REACTIONS OF 11-CHLORO-11-PHENYL-6,11-DIHYDRODIBENZO[*b,e*]-THIEPIN WITH PIPERIDINE AND SOME FURTHER NUCLEOPHILES*

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The title compound *Vb* affords with piperidine normal nucleophilic substitution product and the isomeric 3-piperidino derivative *XXXII*. The structure of *XXXII* was proven by (*1*) the ^{1}H NMR and ^{13}C NMR spectra, (*2*) an independent synthesis *via* the intermediates *XXXV*, *XXXVI*, *XXX*, *IV* and *VIIIa*, and (*3*) with the help of model reactions of the 2-methyl derivative *VIb* and the 3-methyl derivative *VIIb* with piperidine. The rearranged cation *XXXVII* is considered a precursor of the product *XXXII*. Similar mixtures are apparently formed in reactions of the chloro derivative *Vb* with a series of further amines where, however, mostly the normal substitution products (*XV*–*XXI*) were isolated and only in two cases the formation of the 3-substituted compounds (*XXXIII*, *XXXIV*) was noted. The 11-amino derivatives of the type *XIII* are unstable in ethanol in the presence of hydrogen chloride; the product of their acid catalyzed solvolysis is the ethoxy derivative *XIV*. Potassium phthalimide reacts with the compound *Vb* under the formation of the normal product *XXII* accompanied by 9-phenylanthracene (*XXXVIII*). Reaction of *Vb* with 3-dimethylaminopropylmagnesium chloride affords on the one hand the normal product *XXIV*, and the isomer on the other, to which the structure *XXXIX* is ascribed. The biological screening of the amines prepared showed with some compounds a rather significant antimicrobial activity *in vitro* (*e.g. XXXIII*) and some structurally less specific neurotropic effects, especially the spasmolytic (*XXII*, *XXXIX*) and the central depressant one (*XX*, *XXXIII*).

The present paper represents a continuation of our previous systematic pharmaco-chemical investigations in the series of 6,11-dihydrodibenzo[*b,e*]thiepin derivatives[1,2]. Dibenzo[*b,e*]thiepin-11(6*H*)-one (*I*) was the starting compound[3–9] which was transformed *via* the tertiary alcohol *Va* to the chloro compound *Vb* using procedures described recently by Hori and coworkers[10] who devoted a series of five communications[10–14] to studies of the 11-phenyldibenzo[*b,e*]thiepin derivatives. These studies had theoretical orientation and especially dealt with characterization of the cation *IX* which was isolated in the form of the crystalline hexachloroantimonate. By shifting the double bonds and the charge its easy rearrangement to the cation *X* is assumed which explains an interesting cyclization reaction proceeding by treat-

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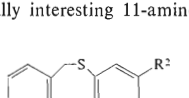
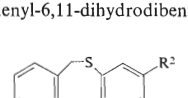
ment of the chloro compound *Vb* with an excess of antimony pentachloride; after the reduction of the intermediate with lithium aluminium hydride the pentacyclic compound *XI* was obtained (ref.[10]). Our own interest in these studies had a practical background: the chloro compound *Vb* was considered a suitable starting material for nucleophilic substitution reactions with amines by which we believed to obtain pharmacologically interesting 11-amino-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepins

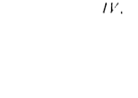


I, $R^1 = R^2 = H$
II, $R^1 = CH_3$, $R^2 = H$
III, $R^1 = H$, $R^2 = CH_3$
IV, $R^1 = H$, $R^2 =$ 

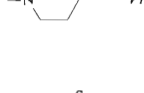


V, $R^1 = R^2 = H$
VI, $R^1 = CH_3$, $R^2 = H$
VII, $R^1 = H$, $R^2 = CH_3$
VIII, $R^1 = H$, $R^2 =$ 

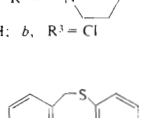
a, $R^3 = OH$; *b*, $R^3 = Cl$



IX



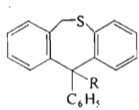
X



XI, R = H
XII, R = CH_3

Piperidine was the first amine used within this project; its reaction with the chloro compound *Vb* in boiling chloroform resulted in an inhomogeneous oily base which was considered to be the crude amine *XIII*. In an attempt at preparing its hydrochloride by treatment with hydrogen chloride in ethanol we obtained on the one hand piperidine hydrochloride[15] and a nitrogen-free substance on the other, which was identified by means of analysis and spectra as the 11-ethoxy derivative *XIV*. Such behaviour of the base *XIII* could indeed be expected: It was clear that the bond of the amino group to the trityl α-carbon atom will be rather unstable. The starting oily base crystallized partly on longer standing and in this way we obtained the compound of the expected elemental composition with the melting point of 192–194°C. Its ^{1}H NMR spectrum, however, showed a singlet at δ 5·15 ppm which could be assigned only to a proton on the trityl α-carbon. In addition, the integration of the

aromatic protons indicated a deficit: Instead of the expected 13 Ar—H only 12 were present. After having found similar phenomena in reactions of *Vb* with some further amines, a hypothesis was formulated suggesting that our oily base is a mixture of two compounds, *i.e.* the expected base *XIII*, the isolation of which in pure state did not succeed first, and the isomeric crystalline base which was tentatively formulated as compound *XXVI* on the basis of the ^{1}H NMR and IR spectra. This spectral evidence could not differentiate whether the piperidine residue is located in position 2 or 3 of the skeleton. Finally we succeeded by combination of chromatography and crystallization in obtaining both of the bases in crystalline state. As far as polarity is concerned, they differ insignificantly and both of them melt practically at the same temperature; in the mixture, however, they melt with a significant depression. From the preparative experiment it was not possible to obtain a clear idea on the quantitative composition of the starting mixture. The ^{1}H NMR spectrum of the mixture of bases was used to this purpose with comparing the area of the 11-H singlet with that of the multiplet of the aromatic protons: Their ratio led to the conclusion that the mixture consists approximately of 75% compound *XIII* and 25% compound *XXVI*.



XIII, R = —N⟨piperidine⟩

XIV, R = OC_2H_5

XV, R = —N⟨pyrrolidine⟩

XVI, R = —N⟨morpholine⟩O

XVII, R = $NHCH_2C_6H_5$

XVIII, R = $NH(CH_2)_2NH_2$

XIX, R = $NH(CH_2)_2N(CH_3)_2$

XX, R = $NH(CH_2)_2N(C_2H_5)_2$

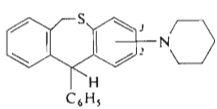
XXI, R = $NH(CH_2)_3$N⟨morpholine⟩O

XXII, R = —N⟨phthalimide⟩O

XXIII, R = H

XXIV, R = $(CH_2)_3N(CH_3)_2$

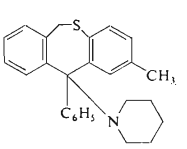
XXV, R = OCH_3



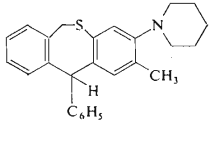
XXVI

For supporting the identification of the substitution product *XXVI* two model experiments were carried out in which first the position 2 and then the position 3 of the skeleton were blocked by a methyl group. The ketone *II* is a known compound[4,6,7,16,17]. Its reaction with phenylmagnesium bromide in ether gave the tertiary alcohol *VIa* which was transformed by treatment with thionyl chloride in boiling dichloromethane to the chloro derivative *VIb*. The preparation of compounds *VIa* and *VIb* by similar methods was mentioned in a patent[18] (experimental details and data on the characterization of the products are not available). When the chloro compound *VIb* was heated to 100°C, decomposition took place and as the sole crystalline product a compound $C_{21}H_{16}S$ was isolated in a small amount and identified by means of the ^1H NMR and IR spectra as 9-methyl-5,13b-dihydrofluoreno[1,9a,9-*c*,*d*]-2-benzothiepin (*XII*). We are thus dealing here with a product of dehydrochlorination of *VIb* in which apparently a cation like *X* appears as an intermediate. The reaction of the chloro compound *VIb* with an excess of piperidine in boiling chloroform resulted in an inhomogenous base which was separated to two isomers. The spectra could definitely differentiate the normal substitution product *XXVII* and the anomalous product to which the structure of the 3-piperidino derivative *XXVIII* could be attributed.

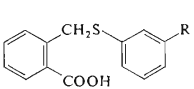
In the 3-methyl series we started from *m*-thiocresol[19] whose sodium salt afforded by a reaction with phthalide in boiling ethanol the acid *XXIX*. The cyclization with polyphosphoric acid at 110°C gave the ketone *III* which was transformed by treatment with phenylmagnesium bromide in ether to the tertiary alcohol *VIIa*. The following reaction with thionyl chloride in dichloromethane under cooling resulted in the very unstable chloro derivative *VIIb* which reacted with excessive



XXVII

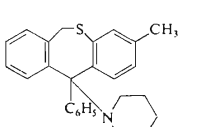


XXVIII



XXIX, R = CH_3

XXX, R = —N

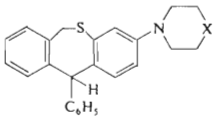


XXXI

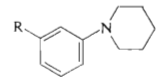
piperidine in boiling dichloromethane and gave a sole crystalline product. It was characterized by means of the ^{1}H NMR and IR spectra as the normal substitution product *XXXI*. The results of both model experiments can be summarized in the sense that while the methyl group in position 2 does not interfere with the course of the anomalous substitution reaction, the methyl group in position 3 prevents this reaction. These results represented a preliminary evidence of the location of the piperidine residue in compound *XXVI* in position 3.

For having a rigorous proof of structure of the compound *XXVI* as the 3-piperidino derivative *XXXII*, an independent "total" synthesis of the compound *XXXII* was carried out. A reaction of 3-bromoaniline with 1,5-dibromopentane[20] in boiling ethanol (analogy, *cf.*[21]) gave 1-(3-bromophenyl)piperidine (*XXXV*) which was converted by treatment with lithium in boiling ether to the lithium derivative. The following reaction with sulfur led to 3-piperidinothiophenol (*XXXVI*). Its sodium salt reacted with phthalide in boiling ethanol and gave the amino acid *XXX* which was cyclized with polyphosphoric acid at 130°C. Chromatography of the oily product afforded in a moderate yield the desired 3-piperidinodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*IV*) which was treated with phenylmagnesium bromide in ether and gave the amino alcohol *VIIIa*. By its reduction with hydroiodic acid in boiling acetic acid the amine *XXXII* was obtained and was found identical with the base, formulated originally as *XXVI*. We try to explain its formation from the chloro compound *Vb* by a rearrangement of the primary cation *IX* to the isomeric cation *XXXVII* which already has the necessary presupposition for being the precursor of compound *XXXII*. The structure *XXXII* was finally confirmed also by means of the ^{13}C NMR spectrum: The signal of the quaternary carbon in position 11a is shifted upfield (to 124·8 ppm) which indicates its *para*-position toward the nitrogen atom on the nucleus; signals at 115·1 and 113·6 ppm correspond to the methine carbons in *ortho*-positions to the nitrogen atom and the difference in their shifts (1·5 ppm) is caused by their unsymmetric position toward the sulfur atom.

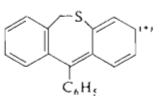
Reactions of the chloro compound *Vb*, with pyrrolidine and morpholine have apparently a similar course like the reaction with piperidine but in these cases only bases of the normal series *XV* and *XVI* could be isolated in crystalline state.The base *XV* is cleaved already in an attempt at preparing the maleate by neutralization with maleic acid in boiling ethanol; the ethoxy derivative *XIV* results again as the product and pyrrolidine hydrogen maleate was furhter isolated. The base *XVI* does not show in the ^{1}H NMR spectrum the signal of the trityl α-proton and by treatment with hydrogen chloride in a mixture of ethanol and ether undergoes solvolysis with the formation of the ether *XIV*. From the reaction of compound *Vb* with benzylamine two products were isolated but their ^{1}H NMR spectra are identical. We are dealing here with two crystal modifications of the 11-benzylamino derivative *XVII*, one of which having been already described[12].



XXXII, X = CH_2
XXXIII, X = NCH_3
XXXIV, X = NCH_2CH_2OH



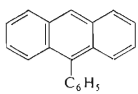
XXXV, R = Br
XXXVI, R = SH



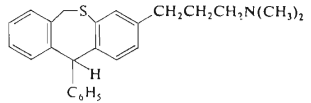
XXXVII

The chloro compound *Vb* was further reacted with the following diamines: (*a*) ethylenediamine, (*b*) N,N-dimethylethylenediamine[22], (*c*) N,N-diethylethylenediamine and (*d*) N-(3-aminopropyl)morpholine. Structures of the 11-amino derivatives *XVIII*–*XXI* were assigned to the products; in cases (*b*) and (*d*) the proof of structure was given by means of the ^{1}H NMR spectra, the structure of products in cases (*a*) and (*c*) is assigned on the basis of analogy. These products reveal a higher stability which enabled the preparation of crystalline maleates. In cases (*c*) and (*d*) it was even possible to isolate the crude bases from the organic solvents into dilute hydrochloric acid without a more substantial decomposition. On the other hand in cases (*a*) and (*b*) the cleavage was observed when this procedure was used; as products of this cleavage ethylenediamine maleate and the 11-ethoxy derivative *XIV* were isolated and characterized.

The opposite results were noted in reactions of the chloro compound *Vb* with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine. Mixtures are apparently formed again but the isolated crystalline bases show in the ^{1}H NMR spectra the singlet of the trityl α-proton. These bases are stable in acid solutions and afford without difficulties crystalline maleates. On the basis of analogy structures *XXXIII* and *XXXIV* were assigned to them. A reaction of compound *Vb* with potassium phthalimide in boiling xylene or in dimethylformamide at 60°C gave a product for which the spectra determined the structure of the phthalimido derivative *XXII*. In the first case (reaction in xylene) there was obtained a hydrocarbon $C_{20}H_{14}$ (mass spectrum) as the less polar by-product and was identified as 9-phenylanthracene[23] (*XXXVIII*) It is a further case of sulfur extrusion with which we encountered in the dibenzo[*b*,*e*]-thiepin series heterofore[24,25].



XXXVIII



XXXIX

In an attempt at reacting the chloro derivative *Vb* with the sodium salt of thiophenol in dimethylformamide an inhomogeneous oily product was formed from which two crystalline substances were isolated in minute amounts. The first is a compound $C_{20}H_{16}S$ which was identified by the ^{1}H NMR spectrum as 11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXIII*). Its formation has to be explained by reduction of a small amount of compound *Vb* with thiophenol; this view is substantiated by the identity of the second crystalline product which is diphenyl disulfide[26], *i.e.* the product of thiophenol oxidation. Compound *XXIII* was also obtained by reduction of the alcohol *Va* with hydroiodic acid in boiling acetic acid and the same compound has previously been prepared[10] by several further procedures. An interesting course was revealed by the reaction of the chloride *Vb* with 3-dimethylaminopropylmagnesium chloride in a mixture of ether and benzene. An oily mixture of bases was obtained in a high yield and was separated by chromatography on aluminium oxide. The main product is the less polar crystalline base $C_{25}H_{27}NS$ whose ^{1}H NMR spectrum and IR spectrum are a reliable basis for its formulation as the 11-(3-dimethylaminopropyl) derivative *XXIV*, *i.e.* the normal product. The minor more polar base is oily and its ^{1}H NMR spectrum shows the typical singlet of the trityl α-proton at 5·20 ppm. On the basis of analogy we assign to this product the structure of the 3-(3-dimethylaminopropyl) derivative *XXXIX*. Both bases afforded crystalline hydrogen maleates. Finally, the reaction of the chloro compound *Vb* with sodium methoxide in a mixture of methanol and benzene was carried out; the expected 11-methoxy derivative *XXV* was formed, which was prepared by a similar procedure heterofore[10].

We have to note that the described formation of unusual products (*XXVIII*, *XXXII*–*XXXIV*, *XXXIX*) of substitution of the chloro derivatives *Vb* and *VIb* has its analogy in results of another group[27–30] who investigated for example the reaction of 9-benzhydrylidene-10-chloro-10-phenyl-9,10-dihydroanthracene with sodium methoxide and described in addition to the normal substitution product also the formation of anomalous isomers. A common feature with our cases is the steric hindrance of the leaving group which causes the rearrangement of the primary cation and location of the substituent in a sterically more favourable position, eventually even on the aromatic nucleus.

Some of the amines prepared and their salts were subjected to pharmacological screening (Dr S. Wildt, affiliated unit of our institute at Rosice n/L). In the test

of acute toxicity in mice (oral administration) compounds *XIII*, *XVI*, *XVIII*, *XX* and *XXXII–XXXIV* were very little toxic; their LD_{50} are above 2·5 g/kg; compound *XXI* has an LD_{50} 2·5 g/kg. These compounds were administered in the screening in basic oral doses of 300 mg/kg. Maleates of some of the bases were water-soluble which enabled their parenteral administration; their LD_{50} in mg/kg on *i.v.* administration and the basic doses D (mg/kg) are given: *XX*, 50, 10; *XXIV*, 20, 4; *XXXIX*, 40, 8. In general, the pharmacodynamic activity of the compounds tested is little significant and the screening showed the following results: *XIII*, in an oral dose of 300 mg/kg an antitussic effect in the test of citric acid aerosol in guinea pigs was noted (36% inhibition in comparison with the control). *XVI*, in doses above 300 mg/kg *p.o.* brings about ptosis in mice lasting for 6 h after the adminstration. *XVIII*, in doses above 300 mg/kg *p.o.* reduced the activity in mice and brought about ptosis lasting for 6 h after the administration. *XIX*, in the oral dose of 300 mg/kg has antiinflammatory effect in the test of caolin arthritis in rats; the highest dose administered (2·5 g/kg) to mice brought about tremor and convulsions in a part of animals, the dose was lethal only for 20% animals. *XX*, on *i.v.* administration doses above 10 mg/kg had convulsant effect and the mice perished within 2 min, on oral administration a dose of 2·5 g/kg is tolerated without toxic symptoms; a dose of 10 mg/kg *s.c.* brings about a mild decrease of motility of mice in known surroundings; an oral dose of 300 mg/kg showed signs of antiinflammatory action in the test of caolin arthritis in rats (a dose of 50 mg/kg was without effect). *XXI*, in oral doses above 300 mg/kg reduced the activity and reactivity of mice, elicited ptosis and hypothermia. *XXIV*, a dose of 4 mg/kg *i.v.* elicited brief and deep drops of blood pressure in normotensive rats, in concentrations of 1 – 10 μg/ml it had spamolytic effects on isolated rat duodenum towards acetylcholine, as well as barium chloride contractions. *XXXII*, oral doses above 300 mg/kg in mice elicited ptosis lasting for 6 h after the administration. *XXXIII*, oral doses above 300 mg/kg in mice brought about reduced activity and ptosis. *XXXIV*, in an oral dose of 300 mg/kg the substance exhibited anorectic effects in mice (in two experiments reduction of food consumption by 83, and 50% respectively, in comparison with the control group). *XXXIX*, a dose of 8 mg/kg *i.v.* elicited brief and deep drops of blood pressure in rats, in concentrations of 1 – 10 μg/ml there was a spasmolytic effect on the isolated rat duodenum towards the acetylcholine and barium chloride contractions.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, Bacteriological department of this institute); the microorganisms and the minimum inhibitory concentrations (MIC in μg/ml) unless they are higher than 100 μg/ml are given: *Streptococcus β-haemolyticus*, *XIII* 12·5, *XVIII* 25, *XIX* 25, *XX* 25, *XXIV* 12·5, *XXXIII* 6·2, *XXXIV* 12·5, *XXXIX* 12·5; *Streptococcus faecalis*, *XVIII* 50, *XIX* 50, *XX* 50, *XXIX* 25, *XXXIII* 12·5, *XXXIV* 100, *XXXIX* 12·5; *Staphylococcus pyogenes aureus*, *XIII* 25, *XVIII* 50, *XIX* 50, *XX* 25, *XXIV* 12·5, *XXXIII* 12·5, *XXXIV* 25, *XXXIX* 12·5; *Escherichia coli*, *XVIII* 50, *XIX* 50, *XX* 25, *XXIV* 25, *XXXIII* 25, *XXXIV* 50, *XXXIX* 12·5; *Proteus vulgaris*, *XXIV* 100, *XXXIX* 100; *Mycobacterium tuberculosis* H37Rv, *XX* 50, *XXXIV* 100; *Saccharomyces pasterianus*, *XXXIII* 50; *Trichophyton*

mentagrophytes, *XVI* 50, *XVIII* 50, *XXIV* 50, *XXXIII* 50, *XXXIV* 50, *XXXIX* 50; *Candida albicans*, *XXXIX* 50; *Aspergillus niger*, *XXXIII* 50. With regard to the significant inhibiting activity of compound *XXXIII*, especially towards cocci, this compound was tested in a multipoint inoculator with the use of 20 strains of *Staphylococcus pyogenes aureus* and 20 strains of *Escherichia coli*. While in the first case the activity was confirmed (MIC 6·2—25 μg/ml), in the second case the substance was found less active (MIC in average above 100 μg/ml) and its investigation was discontinued.

EXPERIMENTAL

The melting points were determined in an automatic Mettler FP-5 melting point recorder or in Kofler's block and are not corrected. The samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in nujol) with a Unicam SP 200G spectrophotometer, the ^{1}H NMR spectra (mostly in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrophotometer and the mass spectra with the spectrometers MCH 1320 and/or MAT 44S. The ^{13}C-NMR spectrum was measured on a Jeol FX-60 NMR spectrometer (15·036 MHz) in FT mode in C^2HCl_3 at 25°C. Chemical shifts are given in the δ-scale referenced to tetramethylsilane (internal standard) with accuracy ±0·08 ppm. They were calculated from the digitally obtained address differences. To improve the signal to noise ratio, the accumulated free induction decays were multiplied by an exponential causing additional line broadening of 1·6 Hz. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol). The column chromatographic separations were carried out either on neutral Al_2O_3 (activity II) or on silica gel (Silpearl).

1-(3-Bromophenyl)piperidine (*XXXV*)

A mixture of 144 g 3-bromoaniline, 77 g 1,5-dibromopentane[20] and 500 ml ethanol was refluxed for 23 h, the solvent was evaporated under reduced pressure, the residue was diluted with 10% NaOH and the product extracted with benzene. The extract was dried with K_2CO_3 and distilled; 55·5 g (70%), b.p. 157—163°C/0·45 kPa. ^{1}H NMR spectrum: δ 6·60—7·30 (m, 4 H, Ar—H), *c.* 3·10 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{11}H_{14}BrN$ (240·2) calculated: 55·01% C, 5·88% H, 33·28% Br, 5·83% N; found: 55·70% C, 6·07% H, 32·62% Br, 5·84% N.

3-Piperidinothiophenol (*XXXVI*)

XXXV (53·8 g) was added dropwise to 3·5 g Li in 250 ml ether and the mixture was refluxed for 3 h under nitrogen. It was then treated over 15 min with 4·8 g S, the mixture was refluxed for 1 h, cooled and decomposed with a mixture of 30 ml hydrochloric acid and 40 ml water. The acid mixture was neutralized with 5% $NaHCO_3$, the organic layer was separated and extracted with 300 ml 10% NaOH. Evaporation of the organic layer recovered 34·1 g starting *XXXV*. The aqueous alkaline solution was acidified with 50 ml hydrochloric acid and 20 ml acetic acid and the amphoteric product was isolated by extraction with benzene. The extract was dried with $MgSO_4$ and distilled; 5·9 g (37% per conversion), b.p. 135—137°C/70 Pa. ^{1}H NMR spectrum: δ 6·50—7·30 (m, 4 H, Ar—H), 3·40 (bs, 1 H, SH), 3·10 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{11}H_{15}NS$ (193·3) calculated: 68·34% C, 7·82% H, 7·25% N, 16·59% S; found: 68·66% C, 7·95% H, 7·28% N, 16·28% S.

2-(3-Methylphenylthiomethyl)benzoic Acid (*XXIX*)

m-Thiocresol[19] (27·8 g) was dissolved in a solution of sodium ethoxide (from 5·15 g Na and 75 ml ethanol) and the solution was treated with 30 g phthalide. The mixture was stirred and refluxed for 3 h, diluted with 100 ml water, ethanol was evaporated, the residue was diluted with another 100 ml hot water and the solution was filtered with charcoal. The filtrate was cooled and acidified with 45 ml 5M-HCl. The precipitated acid was filtered, washed with water and dried *in vacuo*; 51 g (88%), m.p. 90–94°C. Analytical sample, m.p. 97–99°C (Kofler) (aqueous ethanol). UV spectrum: inflexes at 285 nm (log ε 3·45), and 253 nm (3·87). IR spectrum: 695, 715, 770, 778, 892 (4 and 3 adjacent and solitary Ar—H), 925, 1 272, 1 302, **1 690**, 2 480, 2 520, 2 600, infl. 3 120 (ArCOOH), 1 490, 1 570, 1 590 cm^{-1} (Ar). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·76% C, 5·53% H, 12·87% S.

2-(3-Piperidinophenylthiomethyl)benzoic Acid (*XXX*)

Na (0·7 g) was dissolved in 15 ml ethanol and the solution was treated with 5·75 g *XXXVI* and 4·0 g phthalide and the mixture was refluxed for 3·5 h. Ethanol was evaporated under reduced pressure, the residue was dissolved in water and the solution was acidified with 2·5 ml acetic acid. The product was isolated by extraction with benzene. The extract was evaporated and the residue was crystallized from a mixture of benzene and light petroleum; 5·85 g (60%), m.p. 126–129°C (Mettler). UV spectrum: λ_{max} 300 nm (log ε 3·45), 226 nm (4·34), infl. 259 nm (4·14). IR spectrum: 710, 770, 865 (4 and 3 adjacent and solitary Ar—H), 935, 1 240, 1 270, 1 300, **1 685**, infl. 3 160 (ArCOOH), 1 580 (Ar), 2 640 cm^{-1} (NH^+). ^1H NMR spectrum: δ 11·40 (bs, 1 H, COOH), 8·00 (m, 1 H, 6-H), 6·70–7·40 (m, 7 H, remaining Ar—H), 4·52 (s, 2 H, $ArCH_2S$), 3·10 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{19}H_{21}NO_2S$ (327·5) calculated: 69·69% C, 6·46% H, 4·28% N, 9·79% S; found: 69·88% C, 6·48% H, 3·96% N, 9·73% S.

3-Methyldibenzo[*b*,*e*]thiepin-11(6*H*)-one (*III*)

Polyphosphoric acid was prepared by stirring a mixture of 110 ml 85% H_3PO_4 and 180 g P_2O_5 for 1·5 h at 125°C. *XXIX* (50 g) was slowly added under stirring and the mixture was heated for 1·5 h to 110°C. After cooling the mixture was decomposed with 600 ml water and the product was extracted with benzene. The extract was washed with 5% NaOH and water, filtered with charcoal, dried with Na_2SO_4 and evaporated. The residue (44 g) was crystallized from 180 ml ethanol and gave 34·1 g (73%) pure product, m.p. 67–68°C (Kofler). UV spectrum: λ_{max} 350 nm (log ε 3·56), 245 nm (4·37), infl. 278 nm (3·99). IR spectrum: 730, 765, 820, 875, 882 (4 and 2 adjacent and solitary Ar—H), 1 595 (Ar), 1 650 cm^{-1} (ArCOAr'). ^1H NMR spectrum: δ 8·10 (bd, 1 H, 1-H), 6·90–7·70 (m, 6 H, remaining Ar—H), 3·95 (s, 2 H, $ArCH_2S$), 2·23 (s, 3 H, CH_3). For $C_{15}H_{12}OS$ (240·3) calculated: 74·96% C, 5·04% H, 13·34% S; found: 75·14% C, 5·07% H, 13·35% S.

3-Piperidinodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*IV*)

A mixture of 50 g polyphosphoric acid and 5·7 g *XXX* was stirred for 30 min at 130°C and decomposed by pouring on ice. It was made alkaline with 50% NaOH and extracted with chloroform. The extract was dried with K_2CO_3, evaporated and the residue was chromatographed on 200 g silica gel. Benzene eluted 3·18 g (59%) homogeneous product as the least polar component, m.p. 138–138·5°C (Mettler) (benzene–cyclohexane). UV spectrum: λ_{max} 247 nm

(log ε 4·33), 295 nm (3·75), 375 nm (4·42). IR spectrum: 740, 770, 840, 860 (4 and 2 adjacent and solitary Ar—H), 1 570, 1 595 (Ar), 1 610 cm^{-1} (ArCOAr—NR_2). ^1H NMR spectrum: δ 8·25 (d, J = 8·0 Hz, 1 H, 1-H), 7·65 (m, 2 H, 4,10-H_2), 7·00—7·40 (m, 3 H, 7,8,9-H_3), 6·71 (q, J = 2·5; 8·0 Hz, 1 H, 2-H), 3·98 (s, 2 H, $ArCH_2S$), 3·30 (bm, 4 H, CH_2NCH_2), 1·60 (bm, 6 H, remaining 3 CH_2 of piperidine). For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N 10·36% S; found: 73·76% C, 6·20% H, 4·16% N, 10·60% S.

11-Phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*Va*)

The Grignard reagent was prepared by treatment of 5·86 g Mg with 41·6 g bromobenzene in 190 ml boiling ether. After cooling to 20—25°C it was treated dropwise over 30 min with a solution of 27·1 g *I* (ref.[3-9]) in 120 ml benzene and the mixture was refluxed for 4 h. After cooling it was decomposed with 200 ml 10% NH_4Cl. Usual processing of the organic layer gave 30·0 g (82%) *Va*, m.p. 200—204°C. Crystallization from ethanol gave a product melting at 204—205°C (Kofler). Lit.[10], m.p. 206—207°.

2-Methyl-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VIa*)

The Grignard reagent prepared from 12·2 Mg and 87·5 g bromobenzene in 380 ml ether was stirred and treated dropwise at room temperature over 40 min with a solution of 60 g *II* (ref.[16,17]) in 250 ml benzene. The mixture was refluxed for 4 h, cooled and decomposed with 400 ml 20% NH_4Cl. Processing of the organic layer yielded 70·5 g (89%) product, m.p. 156—158°C. Analytical sample, m.p. 159—160°C (Mettler) (ethanol). IR spectrum (KBr): 704, 753, 772, 812, 872, 885 (5, 4 and 2 adjacent and solitary Ar—H), 1 015 (R_3C—OH in a ring), 1 472, 1 482, 1 492, 1 594, 3 020 (Ar), 3 390, 3 490 cm^{-1} (OH). ^1H NMR spectrum: δ 8·00 (m, 1 H, 10-H), 7·78 (bs, 1 H, 1-H), 6·80—7·40 (m, 10 H, remaining Ar—H), 3·60 and 3·10 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 2·22 (s, 4 H, CH_3 and OH). For $C_{21}H_{18}OS$ (318·4) calculated: 79·21% C, 5·70% H, 10·07% S; found: 79·14% C, 5·83% H, 10·20% S.

3-Methyl-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VIIa*)

A similar reaction of the Grignard reagent (prepared from 4·15 g Mg and 29·5 g bromobenzene in 130 ml ether) with 20·4 g *III* in 90 ml benzene gave a crude product which was crystallized from 85 ml toluene; 21·9 g (81%), m.p. 183—186°C. Analytical sample, m.p. 184·5—186°C (Kofler) (toluene). IR spectrum: 704, 750, 765, 775, 805, 825, 865, 886 (5, 4 and 2 adjacent and solitary Ar—H), 1 155 (R_3C—OH), 1 480, 1 595 (Ar), 3 480 cm^{-1} (OH). For $C_{21}H_{18}OS$ (318·4) calculated: 79·21% C, 5·70% H, 10·07% S; found: 79·01% C, 5·72% H, 10·20% S.

11-Phenyl-3-piperidino-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VIIIa*)

A similar reaction of the Grignard reagent (prepared from 0·73 g Mg and 4·71 g bromobenzene in 30 ml ether) with 2·9 g *IV* in 20 ml benzene gave a crude product which was recrystallized from a mixture of benzene and light petroleum; 2·70 g (74%), m.p. 215—220°C. Analytical sample. m.p. 218—221°C (Mettler) with decomposition (benzene–light petroleum). IR spectrum: 710, 768, 774, 820, 867 (5, 4 and 2 adjacent and solitary Ar—H), 1 154 (R_3C—OH), 1 545, 1 594 (Ar), 3 040 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·00 (m, 1 H, 10-H), 7·82 (d, J = 8·5 Hz, 1 H, 1-H), 7·00—7·40 (m, 8 H, C_6H_5 and 7,8,9-H_3), 6·71 (q, J = 8·5; 2·0 Hz, 1 H, 2-H), 6·52 (d, J = 2·0 Hz, 1 H, 4-H), 6·21 (s, 1 H, OH), 3·52 and 3·25 (ABq, J = 13·0 Hz, 2 H,

$ArCH_2S$), 3·05 (bs, 4 H, CH_2NCH_2), 1·50 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{25}H_{25}NOS$ (387·5) calculated: 77·48% C, 6·50% H, 3·62% N, 8·27% S; found: 77·16% C, 6·66% H, 3·30% N, 8·38% S.

11-Chloro-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*Vb*)

A solution of 25·8 g *Va* in 230 ml dichloromethane was stirred and treated dropwise with 69 ml $SOCl_2$ and the mixture was refluxed for 3 h. After standing overnight the mixture was diluted with 150 ml benzene and the volatile components were completely evaporated *in vacuo* at 40°C. The residue was mixed with 100 ml light petroleum and filtered; 23·9 g (91%), m.p.143—146°C (Mettler). Crystallization from a mixture of benzene and light petroleum gave a product melting at 143—145·5°C. Lit.[10], m.p. 144—145·5°C.

11-Chloro-2-methyl-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*VIb*)

A solution of 35·0 g *VIa* in 350 ml dichloromethane was stirred and treated dropwise at 30°C over 45 min with 90 ml $SOCl_2$. The mixture was refluxed for 3 h, allowed to stand overnight at room temperature and evaporated *in vacuo*. The residue was diluted with 200 ml benzene and the solution was completely evaporated *in vacuo* at 40°C. The residue crystallized from 100 ml light petroleum and the crude product was recrystallized from a mixture of 25 ml benzene and 75 ml light petroleum; 24·8 g (67%), m.p. 137—139°C. Repeating the crystallization gave the analytical sample, m.p. 140—142°C (Mettler). ^{1}H NMR spectrum: δ 8·15 (m, 1 H, 10-H), 8·10 (d, 1 H, 1-H), 6·80—7·50 (m, 10 H, remaining Ar—H), 3·60 and 3·25 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 2·30 (s, 3 H, CH_3). For $C_{21}H_{17}ClS$ (336·9) calculated: 74·87% C, 5·09% H, 10·53% Cl, 9·52% S; found: 75·12% C, 5·22% H, 10·59% Cl, 9·70% S.

11-Chloro-3-methyl-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*VIIb*)

A solution of 1·78 g $SOCl_2$ in 10 ml dichloromethane was added dropwise over 3 h to a stirred and cooled solution of 4·8 g *VIIa* in 50 ml dichloromethane at a maximum temperature of 20°C. The mixture was stirred for 3 h and allowed to stand overnight at room temperature. It was then evaporated *in vacuo* at 22°C, the residue was mixed with 50 ml light petroleum and the crystalline product was filtered; 3·9 g (77%), m.p. 111—113°C (Kofler) with decomposition. A recrystallization was impossible because of an extreme instability of the compound. ^{1}H NMR spectrum: δ 6·60—8·00 (m, 12 H, Ar—H), 3·40 (bs, 2 H, $ArCH_2S$), 2·20 (s, 3 H, CH_3). For $C_{21}H_{17}ClS$ (336·9) calculated: 74·87% C, 5·09% H, 9·52% S; found: 74·62% C, 5·25% H, 9·28% S.

9-Methyl-5,13b-dihydrofluoreno[1,9a,9-*cd*]-2-benzothiepin (*XII*)

The crude *VIb* prepared from 35 g *VIa*, was heated on the water bath for a short time to 100°C. Decomposition took place and from the oily product only 1·8 g crystalline solid could be obtained by crystallization from a mixture of 30 ml benzene and 60 ml light petroleum. This product was recrystallized from benzene and melted at 212—216°C (Mettler). Mass spectrum, m/z (%): 300 (M^+ corresponding to $C_{21}H_{16}S$), 285 ($C_{20}H_{13}S$, 100), 267 ($C_{21}H_{15}$, 29), 252 ($C_{20}H_{12}$, 63), 239 ($C_{19}H_{11}$), 126 ($C_{10}H_6$, 37). IR spectrum (KBr): 730, 740, 800 (4 and 2 adjacent Ar—H), 1 480, 1 577, 1 608, 3 020, 3 050 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·60—7·90 (m, 10 H, Ar—H), 5·70 (s, 1 H, 13b-H), 5·30 and 3·50 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 2·55 (s, 3 H, $ArCH_3$). For $C_{21}H_{16}S$ (300·3) calculated: 83·98% C, 5·37% H, 10·65% S; found: 83·84% C, 5·47% H, 10·70% S.

11-Phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXIII*)

A) Thiophenol (1·88 g) was converted to the sodium salt by treatment with sodium ethoxide prepared from 0·39 g Na and 10 ml ethanol. The solution was completely evaporated *in vacuo*, the residue was dissolved in 15 ml dimethylformamide and 5·0 g *Vb* were added. The mixture was stirred for 8 h at 60°C, diluted with 50 ml water and extracted with benzene. The extract was dried with K_2CO_3 and evaporated. The residue was chromatographed on 400 g Al_2O_3 (elution with the mixture of benzene and light petroleum and then only with benzene). From the least polar fractions 0·29 g *XXIII* were isolated which melted at 172—175°C (Mettler) (ethanol–benzene). Mass spectrum, *m/z* (%): 288 (M^+ corresponding to $C_{20}H_{16}S$, 45), 255 (100), 210 (17), 197 (18), 178 (68), 165 (10). ^{1}H NMR spectrum: δ 6·80—7·50 (m, 13 H, Ar—H), 5·20 (s, 1 H, 11-H), 4·08 and 3·04 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$). The analysis corresponds to $C_{20}H_{16}S$. Lit.[10], m.p. 178—179°C.

The mother liquors were combined and distilled. The fraction boiling at 150—195°C/80 Pa crystallized from ethanol and gave 0·4 g solid, m.p. 57—59°C (Mettler) which is the crude diphenyl disulfide. Lit.[26], m.p. 62°C.

B) A solution of 15·2 g *Va* in 50 ml acetic acid was added at 50°C to a mixture of 50 ml 57% hydroiodic acid, 0·75 $NaH_2PO_2.H_2O$ and 5·1 g red P and the mixture obtained was stirred and refluxed for 4 h. It was diluted with 100 ml benzene and filtered with charcoal. The filtrate was extracted with benzene, the extract was washed with 5% $NaHSO_3$ and water, dried with $MgSO_4$ and evaporated; 13·6 g (94%), m.p. 170—175°C. Crystallization from ethanol gave the pure product melting at 175—177·5°C (Kofler), identical with the compound obtained according to *A*.

11-Phenyl-11-piperidino-6,11-dihydrodibenzo[*b,e*]thiepin (*XIII*)

A) A solution of 25·5 g *Vb* and 30 g piperidine in 55 ml chloroform was refluxed for 8 h and evaporated under reduced pressure. The residue was dissolved in 250 ml benzene, the solution was washed with water, filtered with charcoal, dried with K_2CO_3 and evaporated. The, oily residue crystallized from 60 ml cyclohexane giving 12 g inhomogeneous crystalline product melting at 180—190°C. Further two crystallizations from a mixture of benzene and light petroleum gave 5·78 g (20%) homogeneous compound melting at 191—194°C (Kofler). It was identified as 11-phenyl-3-piperidino-6,11-dihydrodibenzo[*b,e*]thiepin (*XXXII*). UV spectrum: λ_{max} 251 nm ($\log \varepsilon$ 4·42), infl. 304 nm (3·37). IR spectrum: 700, 730, 760, 800, 860 (5, 4 and 2 adjacent and solitary Ar—H), 1 490, 1 590 (Ar), 2 790 cm^{-1} (CH_2—N). ^{1}H NMR spectrum: δ 6·80—7·40 (m, 9 H, C_6H_5 and 7,8,9,10-H_4), 7·00 (d, J = 8·5 Hz, 1 H, 1-H), 6·65 (bs, 1 H, 4-H), 6·59 (q, J = 8·5; 3·0 Hz, 1 H, 2-H), 5·15 (s, 1 H, 11-H), 4·12 and 3·03 (ABq, J = 13·0 Hz. 2 H, $ArCH_2S$), 3·05 (bm, 4 H, CH_2NCH_2), 1·56 (bs, 6 H, remaining 3 CH_2 of piperidine). ^{13}C NMR spectrum: 151·1 (C-3), 124·8 (C-11a), 144·5, 142·3, 136·3 (remaining quaternary carbons), 57·6 (C-11) 134·0, 130·7, 129·0, 128·4, 127·9, 127·6, 127·1, 115·1, 113·6 (12 aromatic methine carbons), 50·2 (2 methylene carbons adjacent to piperidine N), 33·0 (C-6), 25·7 (2 methylene carbons in positions 3 and 5 of piperidine), 24·3 (methylene carbon in position 4 of piperidine) ppm. For $C_{25}H_{25}NS$ (371·5) calculated: 80·82% C, 6·78% H, 3·77% N, 8·63% S; found: 80·90% C, 6·85% H, 4·08% N, 8·58% S.

The mother liquors were combined, evaporated and chromatographed on 400 g Al_2O_3. Fractions obtained by elution with a mixture 1 : 1 of benzene and light petroleum were repeatedly crystallized from ethanol and from a mixture of ethanol and benzene and finally yielded 5·3 g (18%) *XIII*, m.p. 192—195°C (Mettler). ^{1}H NMR spectrum: δ 7·90 (m, 2 H, 1,10-H_2), 6·80 to 7·40 (m, 11 H, remaining Ar—H), 3·78 and 3·45 (ABq, J = 12·0 Hz, 2 H, $ArCH_2S$), 3·10—3·40 (bm, 4 H, CH_2NCH_2), 1·00—2·00 (m, 6 H, remaining 3 CH_2 of piperidine). For $C_{25}H_{25}NS$

(371·5) calculated: 80·82% C, 6·78% H, 3·77% N, 8·63% S; found: 81·02% C, 7·01% H, 3·86% N, 8·37% S. A mixture of compounds *XIII* and *XXXII* melts with a deep depression (162—177°C).

An attempt at preparing the hydrochloride of *XIII* was carried out: A solution of 1·2 g *XIII* in 12 ml ethanol was treated with a slight excess of a solution of HCl in ether and the solution was diluted with 25 ml ether. The separated product (0·4 g) was identified as piperidine hydrochloride, m.p. 244—246°C (Kofler) with decomposition (2-propanol–ether). The analysis corresponded to $C_5H_{12}ClN$. Lit.[15], m.p. 244—245°C. The mother liquor was evaporated, the residue was dissolved in chloroform, the solution was washed with water, dried and evaporated again; 0·9 g 11-ethoxy-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XIV*), m.p. 153·5—154·5°C (Kofler) (ethanol). IR spectrum: 701, 748, 758 (5 and 4 adjacent Ar—H), 1 058 (ROR'), 1 480, 1 492, 1 600, 3 030, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·05 (m, 1 H, 1-H), 7·80 (m, 1 H, 4-H), 7·00—7·50 (m, 11 H, remaining Ar—H), 3·65 and 3·30 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), *c.* 3·10 (m, 2 H, OCH_2), 1·31 (t, 3 H, CH_3 of ethyl). For $C_{22}H_{22}OS$ (332·5) calculated: 79·48% C, 6·06% H, 9·65% S; found: 79·46% C, 6·07% H, 9·68% S. The same compound *XIV* was isolated in an attempt at preparing similarly the hydrochloride of the crude oily mixture of *XIII* and *XXXII*.

B) A solution of 10·0 g *Vb* and 12 g piperidine in 22 ml chloroform was refluxed for 8 h and after cooling, the mixture was separated between 200 ml water and 300 ml benzene. The organic layer was washed with water, dried with K_2CO_3 and evaporated. The oily residue (11·5 g, 100%) was dissolved in benzene and the solution was filtered through a column of 30 g Al_2O_3. The filtrate was evaporated and the residue (11·25 g, 98%) used for evaluation by the ^1H NMR method. The areas of the multiplet at 6·60—7·90 ppm (Ar—H) and of the singlet at 5·15 ppm (11-H) were in a ratio of 50 : 1 which corresponds approximately to the presence of 75% *XIII* and 25% *XXXII*.

11-Phenyl-3-piperidino-6,11-dihydrodibenzo[*b,e*]thiepin (*XXXII*)

A mixture of 10 ml 57% hydroiodic acid, 0·5 g $NaH_2PO_2.H_2O$, 1·0 g *VIIIa* and 10 ml acetic acid was heated for 4 h under reflux in a bath of 120°C. After cooling, 10 ml water were added and the mixture was made alkaline with 50% NaOH. The product was extracted with chloroform, the extract was dried and evaporated. The residue (m.p. 189—193°C) was crystallized from a mixture of ethanol and benzene; 0·50 g (52%), m.p. 192—194°C (Mettler). The compound proved identical (mixed melting point, analysis, spectra) with *XXXII* obtained under *A*.

2-Methyl-11-phenyl-11-piperidino-6,11-dihydrodibenzo[*b,e*]thiepin (*XXVII*)

A solution of 5·05 g *VIb* and 18 ml piperidine in 10 ml chloroform was refluxed for 8 h. After cooling the mixture was diluted with 100 ml water and extracted with benzene. Processing of the extract gave 5·8 g residue which was dissolved in 12 ml cyclohexane and the solution was treated with 25 ml light petroleum. Crystallization led to 2·85 g (49%) crude *XXVII*, m.p. at 148—209°C. Repeated crystallization from a mixture of ethanol and benzene gave the homogeneous product, m.p. 215—218°C (Mettler.) Mass spectrum, m/z (%): 385 (M^+ corresponding to $C_{26}H_{27}NS$), 384, 300 ($C_{21}H_{15}S$, 100), 268 ($C_{21}H_{16}$, 56), 253 ($C_{20}H_{13}$, 29), 252 ($C_{20}H_{12}$, 29), 178 ($C_{14}H_{10}$, 24). IR spectrum: 713, 772, 816, 895 (5, 4 and 2 adjacent and solitary Ar—H), 1 479, 1 491, 1 558, 1 598, 3 020, 3 043 (Ar), 2 793 cm^{-1} (CH_2—N). ^1H NMR spectrum: δ 7·88 (q, 1 H, 10-H), 7·75 (d, 1 H, 1-H), 6·70—7·40 (m, 10 H, remaining Ar—H), 3·75 and 3·45 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·00—3·50 (bm, 4 H, CH_2NCH_2), 2·28 (s, 3 H, CH_3), 0·90—2·20 (m, 6 H, remaining 3 CH_2 of piperidine). For $C_{26}H_{27}NS$ (385·6) calculated: 80·99% C, 7·06% H, 3·63% N, 8·32% S; found: 81·56% C, 7·26% H, 3·54% N, 9·13% S.

The mother liquors after the crude *XXVII* were chromatographed on 200 g silica gel. Benzene eluted 1·73 g (30%) product, m.p. 163–176°C. Repeated crystallization from a mixture of ethanol and benzene gave the homogeneous compound melting at 176–178°C (Mettler) which proved to be 2-methyl-11-phenyl-3-piperidino-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXVIII*). Mass spectrum, *m*/*z* (%): 385 (M^+ corresponding to $C_{26}H_{27}NS$), 370 ($C_{25}H_{24}NS$, 62), 352 ($C_{26}H_{26}N$, 51), 308 ($C_{20}H_{22}NS$, 32), 294 ($C_{22}H_{16}N$, 42), 179 (24), 178 (27), 84 (22). IR spectrum: 702, 737, 751, 780, 860 (5 and 4 adjacent and solitary Ar—H), 1 494, 1 550, 1 581, 1 603, 3 023 (Ar), 2 788 cm^{-1} (CH_2—N). ^1H NMR spectrum: δ 6·78 (s, 1 H, 4-H), 6·90–7·50 (m, 10 H, remaining Ar—H), 5·20 (s, 1 H, 11-H), 4·15 and 3·10 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 2·80 (bm, 4 H, $CH_2.NCH_2$), 2·20 (s, 3 H, CH_3), 1·60 (bm, 6 H, remaining 3 CH_2 of piperidine). For $C_{26}H_{27}NS$ (385·6) calculated: 80·99% C, 7·06% H, 3·63% N, 8·32% S; found: 81·53% C, 7·26% H, 3·55% N, 8·15% S.

3-Methyl-11-phenyl-11-piperidino-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXXI*)

A solution of 3·0 g *VIIb* in 10 ml dichloromethane was stirred and treated dropwise with a solution of 3·6 g piperidine in 10 ml dichloromethane at 20°C. The mixture was stirred for 20 h at 20–23°C, refluxed for 1 h and evaporated *in vacuo*. The residue was diluted with 50 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue crystallized from 10 ml cyclohexane; 1·1 g (32%), m.p. 182–185°C (Kofler). IR spectrum (KBr): 710, 765, 818, 887 (5, 4 and 2 adjacent and solitary Ar—H), 1 473, 1 595, 3 015, 3 050 (Ar), 2 828, 2 840 cm^{-1} (CH_2—N). ^1H NMR spectrum: δ 6·80–8·00 (m, 12 H, Ar—H), 3·78 and 3·45 (ABq, 2 H, $ArCH_2S$), 2·20 (s, 3 H, CH_3), 0·90–3·50 (m, 10 H, 5 CH_2 of piperidine). For $C_{26}H_{27}NS$ (385·6) calculated: 80·99% C, 7·06% H, 3·63% N, 8·32% S; found: 79·64% C, 7·11% H, 3·32% N, 8·24% S.

11-Phenyl-11-pyrrolidino-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XV*)

A solution of 4·85 g *Vb* and 17·4 g pyrrolidine in 10 ml chloroform was refluxed for 5 h, diluted with 60 ml chloroform, washed with water, filtered with charcoal and evaporated. The residue crystallized from a mixture of 15 ml benzene and 15 ml light petroleum; 2·3 g (43%), m.p. 234 to 238°C. Analytical sample, m.p. 243–244°C (Kofler) (benzene–light petroleum). UV spectrum (saturated solution): λ_{max} 252 and 322 nm. IR spectrum: 698, 728, 748 (5 and 4 adjacent Ar—H), 1 482, 1 500, 1 597, 3 020, 3 045 cm^{-1} (Ar). For $C_{24}H_{23}NS$ (357·5) calculated: 80·63% C, 6·48% H, 3·92% N, 8·97% S; found: 80·53% C, 5·76% H, 3·76% N, 8·76% S.

A boiling solution of 2·0 g *XV* in 25 ml ethanol was neutralized with a solution of 0·75 g maleic acid in 5 ml ethanol. After cooling the precipitated compound (0·4 g) was filtered and identified as the recovered starting *XV*. The filtrate was evaporated *in vacuo*, the residue dissolved in 5 ml ethanol and the solution treated with 20 ml ether. There crystallized 0·65 g compound melting at 92–96°C (Kofler) (2-propanol–ether) which was identified as pyrrolidine hydrogen maleate. For $C_8H_{13}NO_4$ (187·2) calculated: 51·33% C, 7·00% H, 7·48% N; found: 51·38% C, 7·00% H, 6·98% N. Evaporation of the mother liquor gave 0·9 g *XIV*, m.p. 147·5–151·5°C (Kofler) (ethanol), identical with the compound described above (mixed melting point, analysis, IR spectrum).

11-Morpholino-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XVI*)

A solution of 4·85 g *Vb* and 15 ml morpholine in 10 ml chloroform was refluxed for 13 h, diluted with benzene, washed with water, the organic layer was filtered with charcoal, dried with K_2CO_3

and evaporated. The semi-solid residue crystallized from 15 ml benzene; 3·1 g (55%), m.p. 200 to 204°C. Analytical sample, m.p. 211·5°C (Kofler) (benzene). ^{1}H NMR spectrum: δ 6·70–8·00 (m, 13 H, Ar—H), 1·20–4·00 (m, 10 H, 5 CH_2). For $C_{24}H_{23}NOS$ (373·5) calculated: 77·17% C, 6·21% H, 3·75% N; found: 77·43% C, 6·02% H, 3·59% N. An attempt at preparing the hydrochloride led again to *XIV* (0·7 g from 1·3 g *XVI*), m.p. 153·5–154·5°C (ethanol), identical with compound described above (mixed m.p., chromatography, analysis, spectra).

11-Benzylamino-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XVII*)

A solution of 5·0 g *Vb* and 7·0 g benzylamine in 10 ml chloroform was refluxed for 8 h and processed similarly like in the preceding cases. The crude product crystallized from ethanol and was recrystallized from a mixture of ethanol and benzene giving 2·44 g lower melting modification, m.p. 160–162°C (Mettler). UV spectrum: λ_{max} 266 nm (log ε 3·85), infl. 289 nm (3·33) and 301 nm (3·15). IR spectrum: 702, 730, 750, 760 (5 and 4 adjacent Ar—H), 1 490, 1 559, 1 580, 1 595, 1 604, 3 050, 3 070 (Ar), 3 300 cm^{-1} (NH). Its ^{1}H NMR spectrum was identical with that of the higher melting modification. For $C_{27}H_{23}NS$ (393·5) calculated: 82·40% C, 5·89% H, 3·56% N, 8·15% S; found: 82·37% C, 5·97% H, 3·40% N, 8·17% S.

Evaporation of the mother liquors and crystallization of the residue from a mixture of ethanol and benzene gave 1·07 g of the higher melting modification, m.p. 182–183°C (Mettler). ^{1}H NMR spectrum: δ 6·90–8·10 (m, 18 H, Ar—H), 3·65 and 3·30 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·48 and 3·00 (ABq, J = 13·0 Hz, 2 H, $ArCH_2N$), 1·95 (bs, disappears after ^2H_2O, 1 H, NH). For $C_{27}H_{23}NS$ (393·5) calculated: 82·40% C, 5·89% H, 3·56% N, 8·15% S; found: 82·84% C, 5·97% H, 3·57% N, 8·16% S. The total yield of both modifications was 3·51 g (58%). Hori and coworkers[12] described the lower melting modification and reported the m.p. of 165–166°C.

11-(2-Aminoethylamino)-11-phenyl-6,11-dihydrodibenzo[*b e*]thiepin (*XVIII*)

A mixture of 3·35 g *Vb*, 25 ml chloroform and 9·0 g anhydrous ethylenediamine was stirred for 3 h at 50°C and refluxed for 3·5 h. Chloroform was evaporated under reduced pressure, the residue was dissolved in 75 ml toluene, the solution washed with water, dried with K_2CO_3 and evaporated. The inhomogeneous residue was dissolved in 6 ml benzene and the solution was treated with 5 ml light petroleum. There crystallized 3·2 g (62%) crude base (m.p. 105–112°C) which was dissolved in 40 ml ethanol, neutralized with a solution of 2·0 g maleic acid in 20 ml ethanol and the product precipitated by treatment with ether. There crystallized 2·6 g maleate solvated with 0·5 H_2O, m.p. 177–179°C (Kofler) (95% ethanol–ether). For $C_{26}H_{26}N_2O_4S$ + + 0·5 H_2O (471·6) calculated: 66·22% C, 5·77% H, 5·94% N, 6·80% S; found: 66·30% C, 5·66% H, 5·93% N, 6·87% S.

In another experiment the attempt was made to extract the crude base from the organic solvent into 1M-HCl. The base was then relaesed with 2·5M-NaOH and isolated in the usual way. Its neutralization with maleic acid in ethanol gave a compound melting at 172–172·5°C (Kofler) (90% ethanol) which proved to be ethylenediamine maleate. For $C_{10}H_{16}N_2O_8$ (282·2) calculated: 41·10% C, 5·52% H, 9·59% N; found: 41·42% C, 5·41% H, 9·43% N.

11-(2-Dimethylaminoethylamino)-11-phenyl-6,11-dihydrobenzo[*b,e*]thiepin (*XIX*)

A mixture of 4·85 g *Vb*, 8 ml chloroform and 4·9 g N,N-dimethylethylenediamine[22] was refluxed for 6·5 h and processed similarly like in the preceding cases. There were obtained 5·7 g (100%) crude base which was neutralized with 3·5 g maleic acid in 25 ml ethanol and the maleate was precipitated by 40 ml ether; 4·7 g (64%), m.p. 190–191°C (Kofler) (ethanol–ether). Mass spec-

trum, *m/z* (%): 374 (M^+ corresponding to $C_{24}H_{26}N_2S$), 287 (19), 286 (9), 254 (12), 212 (7), 178 (6), 72 (11), 58 (100). For $C_{28}H_{30}N_2O_4S$ (490·6) calculated: 68·54% C, 6·16% H, 5·71% N, 6·54% S; found: 68·42% C, 6·06% H, 5·89% N, 6·40% S.

A sample of the maleate was decomposed with NH_4OH and the pure oily base was isolated by extraction with ether. It was used for recording the ^1H NMR spectrum: δ 7·00—8·00 (m, 13 H, Ar—H), 3·62 and 3·30 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 1·90—2·60 (m, 5 H, $NHCH_2CH_2$), 2·05 (s, 6 H, CH_3NCH_3).

In another experiment, the cooled reaction mixture was shaken with 2·5M-HCl and the precipitated hydrochloride was crystallized from ethanol. A cleavage took place and *XIV* (m.p. 150—152·5°C) was isolated as the product. Its identity with the compound described previously was corroborated by the mixed melting point.

11-(2-Diethylaminoethylamino)-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XX*)

A mixture of 4·85 g *Vb*, 12 ml chloroform and 17·5 g N,N-diethylethylenediamine was refluxed for 5·5 h and evaporated under reduced pressure. The residue was dissolved in 100 ml toluene, the solution was washed with water and the basic product was extracted into 150 ml cooled 1M-HCl. The aqueous acid layer was immediately made alkaline with 50 ml 5M-NaOH, the base was extracted with ether, the extract dried with K_2CO_3 and evaporated; 6·0 g oil. It was neutralized with 3·5 g maleic acid in 30 ml ethanol and the maleate was precipitated with ether; 3·7 g (39%), m.p. 158—162°C (Kofler). Analytical sample, m.p. 167·5—169°C (ethanol). For $C_{30}H_{34}N_2O_4S$ (518·7) calculated: 69·47% C, 6·61% H, 5·40% N, 6·18% S; found: 69·10% C, 6·81% H, 5·24% N, 6·17% S.

11-(3-Morpholinopropylamino)-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXI*)

A mixture of 4·85 g *Vb*, 10 ml chloroform and 14·4 g N-(3-aminopropyl)morpholine was stirred and refluxed for 6 h. Chloroform was evaporated *in vacuo*, the residue was dissolved in 100 ml toluene, the solution was washed with water and the product was extracted into 100 ml 1M-HCl. The separated aqueous layer was immediately made alkaline with 5M-NaOH and the base isolated by extraction with ether. Drying of the extract (K_2CO_3) and evaporation yielded 4·3 g (67%) base, m.p. 160—170°C. Analytical sample, m.p. 171·5—174·5°C (Kofler) (benzene–cyclohexane–light petroleum). ^1H NMR spectrum: δ 6·80—7·90 (m, 13 H, Ar—H), 3·55 and 3·28 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 1·50—2·50 (m, 15 H, 7 CH_2 and NH). For $C_{27}H_{30}N_2OS$ (430·6) calculated: 75·30% C, 7·05% H, 6·50% N, 7·44% S; found: 75·79% C, 6·99% H, 6·30% N, 7·35% S.

Maleate, m.p. 166·5—167·5°C (Kofler) (aqueous ethanol). For $C_{31}H_{34}N_2O_5S$ (546·7) calculated: 68·10% C, 6·26% H, 5·13% N, 5·87% S; found: 68·10% C, 6·04% H, 5·08% N, 5·84% S.

3-(4-Methylpiperazino)-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXXIII*)

A mixture of 4·85 g *Vb*, 12 ml chloroform and 15·2 g 1-methylpiperazine was refluxed for 6 h, diluted with 100 ml benzene, washed with water and shaken with 100 ml 1M-HCl. The precipitated hydrochloride was filtered, combined with the acid aqueous layer of the filtrate and the suspension was made alkaline with 30 ml 5M-NaOH. It was extracted with benzene, the extract was dried (K_2CO_3) and evaporated; 3·6 g (62%) crude product, m.p. 188—194°C. Analytical sample of the base, m.p. 207·5—209·5°C (Kofler) (benzene–light petroleum). ^1H NMR spectrum: δ 6·60 (m, 2 H, 2,4-H_2), 6·90—7·50 (m, 10 H, remaining Ar—H), 5·20 (s, 1 H, 11-H), 4·11 and

3·09 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·15 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (s, 3 H, NCH_3). For $C_{25}H_{26}N_2S$ (386·6) calculated: 77·67% C, 6·78% H, 7·25% N, 8·28% S; found: 77·96% C, 6·93% H, 7·27% N, 8·29% S.

Maleate hydrate, m.p. 169·5–172°C (Kofler) (ethanol–ether). For $C_{29}H_{30}N_2O_4S + H_2O$ (520·6) calculated: 66·89% C, 6·19% H, 5·38% N, 6·16% S; found: 67·13% C, 5·83% H, 5·57% N, 6·23% S.

3-[4-(2-Hydroxyethyl)piperazino]-11-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXXIV*)

A mixture of 4·85 g *Vb*, 12 ml chloroform and 22 g 1-(2-hydroxyethyl)piperazine was refluxed for 6 h and processed like in the preceding case; 2·8 g (45%) base which was repeatedly crystallized from ethanol, m.p. 156–160°C (Kofler). IR spectrum: 700, 711, 730, 771 (Ar—H), 1 050 (CH_2.OH), 1 592, 1 600, 3 020 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum: δ 6·50–7·40 (m, 12 H, Ar—H), 5·15 (s, 1 H, 11-H), 4·10 and 3·05 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·60 (t, 2 H, CH_2O), 3·10 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (m, 6 H, $CH_2N^4CH_2$ of piperazine and NCH_2 in the chain). For $C_{26}H_{28}N_2OS$ (416·6) calculated: 74·96% C, 6·77% H, 6·72% N, 7·70% S; found: 74·92% C, 6·70% H, 6·58% N, 7·80% S.

Bis(hydrogen maleate) solvated with 2·5 H_2O, m.p. 102–104°C (Kofler) (acetone–ether). For $C_{34}H_{36}N_2O_9S + 2{\cdot}5\ H_2O$ (693·8) calculated: 58·96% C, 5·96% H, 4·62% S; found: 59·03% C, 5·74% H, 4·53% S.

11-Phenyl-11-phthalimido-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXII*)

A) A mixture of 5·2 *Vb*, 3·0 g potassium phthalimide and 50 ml xylene was refluxed for 10 h, cooled and the insoluble material was filtered off. The filtrate was evaporated, the residue dissolved in benzene and the solution chromatographed on 50 g silica gel. Elution with benzene removed first 3·7 g less polar products from which repeated crystallization from cyclohexane and then ethanol gave 0·3 g substance melting at 151–154°C (Mettler) which was identified as 9-phenylanthracene (*XXXVIII*). Mass spectrum, m/z: 254·1098 (M^+ corresponding to $C_{20}H_{14}$, calculated 254·1095, 100%), 126 ($C_{10}H_6$), 113 (C_9H_5). Lit.[23], m.p. 151–152°C.

Continued elution with benzene yielded 2·0 g (29%) *XXII* which was crystallized from ethanol and then acetone and melted at 218–219°C (Mettler). Mass spectrum, m/z (%): 433·1145 (M^+ corresponding to $C_{28}H_{19}NO_2S$, calculated 433·1137, 40%), 400·1303 ($C_{28}H_{18}NO_2$, 100), 324 (32), 323·0936 ($C_{22}H_{13}NO_2$, 11), 286·0794 ($C_{20}H_{14}S$, 45), 253·0999 ($C_{20}H_{13}$, 82), 252 (83), 178·0771 ($C_{14}H_{10}$, 60). UV spectrum: inflexes at 270 nm (log ε 3·80), 290 nm (3·60), 300 nm (3·56). IR spectrum: 701, 728, 748 (5 and 4 adjacent Ar—H), 1 488, 1 508, 1 608, 3 055 (Ar), 1 712, 1 768 cm^{-1} (Ar  N). ^1H NMR spectrum: δ 6·90–8·00 (m, 17 H, Ar—H), 4·08 and 3·81 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$). For $C_{28}H_{19}NO_2S$ (433·5) calculated: 77·57% C, 4·42% H, 3·23% N, 7·40% S; found: 77·32% C, 4·50% H, 3·00% N, 7·54% S.

B) A mixture of 3·2 g *Vb*, 10 ml dimethylformamide and 2·04 g potassium phthalimide was stirred for 24 h at 25°C and then for 1 h at 65°C. It was diluted with benzene, the solution washed with 0·2M-NaOH and water, dried with Na_2SO_4 and evaporated *in vacuo*. The residue (3·6 g, 83%) melted at 204–207°C. Recrystallization from ethanol and then from a mixture of ethanol and benzene gave the pure product, m.p. 217–219°C (Kofler), identical with the compound obtained according to *A*.

11-(3-Dimethylaminopropyl)-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXIV*)

The Grignard reagent was prepared from 3·6 g Mg and 19·5 g 3-dimethylaminopropyl chloride in 60 ml ether (initiation of the reaction with a grain of I_2 and 0·45 .ml 1,2-dibromoethane) and by refluxing for 5 h. It was stirred and treated over 25 min with a solution of 19·5 g *Vb* in 100 ml benzene and refluxed for 3·5 h. After cooling it was diluted with benzene and decomposed by 100 ml 10% NH_4Cl solution, added dropwise. The organic layer was washed with water and the basic products were extracted into 200 ml 1M-HCl. The acid aqueous solution was separated, made alkaline with 2·5M-NaOH and the bases were extracted with benzene. The extract was dried (K_2CO_3) and evaporated. The remaining oil (21·1 g) was chromatographed on a column of 1·2 kg Al_2O_3; a 9 : 1 mixture of benzene and light petroleum was used for the elution. After the separation of 0·6 g inhomogeneous oil there were obtained 7·1 g (32%) product with an R_F 0·6 which crystallized from ethanol and was identified as *XXIV*, m.p. 153—156°C (Kofler). IR spectrum: 700, 746 (5 and 4 adjacent Ar—H), 1 490, 1 596, 3 030, 3 060 (Ar), 2 775, 2 820 cm^{-1} [R—N$(CH_3)_2$]. ^{1}H NMR spectrum: δ 7·00—7·80 (m, 13 H, Ar—H), 3·60 and 3·23 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 2·40—3·10 (m, 2 H, 11-CH_2), 2·20 (t, 2 H, CH_2N), 2·12 (s, 6 H, CH_3NCH_3), 1·35 and 0·80 (2 m, 2 H, CH_2 in the middle of the propane chain). For $C_{25}H_{27}NS$ (373·5) calculated: 80·38% C, 7·28% H, 3·75% N, 8·59% S; found: 80·74% C, 7·38% H, 4·00% N, 8·48% S.

Hydrogen naleate, m.p. 197·5—199·5°C (Kofler) (ethanol). For $C_{29}H_{31}NO_4S$ (489·6) calculated: 71·13% C, 6·38% H, 2·86% N, 6·55% S; found: 71·19% C, 6·28% H, 2·79% N, 6·38% S.

Continued chromatography with the same eluent gave 4·8 g mixture and then 2·1 g (10%) homogeneous oil with the R_F 0·4 which was identified as 3-(3-dimethylaminopropyl)-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXXIX*). Neutralization with maleic acid in ethanol and treatment with ether gave the hydrogen maleate crystallizing from a mixture of ethanol and ether and melting at 169·5—172°C (Kofler). For $C_{29}H_{31}NO_4S$ (489·6) calculated: 71·12% C, 6·38% H, 2·86% N, 6·55% S; found: 70·80% C, 6·41% H, 2·62% N, 6·60% S.

A sample of the maleate was decomposed with NH_4OH and the pure base, isolated by extraction with ether, was used for recording the ^{1}H NMR spectrum: δ 6·70—7·40 (m, 12H, Ar—H), 5·20 (s, 1 H, 11-H), 4·10 and 3·02 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·20—2·70 (m, 4 H, $ArCH_2$ and NCH_2), 2·18 (s, 6 H, CH_3NCH_3), *c.* 1·72 (m, 2 H, CH_2 in the middle of the propane chain).

11-Methoxy-11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XXV*)

Na (0·6 g) was dissolved in 50 ml methanol and the solution was treated with a solution of 4·9 g *Vb* in 50 ml benzene. The mixture was stirred and refluxed for 1 h, cooled, diluted with benzene and washed with water. After drying with K_2CO_3 the solvent was evaporated and the residue was crystallized from a mixture of methanol and benzene; 3·14 g (65%) *XXV*, m.p. 146·5—148·5°C (Mettler). UV spectrum: λ_{max} 265 nm (log ε 3·87), inflexes at 289 nm (3·28) and 298 nm (3·07). IR spectrum: 704, 749, 769 (5 and 4 adjacent Ar—H), 1 059, 1 070 (R—O—R'), 1 478, 1 489, 1 534, 1 585, 3 020, 3 040, 3 054, 3 078 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·90—8·00 (m, 13 H, Ar—H), 3·58 and 3·22 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·98 (s, 3 H, OCH_3). Lit.[10], m.p. 150·5—152°C.

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