BUTACLAMOL-LIKE NEUROLEPTIC AGENTS: SYNTHESIS OF 1-(11*H*-DIBENZ[*b*,*f*]-1,4-OXATHIEPIN-11-YL)METHYL-4-ISOBUTYLPIPERIDIN-4-OL AND OF SOME RELATED COMPOUNDS

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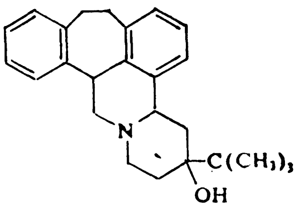
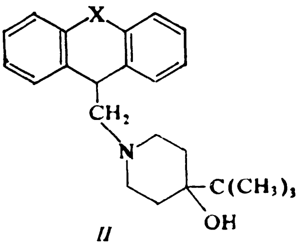
1-(11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-11-yl)methyl-4-piperidone (*XIII*), which was obtained from 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxylic acid (*VIII*) in four steps, was treated with isobutylmagnesium bromide and gave the title compound *V* in addition to the prevailing quantity of the secondary alcohol *VI*, *i.e.* the product of reduction. Synthesis of a series of trisubstituted benzyl phenyl sulfide derivatives *XVIII*–*XXIV*, *XXVI*–*XXXI* is described; these compounds are potential intermediates in the preparation of 11*H*-dibenz[*b*,*f*]-1,4-oxathiepinacetic acids *XVI* and *XVII*. Chloromethylation of 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*VII*) and two further usual steps gave an acid to which structure *XVI* is assigned. Compound *V* is an open model of "oxathiaisobutaclamol" and in agreement with this fact it behaves like a neuroleptic agent: it increases the turnover and metabolism of dopamine in the rat brain striatum which is manifested by a significant rise of homovanillic acid level.

Butaclamol (*I*) is a pentacyclic neuroleptic agent with three chiral centers in the molecule and with a high degree of stereoselectivity of effects[1,2]. There was described the synthesis of four open models of butaclamol of formula *II* (X = $—CH_2CH_2—$, —CH=CH—, —S—, —O—) with strongly simplified stereochemical situation but maintaining, nevertheless, some degree of neuroleptic activity[3,4]. This activity is also shown by isobutaclamol (*III*) (ref.[5]) and by the recently described thiaisobutaclamol (*IV*) (ref.[6]). Using structures *I*–*IV* we have now designed the title compound *V* as a new open model; its molecule contains two chalcogen atoms as hetero atoms in the basic tricycle. The tert-butyl was substituted by isobutyl after unfavourable experiences with reactions of tert-butylmagnesium chloride[6]; isobutyl, besides, is present in a very similar situation in the molecule of the neuroleptic agent tetrabenazine[7]. The synthesis of compound *V*, which is being described in the present communication, represents a continuation of our previous work in the 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin series[8].

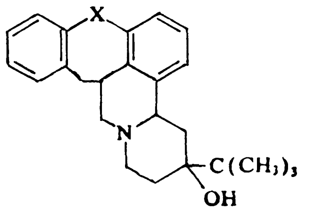
Our synthesis started from 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxylic acid (*VIII*) (ref.[8]) which was obtained from 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*VII*) (ref.[8]) by treatment with butyllithium followed by carbon dioxide. The ethyl ester *IX* was obtained in an attempt to prepare the 4-hydroxypiperidide of the acid *VIII via* the mixed anhydride with monoethyl carbonate; the reaction of the acid *VIII* with ethyl chloroformate in chloroform in the presence of triethylamine resulted in the ethyl ester *IX* in a good yield. Similar reactions were described in our previous communications[9-12]. 4-Hydroxypiperidine[13-17], which should react in the mentioned attempt, was obtained instead of the wanted 4-isobutylpiperidin-4-ol by reaction of 1-ethoxycarbonyl-4-piperidone[18] with isobutylmagnesium bromide in ether and by the following hydrolysis of the crude product with potassium hydroxide in boiling ethanol; the Grignard reagent only reduced the ketone. Similar results gave reactions of 1-ethoxycarbonyl-4-piperidone[18] with isopropylmagnesium chloride or with tert-butylmagnesium chloride and the following alkaline hydrolyses: only mixtures of the desired tertiary alcohols with prevailing 4-hydroxypiperidine were obtained.



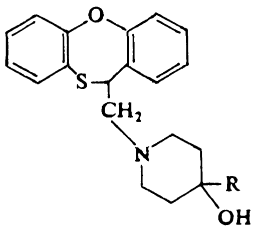
I



II

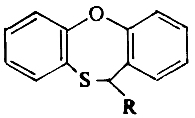


III, $X = CH_2$
IV, $X = S$

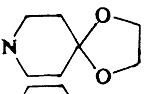
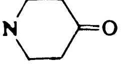


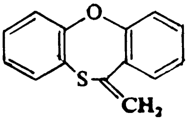
V, $R = CH_2CH(CH_3)_2$
VI, $R = H$

The acid *VIII* was reduced with diborane to the primary alcohol *X*. Its treatment with phosphorus tribromide gave the bromide *XI* which was subjected to the substitution reaction with 1,4-dioxa-8-azaspiro[4,5]decane[18] in boiling acetone in the presence of potassium carbonate. The desired product *XII* was obtained in a moderate yield and was characterized as the hydrochloride. Dehydrobromination was an important side reaction. Its product *XV* was oily and was characterized by the ^1H NMR spectrum. The same substitution reaction, carried out in chloroform, gave a better yield of *XII*. The hydrolysis of the ketal *XII* with dilute hydrochloric acid in boiling dioxane does not proceed easily; only after 25 h most of it reacted and the crystalline amino keton *XIII* was isolated and characterized by spectra. Reaction of this compound with isobutylmagnesium bromide gave a mixture which was separated by chromatography on silica gel. Chloroform eluted the less polar minor product which proved to be the title compound *V*. Ethanol eluted then the more polar main product which was identified as the secondary alcohol *VI*, *i.e.* the product of reduction. Both compounds were prepared as hydrochlorides and their identity was corroborated by spectra (mass spectra included). A similar reaction with tert-butylmagnesium chloride gave after chromatography an amorphous hydrochloride which was shown by the mass spectrum to be a mixture of the desired tertiary alcohol and the starting amino ketone *XIII*; the more polar product was again the secondary alcohol *VI*. Reaction of the previously described[8] 11-(dimethylaminomethyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin with methyl iodide in ether gave the quaternary salt *XIV*.



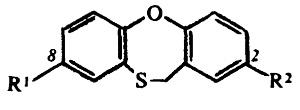
VII, R = H
VIII, R = COOH
IX, R = $COOC_2H_5$
X, R = CH_2OH
XI, R = CH_2Br

XII, R = CH_2N 
XIII, R = CH_2N 
XIV, R = $CH_2\overset{+}{N}(CH_3)_3$ I^-

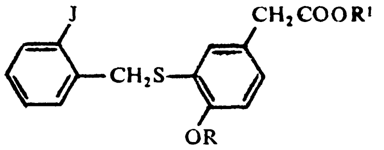


XV

The second part of this paper describes experiments aiming at the synthesis of the two isomeric 11*H*-dibenz[*b*,*f*]-1,4-oxathiepinacetic acids *XVI* and *XVII* considered potential antiinflammatory agents[19]. These experiments were discontinued in the final cyclization steps because of unexpected difficulties. The first of these experiments started from (3-chlorosulfonyl-4-methoxyphenyl)acetic acid[20] which was reduced to (3-mercapto-4-methoxyphenyl)acetic acid[20] with phosphorus and iodine in boiling acetic acid (a new application of the Wagner's method[21]). Reaction of this thiol with 2-iodobenzyl bromide[22] in dimethylformamide in the presence of potassium carbonate at room temperature gave the acid *XVIII*. Attempts to demethylate this methoxy acid with boron tribromide in dichloromethane or with iodotrimethylsilane[23,24] (generated *in situ* from chlorotrimethylsilane and sodium iodide in acetonitrile) led neither to the desired hydroxy acid nor to any crystalline product. In the former case a small amount of an oily product was isolated from the chromatography of the crude product on silica gel as the least polar fraction and was characterized by spectra as the methyl ester of the desired hydroxy acid; methyl bromide formed, together with sodium carbonate used during the processing of the reaction mixture, could have effected the esterification. Finally, a mixture of two acids $C_{15}H_{12}O_3S$ was obtained in low yield by the sequence starting with the chloromethylation of compound *VII*, followed by treatment with potassium cyanide and concluded by hydrolysis with sodium hydroxide in boiling aqueous ethanol. The mixture of the acids obtained was chromatographed on silica gel which led to the isolation of the main component to which the structure *XVI* was assigned (spectra not at variance). The minor isomer, obtained from the mother liquors, is tentatively formulated as the acid *XVII*. The whole procedure is not of preparative value.

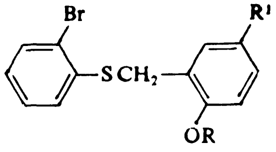


XVI, $R^1 = CH_2COOH$, $R^2 = H$
XVII, $R^1 = H$, $R^2 = CH_2COOH$

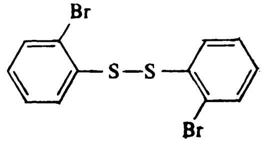


XVIII, $R = CH_3$, $R^1 = H$
XIX, $R = H$, $R^1 = CH_3$

In the second experiment 2-bromothiophenol[25] was reacted with 3-chloromethyl-4-methoxybenzaldehyde[26] in dimethylformamide in the presence of potassium carbonate at 100°C; the aldehyde *XX* was obtained in a good yield. It was reduced with sodium borohydride in aqueous ethanol to the alcohol *XXI* which was transformed to the crude nitrile *XXII* by treatment with hydrogen chloride in benzene and by the following reaction of the crude chloride with sodium cyanide in dimethylformamide at 100°C. In the effort to effect demethylation the nitrile *XXII* was subjected to treatment with a boiling mixture of acetic acid, acetic anhydride and hydrobromic acid under saturation with hydrogen bromide. The crude product obtained was separated by extraction into aqueous sodium hydroxide. The main part was not soluble and its crystallization gave the methoxy amide *XXIII* as the main product.



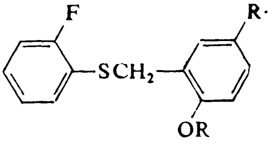
XX, $R = CH_3$, $R^1 = CHO$
XXI, $R = CH_3$, $R^1 = CH_2OH$
XXII, $R = CH_3$, $R^1 = CH_2CN$
XXIII, $R = CH_3$, $R^1 = CH_2CONH_2$
XXIV, $R = H$, $R^1 = CH_2CONH_2$



XXV

From the soluble part the minor product was isolated, purified by chromatography on silica gel and was identified as the hydroxy amide *XXIV*. Hydration of the nitrile to amide was thus the main reaction; demethylation took place only in a lesser extent. An attempt to cyclize the hydroxy amide *XXIV* by refluxing in dimethylformamide with potassium carbonate and copper led – at least partly – to a cleavage of the benzyl–S bond since the only crystalline product isolated was identified as bis(2-bromophenyl) disulfide (*XXV*) (ref.[27]).

The third experiment, similarly like the second one, was directed to compound *XVII*; fluorine atom substituted here the bromine atom of the preceding series. 2-Fluorothiophenol[28] reacted with 3-chloromethyl-4-methoxybenzaldehyde[26] similarly like in the preceding series and gave the aldehyde *XXVI* which was reduced to the alcohol *XXVII*. Treatment with hydrogen chloride in benzene and then with sodium cyanide in dimethylformamide gave in a good yield the nitrile *XXVIII*. An attempt to demethylate it with boron tribromide in dichloromethane at −10°C led to the recovery of most of the starting *XXVIII* and to isolation of the methoxy amide *XXIX* as the only product formed. A similar reaction at room temperature resulted in the desired demethylation combined again with hydration: the hydroxy amide *XXX* was obtained in a moderate yield and its identity was corroborated by spectra. A rather clean demethylation of the methoxy nitrile *XXVIII* was effected with iodotrimethylsilane (generated from chlorotrimethylsilane and sodium iodide) in acetonitrile at 60°C (*cf.*[23,24]); the hydroxy nitrile *XXXI* was obtained in a satisfactory yield. An attempt at its cyclization with sodium hydride in dimethylformamide at 80–90°C (for similar cyclization reactions of fluorinated alcohols in dimethylformamide, *cf.*[29]) was not successful: a crystalline compound melting at 130–134°C was obtained in a yield of about 20%; its analysis indicated the presence of two nitrogen atoms per one atom of sulfur (two CN bands in the IR spectrum at 2 220 and 2 240 cm^{-1}) and the mass spectrum did not disclose the molecular ion. We presume that the cleavage of the benzyl–S bond took partly place and the phenylacetonitrile fragment combined somehow with the molecule of the starting *XXXI*. The data available do not allow to assign the structure.



XXVI, R = CH_3, R^1 = CHO
XXVII, R = CH_3, R^1 = CH_2OH
XXVIII, R = CH_3, R^1 = CH_2CN

XXIX, R = CH_3, R^1 = CH_2CONH_2
XXX, R = H, R^1 = CH_2CONH_2
XXXI, R = H, R^1 = CH_2CN

Compounds *V* and *VI* were considered potential neuroleptics and were compared with butaclamol in the test following the influence on the dopamine metabolism in the striatum of the rat brain. Both compounds showed the neuroleptic activity, *i.e.* they raise the level of homovanillic acid in the striatum. Quantitatively they are much weaker than butaclamol[1]. While an oral dose of 5 mg/kg of butaclamol (*I*) raised the homovanillic acid level to 644% (control value 100%), the same doses of compounds *V* and *VI* raised the level to 228%, and 207%, respectively. The quaternary salt *XIV* was evaluated in the general pharmacological screening. It is rather toxic in mice, $LD_{50} = 7$ mg/kg *i.v.* A dose of 1·5 mg/kg *i.v.* was without effect in a series of *in vivo* tests. In a concentration of 1 – 10 μg/ml it showed spasmolytic (anticholinergic) effect on the isolated rat duodenum and in a similar concentration (10 μg/ml) it exhibited a positively inotropic effect on the isolated rabbit atrium.

EXPERIMENTAL

The melting points of analytical samples were determined in the Mettler FP-5 melting point recorder. The samples were dried *in vacuo* of 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, IR spectra (mostly in Nujol) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with the spectrometers MCH-1320 and Varian MAT 44S. The homogeneity of the compound and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). All extracts were processed by drying with $MgSO_4$ or K_2CO_3 and by evaporation *in vacuo*.

4-Hydroxypiperidine

Grignard reagent was prepared from 110 g isobutyl bromide and 19·5 g Mg in 380 ml ether. Under stirring it was treated with a solution of 34·2 g 1-ethoxycarbonyl-4-piperidone[18] in 40 ml ether. The mixture was refluxed for 10 h, after cooling decomposed by addition of 650 ml 20% NH_4Cl and extracted with ether. Processing of the extract gave 21·0 g (61%) product, b.p. 120 to 130°C/13 Pa, consisting mainly of 1-(ethoxycarbonyl)piperidin-4-ol. For $C_8H_{15}NO_3$ (173·2) calculated: 8·09% N; found: 7·68% N. This product (20·2 g), 25 g KOH and 25 ml ethanol were refluxed for 3 h in a bath of 130°C. Ethanol was evaporated *in vacuo*, the residue was diluted with 25 ml water and extracted with ether. Processing of the extract and distillation gave 9·8 g (83%) 4-hydroxypiperidine, b.p. 110°C/70 Pa or 80°C/30 Pa, crystallizing on standing to a low-melting solid. B.p. 211–212°C/100 kPa (ref.[13]), 106°C/1·7 kPa (ref.[16]). Hydrochloride, m.p. 154–156°C (aqueous ethanol–ether). Lit.[15], m.p. 151–153°C.

Ethyl 11*H*-Dibenz[*b,f*]-1,4-oxathiepin-11-carboxylate (*IX*)

A solution of 14·7 g *VIII* (ref.[8]) in 50 ml chloroform was treated with 5·75 g triethylamine and then dropwise over 30 min with 6·2 g ethyl chloroformate under stirring and cooling with ice and water. The mixture was stirred for 1 h, treated with a solution of 9·0 g 4-hydroxypiperidine in 25 ml chloroform, stirred for 2 h, allowed to stand overnight, washed with water, dilute NaOH, dilute hydrochloric acid, dried with K_2CO_3, and evaporated *in vacuo*. The residue was crystallized from a mixture of benzene and light petroleum; 14·6 g (79%) 2 : 1 solvate of *IX* with benzene, m.p. 55—60°C (benzene–cyclohexane). Mass spectrum, *m/z*: 286·0694 (M^+ corresponding to $C_{16}H_{14}O_3S$, calculated 286·0664), 213 ($M-COOC_2H_5$), 181 ($C_{13}H_9O$), 152 ($C_{12}H_8$). For $C_{16}H_{14}O_3S$ + 0·5 C_6H_6 (325·4) calculated: 70·12% C, 5·27% H, 9·85% S; found: 69·84% C, 5·64% H, 10·14% S.

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

A stirred solution of 38·1 g *VIII* (ref.[8]) in 180 ml tetrahydrofuran was treated under nitrogen with 7·7 g $NaBH_4$ and then over 20 min at 15—25°C with 25 ml $BF_3.O(C_2H_5)_2$. The mixture was allowed to stand overnight at room temperature, decomposed under stirring by a slow addition of 100 ml 5% hydrochloric acid and extracted with benzene. The extract was washed with 5% Na_2CO_3, dried and evaporated. The residue was distilled; 32·5 g (90%), b.p. 195°C/80 Pa. For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·83% C, 4·95% H, 13·12% S; found: 69·18% C, 5·03% H, 13·13% S.

11-Bromomethyl-11*H*-dibenz[*b,f*]-1,4-oxathiepin (*XI*)

X (32·4 g), 2·0 g pyridine and 10 ml benzene were added dropwise over 1 h to a stirred mixture of 12·9 g PBr_3, 5 ml benzene and 1·0 g pyridine at −5°C, the mixture was stirred for 5 h at this temperature and then allowed to stand for 1 week at room temperature. It was diluted with benzene, decomposed and washed with water, the benzene solution was dried and evaporated; 35·0 g (86%), m.p. 94—104°C. Analytical sample, m.p. 106—109°C (cyclohexane–hexane). IR spectrum: 750, 761 (4 adjacent Ar—H), 1 220, 1 260 (Ar—O—Ar), 1 488, 1 564, 1 579, 1 589, 1 600, 3 053, 3 082 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80—7·50 (m, 8 H, ArH), 5·25 (dd, $J = 10·0; 7·0$ Hz, 1 H, Ar—CH—S), 4·35 and 3·70 (2 dd, $J = 15·0; 10·0$ and 15·0; 7·0 Hz, 1 + 1 H, CH_2Br). For $C_{14}H_{11}BrOS$ (307·2) calculated: 54·73% C, 3·61% H, 26·01% Br, 10·44% S; found: 54·52% C, 3·81% H, 25·50% Br, 10·49% S.

8-(11*H*-Dibenz[*b,f*]-1,4-oxathiepin-11-yl)methyl-1,4-dioxa-8-azaspiro[4,5]decane (*XII*)

A) A mixture of 15·4 g *XI*, 8·6 g 1,4-dioxa-8-azaspiro[4,5]-decane[18], 7·0 g K_2CO_3 and 100 ml acetone was stirred and refluxed for 12 h. After cooling it was filtered, the filtrate was evaporated and the residue treated with dilute hydrochloric acid and ether. There crystallized 7·0 g (34%) crude hydrochloride of *XII* which was crystallized from a mixture of ethanol and ether, m.p. 210—227°C with decomposition. For $C_{21}H_{24}ClNO_3S$ (406·0) calculated: 62·13% C, 5·96% H, 8·73% Cl, 3·45% N, 7·90% S; found: 62·06% C, 5·94% H, 8·46% Cl, 3·19% N, 7·85% S.

Decomposition of the hydrochloride with NH_4OH and extraction with chloroform gave the pure base *XII*, m.p. 160·5—162°C (cyclohexane). IR spectrum: 750 (4 adjacent Ar—H), 1 080 (R—O—R), 1 200 (Ar—O—Ar), 1 462, 1 485, 1 561, 1 572, 1 585, 1 599, 3 045 (Ar), 2 810 cm^{-1} (CH_2—N). ^1H NMR spectrum: δ 6·80—7·40 (m, 8 H, ArH), 3·20—4·30 (m, 3 H, $ArCHCH_2N$), 3·86 (s, 4 H, OCH_2CH_2O), c. 2·65 (m, 4 H, CH_2NCH_2 in the ring), 1·75 (t, 4 H, remaining 2 CH_2). For $C_{21}H_{23}NO_3S$ (369·5) calculated: 68·26% C, 6·27% H, 3·79% N, 8·68% S; found: 68·53% C, 6·45% H, 3·56% N, 8·73% S.

The ethereal layer after removal of the base with dilute hydrochloric acid was evaporated, the residue (8·3 g neutral components) was dissolved in benzene, the solution was washed with dilute NaOH and water, dried and evaporated. The residue was treated with cyclohexane, the solution was separated from the undissolved part by decantation and evaporated; 6·1 g oil which could not be distilled *in vacuo* (decomposition). It was characterized by the ^1H NMR spectrum as 11-methylene-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin (*XV*): δ 6·90—7·50 (m, 8 H, ArH), 5·49 and 5·38 (2 s, 1 + 1 H, $=CH_2$).

B) A mixture of 19·0 g *XI*, 21 g 1,4-dioxa-8-azaspiro[4,5]decane[18] and 20 ml chloroform was warmed to achieve dissolution, the solution was then allowed to stand for 1 week at room temperature, refluxed for 8 h, after cooling diluted with benzene and washed with water. Shaking of the benzene solution with dilute hydrochloric acid gave the crystalline hydrochloride which was processed similarly like under *A*) giving 9·25 g (40%) base, m.p. 160·5—162°C.

1-(11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-11-yl)methyl-4-piperidone (*XIII*)

A mixture of 10·5 g *XII*, 180 ml dioxane and 80 ml 1 : 1 dilute hydrochloric acid was refluxed for 25 h, dioxane was evaporated *in vacuo*, the residue was treated with NH_4OH and extracted with benzene. The extract was evaporated and chromatographed on a column of 200 g silica gel. Benzene and the first fractions of chloroform removed the impurities and chloroform eluted then 5·37g (58%) homogeneous base which crystallized from a mixture of benzene and light petroleum, m.p. 185—189°C. IR spectrum: 750, 775 (4 adjacent Ar—H), 1 210 (Ar—O—Ar), 1 483, 1 565, 1 574, 1 585, 1 600, 3 045 (Ar), 1 702 (C=O), 2 805, 2 820 cm^{-1} ($N—CH_2$). ^1H NMR spectrum: δ 6·80—7·50 (m, 8 H, ArH), 4·25 (dd, J = 10·0; 7·0 Hz, 1 H, Ar—CH—S), 2·20—4·00 (m, 10 H, remaining 5 CH_2). For $C_{19}H_{19}NO_2S$ (325·4) calculated: 70·12% C, 5·89% H, 4·30% N, 9·85% S; found: 70·10% C, 6·03% H, 4·07% N, 9·71% S.

1-(11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-11-yl)methyl-4-isobutylpiperidin-4-ol (*V*)

Grignard reagent was prepared from 13·7 g isobutyl bromide and 2·4 g Mg in 90 ml ether, it was treated under stirring over 10 min with a solution of 5·0 g *XIII* in a mixture of 50 ml benzene and 30 ml tetrahydrofuran. The mixture was refluxed for 4 h, cooled, decomposed with 20% NH_4Cl, the organic layer was dried and evaporated. The residue was dissolved in chloroform and chromatographed on 200 g silica gel. Chloroform eluted in the first fractions the homogeneous desired product *V*; 1·55 g (26%) oil. The base was transformed by hydrogen chloride in ether to the hydrochloride, m.p. 219—223°C (acetone–ethanol–ether). Mass spectrum, m/z (%): 383·1896 (M^+ corresponding to $C_{23}H_{29}NO_2S$, calculated 383·1919, 13%), 350, 290, 258 (75), 227 (89), 226 (73), 195 (30), 181 (100), 158 (42). IR spectrum: 750, 769 (4 adjacent Ar—H), 1 050 (C—OH), 1 490, 1 578, 1 600 (Ar), 2 520, 2 545 (NH^+), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·50 (m, 8 H, ArH), 4·60 (m, 1 H, Ar—CH—S), 4·10 (m, 2 H, 11-CH_2N), 2·68 (bs, 1 H, OH), 1·48 (d, J = 6·5 Hz, 2 H, CH_2 of isobutyl), 0·95 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isobutyl). For $C_{23}H_{30}ClNO_2S$ (420·0) calculated: 65·77% C, 7·20% H, 8·44% Cl, 3·34% N, 7·63% S; found: 65·85% C, 7·16% H, 8·70% Cl, 3·31% N, 7·78% S.

The chromatography was continued and elution with ethanol gave 2·65 g (53%) of a second homogeneous oily product which was identified as 1-(11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-yl)-methylpiperidin-4-ol (*VI*). Hydrochloride, m.p. 254°C (acetone). Mass spectrum, m/z (%): 327·1289 (M^+ corresponding to $C_{19}H_{21}NO_2S$, calculated 327·1293, 10%), 294, 227 (54), 226 (50), 203 (21), 202 (100), 195 (21), 181 (83). IR spectrum: 761 (4 adjacent Ar—H), 1 033 (C—OH), 1 190 (Ar—O—Ar), 1 491, 1 561, 1 579, 1 602 (Ar), 2 420, 2 520, 2 547, 2 620 (NH^+), 3 300 cm^{-1} (OH). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 63·02% C, 6·20% H, 9·87% Cl, 3·92% N, 8·80% S.

N-(11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-11-yl)methyl-trimethylammonium Iodide (*XIV*)

11-(Dimethylaminomethyl)-11*H*-dibenz[*b*,*f*]-1,4-oxathiepin oxalate[8] (0·93 g) was decomposed with NH_4OH and the oily base was isolated by extraction with ether and processing of the extract.

It was dissolved in 10 ml ether, the solution was treated with 5 ml methyl iodide and the mixture allowed to stand for 48 h at room temperature. The precipitated product was filtered and recrystallized from a mixture of ethanol and ether; 0·91 g (86%), m.p. 204·5–205·5°C. For $C_{17}H_{20}$.INOS (413·3) calculated: 49·40% C, 4·88% H, 30·70% I, 3·39% N, 7·76% S; found: 49·23% C, 4·83% H, 30·78% I, 2·99% N, 7·93% S.

(3-Mercapto-4-methoxyphenyl)acetic Acid

A refluxing mixture of 40 ml acetic acid, 9·2 g red P and 0·5 g *I* was treated over 40 min with 33·0 g (3-chlorosulfonyl-4-methoxyphenyl)acetic acid[20], the mixture was refluxed for 3 h, slowly treated with 8 ml water, refluxed for 1 h, mixed with 100 ml water and 100 ml ether and filtered. The filtrate was extracted with ether, the extract was washed with 300 ml 10% NaOH, the washings were separated, acidified with hydrochloric acid and extracted with ether. Processing of the extract and crystallization of the residue gave 17·1 g (69%) product, m.p. 79–83°C. Lit.[20], m.p. 83–84°C.

[3-(2-Iodobenzylthio)-4-methoxyphenyl]acetic Acid (*XVIII*)

A reaction of 24·4 g (3-mercapto-4-methoxyphenyl)acetic acid with 36·5 g 2-iodobenzyl bromide[22] in 400 ml dimethylformamide in the presence of 34 g K_2CO_3 gave 41·6 g crude product which was dissolved in 40 ml chloroform and the solution was filtered through a column of 50 g silica gel. Washing with chloroform, evaporation, and crystallization from aqueous ethanol gave 29·9 g (59%) crude substance, m.p. 99–107°C. Analytical sample, m.p. 104–106°C (aqueous ethanol). IR spectrum: 740, 770, 811, 880 (4 and 2 adjacent and solitary Ar—H), 1 015, 1 249 ($ArOCH_3$), 910, 1 249, 1 708, 2 640, 2 725 (R—COOH), 1 489, 1 598, infl. 3 100 cm^{-1} (Ar). ^1H NMR spectrum: δ 10·80 (bs, 1 H, COOH), 6·70–7·80 (m, 7 H, ArH), 4·13 (s, 2 H, $ArCH_2S$), 3·84 (s, 3 H, OCH_3), 3·50 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{15}IO_3S$ (414·3) calculated: 46·39% C, 3·65% H, 30·64% I, 7·74% S; found: 47·04% C, 3·70% H, 29·87% I, 7·55% S.

Methyl [4-Hydroxy-3-(2-iodobenzylthio)phenyl]acetate (*XIX*)

A solution of 5·6 g *XVIII* in 50 ml dichloromethane was stirred and treated at −10°C over 10 min with 6·8 g BBr_3, added dropwise. The mixture was stirred for 7 h under cooling, allowed to stand for 48 h at room temperature, decomposed with water and filtered. The filtrate was evaporated, the residue was dissolved in benzene and the solution was washed with 10% Na_2CO_3. Acidification of the aqueous solution recovered 3·5 g starting *XVIII*. The benzene layer was evaporated and the residue (2·0 g) was chromatographed on 20 g silica gel. Benzene eluted 0·76 g oil which was identified as *XIX*. Mass spectrum, *m*/*z* (%): 414 (M^+ corresponding to $C_{16}H_{15}$.IO_3S, 3%), 355 ($C_{14}H_{12}IOS$, 2), 227 ($C_{14}H_{11}OS$, 6), 217 (C_7H_6I, 100), 90 (C_7H_6, 55). IR spectrum (film): 725, 760, 828, 873, 888 (4 and 2 adjacent and solitary Ar—H), 1 010, 1 250, 1 290, 1 730 (RCOOR'), 1 155 (ArOH), 1 483, 1 560, 1 580, 1 600, 3 020, 3 045 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum: δ 6·55–7·80 (m, 8 H, ArH and OH), 3·97 (s, 2 H, $ArCH_2S$), 3·69 (s, 3 H, OCH_3), 3·48 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{15}IO_3S$ (414·3) calculated: 46·39% C, 3·65% H, 30·64% I, 7·74% S; found: 47·02% C, 3·96% H, 30·10% I, 8·00% S.

3-(2-Bromophenylthiomethyl)-4-methoxybenzaldehyde (*XX*)

A mixture of 51·1 g 2-bromothiophenol[25], 300 ml dimethylformamide, 49·8 g 3-chloromethyl-4-methoxybenzaldehyde[26] and 38 g K_2CO_3 was stirred and heated for 3 h to 100°C. After cooling the mixture was filtered, the filtrate was evaporated *in vacuo*, the residue was dissolved in 300 ml benzene, the solution was washed with water, 5% NaOH and water, dried and evaporated. The residue was crystallized from ethanol; 72·1 g (79%), m.p. 85—86°C. For $C_{15}H_{13}BrO_2S$ (337·2) calculated: 53·42% C, 3·88% H, 23·70% Br, 9·51% S; found: 53·59% C, 3·94% H, 23·72% Br, 9·58% S.

3-(2-Fluorophenylthiomethyl)-4-methoxybenzaldehyde (*XXVI*)

XXVI was prepared similarly by a reaction of 17·3 g 2-fluorothiophenol[28], 24·9 g 3-chloromethyl-4-methoxybenzaldehyde[26] and 19 g K_2CO_3 in 150 ml dimethylformamide; the crude product was distilled, 31·7 g (85%), b.p. 180—185°C/80 Pa. UV spectrum: λ_{max} 275 nm (log ε 4·26). IR spectrum (film): 756, 820, 880 (4 and 2 adjacent and solitary Ar—H), 1 025, 1 260 ($ArOCH_3$), 1 470, 1 500, 1 580, 1 600, 3 005, 3 060 (Ar), 1 688, 2 730 cm^{-1} (ArCHO). ^1H NMR spectrum: δ 9·80 (s, 1 H, CHO), 7·75 (dd, $J = 8·5$; 2·5 Hz, 1 H, 6-H of benzaldehyde), 7·50 (d, $J = 2:5$ Hz, 1 H, 2-H of benzaldehyde), 6·90 (d, $J = 8·5$ Hz, 1 H, 5-H of benzaldehyde), 6·90—7·40 (m, 4 H, remaining ArH), 4·12 (s, 2 H, $ArCH_2S$), 3·88 (s, 3 H, OCH_3). For $C_{15}H_{13}FO_2S$ (276·3) calculated: 65·20% C, 4·74% H, 6·88% F, 11·60% S; found: 65·39% C, 4·63% H, 6·65% F, 11·40% S.

3-(2-Bromophenylthiomethyl)-4-methoxybenzyl Alcohol (*XXI*)

A stirred solution of 70·1 g *XX* in 130 ml ethanol was treated dropwise at 70°C with a solution of 5·9 g $NaBH_4$ in 27 ml water containing 1 drop 20% NaOH. The mixture was refluxed for 3 h, ethanol was evaporated *in vacuo*, and the residue distributed between 150 ml water and 150 ml benzene. The organic layer was washed with 3% NaOH and water, dried and evaporated; 67·0 g (95%), m.p. 54—55·5°C (aqueous ethanol). IR spectrum: 734, 820, 904 (4 and 2 adjacent and solitary Ar—H), 1 020, 1 255, 2 830 ($ArOCH_3$), 1 030 (CH_2OH), 1 503, 1 575, 1 590, 1 612 (Ar), 3 250 cm^{-1} (OH). ^1H NMR spectrum: δ 6·60—7·60 (m, 7 H, ArH), 4·45 (bd, $J = 5·0$ Hz, 2 H, $ArCH_2O$), 4·10 (s, 2 H, $ArCH_2S$), 3·78 (s, 3 H, OCH_3), 1·80 (bt, $J = 5·0$ Hz, 1 H, OH). For $C_{15}H_{15}BrO_2S$ (339·3) calculated: 53·10% C, 4·46% H, 23·56% Br, 9·45% S; found: 53·21% C, 4·42% H, 23·50% Br, 9·35% S.

3-(2-Fluorophenylthiomethyl)-4-methoxybenzyl Alcohol (*XXVII*)

A similar reduction of 31·7 g *XXVI* in 70 ml ethanol with 3·2 g $NaBH_4$ in 15 ml water gave 31·0 g (97%) *XXVII*, b.p. 185—187°C/50 Pa. IR spectrum: 755, 820, 896 (4 and 2 adjacent and solitary Ar—H), 1 030 (CH_2OH), 1 030, 1 260, 2 835 ($ArOCH_3$), 1 500, 1 588, 1 595, 1 610, 3 000, 3 065 (Ar), 3 360 cm^{-1} (OH). ^1H NMR spectrum: δ 7·10—7·40 (m, 6 H, ArH of fluorophenyl and 2,6-H_2 of benzyl alcohol), 6·80 (d, $J = 8·5$ Hz, 1 H, 5-H of benzyl alcohol), 4·48 (bd, $J = 5·0$ Hz, 2 H, $ArCH_2O$), 4·10 (s, 2 H, $ArCH_2S$), 3·80 (s, 3 H, OCH_3), 1·80 (bt, $J = 5·0$ Hz, 1 H, OH). For $C_{15}H_{15}FO_2S$ (278·4) calculated: 64·73% C, 5·43% H, 6·83% F, 11·52% S; found: 64·33% C, 5·37% H, 6·83% F, 11·60% S.

[3-(2-Bromophenylthiomethyl)-4-methoxyphenyl]acetonitrile (*XXII*)

A solution of 71·2 g *XXI*, in 350 ml benzene was treated with 30 g powdered $CaCl_2$ and saturated with HCl for 2 h. After standing overnight it was filtered and benzene was evaporated. The residue (70·9 g of the crude chloride) was dissolved in 240 ml dimethylformamide, the solution was treated with 23 g NaCN and stirred for 1·5 h without heating and then for 4 h at 100°C. The solvent was evaporated *in vacuo*, the residue was distributed between water and benzene, the organic layer was dried and evaporated; 70·6 g (97%) crude *XXII*. A sample was distilled for analysis with signs of decomposition; b.p. 240—250°C/50 Pa. For $C_{16}H_{14}BrNOS$ (348·3) calculated: 55·18% C, 4·05% H, 22·95% Br, 4·02% N, 9·21% S; found: 55·58% C, 4·20% H, 22·25% Br, 4·52% N, 9·01% S.

[3-(2-Fluorophenylthiomethyl)-4-methoxyphenyl]acetonitrile (*XXVIII*)

A reaction of 30·8 g *XXVII* with HCl in 130 ml benzene followed by treatment of the crude chloride with 20 g NaCN in 100 ml dimethylformamide gave 27·5 g (87%) *XXVIII*, b.p. 193 to 195°C/50 Pa (distills without decomposition). IR spectrum (film): 755, 815, 882 (4 and 2 adjacent and solitary Ar—H), 1 030, 1 220, 1 255 ($ArOCH_3$), 1 503, 1 570, 1 595, 1 612, 3 000, 3 065 (Ar), 2 248 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·60—7·30 (m, 7 H, ArH), 4·05 (s, 2 H, $ArCH_2S$), 3·75 (s, 3 H, OCH_3), 3·52 (s, 2 H, $ArCH_2CN$). For $C_{16}H_{14}FNOS$ (287·4) calculated: 66·88% C, 4·91% H, 6·61% F, 4·87% N, 11·16% S; found: 67·38% C, 4·87% H, 6·53% F, 5·23% N, 11·27% S.

[3-(2-Bromophenylthiomethyl)-4-methoxyphenyl]acetamide (*XXIII*)

A mixture of 64 g crude *XXII*, 180 ml acetic acid, 60 ml acetic anhydride and 120 ml 50% HBr was stirred and saturated with HBr for 1·5 h at 60—70°C. The stirring was continued for 2 h, the mixture was poured into 2 l water and extracted with chloroform. The extract was washed with 5% NaOH and water, dried and evaporated. The residue gave by crystallization from benzene 16·1 g (24%) *XXIII*, m.p. 129—133°C. Mass spectrum, *m*/*z* (%): 367 (3), 365 (M^+ corresponding to $C_{16}H_{16}BrNO_2S$, 3%), 178 (100). IR spectrum: 739, 749, 788, 818 (ArH), 1 020, 1 034, 1 253, 1 282 ($ArOCH_3$), 1 500 (Ar), 1 647 ($CONH_2$), 3 190, 3 375 cm^{-1} (NH_2). ^1H NMR spectrum: δ 6·30—7·70 (m, 9 H, ArH and NH_2), 4·15 (s, 2 H, $ArCH_2S$), 3·75 (s, 3 H, OCH_3), 3·29 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{16}BrNO_2S$ (366·3) calculated: 52·46% C, 4·40% H, 21·82% Br, 3·82% N, 8·75% S; found: 52·78% C, 4·52% H, 21·49% Br, 3·96% N, 8·75% S.

The alkaline washings were acidified with hydrochloric acid and extracted with chloroform. Processing of the extract gave 16·7 g residue which was chromatographed on 200 g silica gel. Chloroform eluted some less polar noncrystallizing components and then ethyl acetate eluted 8·37 g (13%) homogeneous [3-(2-bromophenylthiomethyl)-4-hydroxyphenyl]acetamide (*XXIV*), m.p. 139—143·5°C (benzene–ethanol). IR spectrum: 745, 790, 835, 900 (4 and 2 adjacent and solitary ArH), 1 270, 1 375 (ArOH), 1 508, 1 600 (Ar), 1 650 ($CONH_2$), 3 180, 3 230, 3 360, 3 480 cm^{-1} (OH, NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·60 (s, 1 H, OH), 6·60—7·70 (m, 9 H, ArH and $CONH_2$), 4·15 (s, 2 H, $ArCH_2S$), 3·21 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{14}Br.NO_2S$ (352·3) calculated: 51·14% C, 4·01% H, 22·69% Br, 3·98% N, 9·10% S; found: 51·27% C, 4·12% H, 23·03% Br, 3·87% N, 8·80% S.

XXIV (8·1 g) was refluxed with 5·5 g K_2CO_3 and 1·5 g Cu in 150 ml dimethylformamide (7 h, nitrogen atmosphere). The solvent was evaporated *in vacuo* and the residue distributed between dilute NaOH and chloroform. Processing of the organic layer gave 0·40 g bis (2-bromophenyl) disulfide (*XXV*), m.p. 93—96°C (ethanol). Mass spectrum, *m*/*z* (%): 378, 376, 374 (M^+ corresponding to $C_{12}H_8Br_2S_2$, 7%), 216 ($C_{12}H_8S_2$, 30), 189 (12), 187 (12), 108 (C_6H_4S, 100). ^1H NMR spectrum: δ 7·50 (dd, 4 H, 3,6,3′,6′-H_4), 6·90—7·40 (m, 4 H, remaining ArH). For $C_{12}H_8Br_2S_2$ (376·2) calculated: 38·32% C, 2·14% H, 17·05% S; found: 38·56% C, 2·18% H, 16·80% S. Lit.[27], m.p. 97·5—98°C. Acidification of the alkaline washings gave only amorphous and polymeric material.

[3-(2-Fluorophenylthiomethyl)-4-methoxyphenyl]acetamide (*XXIX*)

A solution of 7·7 g *XXVIII* in 40 ml dichloromethane was stirred and treated over 30 min with 15·5 g BBr_3 at −10°C, the mixture was stirred and cooled for 5 h, decomposed with 50 ml water at 20°C, allowed to stand overnight, filtered and the organic layer of the filtrate was dried and evaporated. From the oily residue, consisting mainly of the starting *XXVIII*, 1·1 g (13%) *XXIX* crystallized, m.p. 96—104°C (benzene). IR spectrum (KBr): 750, 820, 872 (4 and 2 adjacent and solitary ArH), 1 070, 1 225, 1 250 ($ArOCH_3$), 1 470, 1 500, 1 570, 1 590 (Ar), 1 610, 1 655 ($CONH_2$), 3 170, 3 360 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·60—7·50 (m, 9 H, 7 ArH and NH_2), 4·11 (s, 2 H, $ArCH_2S$), 3·70 (s, 3 H, OCH_3), 3·25 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{16}FNO_2S$ (305·4) calculated: 62·93% C, 5·28% H, 6·22% F, 4·59% N, 10·50% S; found: 63·11% C, 5·22% H, 6·33% F, 4·94% N, 10·70% S.

[3-(2-Fluorophenylthiomethyl)-4-hydroxyphenyl]acetamide (*XXX*)

A stirred solution of 6·6 g *XXVIII* in 40 ml dichloromethane was treated dropwise with 15·5 g BBr_3 at −10°C, the mixture was allowed to stand overnight at room temperature, decomposed with water, and extracted with chloroform. Processing of the extract gave 2·6 g (39%) *XXX*, m.p. 104—106°C (chloroform). IR spectrum: 750, 790, 833, 900 (4 and 2 adjacent and solitary ArH), 1 070, 1 212 (ArOH), 1 470, 1 510, 1 568, 3 020 (Ar), 1 608, 1 648 ($CONH_2$), 3 200, 3 260, 3 360, 3 484 cm^{-1} (NH_2, OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·55 (s, 1 H, OH), 6·60—7·50 (m, 9 H, 7 ArH and $CONH_2$), 4·12 (s, 2 H, $ArCH_2S$), 3·20 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{14}$.FNO_2S (291·4) calculated: 61·84% C, 4·84% H, 6·52% F, 4·81% N, 11·01% S; found: 61·72% C, 4·73% H, 6·47% F, 4·62% N, 10·80% S.

[3-(2-Fluorophenylthiomethyl)-4-hydroxyphenyl]acetonitrile (*XXXI*)

A solution of 19·4 g *XXVIII* in 90 ml acetonitrile was treated with 21·4 g NaI and 18·6 g chlorotrimethylsilane and the mixture was stirred and heated to 60°C for 5·5 h. After standing overnight 10·0 g chlorotrimethylsilane were added and the stirring and heating was continued for 8 h. It was then decomposed with water and extracted with ether. The extract was washed with a solution of $Na_2S_2O_3$, dried and evaporated. The residue was chromatographed on 200 g silica gel. Benzene eluted 9·1 g starting *XXVIII* and chloroform eluted then 8·90 g (91% per conversion) of homogeneous *XXXI*, m.p. 103·5—104·5°C (benzene–cyclohexane). UV spectrum: λ_{max} 285 nm (log ε 3·52). IR spectrum: 770, 837, 889 (4 and 2 adjacent and solitary ArH), 1 260, 1 270 (ArOH), 1 470, 1 515, 1 570, 1 595, 1 615 (Ar), 2 270 (R—CN), 3 290 cm^{-1} (OH). ^1H NMR spectrum: δ 6·60—7·40 (m, 7 H, ArH), 6·19 (s, 1 H, OH), 4·08 (s, 2 H, $ArCH_2S$), 3·52 (s, 2 H, $ArCH_2CN$). For $C_{15}H_{12}FNOS$ (273·3) calculated: 65·91% C, 4·43% H, 6·95% F, 5·12% N, 11·73% S; found: 65·65% C, 4·41% H, 7·19% F, 5·19% N, 11·98% S.

11*H*-Dibenz[*b*,*f*]-1,4-oxathiepin-8-acetic Acid (*XVI*)

A solution of 27·4 g *VII* (ref.[8]) in 40 ml acetic acid was treated with 4·7 g paraformaldehyde, 20 ml hydrochloric acid, and 15 ml 85% H_3PO_4 and the mixture was stirred and heated to 100—105°C for 7 h. After cooling it was distributed between water and benzene, the benzene layer was dried and evaporated; 32·6 g oil. It was dissolved in 150 ml dimethylformamide, treated with 15·0 g KCN and heated for 4 h to 100°C. The solvent was evaporated *in vacuo*, the residue distributed between water and benzene and the benzene layer was evaporated giving 35·1 g oil. It was dissolved in 400 ml ethanol, 100 ml 20% NaOH were added and the mixture was refluxed for 6·5 h. Ethanol was evaporated *in vacuo*, the residue dissolved in water and the solution washed with benzene. The aqueous alkaline solution was acidified with hydrochloric acid and the product extracted with ether. Evaporation gave 10·2 g mixture of acids which was chromatographed on 180 g silica gel. Elution with chloroform gave 7·65 g mixture of acids from which crystallization from a mixture of benzene and cyclohexane gave only 1·05 g (3%) homogeneous acid melting at 138—141·5°C to which the structure *XVI* was assigned; it appears to be a 3 : 1 solvate with benzene. Mass spectrum, *m/z* (%): 272 (M^+ corresponding to $C_{15}H_{12}O_3S$, 100%), 254 (21), 226 (62), 184 (35), 165 (30), 134 (40). IR spectrum (KBr): 750, 760, 767, 790, 880, 888 (4 and 2 adjacent and solitary ArH), 910, 1 693, 2 540, 2 600, 2 650, 2 720, infl. 3 100 (R—COOH), 1 232 (ArOAr), 1 482, 1 550, 1 582, 1 600, 3 020, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·05 (bs, 1 H, COOH), 6·70—7·35 (m, 7 H, ArH), 4·25 (s, 2 H, $ArCH_2S$), 3·54 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{12}O_3S + 1/3\ C_6H_6$ (298·4) calculated: 68·43% C, 4·73% H, 10·75% S; found: 68·46% C, 4·69% H, 10·58% S.

The mother liquors were evaporated and the residue was crystallized from benzene; 0·17 g isomeric acid to which the structure of 11*H*-dibenz[*b,f*]-1,4-oxathiepin-2-acetic acid (*XVII*) was tentatively assigned, m.p. 170—174°C. Mass spectrum, *m/z* (%): 272 (M^+ corresponding to $C_{15}H_{12}O_3S$, 100%), 226 (45), 213 (39), 197 (22), 184 (25), 165 (20), 134 (18). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90—7·40 (m, 7 H, ArH), 4·34 (s, 2 H, $ArCH_2S$), 3·55 (s, 2 H, $ArCH_2$. .CO). For $C_{15}H_{12}O_3S$ (272·3) calculated: 66·17% C, 4·44% H, 11·76% S; found: 65·98% C, 4·60% H, 11·66% S.

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