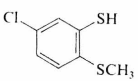
As a potential intermediate of the synthesis of 7-fluorodepsidan derivatives, 4-fluoro-2-(2-methylphenoxy)anisole (*XII*) has been prepared but further work was discontinued because of low yields. It was obtained from 4-fluoro-2-nitroanisole[27] which was reduced with hydrazine in ethanol in the presence of ferric chloride and charcoal to 2-amino-4-fluoroanisole (for a different method of reduction, *cf.*[28]). The transformation to 4-fluoro-2-iodoanisole was carried out using a described procedure[29] and the product was reacted with *o*-cresol in boiling dimethylformamide in the presence of potassium carbonate and copper; compound *XII* was obtained in a yield of only 17%.



XII

The chemistry of derivatives of the other system, *i.e.* 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*II*), can be designated as practically unknown. In the literature[30] we meet only with one mention relating to *cis*-1,2,3,4,4a,11a-hexahydro-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin which was formed in a minute yield by a photochemical reaction of 2,3-benzo-1,5-dithiaspiro[5,5]undecane in cyclohexane and identified only on the basis of spectral data. Synthetic approaches, used by us, included three variants: (*a*) the use of a benzene-1,2-dithiol precursor, (*b*) the use of a benzyl phenyl sulfide precursor with a thiol group on one of the nuclei, (*c*) the use of a diphenyl sulfide precursor with a thiol group on one of the nuclei. The preparation of benzene-1,2-dithiol (*XIII*) was described in the literature[31–36] by several tedious procedures. We did obtain it unexpectedly in the effort to prepare the corresponding 4-chloro derivative according to an abstract of patent[37]. 4-Chlorothioanisole[38] was processed by treatment with chlorosulfonic acid in chloroform and the crude 5-chloro-2-(methylthio)benzenesulfonyl chloride[37] was reduced with zinc and hydrochloric acid in dioxane at 80–90°C; instead of the described 4-chlorobenzene-1,2-dithiol[37] a product was obtained whose analysis indicated that we were dealing here with a non completely homogeneous 5-chloro-2-(methylthio)thiophenol (*XIV*). The reaction of this compound with sodium in liquid ammonia resulted not only in demethylation (analogous S-dealkylations are commonly used for preparative purpose[33,34]) but also in a hydrogenolytic removal of the atom of chlorine; benzene-1,2-dithiol (*XIII*) resulted in a moderate yield. Its reaction with 2-bromobenzyl bromide[39] in dimethylformamide in the presence of potassium carbonate, first at room temperature and after the addition of copper at the boiling point of the mixture, resulted in the desired 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*II*) whose identity was confirmed by analyses and spectra.

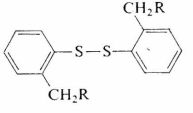
XIII



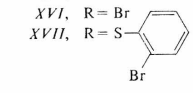
XIV

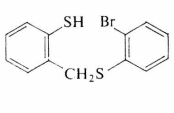
The alternative approach to compound *II*, which used the variant (*b*), proved less favourable and in the last step resulted in a mixture of products. Bis[2-(hydroxymethyl)phenyl]disulfide (*XV*) (ref.[40]) was transformed according to the literature[41] to bis[2-(bromomethyl)phenyl]disulfide (*XVI*) which was condensed with 2-bromothiophenol[42] in a boiling ethanolic solution of potassium hydroxide. The obtained, not completely homogeneous product of the presumed structure *XVII*, was reduced with triphenylphosphine and water (method, *cf.*[43]); the mixture obtained was separated by distillation and crystallization of the distillate giving 2-(2-bromophenylthiomethyl)thiophenol (*XVIII*). A crude product was used for the following cycliza-

tion and the reaction was carried out by boiling in dimethylformamide in the presence of potassium carbonate and copper. Crystallization of the crude product from ethanol separated a substance $C_{14}H_{12}S_2$, *i.e.* a higher homologue of the desired compound *II*, which was identified as the known 6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin (*XIX*) (ref.[44–49]). Evaporation of the mother liquor and crystallization of the residue from a mixture of benzene and light petroleum gave a small amount of triphenylphosphine oxide[50,51], a by-product of the preceding reaction stage. The combined mother liquors were evaporated again and the residue was chromatographed on a column of silical gel. In a small amount, the least polar product was isolated, whose ^{1}H-NMR spectrum shows only signals of aromatic protons; it was identified as thianthrene (*XX*) (ref.[52]). As the more polar product, obtained in a moderate yield, the desired compound *II* was eluted and found identical with the product of the first described method. The simultaneous formation of homologues *XX*, *II* and *XIX* indicates that in addition to the cyclization of compound *XVIII* by the mechanism of the aromatic nucleophilic substitution catalyzed by copper, a fragmentation by the cleavage of the CH_2—S bond takes place and is followed by recombination of the fragments formed (of unclear character) by all the three routes possible[53].

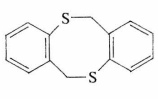


XV, R = OH
XVI, R = Br
XVII, R = S

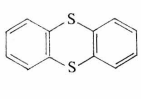




XVIII



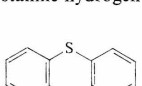
XIX



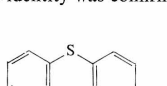
XX

It could be expected that reaction of 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*II*) with sufficiently hard bases will result in cleavage of one proton in position 11 under the formation of the corresponding carbanion or the organometallic compound useful for further reactions and introduction of the necessary substituents to position 11. The reaction of compound *II* with n-butyllithium (solution in hexane) in ether proceeds first under the formation of a dark red coloration (formation of the ion)

and then under separation of a precipitate. The following action of an excess of carbon dioxide gave 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin-11-carboxylic acid (*XXI*). Reactions of the organolithium compound with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride led to the title aminoalkyl derivatives *VI* and *VII* which were isolated as crystalline hydrogen oxalates and their identity was confirmed by spectra.

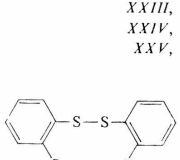


XXI



XXII

XXIII, $R^1 = COOH$, $R^2 = NH_2$
XXIV, $R^1 = CH_2OH$, $R^2 = SH$
XXV, $R^1 = CH_2Cl$, $R^2 = SH$



XXVI, R = COOH
XXVII, $R = CH_2OH$

XXVIII, $R = CH_2OH$
XXIX, R = COOH

Another alternative approach to the 11*H*-dibenzo[*b*,*e*]-1,4-dithiepin skeleton used the variant (*c*) and its goal was the synthesis of 2-chloro-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*XXII*). Reaction of 5-chloro-2-iodobenzoic acid[54] with 2-aminothiophenol in a boiling aqueous solution of potassium hydroxide in the presence of copper gave the acid *XXIII* which was diazotized and the diazonium chloride solution was processed by treatment with a solution of sodium disulfide. The desired diacid *XXVI* was obtained and a sample was purified and characterized. The crude compound was reduced with lithium aluminium hydride in ether and the mixture

obtained was separated to a compound of acid character (soluble in a 5% sodium hydroxide solution) and to a neutral compound. The acid product is oily; it was purified by distillation and identified as the desired 2-(4-chloro-2-hydroxymethylphenylthio)thiophenol (*XXIV*). The neutral product was identified as 2-chlorodibenzothiophene-4-methanol (*XXVIII*). This compound was formed evidently by reduction of 2-chlorodibenzothiophene-4-carboxylic acid (*XXIX*), present in the crude diacid *XXVI*. It is a new example of the formation of a dibenzothiophene derivative by diazotization of a 2-aminodiphenyl sulfide derivative (for preceding cases, *cf.*[54,55]). In order to transform compound *XXIV* into the corresponding benzyl chloride *XXV*, the compound was subjected to treatment with hydrochlorid acid at 45°C and the crude product (without characterization) was cyclized at room temperature in dimethylformamide in the presence of potassium carbonate. The resulting mixture was separated by chromatography on alumina and the desired 2-chloro-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*XXII*) was obtained in a poor yield as the least polar component. A more polar product was the crystalline substance $C_{26}H_{20}Cl_2O_2S_4$ (mass spectrum, analysis) having evidently the structure of the diol *XXVII*. The conversion of the alcohol *XXIV* to the chloride *XXV* proceeded apparently under the conditions used only partially and the side reaction was the oxidation of the thiol *XXIV* to the disulfide *XXVII* which remained unchanged in the final cyclization reaction.

Compounds *V*–*VII* 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.

Compound V: Acute toxicity in mice, LD_{50} = 500 mg/kg. Incoordination effect in the rotarod test in mice as a criterion of the central depressant action[56] (medium effective dose bringing about ataxia in the time of optimum activity), ED_{50} = 21 mg/kg (for chlorpromazine, ED_{50} = 8·2 mg/kg). In a dose of 50 mg/kg it does not antagonize the perphenazine catalepsy in rats and has not the antiapomorphine effect in rats[57,58]. In a dose of 100 mg/kg it does not influence significantly the gastric ulcers in rats elicited with reserpine[59].

Compound VI: Acute toxicity in mice, LD_{50} between 200 (nontoxic dose) and 500 mg/kg (lethal for 60% of the animals). Incoordination effect, ED_{50} = 143 mg/kg, Inhibition of motility in mice in the test of Ther[60] (dose bringing about an effect corresponding to 50% of the control value), D_{50} = 17 mg/kg (for chlorpromazine, D_{50} = 4·8 mg/kg). In a dose of 50 mg/kg it is inactive in the test of catalepsy and has not the antiapomorphine effect in rats. It antagonizes the hypothermic effect of reserpine in mice which is typical for tricyclic antidepressants[59]; a dose of 10 mg/kg elevates the body temperature (measured rectally) by 4·22°C (maximum effect) as compared with the reserpine control group (the same dose of imipramine elevates the temperature by 2·97°C and the same dose of amitriptyline by 2·51°C). In a dose

of 20 mg/kg it is inactive in the test of reserpine ptosis in mice[59] and in a dose of 50 mg/kg it does not influence the reserpine gastric ulcers in rats.

Compound VII: Acute toxicity, LD_{50} between 200 (nontoxic dose) and 500 mg/kg (lethal for 60% animals). Incoordination effect. ED_{50} = 134 mg/kg. Inhibition of motility (Ther), D_{50} = 20 mg/kg. In a dose of 50 mg/kg it is inactive in the test of catalepsy and has not antiapomorphine effect in rats. It antagonizes intensively the hypothermic action of reserpine in mice; a dose of 10 mg/kg elevates the rectal temperature by 3·80°C (in comparison with the reserpine control group) which is higher than the effect of imipramine and amitriptyline. Similarly like the preceding compound, it is inactive in a dose of 20 mg/kg in the test of reserpine ptosis in mice and in a dose of 50 mg/kg it does not influence the reserpine ulcers in rats.

In conclusion: whereas compound *V* shows only a mild incoordinating action in mice, compounds *VI* and *VII* have an intensive antireserpine activity in the test of hypothermia in mice; on the other hand they influence in the used high doses neither the reserpine ptosis in mice nor the reserpine gastric ulcers in rats.

Compounds *V*—*VII* 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*, *VI* 25, *VII* 12·5; *Streptococcus faecalis*, *VI* 100, *VII* 50; *Staphylococcus pyogenes aureus*, *VI* 50, *VII* 25; *Escherichia coli*, *VI* 50, *VII* 25; *Proteus vulgaris*, *VI* 100, *VII* 100; *Mycobacterium tuberculosis* H37Rv, *VI* 12·5, *VII* 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 registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in C^2HCl_3 unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer and ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{(CFCl_3)} = 0$) with the same instrument. The mass spectra were recorded with MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

2-Fluorophenol

A solution of 250 ml pyridine in 200 ml ethanol was stirred, treated dropwise with 310 ml hydrochloric acid and evaporated *in vacuo*. 2-Fluoroanisole[18,19] (82·8 g, b.p. 158—160°C) was added to the residue and the mixture was heated for 10 h in a nitrogen atmosphere to 200°C under a reflux condenser. After cooling, the mixture was diluted with 500 ml water, acidified with 50 ml hydrochloric acid and extracted with ether. The organic layer was washed with water and the product was extracted into 10% NaOH. The alkaline solution was acidified with hydrochloric acid and extracted with ether. The extract was dried with $MgSO_4$ and distilled; 60·0 g (82%), b.p. 149—152°C. Lit.[21], b.p. 151—152°C.

2-(2-Fluorophenoxy)benzoic Acid (*VIII*)

A mixture of 54·4 g 2-fluorophenol, 50 ml dimethylformamide, 120·3 g 2-iodobenzoic acid[22], 100 g K_2CO_3 and 1 g Cu was heated under reflux for 2·5 h in a bath of 170°C. The mixture was poured into 1 l water, the solution was filtered, the filtrate acidified with hydrochloric acid, the precipitated product was filtered and crystallized from 100 ml 70% aqueous ethanol; 44·2 g (45% per conversion), m.p. 130—134°C. A sample was recrystallized from aqueous ethanol, m.p. 140°C. Lit.[23], m.p. 140°C. Processing of the mother liquors led to recovery of 15·2 g 2-iodobenzoic acid, m.p. 157°C (lit.[22], m.p. 162°C).

2-(2-Fluorophenoxy)benzyl Alcohol (*IX*)

A solution of 44·2 g crude *VIII* in 65 ml tetrahydrofuran was treated at 10—20°C with 7·22 g $NaBH_4$, the mixture was stirred for 30 min and treated dropwise under cooling with a solution of 35·9 g boron trifluoride etherate in 20 ml tetrahydrofuran. The mixture was stirred for 3 h at 15—20°C, decomposed at 8°C with 20 ml 5% hydrochloric acid added dropwise, diluted with water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and distilled; 31·7 g (76%), b.p. 127—129°C/27 Pa. A sample for analysis was redistilled, b.p. 128°C/27 Pa. IR spectrum (film): 750 (4 adjacent Ar—H), 1 042 (CH_2OH), 1 196, 1 218, 1 267 (ArOAr), 1 500, 1 588, 1 608, 3 010, 3 042 (Ar), 3 330 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·50—7·50 (m, 8 H, Ar—H), 4·80 (s, 2 H, $ArCH_2O$), 2·45 (s, 1 H, OH). ^{19}F-NMR spectrum: δ −131·9 (m). For $C_{13}H_{11}FO_2$ (218·2) calculated: 71·54% C, 5·09% H, 8·71% F; found: 71·59% C, 5·35% H, 8·64% F.

2-(2-Fluorophenoxy)benzaldehyde (*X*)

A stirred solution of 31·5 g *IX* in 30 ml acetic acid was treated dropwise over 30 min with a solution of 160 g ceric ammonium nitrate in 600 ml 50% aqueous acetic acid. The mixture was stirred for 1 h at room temperature, heated for 2 h to 100°C, cooled and extracted with benzene. The extract was washed with 5% Na_2CO_3, dried with K_2CO_3 and distilled; 27·6 g (88%), b.p. 120 to 123°C/105 Pa. UV spectrum: λ_{max} 243 nm (log ε 3·99), 308 nm (3·82). IR spectrum (film): 755 (4 adjacent Ar—H), 1 220, 1 265 (ArOAr), 1 480, 1 500, 1 583, 1 602, 3 060 (Ar), **1 695**, 2 750 cm^{-1} (ArCHO). ^{1}H-NMR spectrum: δ 10·60 (d, J = 1·0 Hz, 1 H, CHO), 7·92 (q, J = 8·5; 2·0 Hz, 1 H, 6-H), 7·45 (q, J = 8·5; 2·0 Hz, 1 H, 4-H), *c.* 7·18 (m, 5 H, 5-H and 4 Ar—H of 2-fluorophenoxy), 6·75 (bd, J = 8·5 Hz, 1 H, 3-H). ^{19}F-NMR spectrum: δ −130·8 (m). For $C_{13}H_9FO_2$ (216·2) calculated: 72·22% C, 4·20% H, 8·79% F; found: 72·53% C, 4·53% H, 8·34% F.

1-[2-(2-Fluorophenoxy)phenyl]-4-dimethylaminobutanol (*XI*)

3-Dimethylaminopropyl chloride (8·5 g) was transformed by treatment with 1·7 g Mg in 30 ml tetrahydrofuran (the reaction was started with a grain of iodine and a few drops of 1,2-dibromoethane and finished by refluxing for 2 h) to the Grignard reagent. This was treated at room temperature with a solution of 10·8 g *X* in 20 ml tetrahydrofuran and the mixture was refluxed for 4 h. After cooling it was decomposed by a slow addition of 100 ml 20% NH_4Cl and extracted with ether. The extract was dried with K_2CO_3 and evaporated; 15·1 g (100%) oily crude *XI*, which was used for the last step without purification. A sample was chromatographed on a column of neutral Al_2O_3 (activity II). Benzene eluted a small quantity of a less polar product and chloroform eluted the homogeneous oily *XI*. It was characterized as the 2,4,6-trinitrobenzoate, m.p. 96—98°C with decomposition (ethanol–ether). For $C_{25}H_{25}FN_4O_{10}$ (560·5) calculated: 53·57% C, 4·50% H, 3·39% F, 10·00% N; found: 53·53% C, 4·57% H, 2·85% F, 10·16% N.

11-(3-Dimethylaminopropyl)-11*H*-dibenzo[*b,e*]-1,4-dioxepin (*V*)

Crude *XI* (15·1 g) was added over 6 h to a stirred mixture of 3·4 g NaH and 100 ml dimethylformamide at 70°C in a nitrogen atmosphere. The mixture was heated for 6 h to 70°C, allowed to stand overnight at room temperature, poured into 2·5 l water and extracted with ether. The extract was dried with K_2CO_3 and evaporated. The oily residue (14·5 g) was shown by TLC to be a mixture of the product with the starting *XI*. It was dissolved in benzene and chromatographed on a column of 500 g neutral Al_2O_3 (activity II). Benzene eluted 3·43 g (55% per conversion) of the homogeneous oily base *V* which was converted by neutralization with maleic acid in ether to the hydrogen maleate, m.p. 82—84°C (acetone–ether). For $C_{22}H_{25}NO_6$ (399·4) calculated: 66·15% C, 6·31% H, 3·51% N; found: 65·94% C, 6·28% H, 3·37% N. A sample of the maleate was decomposed with NH_4OH and the pure base isolated by extraction with ether, oil. ^{1}H-NMR spectrum: δ 6·70—7·30 (m, 8 H, Ar-H), 5·40 (dd, J = 5·0; 8·0 Hz, 1 H, Ar—CH—O), 2·25 (t, J = 7·0 Hz, 2 H, CH_2N), 2·15 (s, 6 H, CH_3NCH_3), *c.* 2·00 (m, 2 H, CH_2 of the side chain adjacent to the tricycle), 1·70 (m, 2 H, CH_2 in the middle of the propane side chain). Continuation of the chromatography with elution with chloroform led to recovery of 8·49 g starting *XI*.

2-Amino-4-fluoroanisole

A solution of 176 g 4-fluoro-2-nitroanisole[27] (m.p. 61—62°C) in 480 ml ethanol was treated with 10 g charcoal, 25 ml 80% hydrazine hydrate and a solution of 4·8 g $FeCl_3$ in 50 ml ethanol, the mixture was refluxed and treated over 1·5 h with 77 ml 80% hydrazine hydrate, added dropwise. The mixture was stirred and refluxed for 12 h, ethanol was evaporated under reduced pressure, the residue was diluted with 150 ml water and extracted with benzene. The extract was dried with $MgSO_4$ and distilled; 134 g (92%), b.p. 105—107°C/1 kPa. Lit.[28], b.p. 105 to 106°C/1 kPa (for a product obtained by a different method).

4-Fluoro-2-(2-methylphenoxy)anisole (*XII*)

A mixture of 22·9 g 4-fluoro-2-iodoanisole[29] (b.p. 112—113°C/1·3 kPa), 10·8 g *o*-cresol, 13·8 g K_2CO_3, 1 g Cu and 40 ml dimethylformamide was refluxed for 14 h, poured into water and extracted with benzene. The extract was washed with 5% NaOH and dilute hydrochloric acid, dried with $MgSO_4$ and distilled; 3·48 g (17%), b.p. 115—125°C/0·15 kPa. A sample was redistilled for analysis, b.p. 110—115°C/0·1 kPa. ^{1}H-NMR spectrum: δ 6·20—7·20 (m, 7 H, Ar—H), 3·81 (s, 3 H, OCH_3), 2·20 (s, 3 H, $ArCH_3$). ^{19}F-NMR spectrum: δ —121·7 (dt, $J_{F(o-H)}$ = 7·5 Hz, $J_{F(m-H)}$ = 6·0 Hz). For $C_{14}H_{13}FO_2$ (232·3) calculated: 72·40% C, 5·64% H, 8·18% F; found: 71·86% C, 6·28% H, 7·85% F.

5-Chloro-2-(methylthio)thiophenol (*XIV*)

A solution of 108·5 g 4-chlorothioanisole[38] (b.p. 105°C/1·3 kPa) in 450 ml chloroform was stirred and treated at room temperature over 2·5 h with 410 g chlorosulfonic acid, the mixture was stirred for another 0·5 h, refluxed for 2 h, poured on ice and extracted with chloroform. The extract was dried with $CaCl_2$ and evaporated *in vacuo*. The obtained crude oily 5-chloro-2-(methylthio)benzenesulfonyl chloride[37] (81 g) was dissolved in 400 ml dioxane, 120 g Zn dust were added and the stirred mixture was treated over 75 min with 360 ml hydrochloric acid, added dropwise. The temperature rose spontaneously to 60°C, the mixture was stirred for 90 min at 80 to 90°C and processed by steam distillation. The distillate was extracted with ether, the extract was dried with $CaCl_2$ and distilled; 23·6 g (18%), b.p. 95—100°C/53 Pa. For analysis the product

was redistilled but even then is not completely homogeneous; b.p. 92—94°C/50 Pa. For $C_7H_7ClS_2$ (190·7) calculated: 44·08% C, 3·70% H, 18·59% Cl, 33·63% S; found: 44·69% C, 3·67% H, 20·40% Cl, 32·69% S.

Benzene-1,2-dithiol (*XIII*)

Crude *XIV* (26·1 g) was added to 450 ml liquid NH_3 and the solution was treated over 1 h with 12·1 g Na in small pieces under moderate refluxing. The blue mixture was stirred for 40 min, decomposed by addition of 8·0 g NH_4Cl, NH_3 was allowed to evaporate, the residue was dissolved in water, the solution was acidified with hydrochloric acid and the product extracted with ether. The extract was dried with $CaCl_2$ and distilled; 9·8 g (50%) crude *XIII*, b.p. 107—109°C/1·3 kPa. The product was used for further work without purification. A sample was redistilled, b.p. 108°C/1·3 kPa. For $C_6H_6S_2$ (142·2) calculated: 50·66% C, 4·25% H, 45·09% S; found: 51·40% C, 4·18% H, 44·34% S; the product is practically chlorine-free. Lit.[36], b.p. 110—111°C/1·6 kPa for a product obtained differently.

2-(2-Bromophenylthiomethyl)thiophenol (*XVIII*)

2-Bromothiophenol[42] (18·4 g) and 19·6 g bis[2-(bromomethyl)phenyl] disulfide[41] (m.p. 65—68°C) were added to a solution of 6·1 g KOH in 200 ml ethanol and the mixture was refluxed for 6 h under nitrogen. Ethanol was evaporated under reduced pressure, the residue diluted with 100 ml water and extracted with benzene. The extract was dried with Na_2SO_4 and evaporated; 31 g (100%) oily crude *XVII*. According to TLC, the product contained at least two impurities but was processed without further purification.

It was dissolved in 80 ml dioxane, a solution of 13·2 g triphenylphosphine in 70 ml dioxane was added and the stirred mixture was treated over 5 min with 30 ml water acidified with 4 drops hydrochloric acid. The mixture was stirred under nitrogen for 1 h at 40°C, dioxane was evaporated *in vacuo*, the residue was dissolved in 150 ml ether and the solution extracted into 200 ml 5% NaOH. The aqueous alkaline solution was acidified with 100 ml 3M-HCl and the product was extracted with benzene. The extract was dried with Na_2SO_4 and distilled; 18·5 g (60%), b.p. 168—172°C/27 Pa, m.p. 66—68°C (ethanol). ^{1}H-NMR spectrum: δ 6·90—7·70 (m, 8 H, Ar—H), 4·20 (s, 2 H, $ArCH_2S$), 3·75 (s, 1 H, SH). For $C_{13}H_{11}BrS_2$ (311·2) calculated: 50·16% C, 3·56% H, 25·67% Br, 20·60% S; found: 50·56% C, 3·55% H, 25·90% Br, 20·41% S.

11*H*-Dibenzo[*b*,*e*]-1,4-dithiepin (*II*)

A) A mixture of 9·4 g crude *XIII*, 200 ml dimethylformamide, 13·3 g 2-bromobenzyl bromide[39] and 7·35 g K_2CO_3 was stirred for 1 h at room temperature. K_2CO_3 (10 g) and 0·8 g Cu were added and the mixture was refluxed for 6 h. Dimethylformamide was evaporated *in vacuo*, the residue was diluted with water and extracted with benzene (filtration before separation of the layers). The extract was washed with water, dried with K_2CO_3 and distilled; 7·1 g almost homogeneous oil, b.p. 170—180°C/0·15 kPa. The distillate was chromatographed on a column of 200 g silica gel. Light petroleum eluted first 0·35 g of a very little polar impurity and then 6·58 g (54%, calculated for the starting 2-bromobenzyl bromide) homogeneous *II*, m.p. 44—45·5°C (lower melting modification). Single recrystallization from methanol gave the higher melting modification, m.p. 55·5—56°C which was analyzed and characterized by spectra. Mass spectrum, *m/z*: 230 (M^+ corresponding to $C_{13}H_{10}S_2$), 197 (M—SH), 166 (M—2 S), 165 (197—S), 153, 152 (166—CH_2). ^{1}H-NMR spectrum: δ 6·80—7·70 (m, 8 H, Ar—H), 4·52 (s, 2 H, $ArCH_2S$). For $C_{13}H_{10}S_2$ (230·3) calculated: 67·78% C, 4·38% H, 27·84% S; found: 68·19% C, 4·40% H, 28·01% S.

B) A mixture of 17·1 g oily *XVIII*, 8·3 g K_2CO_3, 1·5 g Cu and 300 ml dimethylformamide was refluxed for 6 h under nitrogen. Dimethylformamide was evaporated ***in vacuo***, the residue diluted with 200 ml water and extracted with benzene (filtration prior to separation of the layers). The extract was dried with $MgSO_4$ and evaporated. The residue (12·3 g) was dissolved in 25 ml ethanol and allowed to crystallize on standing; 2·1 g 6*H*,12*H*-dibenzo[*b*,*f*]-1,5-dithiocin (*XIX*), m.p. 171—172°C (benzene–ethanol). Mass spectrum, *m*/*z*: 244 (M^+ corresponding to $C_{14}H_{12}S_2$), 211 (M—SH), 178 (M—2 SH), 165 (178—CH), 153, 144, 121. UV spectrum: λ_{max} 259 nm (log ε 3·84), infl. 225 nm (4·30), 248 nm (3·91), 283 nm (3·46). IR spectrum: 742, 760, 770 (4 adjacent Ar—H), 3 048 cm^{-1} (Ar). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·70—7·40 (m, 8 H, Ar—H), 4·36 (s, 4 H, 2 $ArCH_2S$). For $C_{14}H_{12}S_2$ (244·4) calculated: 68·81% C, 4·95% H, 26·24% S; found: 69·28% C, 4·99% H, 25·84% S. Lit.[44,45], m.p. 174—176°C, and 175—176°C, respectively (for *XIX* obtained differently).

The mother liquor was evaporated *in vacuo* and the residue was dissolved in benzene and the solution treated with light petroleum; 1·4 g triphenylphosphine oxide (a by-product of the preparation of the starting *XVIII*), m.p. 157—158°C. UV spectrum: λ_{max} 223·5 nm (log ε 4·42), 260 nm (3·24), 265 nm (3·34), 272 nm (3·27), infl. 255 nm (3·09). IR spectrum: 700, 725, 759 (C_6H_5). 1 124, 1 188, 1 193 (P—O), 1 477, 1 592, 3 020, 3 040, 3 060 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·20—7·80 (m, Ar—H). For $C_{18}H_{15}OP$ (278·3) calculated: 77·69% C, 5·43% H; found: 77·83% C, 5·47% H, Lit.[51], m.p. 156°C.

The mother liquor was evaporated again, the residue was dissolved in 150 ml boiling light petroleum (the undissolved part filtered off) and the cold solution was chromatographed on a column of 270 g silica gel. Elution with light petroleum gave first 0·50 g thianthrene (*XX*), m.p. 155—157·5°C (light petroleum). UV spectrum: λ_{max} 256·8 nm (log ε 4·58), infl. 241·5 nm (4·25). IR spectrum: 753, 763 (4 adjacent Ar—H), 1 558, 3 035, 3 050 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·54 (m, 4 H, 1,4,6,9-H_4), 7·20 (m, 4 H, 2,3,7,8-H_4). For $C_{12}H_8S_2$ (216·3) calculated: 66·63% C, 3·73% H, 29·65% S; found: 66·82% C, 3·91% H, 29·80% S. Lit.[52], m.p. 160°C.

Continued elution with light petroleum gave 2·19 g (17%) *II*, m.p. 44—45°C, after crystallization from methanol 55·5—56°C, identical with the product prepared according to *A*.

11*H*-Dibenzo[*b*,*e*]-1,4-dithiepin-11-carboxylic Acid (*XXI*)

A stirred solution of 1·90 g *II* in 30 ml ether was treated dropwise over 25 min with 6 ml 15% n-butyllithium solution in hexane under nitrogen (the solution turned dark red, after 15 min a solid precipitated). The stirring was continued at room temperature for 20 min, the mixture was treated with an excess of solid CO_2 and stirred for 1·5 h. It was then decomposed with water, acidified with hydrochloric acid and extracted with ether. The extract was shaken with 5% NaOH and water, the separated aqueous alkaline layers were acidified with hydrochloric acid and the precipitated product was filtered after two days standing; 1·77 g (78%), m.p. 181—181·5°C (benzene–ethanol). UV spectrum: λ_{max} 249 nm (log ε 4·27), infl. 275 nm (3·76), 300 nm (3·56). IR spectrum: 742 (4 adjacent Ar—H), 930, 1 270, 1 693, 1 716, 2 605, 2 775 (COOH), 1 578, 3 040 cm^{-1} (Ar). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90—7·70 (m, 8 H, Ar—H), 5·78 (s, 1 H, Ar—CH—S). For $C_{14}H_{10}O_2S_2$ (274·4) calculated: 61·29% C, 3·67% H, 23·37% S; found: 61·78% C, 3·72% H, 23·44% S.

11-(2-Dimethylaminoethyl)-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*VI*)

A solution of 3·40 g *II* in 50 ml ether was stirred and treated under nitrogen over 20 min with 10 ml 15% n-butyllithium solution in hexane, added dropwise. The mixture was stirred for 30 min and treated slowly with 10 g 2-dimethylaminoethyl chloride under cooling with cold water. The

mixture was stirred for 2 h, washed with water and the product was extracted into 1 : 1 dilute hydrochloric acid. The separated solution of the hydrochloride was made alkaline with NH_4OH and the base extracted with ether. Processing of the extract gave 4·33 g (97%) oily base which was dissolved in 7 ml acetone and neutralized with a solution of 1·81 g oxalic acid dihydrate in 5 ml acetone; 5·31 g hydrogen oxalate, m.p. 185–192°C. Analytical sample, m.p. 195–197°C (ethanol). Mass spectrum, *m/z*: 301 (M^+ corresponding to $C_{17}H_{19}NS_2$), 69, 58 (base peak, $CH_2{=}\overset{+}{N}(CH_3)_2$). For $C_{19}H_{21}NO_4S_2$ (391·5) calculated: 58·29% C, 5·40% H, 3·58% N, 16·38% S; found: 58·52% C, 5·69% H, 3·64% N, 16·26% S.

11-(3-Dimethylaminopropyl)-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*VII*)

A solution of 3·10 g *II* in 50 ml ether was treated similarly like in the preceding case with 10 ml 15% n-butyllithium in hexane and after 30 min stirring the mixture was treated with 10 g 3-dimethylaminopropyl chloride. Similar processing gave 3·70 g (87%) crude oily base which was chromatographed on a column of 200 g neutral Al_2O_3 (activity II). Benzene eluted 2·89 g homogeneous base which was neutralized with oxalic acid in a mixture of acetone and ether; hydrogen oxalate, m.p. 181–182°C (ethanol). Mass spectrum, *m/z*: 315 (M^+ corresponding to $C_{18}H_{21}NS_2$), 282 (M–SH), 58 [$CH_2{=}\overset{+}{N}(CH_3)_2$], 45. For $C_{20}H_{23}NO_4S_2$ (405·5) calculated: 59·23% C, 5·72% H, 3·45% N, 15·81% S; found: 59·50% C, 6·01% H, 3·38% N, 15·58% S.

A sample of the pure hydrogen oxalate was decomposed with NH_4OH and the base isolated by extraction with ether, oil. ^{1}H-NMR spectrum: δ 6·80–7·70 (m, 8 H, Ar—H), 5·82 (t, $J = 7·0$ Hz, 1 H, Ar—CH—S), 2·38 (t, 2 H, CH_2N), 2·24 (s, 6 H, CH_3NCH_3), 1·60–2·10 (m, 4 H, remaining CH_2CH_2 of the side chain).

2-(2-Aminophenylthio)-5-chlorobenzoic Acid (*XXIII*)

A mixture of 125 g 5-chloro-2-iodobenzoic acid[54], 57·5 g 2-aminothiophenol, 92 g KOH, 6 g Cu and 920 ml water was stirred and refluxed for 6·5 h. It was filtered while hot and the filtrate was acidified with acetic acid. The precipitated product was filtered and crystallized from 750 ml aqueous acetic acid; 112 g (91%), m.p. 172–175°C. Analytical sample, m.p. 174–176°C (acetic acid). UV spectrum: λ_{max} 222·5 nm (log ε 4·40), 248 nm (4·19), 318 nm (3·83), infl. 261 nm (4·10). IR spectrum: 721, 730, 748 (4 adjacent Ar—H), 783, 800, 819 (2 adjacent Ar—H), 855, 869 (solitary Ar—H), 960, 1 220, **1 690** (ArCOOH), 1 480, 1 550, 1 590, 3 030, 3 060 (Ar), 2 480, 2 545 (COOH), 3 260, 3 332 cm^{-1} (NH_2). For $C_{13}H_{10}ClNO_2S$ (279·7) calculated: 55·81% C, 3·60% H, 12·68% Cl, 5·01% N, 11·46% S; found: 56·03% C, 3·94% H, 12·66% Cl, 4·90% N, 11·28% S.

Bis[2-(2-carboxy-4-chlorophenylthio)phenyl] Disulfide (*XXVI*)

A mixture of 110 g *XXIII*, 130 ml water, 130 g ice and 80 ml hydrochloric acid was diazotized at 0–5°C under stirring with a solution of 27·6 g $NaNO_2$ in 105 ml water. The mixture was stirred for 1 h at 0–5°C and poured into a cooled solution prepared from 102 g $Na_2S.9\,H_2O$, 13·4 g S and 120 ml water (dissolved by heating and then cooled) and 16 g NaOH in 40 ml water. It was stirred for 2 h without cooling, acidified with 80 ml hydrochloric acid, the separated solid was filtered, suspended in a hot solution of 26 g Na_2CO_3 in 250 ml water, the undissolved part (sulfur) was filtered off while hot and the filtrate was acidified with hydrochloric acid. The separated solid was filtered and suspended in 700 ml ethanol; 17·1 g product melting at 300°C did not dissolve and was filtered. The filtrate was evaporated and the residue treated with benzene; there were obtained 16·9 g product melting at about 270°C. Both high-melting products were

combined (34 g, 29%) and considered to be the crude *XXVI*. Repeated crystallization of a sample from a mixture of dimethylformamide and water led to the homogeneous product, m.p. 305 to 307°C. UV spectrum: λ_{max} 257·5 nm (log ε 4·49), 325 nm (4·02). IR spectrum: 730, 750, 780, 820, 859 (4 and 2 adjacent and solitary Ar—H), 895, 1 250, **1 690**, 2 515, 2 575, 2 620, 2 680, infl. 3 100 (ArCOOH), 1 542, 1 568, 1 580 cm^{-1} (Ar). For $C_{26}H_{16}Cl_2O_4S_4$ (591·5) calculated: 52·78% C, 2·73% H, 11·98% Cl, 21·68% S; found: 52·61% C, 3·08% H, 11·48% Cl, 21·31% S.

2-(4-Chloro-2-hydroxymethylphenylthio)thiophenol (*XXIV*)

Crude *XXVI* (31·5 g) was slowly added to a stirred suspension of 12·5 g $LiAlH_4$ in 325 ml ether and the mixture was refluxed for 12 h. After standing overnight it was decomposed by addition of 50 ml ether saturated with water, 15 ml water added dropwise and 300 ml 10% hydrochloric acid. The organic layer was separated, washed with water and the acidic product *XXIV* was extracted into 200 ml 5% NaOH. The alkaline solution was acidified with 3M-HCl and extracted with ether. The extract was dried with $MgSO_4$ and distilled; 13·0 g (43%), b.p. 215—217°C/0·16 kPa. A sample for analysis was redistilled, b.p. 200°C/65 Pa. IR spectrum (film): 750, 815, 881 (4 and 2 adjacent and solitary Ar—H), 1 035, 3 340 (CH_2OH), 1 555, 1 570, 1 580, 3 010 (Ar), 2 515 cm^{-1} (SH). ^{1}H-NMR spectrum: δ 7·50 (d, J = 2·5 Hz, 1 H, 3′-H), 6·90—7·40 (m, 6 H, remaining Ar—H), 4·74 (s, 2 H, $ArCH_2O$), 3·99 (s, 1 H, SH), 2·30 (bs, 1 H, OH). For $C_{13}H_{11}ClOS_2$ (282·8) calculated: 55·21% C, 3·92% H, 12·54% Cl, 22·67% S; found: 55·64% C, 3·93% H, 12·30% Cl, 22·64% S.

The ethereal solution, from which the acidic product was removed by extraction with 5% NaOH, was evaporated and the residue was crystallized from benzene; 4·9 g 2-chlorodibenzothiophene-4-methanol (*XXVIII*), m.p. 161—162°C. UV spectrum: λ_{max} 231 nm (log ε 4·74), 254 nm (4·27), 285 nm (4·00), 315 nm (3·45), 327·5 nm (3·52), infl. 236 nm (4·71), 277·5 nm (3·83). IR spectrum: 731, 761, 866 (4 adjacent and solitary Ar—H), 1 009 (CH_2OH), 1 580, 1 594 (Ar), 3 155 cm^{-1} (OH). ^{1}H-NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·45 (m, 1 H, 9-H), 8·39 (d, J = 2·5 Hz, 1 H, 1-H), 8·00 (m, 1 H, 6-H), 7·58 (d, J = 2·5 Hz, 1 H, 3-H), *c.* 7·50 (m, 2 H, 7,8-H_2), 5·71 (bt, J = 5·0 Hz, 1 H, OH), 4·79 (bd, J = 5·0 Hz), 2 H, $ArCH_2O$). For $C_{13}H_9ClOS$ (248·4) calculated: 62·76% C, 3·64% H, 14·26% Cl, 12·89% S; found: 62·27% C, 3·49% H, 14·38% Cl, 13·02% S.

2-Chloro-11*H*-dibenzo[*b*,*e*]-1,4-dithiepin (*XXII*)

A mixture of 12·7 g *XXIV* and 30 ml hydrochloric acid was stirred for 14 h at 45°C. After cooling, it was extracted with ether, the extract dried with $CaCl_2$ and evaporated; 12·8 g oily inhomogeneous product assumed to consist mainly of *XXV*. It was dissolved in 125 ml dimethylformamide, 5·90 g K_2CO_3 were added and the mixture was stirred for 6 h without heating. The solvent was evaporated *in vacuo*, the residue diluted with 150 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated. The residue (9·0 g) was disolved in 16 ml light petroleum and chromatographed on a column of 400 g neutral Al_2O_3 (activity II). A mixture of benzene and light petroleum (1 : 1) eluted 1·90 g (16% calculated for *XXIV*) desired *XXII*, m.p. 106—109°C (ethanol). ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 7 H, Ar—H), 4·50 (s, 2 H, $ArCH_2S$). For $C_{13}H_9ClS_2$ (264·8) calculated: 58·96% C, 3·43% H, 13·39% Cl, 24·22% S; found: 59·32% C, 3·65% H, 13·07% Cl, 23·53% S.

The chromatography was continued by elution with chloroform giving 6·42 g bis[2-(4-chloro-2-hydroxymethylphenylthio)phenyl] disulfide (*XXVII*), m.p. 131—133°C (aqueous ethanol). Mass spectrum, m/z: 562 (M^+ corresponding to $C_{26}H_{20}Cl_2O_2S_4$), 560, 280. For $C_{26}H_{20}Cl_2O_2S_4$ (563·6) calculated: 55·41% C, 3·58% H, 12·58% Cl, 22·76% S; found: 55·40% C, 3·69% H, 12·90% Cl, 22·43% S.

The fact that tricyclic psychotropic agents containing two chalcogen atoms in the central ring escaped to the attention was found out during a very stimulating discussion of the author (M. P.) with Dr Paul Janssen (Janssen Pharmaceutica, Beerse, Belgium) relating to the preparation of a symposium "Inventory and classification of psychotropic drugs" for the 9th International Congress of Collegium Internationale Neuropsychopharmacologicum, Paris, July 1974.

The analyses were carried out by Mrs J. Komancová. Mrs V. Šmídová, Mr M. Čech, Mrs J. Kropáčová and Dr Z. Volková (analytical department of this institute). Mrs L. Machová participated on the preparation of some intermediates.

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