5-SUBSTITUTED AND 5,7-DISUBSTITUTED 5,7-DIHYDRODIBENZO-[*c*,*e*]THIEPINS AND THE CORRESPONDING S-OXYGENATED COMPOUNDS: ALKYLAMINES, CARBOXYLIC ACIDS, AND CARBOXAMIDES; SYNTHESIS AND PHARMACOLOGICAL SCREENING

Karel ŠINDELÁŘ, Jiří HOLUBEK, Miroslav RYSKA, Ivan KORUNA and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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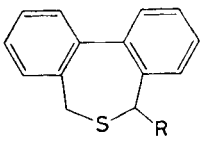
Reaction of 5,7-dihydrodibenzo[*c*,*e*]thiepin (*I*) with n-butyllithium resulted in the partial sulfur extrusion and in the formation of the 9,10-dihydrophenanthrene-9-thiolate anion (*B*). Its further transformations (by hydrolysis, aminoalkylation and spontaneous dehydrogenation) led to phenanthrene-9-thiol (*IX*), the corresponding disulfide *X*, and the S-(2-dimethylaminoethyl) derivatives *XI* and *XIV*. Reactions of 5-chloro-5,7-dihydrodibenzo[*c*,*e*]thiepin (*II*) with the corresponding Grignard reagents were only a poor source of the amines *III* and *IV*. Reaction of the sulfoxide *XVIII* with n-butyllithium or with sodium hydride and the following treatment with 2-dimethylaminoethyl chloride gave the amine *XIX* in a low yield. Only the sulfone *X* was found more useful for preparing the 5- and 5,7-substituted derivatives. Treatment with n-butyllithium and following carbonation afforded mixtures of the monocarboxylic acid *XXI* and dicarboxylic acid *XXVIII*. *Via* acid chlorides they were transformed to the methylamides *XXII* and *XXIX*, and to the dimethylamides *XXIII* and *XXX*. The amide *XXIII* was reduced to the 5-(dimethylaminomethyl) compound *XXV*. Lithiation of the sulfone *XX* or treatment with sodium hydride, and the following action of 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride gave the amines *XXVI*, *XXVII*, and *XXXI*. Only the phenanthrene derivatives *XI* and *XIV*, and the amino sulfone *XXVII* showed clear indications of thymoleptic activity as potential antidepressants.

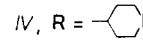
Our interest in amines derived from the dibenzothiepin systems started in the dibenzo[*b*,*e*]thiepin series and the synthetic work led to finding very useful antidepressant and antihistamine agents[1]. Shifting into the dibenzo[*b*,*f*]thiepin series resulted in very extensive investigations with some contributions to the experimental organic chemistry in this field[2] as well as with development of very potent neuroleptic agents and tranquillizers which proved practical usefulness in the treatment of schizophrenic psychoses[1,3]. In both of the mentioned series, the dibenzothiepin systems proved very suitable carrier systems for molecules with neurotropic and psychotropic potency. Encouraged by this fact we have now attempted to tackle a further dibenzothiepin, *i.e.* dibenzo[*c*,*e*]thiepin, having again in view the line of medicinal chemistry. Report on our experience in this series is the object of the present communication.

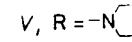
In fact, the chemistry of dibenzo[*c*,*e*]thiepins has not been much developed. The completely unsaturated dibenzo[*c*,*e*]thiepin has not been reported and all the work in this area deals with its 5,7-dihydro derivative *I*, its substituted derivatives (almost exclusively Ar-substituted), and their corresponding sulfoxides and sulfones. The literature until 1969 was comprehensively reviewed[4]. Compound *I* and its derivatives, having the dissymmetrically twisted ring system, attracted the attention of theoretical organic chemists because of the predicted and proven optical isomerism in the series, of the magnetic nonequivalency of the four benzylic protons, and of the easy sulfur extrusion reactions leading to phenanthrenes. Only two more recent papers[5,6] showed indication of interest in direction to medicinal chemistry.

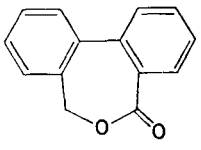
The aim of the present work was to functionalize compound *I* in position 5 or in positions 5 and 7 with carboxyl groups, aminocarbonyl groups, and aminoalkyl side chains. The starting 5,7-dihydrodibenzo[*c*,*e*]thiepin (*I*) was prepared by the described route[7] with some minor modifications. Diphenic acid[8] was reduced with diborane, generated by reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran (method, *cf.*[9]) to 2,2′-bis(hydroxymethyl)biphenyl. In most cases the yield was over 90%. In one case we noted uncomplete reduction: the yield on the diol was only 73% and from the mother liquor a different higher melting compound was isolated and identified as dibenz[*c*,*e*]oxepin-5(7*H*)-one (*VI*) (analysis and the lactone band in the IR spectrum at 1 703 cm^{-1}). The literature described the preparation of 2,2′-bis(hydroxymethyl)biphenyl by reduction of methyl or ethyl diphenate with lithium aluminium hydride[10]; the lactone *VI* was previously obtained by heating 2′-hydroxymethylbiphenyl-2-carboxylic acid to 110°C[11,12]. 2,2′-Bis(hydroxymethyl)-



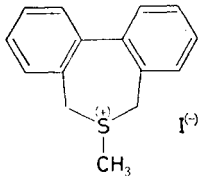
I, R = H
II, R = Cl
III, R = $(CH_2)_3N(CH_3)_2$

IV, R = 

V, R = 



VI



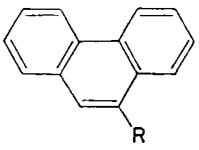
VII

biphenyl was transformed to 2,2'-bis(bromomethyl)biphenyl by treatment with hydrobromic acid in the presence of sulfuric acid[10,13]. The cyclization of the dibromo compound to 5,7-dihydrodibenzo[*c*,*e*]thiepin (*I*) was carried out by heating with sodium sulfide in methanol[7] (yield over 80%). Treatment of compound *I* with methyl iodide in boiling ethanol resulted in the known[7] 6-methyl-5,7-dihydrodibenzo[*c*,*e*]-thiepinium iodide (*VII*) which was prepared for pharmacological testing.

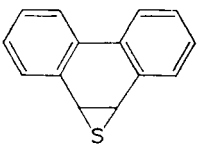
The first reaction we tried with compound *I* was the abstraction of one proton from position 5 by treatment with n-butyllithium in a mixture of ether and hexane in order to form the corresponding carbanion, and the following treatment with carbon dioxide which was expected to lead to the 5-carboxylic acid. Decomposition with water, extraction with dilute sodium hydroxide and acidification of the alkaline extract did not afford any acidic product. The organic solution, containing neutral compounds, was evaporated and chromatographed on silica gel. The first to be eluted with light petroleum was phenanthrene (*VIII*) (analysis, mass spectrum, and the melting point, *cf.*[14,15]). It was followed by the starting compound *I*, more than 50% of which having been recovered. Elution with benzene led to a third compound, melting at 120–125°C, and having the composition $C_{14}H_{10}S$ (analysis and mass spectrum). It is the composition of phenanthrene-9-thiol (*IX*) but this was excluded by the neutral character of the product. The fact, that in the mass spectrum the base peak corresponds to phenanthrene, suggests the possibility that this compound could be 9,10-dihydrophenanthrene 9,10-episulfide (*XIII*) because this should extrude the sulfur atom most easily. The unclear ^{1}H NMR spectrum makes this structure assignment only a tentative one.

The second experiment was carried out in that way that the reaction mixture, obtained by treatment of compound *I* with n-butyllithium in ether–hexane, was allowed to stand for 24 h at room temperature, decomposed with water and separated into acidic and neutral products (extraction with diluted sodium hydroxide). In this case, acidification of the alkaline solution gave an acidic product which was isolated by extraction with benzene and which crystallized from ethanol. It was accompanied by a high-melting compound, being less soluble in ethanol and, therefore, easy to be isolated. The mass spectrum and analysis of the lower melting compound disclosed the elemental composition to $C_{14}H_{10}S$; in the mass spectrum, the molecular ion is the base peak. The UV spectrum showed a high degree of conjugation – like in phenanthrene. The band at 2 560 cm^{-1} in the IR spectrum corresponds to the SH group. All the data available (including the ^{1}H NMR spectrum) allow to assign to this compound the structure of phenanthrene-9-thiol (*IX*). In the literature we may find four references dealing with the thiol *IX*: According to the first one[16], the thiol was obtained from potassium phenanthrene-9-sulfonate by treatment with phosphorus pentachloride and phosphoryl chloride and by the following reduction of the sulfonyl chloride with zinc and dilute sulfuric acid at 100°C; the melting point of 67°C was given (not in agreement with our value). The second

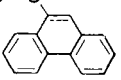
reference[17] deals only with the use of the thiol *IX* in reactions with alicyclic 2-chloroketones. The third reference[18] mentioned the previous papers and had a critical comment on the "inadequate descriptions in the literature". The thiol *IX* was prepared by reaction of 9-phenanthrylmagnesium bromide with sulfur; unfortunately it was not isolated and characterized but directly used in the form of solution of the corresponding sodium thiolate. The last reference available[19] is very similar to the foregoing one: the thiol was prepared from 9-bromophenanthrene, was not isolated and characterized in the pure form but directly processed in the form of solution of the sodium salt. It thus remains unclear what the product of the Indian authors[16] was. There can be hardly any doubts about our assignment and characterization. The high-melting compound, accompanying the thiol *IX*, was identified as the disulfide *X* (analysis, mass spectrum). There is again discrepancy in the melting points of our product and the product of the Indian authors[16]. The disulfide is evidently formed by the spontaneous oxidation of the thiol *IX* with air oxygen. The neutral fraction, obtained from the original organic layer, was characterized by TLC as a mixture of phenanthrene (*VIII*), the starting compound *I* and the mentioned compound $C_{14}H_{10}S$ melting at 120–125°C.



VIII, R = H
IX, R = SH
X, R = S–S



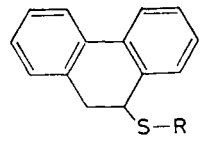
XIII

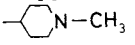


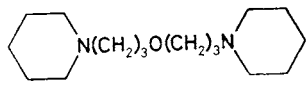
XI, R = $SCH_2CH_2N(CH_3)_2$
XII, R = $S(CH_2)_3N(CH_3)_2$

The next experiment aimed at trapping the primarily formed carbanion by immediate treatment with 2-dimethylaminoethyl chloride. The reaction of compound *I* with n-butyllithium in ether–hexane proceeded for 3·5 h and the mixture was then treated with 2-dimethylaminoethyl chloride (15 h at room temperature). After decomposition with water, the basic product was isolated by extraction with dilute hydrochloric acid. The neutral fraction consisted mainly of the starting sulfide *I* (c. 20% recovered); some phenanthrene was also present. The basic product was separated by chromatography on alumina in two oily bases, both of them giving crystalline maleates. They were characterized by mass spectra and by the ^1H NMR spectra of the released bases. The first to be eluted was identified as N,N-dimethyl-2-

-(9-phenanthrylthio)ethylamine (*XI*), the second one as N,N-dimethyl-2-(9,10-dihydro-9-phenanthrylthio)ethylamine (*XIV*). The rather high recovery of compound *I* led us to try the use of the potent metalating complex comprised of equimolecular quantities of n-butyllithium and N,N,N',N'-tetramethylethylenediamine (refs[20,21]); it had no influence on our reaction: 20% of the starting *I* were recovered and the basic product consisted of a mixture 3 : 7 of compounds *XI* and *XIV*. A similar reaction of compound *I* with n-butyllithium in ether–hexane and with 3-piperidinopropyl chloride gave a mixture from which 35% of the starting *I* were recovered. The basic product was chromatographed and the only oily fraction, which afforded the crystalline hydrochloride, was identified, somewhat surprisingly, as bis(3-piperidinopropyl) ether (*XVII*) (*cf.*[22]).



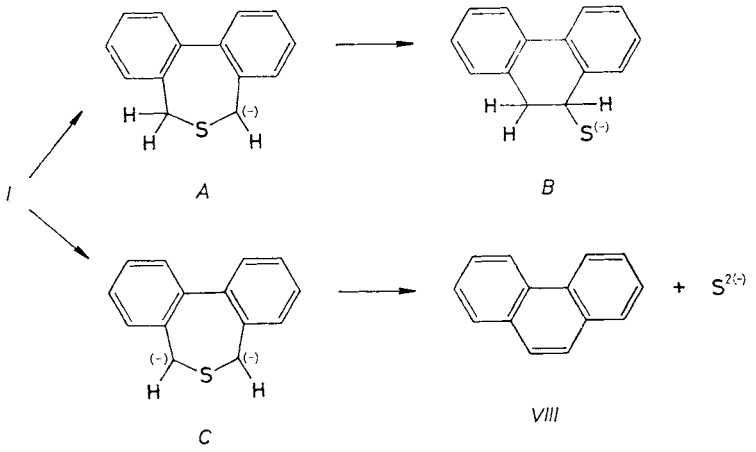
XIV, R = $(CH_2)_2N(CH_3)_2$
XV, R = $(CH_2)_3N(CH_3)_2$
XVI, R = 



XVII

The isolation of compounds *IX*–*XI* and *XIV* in our experiments shows that the primarily formed carbanion *A* is very unstable and rearranges immediately to the 9,10-dihydrophenanthrene-9-thiolate anion *B*. This rearrangement represents, in fact, a partial sulfur extrusion: the sulfur atom leaves the ring but does not leave completely the molecule. This rearrangement is very similar to the Wittig rearrangement[23,24] in the ether series which was, most curiously, observed also with the oxygen analogue of our compound *I*: 5,7-dihydrodibenz[*c*,*e*]oxepin treated with n-butyllithium afforded 9,10-dihydro-9-phenanthrol *via* the two isomeric anions[25]. Potassium amide could also be used as the metalating (proton abstracting) agent[26]. We are not aware of the just observed sulfur analogy of this Wittig rearrangement (*cf.*[27]). Our own experience in this line was negative: 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin afforded by treatment with n-butyllithium and by the following carbonation 84% of 11*H*-dibenz[*b*,*f*]-1,4-oxathiepin-11-carboxylic acid[28]; no isomerization was observed. The isolated phenanthrene derivatives *IX* and *XI* are evidently products of the spontaneous oxidation of the corresponding 9,10-dihydrophenanthrenes by air oxygen (9,10-dihydrophenanthrene-9-thiol was not isolated at all). It is considered unlikely that this aromatization takes place in the stage of the anion *B*; the assumed aromatization of the final products (dihydrothiol and compound *XIV*) is prefered. The formation of phenanthrene as a minor product has to be explained either from the anion *B* during its hydrolysis with concommitant formation of hydrogen sulfide

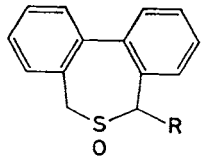
(smell of hydrogen sulfide encountered in the stage of hydrolysis in each experiment), or *via* the dianion *C* again with hydrogen sulfide formation. Neither the involvement of the episulfide *XIII* can be excluded. In any way we were not able to functionalize the position 5 in 5,7-dihydrodibenzo[*c*,*e*]thiepin (*I*) by metallation with n-butyllithium and by the following nucleophilic attack of the carbanion formed; the reason was the immediate rearrangement of the carbanion *A* to the thiolate anion *B*.



Paquette[29] described the chlorination of compound *I* with sulfuryl chloride in tetrachloromethane to the monochloro derivative *II* which was not isolated or characterized but immediately oxidized with 3-chloroperbenzoic acid to the corresponding sulfone. Compound *II* had also to be considered as an intermediate in our attempts to introduce a basic side chain into position 5 of dihydrodibenzo[*c*,*e*]thiepin skeleton. The work of Paquette[29] was repeated and the crude chloro compound *II*, dissolved in a mixture of benzene and tetrahydrofuran, was added to a solution of 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran. Thin-layer chromatography of the isolated basic product showed it to be a mixture of three substances. Chromatography on silica gel separated first as the main product an oily base which afforded the crystalline oxalate. Its analysis and the mass spectrum proved the composition $C_{19}H_{23}NS$. The ^1H NMR spectrum is consistent with the 5,7-dihydrodibenzo[*c*,*e*]thiepin structure *III*. The following product to be eluted was a different oily base $C_{19}H_{23}NS$ (mass spectrum) which afforded also an oxalate. The ^1H NMR spectrum of the released base led to the formulation of the 9,10-dihydrophenanthrene derivative *XV*. The oxalate, prepared from the combined mother liquors, was repeatedly recrystallized, but even then it was characterized by the ^1H NMR spectrum of the released base as the phenanthrene *XII*, strongly contaminated by compound *III*. The appearance of the dihydrophenanthrene *XV* and the phenanthrene *XII* can be explained in the same way like in the foregoing paragraph but we have to assume

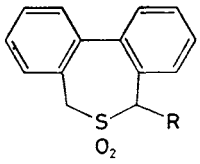
that *1*) the chlorination of compound *I* was not complete and some unchanged *I* remained, *2*) the formation of the Grignard reagent was not complete and some unchanged 3-dimethylaminopropyl chloride remained in the mixture, and *3*) the Grignard reagent formed served as the metallating, *i.e.* the anion forming agent. Similar treatment of the crude chloro compound *II* with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran gave compound *IV* contaminated with the dihydrophenanthrene derivative *XVI* and probably also with its aromatic congener (^{1}H NMR spectrum). Substitution reaction of the crude chloro compound *II* with excessive 1-methylpiperazine in boiling chloroform gave a mixture from which the bases were isolated by extraction into aqueous tartaric acid. It was attempted to transform the released base into the maleate, fumarate and oxalate; none of the salts did crystallize and decomposition of the unstable product *V* took place (repeated appearance of polymeric products); finally the solid picrate was prepared having the composition corresponding to compound *V*. It was not possible to recrystallize the picrate from ethanol without further decomposition. In conclusion, it is necessary to state that neither the way *via* the chloro compound *II* did prove an efficient method for preparing the 5-substituted derivatives of compound *I*.

After the described experience in the sulfide series we turned to the S-oxygenated derivatives. Compound *I* was oxidized with hydrogen peroxide in acetic acid at room temperature; the mixture formed was separated by chromatography on alumina. The minor product, which was first eluted with benzene, was identified as the known sulfone *XX*. It was followed by the sulfoxide *XVIII*, obtained in a reasonable yield. Its IR spectrum showed the sulfoxide band at 1 040 cm^{-1}. In the ^{1}H NMR spectrum four doublets (δ 4·21, 3·83, 3·45, and 3·25 ppm) are differentiated proving the magnetic nonequivalency of the four benzylic protons. The 1,11-dimethyl derivative of this compound is well known[4,30–32] but compound *XVIII* was only mentioned as having been obtained in the yield of 66% by extrusion of sulfur from 5,8-dihydrodibenzo[*c*,*e*]dithiocin 6-oxide; it was not characterized at all[33]. Now it has been metallated either by sodium hydride (suspension in oil) in benzene or by n-butyllithium in benzene and the mixtures were treated with 2-dimethylaminoethyl chloride. In both cases most of the starting sulfoxide *XVIII* was recovered and in both cases a small amount of the base *XIX* was obtained. It was isolated as oxalate. The struc-



XVIII, R = H
XIX, R = $CH_2CH_2N(CH_3)_2$

ture of the released base was corroborated by spectra (sulfoxide bands in the IR spectrum at 1 024, 1 036, and 1 050 cm^{-1}, well differentiated signals of the three benzylic protons in the ^{1}HNMR spectrum). In this case there was no sign of rearrangement but the conversion of compound *XVIII* to the carbanion was very poor. Only in the 5,7-dihydrodibenzo[*c*,*e*]thiepin 6,6-dioxide series it was possible to prepare all the three types of compounds we had in mind: carboxylic acids, carboxamides and aminoalkyl derivatives. The sulfone *XX* was prepared by oxidation of compound *I* with hydrogen peroxide in refluxing acetic acid in agreement with the literature data[7]. Treatment with n-butyllithium in a mixture of benzene, ether and hexane and the following carbonation resulted easily in the 5-carboxylic acid *XXI*. As a very hydrophilic by-product, the 5,7-dicarboxylic acid *XXVIII* was obtained. Only 10% of the sulfone *XX* were recovered. The monocarboxylic acid *XXI* was isolated as a 1 : 1 benzene solvate; the mass spectrum confirmed the expected composition $C_{15}H_{12}O_4S$. The structure *XXI* was fully corroborated by the IR and ^{1}H NMR spectra. The structure of the 5,7-diacid *XXVII* was deduced from the ^{1}H NMR spectrum of its bis(methylamide) *XXIX*. The formation of this diacid proved that some 5,7-dianion, corresponding to *XX*, must have been formed. Treatment of the crude acid *XXI* (containing some diacid *XXVIII*) with thionyl chloride in benzene gave the crude acid chloride which was subjected to the action of methylamine in benzene. After the addition of water, a small quantity of insoluble substance was isolated and identified as the bis(methylamide) *XXIX*; the ^{1}H NMR spectrum led to prefering the structure of the 5,7-disubstituted over that of 5,5-disubstituted compound (the signal of the benzylic protons appears as a singlet at 4·69 ppm). Evaporation of the benzene layer and crystallization of the residue gave the methylamide *XXII* in moderate yield; it crystallized from benzene as a 3 : 1 benzene solvate and from methanol as the nonsolvated substance. Its structure was corroborated by spectra. Chromatography of the mother liquors on silica gel gave a rather important quantity of phenanthrene which must have been formed by extrusion of the elements of SO_2 with simultaneous decarboxylation (analogy of the Ramberg–Bäcklund rearrangement, *cf.*[29,34–36]). A similar reaction sequence, starting from the crude acid *XXI* (containing an important part of the diacid *XXVIII*), and proceeding via



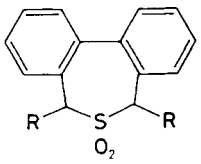
XX, R = H
XXI, R COOH
XXII, R = $CONHCH_3$
XXIII, R = $CON(CH_3)_3$
XXIV, R = CH_2COOH
XXV, R = $CH_2N(CH_3)_2$
XXVI, R = $(CH_2)_2N(CH_3)_2$
XXVII, R = $(CH_2)_3N(CH_3)_2$

the crude acid chloride and its treatment with dimethylamine in benzene, gave a mixture of the dimethylamide *XXIII* and the bis(dimethylamide) *XXX*. This mixture was separated either by crystallization or by chromatography on silica gel.

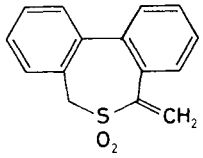
Treatment of the sulfone *XX* with n-butyllithium, the following action of ethyl bromoacetate and hydrolysis gave a mixture consisting of almost 50% of the starting compound *XX*. The acidic fraction was chromatographed on silica gel which led to isolation of 6,6-dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5-acetic acid (*XXIV*) in a low yield; the structure was confirmed by spectra. The dimethylamide *XXIII* was reduced with diborane, generated by reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran. The mixture formed was chromatographed on silica gel. As the first fraction, a small quantity of a nitrogen-lacking substance was obtained and identified by analysis and spectra as 5-methylene-5,7-dihydrodibenzo[*c*,*e*]thiepin 6,6-dioxide (*XXXII*) resulting by dimethylamine elimination from the amine *XXV* (a Mannich base-like behaviour). It was followed by the base XXV, characterized as the oxalate. Its mass spectrum is in agreement with the assigned structure but the ^{1}H NMR spectrum characterized the substance as being a mixture of two isomers (the signal of $N(CH_3)_2$ splitted into two singlets). We are evidently dealing here with two stable conformers because at 150°C the ring inversion is so rapid that the signal of $N(CH_3)_2$ appears as a singlet at 2·00 ppm. Treatment of the sulfone *XX* with sodium hydride in dimethylformamide and the following action of 2-dimethylaminoethyl chloride resulted in the 5-(2-dimethylaminoethyl) derivative *XXVI*; it was characterized by spectra and by the maleate. Sodium hydride does not appear to be a sufficiently hard base for complete abstracting the benzylic proton because most of the starting sulfone *XX* was recovered unchanged. For this reason the similar introduction of 3-dimethylaminopropyl was carried out by making use of n-butyllithium as the metallating agent. 3-Dimethylaminopropyl chloride was used in excess and less than 50% of the starting sulfone *XX* was recovered. The mixture of bases was separated by chromatography on silica gel. The monoalkylated compound *XXVII* was obtained as the major product and was characterized by spectra and by the hydrogen maleate. In a further similar experiment, the chromatographic separation was carried out on alumina. The monoalkylated compound *XXVII* was eluted with benzene and this was followed by elution with chloroform giving the 5,7-dialkylated compound *XXXI* which appeared in this experiment as the major product. There was again the question whether we are dealing here with a 5,7- or 5,5-dialkylated compound. The mass spectrum and especially the ^{1}H NMR spectrum (signal of the benzylic protons appears as the triplet at 3·81 ppm) settled the question again in favour of the 5,7-disubstitution.

The sulfonium salt *VII*, amines *XI*, *XIV*, *XXV*, *XXVI*, and *XXVII* (in the form of salts described in the Experimental), amides *XXII*, *XXIII*, and *XXX*, and the diacid *XXVIII* were subjected to pharmacological screening. They were administered orally (unless stated otherwise) and in the case of the salts, the doses (in mg/kg)

were calculated for the bases. Acute toxicity in mice was studied only with some compounds, LD_{50} in mg/kg: *VII*, 4·0 *i.v.*; *XXII*, >1 000 (no lethality); *XXIII*, >1 000 (10% lethality), *XXVI*, 364, 54·4 *i.v.*; *XXVIII*, >1 000 (no lethality); *XXX*, >1 000 (no lethality).



XXVIII, R = COOH
XIX, R = $CONHCH_3$
XXX, R = $CON(CH_3)_2$
XXXI, R = $(CH_2)_3N(CH_3)_2$



XXXII

The sulfonium salt *VII* in the dose of 1 mg/kg *i.v.* brought about deep and short-lasting drops of blood pressure in anaesthetized normotensive rats. In the dose of 0·5 mg/kg *i.v.* it inhibited the adrenaline pressor reaction in rats by 50%. In the dose of 10 mg/kg *i.v.* it exhibited a myorelaxant effect on the gastrocnemius muscle in rats (*i.e.* 2·5 LD_{50}; the animals were connected to a respiratory pump). In rats it had antitussive action (ED_{50} between 2·5 and 5·0 mg/kg orally) (the coughing activity was elicited by the aerosol of citric acid solution). The compound is rather toxic and its hypotensive, antiadrenaline and myorelaxant activities are typical for onium salts.

The amines were evaluated in a series of tests oriented towards the neuro- and psychopharmacological area; in fact they were specifically evaluated as potential antidepressants. Release of [^{3}H]imipramine from its binding sites in the rat hypothalamus: with compounds *XI*, *XIV*, *XXV*, and *XXVII* the IC_{50} was higher than 100 nanomol; similarly for the release of [^{3}H]desipramine, the IC_{50} with compounds *XIV*, *XXV*, and *XXVI* was higher than 100 nanomol. Discoordinating activity in the rotarod test in mice: *XI*, the dose of 100 mg/kg brought about ataxia in 20% animals; *XIV*, ED_{50} 71 mg/kg; *XXV*, 250 mg/kg, ataxia in 30%, *XXVI*, 40 mg/kg *i.v.*, ataxia in 20%; *XXVII*, inactive at 100 mg/kg. Antireserpine effect in the test of ptosis in mice: *XI* and *XIV*, in the doses of 100 mg/kg antagonized significantly the reserpine effect; *XXV*, inactive at 100 mg/kg; *XXVII*, a significant antireserpine effect at 30 mg/kg. Influence on the ulcerogenic effect of reserpine in rats: *XXVI*, inactive at 50 mg/kg. Potentiation of yohimbine toxicity in mice: *XI*, inactive at 250 mg/kg; *XIV*, ED_{50} 75·7 mg/kg; *XXV*, the dose of 100 mg/kg produced lethality in 40% animals; *XXVII*, 50 mg/kg, lethality in 30%. Anticataleptic effect (towards perphenazine catalepsy) in rats: *XXVI*, the dose of 20 mg/kg was without effect. Effect on locomotor activity in mice: *XIV*, the dose of 100 mg/kg decreased the activity significantly

to 25% of the control group (this effect was not followed with hypermotility); *XXVI*, the dose of 50 mg/kg inhibited the activity significantly. Test of catalepsy in rats: *XIV*, the dose of 50 mg/kg was without effect. Antagonism against climbing behaviour (verticalization) induced by apomorphine (2 mg/kg *s.c.*) in mice: *XIV*, the dose of 30 mg/kg was without effect; *XXVII*, the dose of 30 mg/kg blocked the climbing behaviour in 10% animals. Peripheral antiadrenergic effect in mice: compound *XXV* in the dose of 100 mg/kg and compound *XXVI* in the dose of 50 mg/kg did not protect from the lethal effect of adrenaline. Antihistamine activity: compound *XXVI* in the dose of 10 mg/kg *s.c.* protected 12% of the guinea-pigs from the lethal effect of 5 mg/kg histamine (administered intrajugularly). Peripheral antiserotonin effect: compound *XXVI* in the dose of 10 mg/kg antagonized mildly, but with statistical significance, the serotonin-induced edema of the rat paw. In conclusion: only the phenanthrene derivatives *XI* and *XIV* and the aminosulfone *XXVII* showed clear indications of psychotropic, specifically thymoleptic activity.

The evaluation of the amides was oriented in the line of anticonvulsant and central depressant activities. Electroshock in mice: *XXII*, in the dose of 50 mg/kg practically without effect; XXIII, ED_{50} 20 mg/kg; *XXX*, the dose of 10 mg/kg protected 30% of the animals from the electroshock-induced convulsions but did not protect from the lethal action. Rotarod test in mice: *XXIII*, the dose of 10 mg/kg brought about ataxia in 20% animals; *XXX*, the dose of 50 mg/kg, ataxia in 20% animals. The central activity of the amides is very weak.

The diacid *XXVIII* was evaluated as a potential antiinflammatory agent in rats using two models of the experimental inflammation. The dose of 100 mg/kg inhibited the carrageenan-induced edema by 12% (not significant), the adjuvant edema by 7% (not significant) (for ibuprofen as a standard significant inhibition by 57%, and 31%, respectively, after the dose of 100 mg/kg).

EXPERIMENTAL

The melting points of analytical preparations were determined in the Mettler FP-5 melting point recorder; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, 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 MCH 1 320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3, and evaporated under reduced pressure on a rotating evaporator.

2,2'-Bis(hydroxymethyl)biphenyl

A) A stirred solution of 74·5 g diphenic acid[8] in 200 ml tetrahydrofuran was treated at 20–30°C with 23·2 g $NaBH_4$ under nitrogen, and then at the same temperature with 147 g

$BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 4 h at room temperature, allowed to stand overnight, decomposed with 100 ml 5% hydrochloric acid, and extracted with benzene. The extract was washed with water, 5% NaOH and water, dried and evaporated. The residue crystallized; 62·7 g (95%),m.p. 111—112°C (benzene). Ref.[10], m.p. 112—113°C.

B) In a larger batch from 82·0 g diphenic acid, 220 ml tetrahydrofuran, 25·5 g $NaBH_4$ and 162 g $BF_3.O(C_2H_5)_2$, the crude product obtained (62·8 g) was recrystallized from 250 ml benzene; 53·1 g (73%), m.p. 110—112°C. The mother liquor was evaporated in vacuo and the residue (9·6 g) was crystallized from 20 ml ethanol; 4·1 g (6%) dibenz[*c*,*e*]oxepin-5(7*H*)-one (*VI*), m.p. 133·5—134·5°C. UV spectrum: λ_{max} 248 nm (log ε 4·13), 302 nm (3·46). IR spectrum: 744, 767 (4 adjacent Ar—H), 1 010, 1 110, 1 280, 1 297 (Ar—COO—R), 1 470, 1 560, 1 600, 3 065 (Ar), 1 703 cm^{-1} (Ar—COO—R in the ring). Refs[11,12], m.p. 132, and 134°C, respectively.

5,7-Dihydrodibenzo[*c*,*e*]thiepin (*I*)

Reaction of 61·5 g 2,2′-bis(hydroxymethyl)biphenyl with a boiling mixture of 430 ml 48% hydrobromic acid and 57 ml H_2SO_4 (ref.[13]) gave 95·6 g (98%) 2,2′-bis(bromomethyl)biphenyl, m.p. 90—92°C (ref.[13], m.p. 91—93°C). Cyclization of 81 g of this compound by refluxing with a solution of 172 g $Na_2S.9\,H_2O$ in a mixture of 215 ml water and 4 l methanol gave 42·4 g (84%) *I*, m.p. 90—91°C (ethanol). Ref.[7], m.p. 89—90°C.

A mixture of 4·25 g *I*, 100 ml ethanol and 36 g methyl iodide was refluxed for 8 h to give 5·4 g (76%) 6-methyl-5,7-dihydrodibenzo[*c*,*e*]thiepinium iodide (*VII*), m.p. 138—141°C. Ref.[7], m.p. 139·5—140·5°C.

Attempt at lithiation and carbonation: A solution of 6·4 g *I* in 80 ml ether was stirred and treated under nitrogen with 42 ml 9% n-butyllithium solution in hexane, added dropwise over 15 min. The mixture was stirred for 2 h, poured on solid CO_2, stirred for 1 h, allowed to stand overnight, and decomposed with water. The ether layer was washed with dilute NaOH and evaporated. The residue (6·4 g) was chromatographed on a column of 100 g SiO_2. Light petroleum eluted first 0·94 g (37% per conversion) of phenanthrene (*VIII*), m.p. 97—99°C (ethanol). Mass spectrum, *m/z* (%): 178 (M^+ corresponding to $C_{14}H_{10}$, 100%), 179 (16), 177 (16), 176 (20), 152 (15), 89 (38), 88 (32), 76 (42), 75 (16). Refs[14,15], m.p. 99·5°C. Continued elution with light petroleum recovered 3·37 g (53%) of the starting *I*, m.p. 88—90·5°C. Benzene eluted then 1·34 g (45% per conversion) compound crystallizing from ethanol and melting at 120—125°C to which the structure of 9,10-dihydrophenanthrene-9,10-episulfide (*XIII*) is tentatively assigned. Mass spectrum, *m/z* (%): 210 (M^+ corresponding to $C_{14}H_{10}S$, 4%), 178 ($C_{14}H_{10}$, 100), 176 (21), 150 ($C_{12}H_8$, 14), 89 (23), 88 (20), 76 (27). UV spectrum: λ_{max} 252 nm (log ε 4·37), 257 nm (4·36), 305 nm (3·69), 316 nm (3·58). IR spectrum: 735, 745, 758 (4 adjacent Ar—H), 1 482, 1 570, 1 585, 3 055 (Ar), 1 635 cm^{-1}. For $C_{14}H_{10}S$ (210·2) calculated: 79·98% C, 4·79% H, 15·22% S; found: 80·02% C, 4·91% H, 15·10% S.

Phenanthrene-9-thiol (*IX*)

A solution of 4·6 g *I* in 50 ml ether was stirred under nitrogen and treated at room temperature with 30 ml 9% n-butyllithium solution in hexane. The red solution was allowed to stand for 48 h; during this time the mixture became colourless and some solid precipitated. It was hydrolyzed with water, the ether layer was washed with dilute NaOH and water, dried, and evaporated; 3·0 g mixture containing in addition to starting *I* some *VIII* and *XIII* (TLC). The alkaline washings were acidified with hydrochloric acid (smell of H_2S) and extracted with benzene. Processing of the extract gave 1·8 g residue which was crystallized from ethanol; 50 mg bis(9-phenanthryl) disulfide (*X*), m.p. 202—204°C. Mass spectrum (heating to 300°C), *m/z*: 418

(M^+ corresponding to $C_{28}H_{18}S_2$). UV spectrum (saturated solution in methanol; the solubility is very low): λ_{max} 251·5 nm, infl. 300 nm. IR spectrum: 722, 745, 767 (4 adjacent Ar—H), 1 590, 3 050 cm^{-1} (Ar). For $C_{28}H_{18}S_2$ (418·4) calculated: 80·37% C, 4·34% H, 15·29% S; found: 79·67% C, 4·31% H, 15·39% S. Ref.[16], m.p. 149°C.

The mother liquor was evaporated and crystallization of the residue from ethanol gave 0·25 g *IX*, m.p. 93·5—96·5°C. Mass spectrum, *m/z* (%): 210 (M^+ corresponding to $C_{14}H_{10}S$, 100%), 209 (47), 178 ($C_{14}H_{10}$, 20), 165 ($C_{13}H_9$, 45), 105 (15), 104 (23). UV spectrum: λ_{max} 223 nm (log ε 4·33), 251 (4·58), 258·5 (4·58), 303 (4·00), infl. 312 (3·93). IR spectrum: 720, 748, 760, 875 (4 adjacent and solitary Ar—H), 1 485, 1 570, 1 580, 1 605, 3 045 (Ar), 2 560 cm^{-1} (SH), ^1H NMR spectrum: δ 8·40 (m, 2 H, 4,5-H_2), 8·10 (m, 1 H, 10-H), 7·45 (m, 6 H, remaining ArH), 3·40 (s, 1 H, SH). For $C_{14}H_{10}S$ (210·2) calculated: 79·98% C, 4·79% H, 15·22% S; found: 79·76% C, 4·88% H, 15·13% S. Ref.[16], m.p. 67°C.

N,N-Dimethyl-2-(9,10-dihydro-9-phenanthrylthio)ethylamine (*XIV*)

A solution of 4·6 g *I* in 50 ml ether was stirred under nitrogen and treated with 25 ml 9·3% n-butyllithium solution in hexane, the mixture was stirred for 3·5 h, 10·7 g 2-dimethylaminoethyl chloride were added, and the stirring was continued for 2 h. It was allowed to stand overnight, hydrolyzed with water, the organic layer was washed with 2M HCl and water, dried and evaporated. The residue consisted mainly of the starting *I*; crystallization from ethanol gave 1·0 g substance melting at 88°C. The acid aqueous layer was made alkaline with NH_4OH, and the bases were extracted with benzene. Processing of the extract gave 3·7 g oil which was chromatographed on 150 g silica gel. Elution with chloroform gave 1·03 g (22% per conversion) of a homogeneous oily base which was identified as N,N-dimethyl-2-(9-phenanthrylthio)ethylamine (*XI*). Its neutralization with maleic acid gave the hydrogen maleate which crystallized from a mixture of acetone, ethanol and ether as a 2 : 1 solvate with ethanol, m.p. 109—111°C and after resolidification 115—117°C. Mass spectrum, *m/z* (composition, %): 281 (M^+ corresponding to $C_{18}H_{19}NS$, 1%), 221 ($C_{15}H_9S$, 1), 209 ($C_{14}H_9S$, 1), 176 ($C_{14}H_8$, 1), 165 ($C_{13}H_9$, 3), 72 ($C_4H_{10}N$, 8), 58 (C_3H_8N, 100). For $C_{22}H_{23}NO_4S + 0·5\ C_2H_6O$ (420·5) calculated: 65·69% C, 6·23% H, 3·33% N, 7·63% S; found: 65·72% C, 6·28% H, 3·19% N. 7·68% S.

The released base was used for recording the ^1H NMR spectrum: δ 8·50 (m, 3 H, 4,5,10-H_3), 7·40—7·80 (m, 6 H, remaining ArH), 3·12 (bt, 2 H, CH_2S), 2·58 (bt, 2 H, CH_2N), 2·21 (s, 6 H, $(CH_3)_2N$).

The elution was continued with a mixture of chloroform and ethyl acetate; 1·41 g (29% per conversion) homogeneous oily *XIV*. Its neutralization with maleic acid gave the hydrogen maleate crystallizing from a mixture of acetone, ethanol and ether again as a 2 : 1 solvate with ethanol, m.p. 60—64°C. Mass spectrum, *m/z* (%): 283 (M^+ corresponding to $C_{18}H_{21}NS$, 0·2%), 178 ($C_{14}H_{10}$, 8), 105 (10), 58 (100). For $C_{22}H_{25}NO_4S + 0·5\ C_2H_6O$ (422·6) calculated: 65·38% C, 6·68% H, 3·31% N, 7·59% S; found: 65·34% C, 6·72% H, 3·34% N, 7·70% S. ^1H NMR spectrum of the released base: δ 7·70 (m, 2 H, 4,5-H_2), c. 7·20 (m, 6 H, remaining ArH), 4·15 (dd, J = 4·5; 3·0 Hz, 1 H, Ar—CH—S), 3·35 and 3·00 (2 dd, J = 16·0; 4·5 and 16·0; 3·0 Hz, 1 + 1 H, 10, 10-H_2), 2·40 (m, 4 H, SCH_2CH_2N), 2·14 (s, 6 H, $(CH_3)_2N$).

Attempt to Alkylate *I* with 3-Piperidinopropyl Chloride

A solution of 3·8 g *I* in 50 ml ether was stirred under nitrogen and treated with 25 ml 9% n-butyllithium in hexane. The mixture was stirred for 2 h at 25°C, 7·3 g 3-piperidinopropyl chloride were added, it was stirred for 2 h, allowed to stand for 24 h, washed with water, with dilute hydrochloric acid and water. Evaporation recovered *I*; 1·3 g. Treatment of the aqueous acid

washings with NH_4OH and extraction with ether gave 7·2 g liquid base which was chromatographed on 100 g neutral Al_2O_3 (activity *II*). A mixture of bases (5·5 g) was eluted with the first benzene fraction. Elution with chloroform gave 1·3 g of a homogeneous oily base which was neutralized with HCl in ether; 1·15 g dihydrochloride of bis(3-piperidinopropyl) ether (*XVII*), m.p. 226–230°C (ethanol–ether). Mass spectrum, *m/z* (composition, %): 268 (M^+ corresponding to $C_{16}H_{32}N_2O$, 1%), 170 ($C_{10}H_{20}NO$, 1), 142 ($C_8H_{16}NO$, 11), 110 ($C_7H_{12}N$, 7), 98 ($C_6H_{12}N$, 100), 84 (8). IR spectrum: 1 100, 1 115 (R—O—R), 2 410, 2 520, 2 640 cm^{-1} (NH^+). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·80 (a flat band, 2 NH^+), 1·30–3·60 (m, 6 CH_2). For $C_{16}H_{34}Cl_2N_2O$ (341·4) calculated: 56·29% C, 10·04% H, 20·77% Cl, 8·20% N; found: 56·38% C, 9·89% H, 19·94% Cl 7·93% N. Ref.[22], m.p. 220–221°C.

N,N-Dimethyl-3-(5,7-dihydrodibenzo[*c*,*e*]thiepin-5-yl)propylamine (*III*)

A stirred solution of 6·9 g *I* in 40 ml CCl_4 was treated over 10 min with a solution of 5·5 g SO_2Cl_2 in 20 ml CCl_4, added dropwise. The mixture was heated for 1 h to 60°C and CCl_4 was evaporated *in vacuo*. The yellow crystalline residue (8·5 g), representing crude *II* (*cf.*[29]), was dissolved in a mixture of 30 ml benzene and 20 ml tetrahydrofuran and this solution was added dropwise over 5 min to a stirred Grignard reagent, prepared from 1·6 g Mg and 8·0 g 3-dimethylamino propyl chloride in 50 ml tetrahydrofuran. The mixture was refluxed for 4 h, diluted with ether, and decomposed with a solution of NH_4Cl. The organic layer was extracted with dilute hydrochloric acid, the acid aqueous solution was made alkaline with 20% NaOH and the base was isolated by extraction with benzene. Processing of the extract gave 8·9 g oil characterized by TLC as a mixture of three components. It was chromatographed on 200 g silica gel. The first chloroform eluates were inhomogeneous. Further elution with chloroform and then with a mixture of chloroform and ethyl acetate gave 2·53 g (26%) homogeneous oily *III*. Its neutralization with oxalic acid in a mixture of ethanol and ether gave 2·9 g hydrogen oxalate, m.p. 174·5 to 177·5°C (ethanol). Mass spectrum, *m/z* (composition): 297 (M^+ corresponding to $C_{19}H_{23}NS$), 264 ($C_{19}H_{22}N$), 191 ($C_{15}H_{11}$), 178 ($C_{14}H_{10}$), 165 ($C_{13}H_9$), 72, 58. For $C_{21}H_{25}NO_4S$ (387·5) calculated: 65·09% C, 6·50% H, 3·61% N, 8·28% S; found: 65·15% C, 6·61% H, 3·62% N, 8·02% S. The released base was used for recording the ^1H NMR spectrum: δ 7·30 (m, 8 H, ArH), 3·62 (t, J = 7·0 Hz, 1 H, Ar—CH—S), 3·45 and 3·20 (ABq, J = 12·5 Hz, 1 + 1 H, $ArCH_2S$), 1·80–2·40 (m, 4 H, 2 external CH_2 in propylene), 2·12 (s, 6 H, $(CH_3)_2N$), 1·60 (m, 2 H, CH_2 in the middle of the propane chain).

The elution was continued with ethyl acetate and gave 1·67 g (17%) homogeneous oily N,N-dimethyl-3-(9,10-dihydro-9-phenanthrylthio)propylamine (*XV*). Neutralization with oxalic acid in ethanol gave 1·25 g hydrogen oxalate, m.p. 145–150°C (ethanol). Mass spectrum, *m/z* (composition): 297 (M^+ corresponding to $C_{19}H_{23}NS$), 178 ($C_{14}H_{10}$), 118 ($C_5H_{12}NS$), 72, 58. For $C_{21}H_{25}NO_4S$ (387·5) calculated: 65·09% C, 6·50% H, 3·61% N, 8·28% S; found: 65·12% C, 6·57% H, 3·80% N, 8·02% S. ^1H NMR spectrum of the released base was recorded: δ 7·70 (m, 2 H, 4,5-H_2), 7·20 (m, 6 H, remaining ArH), 4·12 (dd, J = 4·5; 3·5 Hz, 1 H, 9-H), 3·31 and 3·00 (2 dd, J = 12·5; 4·5 and 12·5; 3·5 Hz, 1 + 1 H, 10, 10-H_2), 2·00–2·50 (m, 4 H, 2 external CH_2 of propylene), 2·12 (s, 6 H, $(CH_3)_2N$), 1·68 (m, 2 H, CH_2 in the middle of propane).

The inhomogeneous less polar fractions from the chromatography were combined and also transformed to the hydrogen oxalate; 0·95 g, m.p. 122–126°C after several crystallizations from acetone. According to the ^1H NMR spectrum of the released base, we are dealing here with the hydrogen oxalate of N,N-dimethyl-3-(9-phenanthrylthio)propylamine (*XII*), contaminated with *III* hydrogen oxalate. For $C_{21}H_{23}NO_4S$ (385·5) calculated: 65·43% C, 6·01% H, 3·63% N, 8·32% S; found: 65·15% C, 6·31% H, 3·73% N, 7·99% S.

4-(5,7-Dihydrodibenzo[*c*,*e*]thiepin-5-yl)-1-methylpiperidine (*IV*)

I (6·9 g) in 40 ml CCl_4 was similarly treated with 5·5 g SO_2Cl_2 in 20 ml CCl_4, the mixture was heated for 1 h to 60°C and evaporated *in vacuo*. The remaining crystalline *II* (cf.[29]) was dissolved in 40 ml tetrahydrofuran. The Grignard reagent was prepared from 8·8 g 4-chloro-1-methylpiperidine and 1·6 g Mg in 50 ml tetrahydrofuran by refluxing for 1 h, and after cooling it was added dropwise over 15 min to a stirred solution of *II*. The mixture was refluxed for 3 h, diluted with ether, decomposed with NH_4Cl solution and the organic layer was extracted with dilute hydrochloric acid. The acid aqueous solution was made alkaline with NH_4OH and extracted with ether. Processing of the extract gave 6·75 g mixture of bases which was chromatographed on 200 g silica gel. Chloroform and then ethyl acetate eluted only mixtures of minor basic components. Ethanol eluted 3·60 g (36%) oily base which seemed to be homogeneous and consisted mainly of *IV*; hydrogen oxalate, m.p. 148·5—150·5°C (acetone–ethanol). Mass spectrum, *m/z* (composition and %): 309 (M^+ corresponding to $C_{20}H_{23}NS$, 4%), 276 ($C_{20}H_{22}N$, 26), 178 ($C_{14}H_{10}$, 18), 130 ($C_7H_{12}NS$, 49), 99 (36), 98 ($C_7H_{12}N$, 100), 70 (23), 56 (20), 44 (48). For $C_{22}H_{25}NO_4S$ (399·5) calculated: 66·14% C, 6·31% H, 3·51% N, 8·03% S; found: 65·70% C, 6·24% H, 3·51% N, 7·98% S. The ^1H NMR spectrum of the released base showed contamination with *XVI* and its aromatic congener because the signal of NCH_3 is splitted into 3 singlets: 2·18, 2·16, 2·05 ppm.

1-(5,7-Dihydrodibenzo[*c*,*e*]thiepin-5-yl)-4-methylpiperazine (*V*)

I (6·9 g) in 40 ml CCl_4 was stirred and treated over 30 min with a solution of 5·5 g SO_2Cl_2 in 20 ml CCl_4, the mixture was heated to 60°C for 1 h and evaporated *in vacuo*. The residue was dissolved in 15 ml chloroform, 15 g 1-methylpiperazine were added, and the stirred mixture was refluxed for 8 h. After cooling it was distributed between benzene and water, the benzene layer was washed with water and the bases were extracted into a solution of 5·5 g (+)-tartaric acid in 100 ml water. The aqueous solution was made alkaline with NH_4OH, the base was extracted with benzene, and the extract was processed; 6·7 g (66%) crude *V*. Picrate, m.p. 132—137°C (ethanol). For $C_{25}H_{25}N_5O_7S$ (539·6) calculated: 55·65% C, 4·67% H, 12·98% N, 5·94% S; found: 55·83% C, 4·39% H, 12·91% N, 5·80% S.

5,7-Dihydrodibenzo[*c*,*e*]thiepin 6-Oxide (*XVIII*)

A solution of 6·8 g *I* in 100 ml acetic acid was treated with 5·5 ml 30% H_2O_2 and the mixture was allowed to stand for 24 h at room temperature. It was then diluted with water, extracted with chloroform, the extract was dried and evaporated. The residue was chromatographed on 300 g neutral Al_2O_3 (activity *II*). Benzene eluted first 0·95 g (12%) of the sulfone *XX*, m.p. 208—210°C (ethanol); ref.[7], m.p. 209—210°C. Chloroform eluted then 6·30 g (86%) *XVIII*, m.p. 129—130°C (ethanol). IR spectrum: 744, 755, 775 (4 adjacent ArH), 1 040 (R—S—O), 1 480, 3 020, 3 050, 3 070 cm^{-1} (Ar). ^1H NMR spectrum: δ c. 7·40 (m, 8 H, ArH), 4·21 and 3·25 (ABq, J = 12·0 Hz), 3·83 and 3·45 (ABq, J = 14·0 Hz) (1 + 1 + 1 + 1 H, CH_2SOCH_2). For $C_{14}H_{12}OS$ (228·3) calculated: 73·65% C, 5·30% H, 14·04% S; found: 73·77% C, 5·35% H, 13·94% S.

5-(2-Dimethylaminoethyl)-5,7-dihydrodibenzo[*c*,*e*]thiepin 6-Oxide (*XIX*)

A) A solution of 5·84 g *XVIII* in 120 ml benzene was treated with 0·9 g 80% NaH (suspension in oil), and the mixture was refluxed for 2·5 h. After cooling, 8·6 g 2-dimethylaminoethyl chloride in 20 ml benzene were added dropwise over 90 min, the mixture was refluxed for 2 h, cooled,

hydrolyzed with water, the organic layer was extracted with dilute hydrochloric acid, the organic layer was dried and evaporated; 5·25 g of the starting *XVIII*. The acid aqueous layer was made alkaline with NH_4OH, and the base was isolated by extraction with benzene; 0·50 g (65% *per* conversion) oily *XIX*. Hydrogen oxalate hemihydrate, m.p. 192—193°C (aqueous acetone). For $C_{20}H_{23}NO_5S + 0{\cdot}5\ H_2O$ (398·5) calculated: 60·28% C, 6·07% H, 3·52% N, 8·05% S; found: 60·49% C, 5·72% H, 3·62% N, 8·11% S. The base was released with NH_4OH and isolated by extraction with ether, oil. IR spectrum: 745, 755, 775 (4 adjacent Ar—H), 1 024, 1 036, 1 050 (R—S—O), 1 477, 3 040, 3 070 (Ar), 2 720, 2 760, 2 790, 2 815 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·40 (m, 8 H, ArH), 4·20 and 3·10 (ABq, J = 12·0 Hz, 1 + 1 H, $ArCH_2SO$), 3·40 (m, 1 H, ArCHSO), 2·40 (m, 4 H, CH_2CH_2N), 2·18 (s, 6 H, $(CH_3)_2N$).

B) A solution of 5·25 g *I* in 100 ml benzene was lithiated by treatment with 60 ml 9% butyllithium in hexane, the mixture was stirred for 2 h, treated with 10 g 2-dimethylaminoethyl chloride, stirred for 5 h, and allowed to stand for 48 h. It was washed with water, the organic layer was extracted with dilute hydrochloric acid, dried, and evaporated; 4·80 g recovered *I* (TLC). Treatment of the acid aqueous layer with NH_4OH and extraction with benzene gave 0·40 g *XIX*, identical with the product obtained under *A* (comparison by TLC).

5,7-Dihydrodibenzo[*c*,*e*]thiepin 6,6-Dioxide (*XX*)

A solution of 10·0 g *I* in 100 ml acetic acid was treated with 50 ml 30% H_2O_2, and the mixture was refluxed for 1·5 h. Cooling led to crystallization of 10·2 g (89%) *XX*, m.p. 210—211°C. Ref.[7], m.p. 209—210°C.

6,6-Dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5-carboxylic Acid (*XXI*)

A solution of 3·4 g *X* in 80 ml benzene and 50 ml ether was stirred under nitrogen and treated, with 30 ml 9% n-butyllithium in hexane, the mixture was stirred for 3 h, poured onto solid CO_2, stirred for 1 h, allowed to stand for 48 h, and decomposed with water. The organic layer was washed with dilute NaOH and evaporated; 0·5 g *XX* was recovered, m.p. 208·5—211°C (ethanol). The alkaline solution was acidified with dilute hydrochloric acid, extracted with chloroform, the extract was evaporated, and the residue was induced to crystallize by trituration with benzene; 2·4 g (55% *per* conversion) of the 1 : 1 solvate of *XXI* with benzene, m.p. 118—121°C (benzene–ethanol). Mass spectrum, *m/z* (composition, %): 288 (M^+ corresponding to $C_{15}H_{12}O_4S$, 2%), 244 ($C_{14}H_{12}O_2S$, 17), 224 ($C_{15}H_{12}O_2$, 3), 180 (66), 179 ($C_{14}H_{11}$, 100), 178 ($C_{14}H_{10}$, 62), 165 ($C_{13}H_9$, 51), 152 (20), 89 (23), 44 (29). IR spectrum: 685, 702 (C_6H_6), 763 (4 adjacent Ar—H), 912, 1 720, 2 530, 2 595, 2 640, infl. 3 100 (COOH), 1 130, 1 330 (SO_2), 1 478, 3 030, 3 060, 3 088 cm^{-1} (Ar). ^1H NMR spectrum: δ 9·05 (bs, 1 H, COOH), 7·40—8·00 (m, 8 H, ArH of the biphenyl fragment), 7·60 (s, 6 H, C_6H_6), 4·96 (s, 1 H, 5-H), 4·12 and 3·90 (ABq, J = 13·0 Hz, 1 + 1 H, 7,7-H_2). For $C_{15}H_{12}O_4S + C_6H_6$ (366·4) calculated: 68·83% C, 4·95% H, 8·75% S; found: 68·20% C, 5·00% H, 8·54% S.

6,6-Dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5,7-dicarboxylic Acid (*XXVIII*)

Preparation of *XXI* in a larger batch was carried out similarly from 23·0 g *XX* in a mixture of 500 ml benzene, 100 ml ether and 100 ml tetrahydrofuran, 200 ml 9% n-butyllithium in hexane and excess of CO_2. Similar processing gave 18·4 g (57% per conversion) *XXI*. C_6H_6, m.p. 115 to 120°C (benzene); 1·4 g *XX* were recovered. The aqueous acid solution (after the extraction with chloroform) was allowed to stand for 48 h and deposited 2·8 g (10%) crystals which were purified by recrystallization from a mixture of benzene and ethanol, m.p. 150—152°C. The substance was identified as *XXVIII*. For $C_{16}H_{12}O_6S$ (332·3) calculated: 57·82% C, 3·64% H, 9·65% S; found: 58·02% C, 4·08% H, 9·64% S.

N-Methyl-6,6-dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5-carboxamide (*XXII*)

A mixture of 7·3 g XXI.C_6H_6 (containing some XXVIII), 30 ml benzene and 20 ml $SOCl_2$ was refluxed for 3 h, evaporated *in vacuo*, the residue was dissolved in 80 ml benzene and the solution was added dropwise over 20 min to a stirred and cooled solution (temperature max. +5°C) of 7·7 g methylamine in 50 ml benzene. The mixture was stirred for 2 h at room temperature, allowed to stand overnight, mixed with 50 ml water, the precipitated solid was filtered and crystallized from a mixture of 100 ml chloroform and 30 ml ethanol; 0·72 g N,N'-dimethyl-6,6-dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5,7-dicarboxamide (*XXIX*), m.p. 280–283°C (chloroform). IR spectrum: 753 (4 adjacent Ar—H), 1 125, 1 280, 1 310 (SO_2), 1 545, 1 669 (CONH), 3 290, 3 340 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·40 (bq, J = 2·5 Hz, 2 H, 2 CONH), 8·10 (m, 2 H, 1,11-H_2), 7·50 (m, 6 H, remaining ArH), 4·69 (s, 2 H, 5,7-H_2), 2·45 (t, J = 2·5 Hz, 6 H, 2 NCH_3). For $C_{18}H_{18}N_2O_4S$ (358·4) calculated: 60·32% C, 5·06% H, 7·81% N, 8·95% S; found: 59·44% C, 4·96% H, 7·41% N, 8·50% S.

The benzene layer (after filtration of *XXIX*) was evaporated *in vacuo* and the residue was crystallized from methanol: 2·35 g *XXII*, m.p. 242–244°C. UV spectrum: λ_{max} 243 nm (log ε 4·08). IR spectrum: 746, 765 (4 adjacent Ar—H), 1 130, 1 320 (SO_2), 1 560, 1 650 (CONH), 3 235 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·20–8·50 (m, 9 H, ArH and CONH), 4·80 (s, 1 H, 5-H), 4·56 and 3·85 (ABq, J = 13·0 Hz, 1 + 1 H, 7,7-H_2), 2·62 (bd, 3 H, NCH_3). For $C_{16}H_{15}NO_3S$ (301·3) calculated: 63·77% C, 5·02% H, 4·65% N, 10·64% S; found: 63·73% C, 5·20% H, 4·72% N, 10·43% S.

Crystallization of *XXII* from benzene gave the 3 : 1 solvate with benzene, m.p. 235–240°C. For $C_{16}H_{15}NO_3S + 1/3\ C_6H_6$ (327·4) calculated: 66·03% C, 5·23% H, 4·28% N; found: 65·28% C, 5·13% H, 4·49% N.

The mother liquors after *XXII* and *XXIX* were combined and chromatographed on 100 g silica gel. Elution with chloroform gave in the first fractions 1·0 g phenanthrene (*VIII*), m.p. 93–96°C (benzene–light petroleum). Continued elution with chloroform afforded 2·10 g *XXII*, m.p. 243–246°C (methanol). The total yield on *XXII* was thus 4·45 g (67%).

N,N-Dimethyl-6,6-dioxido-5,7-dihydrodibenzo[*c*,*e*]thiepin-5-carboxamide (*XXIII*)

A) *XXI* (containing a considerable amount of *XXVIII*) (7·3 g), 30 ml benzene and 20 ml $SOCl_2$ were refluxed for 4 h and the mixture was evaporated *in vacuo*. The residue was diluted with 50 ml benzene and the evaporation was repeated. The residue was dissolved in 40 ml benzene and the solution was added dropwise to a stirred and cooled solution of 15 g dimethylamine in 50 ml benzene. It was stirred for 2 h at room temperature, allowed to stand overnight and shaken with 100 ml water. The precipitated solid was filtered and crystallized from a mixture of ethanol and chloroform; 2·65 g N,N,N',N'-tetramethyl-6,6-dioxido-5,7-dihydrodibenzo[*c*,*e*]-thiepin-5,7-dicarboxamide (*XXX*),m.p. 275–278·5°C (ethanol–chloroform). IR spectrum: 760, 765 (4 adjacent Ar—H), 1 140, 1 333 (SO_2), 1 595 (Ar), 1 655 cm^{-1} ($CONR_2$). For $C_{20}H_{22}N_2O_4S$ (386·5) calculated: 62·16% C, 5·74% H, 7·25% N, 8·30% S; found: 61·94% C, 5·98% H, 7·33% N, 8·50% S.

The benzene layer of the filtrate was evaporated and the residue was crystallized from benzene; 2·35 g *XXIII*, m.p. 229·5–230·5°C. IR spectrum: 750, 756, 780, 785 (4 adjacent Ar—H), 1 122, 1 149, 1 320 (SO_2), 1 660 ($CONR_2$), 1 600, 3 020, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·30–7·80 (m, 8 H, ArH), 4·99 (s, 1 H, 5-H), 4·12 and 3·85 (ABq, J = 13·0 Hz, 1 + 1 H, 7,7-H_2), 2·92 and 2·35 (2 s, 3 + 3 H, $(CH_3)_2NCO$). For $C_{17}H_{17}NO_3S$ (315·4) calculated: 64·74% C, 5·43% H, 4·44% N, 10·17% S; found: 65·03% C, 5·52% H, 4·56% N, 9·98% S.

B) Mixture of *XXI* and *XXVIII* (18·1 g) was transformed to the crude acid chloride (50 ml $SOCl_2$ in 75 ml benzene) which was similarly treated with a solution of 45 g dimethylamine in 100 ml benzene. The benzene solution of the crude product was diluted with 300 ml benzene, the solution was washed with water, dried and chromatographed on 250 g silica gel. Elution with benzene removed the least polar impurities and elution with chloroform gave first 9·86 g *XXIII*, m.p. 227–230°C. Continued elution with chloroform gave 2·76 g *XXX*, m.p. 275–279°C (chloroform–ethanol).

6,6-Dioxido-5,7-dihydrodibenzo[*c,e*]thiepin-5-acetic Acid (*XXIV*)

A solution of 6·8 g *XX* in 150 ml benzene was stirred under nitrogen and treated over 5 min at 40–50°C with 60 ml 9% n-butyllithium solution in hexane. The mixture was stirred for 4 h at room temperature, 7·0 g ethyl bromoacetate were added, and the stirring was continued for 3 h. After standing overnight it was hydrolyzed with water and evaporation of the benzene layer recovered 3·87 g of the starting *XX*, m.p. 208–210·5°C (ethanol). Acidification of the aqueous layer with hydrochloric acid and extraction with benzene afforded 1·5 g inhomogeneous product which was chromatographed on 100 g silica gel. Elution with benzene, chloroform and ethyl acetate gave small quantitites of oils which were not characterized. Ethanol eluted 1·0 g (28% per conversion) *XXIV* which crystallized from benzene and melted at 212–213·5°C. Mass spectrum, *m/z* (composition and %): 302 (M^+ corresponding to $C_{16}H_{14}O_4S$, 0·4%), 191 ($C_{15}H_{11}$, 4), 189 ($C_{15}H_9$, 4), 179 (34), 178 ($C_{14}H_{10}$, 100), 165 (10). IR spectrum: 750, 772 (4 adjacent Ar—H), 1 145, 1 167, 1 286, 1 305 (SO_2), 1 105, 1 215, 1 735, 3 200 cm^{-1} (COOH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ c. 7·50 (m, 8 H, ArH), 4·52 and 3·73 (ABq, J = 13·0 Hz, 1 + 1 H, 7,7-H_2), 4·10 (m, 1 H, 5-H), 3·10 (m, 2 H, CH_2CO). For $C_{16}H_{14}O_4S$ (302·4) calculated: 63·56% C, 4·67% H, 10·61% S; found: 64·13% C, 4·75% H, 10·35% S.

5-(Dimethylaminomethyl)-5,7-dihydrodibenzo[*c,e*]thiepin 6,6-Dioxide (*XXV*)

A stirred solution of 3·65 g *XXIII* in 100 ml tetrahydrofuran was treated under nitrogen first with 3·9 g $NaBH_4$, and then with 12 ml $BF_3.O(C_2H_5)_2$, added dropwise (temperature max. 40°C). The mixture was stirred for 1 h at room temperature, refluxed for 8 h, allowed to stand overnight, decomposed with 50 ml 15% hydrochloric acid, made alkaline with NH_4OH, and extracted with benzene. The residue, obtained by processing the extract, was chromatographed on 100 g silica gel. A mixture of benzene and chloroform eluted 70 mg, m.p. 139–140°C (cyclohexane), 5-methylene-5,7-dihydrodibenzo[*c,e*]thiepin 6,6-dioxide (*XXXII*). Mass spectrum, *m/z* (composition): 256 (M^+ corresponding to $C_{15}H_{12}O_2S$), 208 ($C_{15}H_{12}O$), 191 ($C_{15}H_{11}$), 165 ($C_{13}H_9$), 152 ($C_{12}H_8$). IR spectrum: 745 (4 adjacent Ar—H), 1 125, 1 150, 1 300 (SO_2), 1 490, 1 500, 1 596, 3 060, 3 095 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·50 (m, 8 H, ArH), 6·29 and 5·70 (2 s, 1 + 1 H, C=CH_2), 4·22 (s, 2 H, 7,7-H_2). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·30% C, 4·72% H, 12·50% S; found: 70·32% C, 4·87% H, 12·08% S.

Continued elution with benzene–chloroform and then with chloroform alone afforded 2·45 g (70%) base *XXV*, m.p. 199·5–201°C (benzene–light petroleum). Mass spectrum, *m/z* (composition): 301 (M^+ corresponding to $C_{17}H_{19}NO_2S$), 191 ($C_{15}H_{11}$), 178 ($C_{14}H_{10}$), 165 ($C_{13}H_9$), 58 (C_3H_8N), 44 (C_2H_6N). IR spectrum (KBr): 752 (4 adjacent Ar—H), 1 118, 1 131, 1 154, 1 315 (SO_2), 1 485, 3 050, 3 080 (Ar), 2 770, 2 820 cm^{-1} (CH_3N). ^1H NMR spectrum at room temperature: δ 7·50 (m, 8 H, ArH), 2·80–4·30 (m, 5 H, 5,7,7-H_3 and CH_2N), 2·10 and 1·90 (2 s, 78 : 22, 6 H, $(CH_3)_2N$); at 150°C: 2·00 (s, 6 H, $(CH_3)_2N$). For $C_{17}H_{19}NO_2S$ (301·4) calculated: 67·74% C, 6·35% H, 4·65% N, 10·64% S; found: 68·49% C, 6·34% H, 4·71% N, 10·72% S.

Hydrogen oxalate hemihydrate, m.p. 203–204°C (aqueous acetone). For $C_{19}H_{21}NO_6S + 0{\cdot}5\ H_2O$ (400·4) calculated: 56·99% C, 5·54% H, 3·50% N, 8·01% S; found: 57·49% C, 5·44% H, 3·60% N, 8·40% S.

5-(2-Dimethylaminoethyl)-5,7-dihydrodibenzo[*c*,*e*]thiepin 6,6-Dioxide (*XXVI*)

A solution of 3·4 g *XX* in 30 ml dimethylformamide was stirred under nitrogen and treated with 0·7 g 80% NaH (suspension in oil), and the mixture was stirred for 1·5 h. 2-Dimethylaminoethyl chloride (8·3 g) was added, the mixture was stirred for 6 h at room temperature, allowed to stand overnight, decomposed with 50 ml water and extracted with a mixture of benzene and ether. The extract was washed with dilute hydrochloric acid and with water, was dried and evaporated. The residue (2·3 g) was *XX*, m.p. 207·5–210·5°C. The acid aqueous washings were made alkaline with NH_4OH and extracted with benzene; 1·27 g (89% per conversion) *XXVI*, m.p. 134–136·5°C (methanol). IR spectrum: 750, 755 (4 adjacent Ar—H), 1 112, 1 128, 1 310 (SO_2), 1 480, 1 575, 3 025, 3 055 (Ar), 2 780, 2 810 cm^{-1} (CH_3N). ^1H NMR spectrum: δ 7·50 (m, 8 H, ArH), 4·05 and 3·80 (ABq, J = 14·0 Hz, 1 + 1 H, 7,7-H_2), 4·05 (bm, 1 H, 5-H), 2·00 to 2·60 (m, 4 H, CH_2CH_2N), 2·18 (s, 6 H, $(CH_3)_2N$). For $C_{18}H_{21}NO_2S$ (315·4) calculated: 68·54% C, 6·71% H, 4·44% N, 10·17% S; found: 68·56% C, 6·89% H, 4·22% N, 9·95% S.

Hydrogen maleate, m.p. 206–209°C (ethanol). For $C_{22}H_{25}NO_6S$ (431·5) calculated: 61·24% C, 5·84% H, 3·25% N, 7·43% S; found: 61·24% C, 5·86% H, 3·50% N, 7·04% S.

5-(3-Dimethylaminopropyl)-5,7-dihydrodibenzo[*c*,*e*]thiepin 6,6-Dioxide (*XXVII*)

A solution of 5·6 g *XX* in 100 ml benzene was treated with 40 ml 9% n-butyllithium in hexane under nitrogen over 10 min. The mixture was stirred for 3 h at room temperature, 15 g 3-dimethylaminopropyl chloride were added over 10 min, the stirring was continued for 3 h, and the mixture was allowed to stand overnight. It was hydrolyzed with water, the organic layer was washed with dilute hydrochloric acid, dried, and evaporated to recover 2·55 g of the starting *XX*, m.p. 209–211°C (ethanol). The acid washings were made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 5·2 g crude product which was chromatographed on 200 g silica gel. A mixture of ethyl acetate and ethanol and then ethanol alone eluted 4·11 g (100% per conversion) *XXVII*, m.p. 139–142°C (cyclohexane). IR spectrum: 760 (4 adjacent Ar—H), 1 108, 1 120, 1 310 (SO_2), 2 770, 2 820 cm^{-1} (CH_3N). ^1H NMR spectrum: δ 7·50 (m, 8 H, ArH), 4·08 and 3·82 (ABq, J = 14·0 Hz, 1 + 1 H, 7,7-H_2), 4·09 (bt, 1 H, 5-H), c. 2·30 (m, 4 H, 2 external CH_2 of the propane chain), 2·10 (s, 6 H, $(CH_3)_2N$), 1·50 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{19}H_{23}NO_2S$ (329·4) calculated: 69·27% C, 7·04% H, 4·25% N, 9·73% S; found: 69·39% C, 7·12% H, 4·50% N, 9·62% S.

Hydrogen maleate, m.p. 177–178°C (acetone–ether). For $C_{23}H_{27}NO_6S$ (445·5) calculated: 62·00% C, 6·11% H, 3·14% N, 7·20% S; found: 61·64% C, 6·03% H, 2·59% N, 7·43% S.

5,7-Bis(3-dimethylaminopropyl)-5,7-dihydrodibenzo[*c*,*e*]thiepin 6,6-Dioxide (*XXXI*)

XX (2·8 g) in 50 ml benzene was treated with 20 ml 15% n-butyllithium in hexane and after 3 h of stirring with 10 g 3-dimethylaminopropyl chloride. The mixture was stirred under nitrogen for 3·5 h, hydrolyzed with 100 ml water, the organic layer was washed with 50 ml 3M-HCl and water, dried, and evaporated giving 1·25 g of the starting *XX*. The acid solution was treated with NH_4OH, and the bases were extracted with benzene. Processing of the extract gave 2·20 g crude product which was chromatographed on 60 g Al_2O_3. Benzene eluted 0·74 g (35% per conversion) *XXVII*, identical with the product of the preceding experiment. Continued elution

with chloroform afforded 1·06 g (40% *per* conversion) *XXXI*, m.p. 118—121°C (cyclohexane). Mass spectrum, *m/z* (composition, %): 414 (M^+ corresponding to $C_{24}H_{34}N_2O_2S$, 0·2%), 350 ($C_{24}H_{34}N_2$, 0·4), 264 ($C_{19}H_{22}N$, 2), 251 ($C_{18}H_{21}N$, 3), 164 ($C_{16}H_{14}NO_2S$, 4), 84 ($C_5H_{10}N$, 7), 58 (100). IR spectrum: 754 (4 adjacent Ar—H), 1 100, 1 288, 1 305 (SO_2), 1 480, 1 555, 1 578, 3 050 (Ar), 2 750, 2 795, 2 805 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·45 (s, 8 H, ArH), 3·81 (t, J 7·0 Hz, 2 H, 5,7-H_2), c. 2·20 (m, 8 H, 4 external CH_2 in the propane chains), 2·05 (s, 12 H, 2 $(CH_3)_2N$), 1·50 (m, 4 H, remaining 2 CH_2). For $C_{24}H_{34}N_2O_2S$ (414·6) calculated: 69·52% C, 8·27% H, 6·76% N, 7·73% S; found: 69·89% C, 8·29% H, 6·58% N, 7·86% S.

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