11-(DIMETHYLAMINOALKYL)-6,11-DIHYDRODIBENZO[*b,e*]THIEPIN--11-CARBONITRILES AND SOME RELATED COMPOUNDS*

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The title compounds *II* and *III* were obtained by alkylations of 6,11-dihydrodibenzo[*b,e*]thiepin--11-carbonitrile (*I*) with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride in the presence of sodium hydride or sodium amide. Hydrolysis of the nitrile *II* with potassium hydroxide in ethanol resulted in a small amount of the amino acid *X* and in the amine *XI* as the main product. Alkylations of *I* with 1,2-dibromoethane and 1,3-dibromopropane in the presence of sodium hydride gave the bromoalkylnitriles *IV* and *V* and the alkylenebisnitriles *XIII* and *XIV*. The preparation of the methylpiperazinopropyl derivative *VI* proved the usefulness of compounds *IV* and *V* in the synthesis of further aminonitriles of this series. Alkylation of the nitrile *I* with 1,2-dibromoethane in the presence of sodium hydroxide or potassium carbonate and benzyltriethylammonium chloride afforded three isomeric nitriles $C_{17}H_{13}NS$: the vinyl derivative *IX*, the 6,11-ethano-6*H*, 11*H*-dibenzo[*b,e*]thiepin derivative *XV* and finally the 1*a*,11*b*-dihydro--1*H*,7*H*-dibenzo[*b,f*]cyclopropa[*d*]thiocin derivative *XVI*. Compounds *II*, *III*, *VI* and *XII* showed some spasmolytic effects but their central neurotropic activity is insignificant.

The preparation of 2,2-diphenyl-4-piperidinobutyronitrile and some related compounds was described[1] by alkylation of diphenylacetonitrile with 2-piperidinoethyl chloride and similar aminoalkyl halides; sodium amide was used as the reagent generating the corresponding carbanion which is able to react with aminoalkyl halides by a nucleophilic substitution reaction. The salts of these aminonitriles were described[2] as possessing a mild spasmolytic activity of the anticholinergic type which is significantly higher with the corresponding quaternary salts (methiodides).

Our systematic investigations in the series of cyclic analogues of the basic diphenylmethane derivatives and further the accessibility of 6,11-dihydrodibenzo[*b,e*]thiepin--11-carbonitrile (*I*) (ref.[3]) led us to the examination of some alkylation reactions of this nitrile and to the preparation of several title compounds. Our attempt at improving the accessibility of the nitrile *I* by a reaction of dibenzo[*b,e*]thiepin-11(6*H*)--one[4-6] with 4-tolylsulfonylmethyl isocyanide[7] in dimethyl sulfoxide in the presence of potassium tert-butoxide (method, *cf.*[8-10]) was not successful. 9,10-Anthraquinone was isolated as the only crystalline product. In this connection it is necessary to men-

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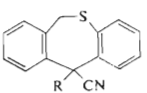
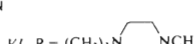
tion that anthracene derivatives were repeatedly reported to appear in reactions of 6,11-dihydrodibenzo[*b*,*e*]thiepin derivatives as products of sulfur extrusion[11-13].

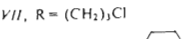
A reaction of the nitrile *I* with sodium hydride in dimethylformamide and the following treatment with 2-dimethylaminoethyl chloride afforded the aminonitrile *II* in a high yield; the product was characterized as the hydrogen oxalate. The same product was obtained in a lower yield by alkylation of the nitrile *I* with 2-dimethylaminoethyl chloride in an aqueous 50% sodium hydroxide solution in the presence of benzyltriethylammonium chloride as the phase-transfer catalyst (method, *cf*[14,15]). The neutral by-product was separated into two substances, obtained in small amounts, 9,10-anthraquinone[16] and dibenzo[*b*,*e*]thiepin-11(6*H*)-one[4-6]. We assume that the last mentioned ketone is the primary by-product and results from the nitrile *I* by the oxidative decyanation[17] of a similar type like that described for the analogous nitrile of the 10,11-dihydrodibenzo[*b*,*f*]thiepin series[18]. 9,10-Anthraquinone is then product of the following oxidative sulfur extrusion. Alkylation of the nitrile *I* with 3-dimethylaminopropyl chloride was carried out using sodium amide in benzene. The desired base *III* was obtained in a 55% yield and characterized by the mass spectrum. Even in this case the alkylation using the phase-transfer catalysis was less favourable and gave rise to an important amount of neutral product which was not separated.



I, R = H
II, R = $CH_2CH_2N(CH_3)_2$
III, R = $(CH_2)_3N(CH_3)_2$
IV, R = CH_2CH_2Br
V, R = $(CH_2)_3Br$



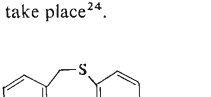
VII, R = $(CH_2)_3Cl$



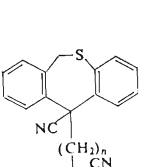
IX, R = $CH{=}CH_2$

While the nitriles like 2,2-diphenyl-4-piperidinobutyronitrile are transformed in high yields by refluxing with potassium hydroxide in aqueous ethanol to the corresponding amides[1], in a similar reaction of *II* the amide was not obtained at all. In addition to a small amount of the high-melting amino acid *X* an oxygen-free base was isolated which was identified as 11-(2-dimethylaminoethyl)-6,11-dihydrodibenzo-[*b*,*e*]thiepin (*XI*). The identity of both products was corroborated by the mass spectra. The formation of compound *XI* by decarboxylation of the amino acid *X* under the conditions used seems unlikely and we prefer the assumption that a similar cleavage of the cyano group took place like that proceeding with substituted phenylacetonitriles by treatment with sodium amide[1,19-21] or with the blue solutions

which are formed by dissolving sodium in liquid ammonia or by dissolving lithium in liquid ethylamine ("solvated electrons", ref.[22]). The synthesis of compound *XI* by a different way was described[23]. In order to prepare the corresponding ethyl ketone, for which the analgesic activity could be expected, nitrile *II* was subjected to treatment with ethylmagnesium bromide in a mixture of ether and benzene. The primary product was heated with a 1 : 1 diluted hydrochloric acid but even then the isolated product appeared to be a base affording the bis(hydrogen maleate). The spectra of the base confirmed that we are dealing here with the ketimine *XII* which is so strongly sterically shielded that its hydrolysis to the ketone under the conditions used did not take place[24].



X, R = COOH
XI, R = H
XII, R = C(=NH)CH$_2$CH$_3$

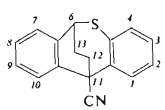


XIII, *n* = 2
XIV, *n* = 3

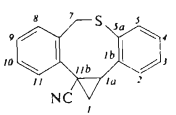
For preparing aminonitriles with more complicated amine residues in their molecules we needed bromoalkylnitriles *IV* and *V*. They were obtained by reactions of the nitrile *I* with sodium hydride and 1,2-dibromoethane or 1,3-dibromopropane in dimethylformamide. They are formed in mixtures with products of double alkylation, *XIII* and *XIV*, which are separated by chromatography on silica gel. Compounds *IV* and *V* are the least polar components of the mixtures and their separation from the starting nitrile *I* is difficult. They were characterized by the ^{1}H NMR spectra. Compounds *XIII* and *XIV* are eluted as the more polar components. Their molecules contain two equivalent chiral centres and they exist as racemates and *meso*-forms. In our reactions mixtures of both forms are formed. In the case of compound *XIII* this mixture was not separated, the elemental composition of the product was confirmed by the mass spectrum. In the case of compound *XIV* two fractions could be separated by chromatography, differing only a little by the polarity, which afforded by recrystallization two homogeneous isomers with different melting points, which are considered stereoisomers of *XIV*. In the case of chromatography of the pair of compounds *IV* and *XIII* an intermediate fraction was isolated in a yield of about 5% which corresponds by its R_F value to dibenzo[*b*,*e*]theipin-11(6*H*)-one[4-6]. We are evidently dealing here with a further case of oxidative decyanation[17] proceeding

without the use of the phase-transfer catalysis method[18]. A reaction of the nitrile *V* with an excess of boiling 1-methylpiperazine gave the aminonitrile *VI*.

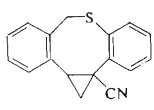
The chloropropylnitrile *VII*, which is a further potential intermediate, has also been prepared making use, however, of a different method. The nitrile *I* was alkylated with 3-(tetrahydro-2-pyranyloxy)propyl chloride[25] in benzene with the help of sodium amide on the one hand, and in a mixture of aqueous sodium hydroxide and tetrahydrofuran in the presence of benzyltriethylammonium chloride on the other. Mixtures were formed in both cases from which the oily tetrahydropyranyl ether *VIII* (diastereoisomeric mixture) was isolated by chromatography on silica gel. Dibenzo-[*b*,*e*]thiepin-11(6*H*)-one[4-6] was separated in both cases in small amounts as the less polar component and evidently again as a product of the oxidative decyanation of the nitrile *I*. In these experiments the sodium amide alkylation method gave higher yields on the desired ether *VIII* than the method using the phase-transfer catalysis. The ether *VIII* was hydrolyzed, without characterization, with dilute methanolic hydrochloric acid and the product was transformed by refluxing with thionyl chloride to the chloro derivative *VII* whose identity was corroborated by spectra.



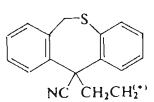
XV



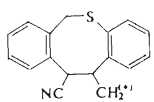
XVI



XVII



A



B

The most complicated reaction course was met in attempts at alkylating the nitrile *I* with excessive 1,2-dibromoethane using benzyltriethylammonium chloride as the phase-transfer catalyst. The reaction was carried out either in a mixture with the aqueous 50% sodium hydroxide (casually in the presence of pyridine) or in dimethyl sulfoxide in the presence of potassium carbonate. The mixtures obtained were separated by chromatography on silica gel, the common point being the fact that the desired bromoethyl derivative *IV* was not isolated at all. Three crystalline products were isolated from the mixtures, all of them having according to the mass spectra and analyses the elemental composition $C_{17}H_{13}NS$. Their IR spectra indicate in all

of them the intact nitrile group. The ^{1}H NMR spectrum identified one of the products as vinyl derivative *IX* (signals of the vinyl protons at δ 6·35, 5·51 and 5·10 ppm), resulting evidently from dehydrobromination of the primarily formed bromoethyl derivative *IV*. The ^{1}H NMR spectrum of the second product indicated the absence of the methylene group in position 6 of the skeleton (between the aromatic ring and the sulfur atom) and further the absence of a proton on $C_{(11)}$, carrying the nitrile group. These facts indicate that the reaction proceeded by bridging between $C_{(6)}$ and $C_{(11)}$ and structure of 6,11-ethano-6*H*,11*H*-dibenzo[*b*,*e*]-thiepin-11-carbonitrile (*XV*) was assigned to the product; we are dealing here with a transannular alkylation. The ^{1}H NMR spectrum of the third product showed the presence of preserved methylene group between the nucleus and the atom of sulfur, the absence of a proton on the carbon carrying the nitrile group and the presence of the fragment CH—CH_2. Structures being conformable to these conditions and to the elemental composition $C_{17}H_{13}NS$ could be derived only by presuming that several isomerizations of the primary carbonium ion *A* took place and were accompanied by the enlargement of the central ring to an eight-membered one by a Wagner–Meerwein rearrangement[26] and anellation of the cyclopropane ring[27]. The results of this procedure were the isomeric structures *XVI* and *XVII*. The ^{1}H NMR spectrum is not able to differentiate between them. On the basis of the ^{13}C NMR spectrum we prefer for our product the structure of 1a,11b-dihydro-1*H*,7*H*-dibenzo[*b*,*f*]cyclopropa[*d*]thiocin-11b-carbonitrile (*XVI*). In the proton-coupled spectrum the signal of the carbon $C_{(5a)}$ is broadened by the influence of numerous long-range interactions to 16 Hz. Structures *XVI* and *XVII* differ in the first line by the long-range interaction with the proton on carbon $C_{(1a)}$. In the experiment of low-power frequency selective decoupling an irradiation frequency corresponding to the resonance frequency of this proton was used and the mentioned signal was contracted to 9 Hz. The result indicates that this interaction really exists and structure *XVI* must be preferred. On the other hand, the proof cannot be considered completely reliable. In the case of correctness of structure *XVI* the cation *B* would be the immediate precursor of the final cyclopropanation reaction which would mean that in the stage of the Wagner–Meerwein rearrangement the thiophenyl fragment was the migrating residue. Dreiding's models confirmed the possibility of existence of two stable diastereoisomeric racemates *XVI* (1a,11b-*cis*-isomer with the planes of the aromatic nuclei in a very sharp angle and 1a,11b-*trans*-isomer with almost coplanar aromatic nuclei). The experimental material available does not allow the configuration assignment but the character of the signal of proton on the carbon $C_{(1a)}$ indicates that we are not dealing with a mixture of both isomers, *i.e.* that our product is homogeneous.

Compounds *II*, *III*, *VI* and *XII* were pharmacologically tested in the form of salts described in the Experimental. The acute toxicity was determined in mice on intravenous administration and the LD_{50} in mg/kg are given: *II* 45, *III* 38, *VI* 50, *XII* 100. The basic intravenous doses (D) in mg/kg used in the general screening were the

following ones: *II* 7, *III* 7, *VI* 10, *XII* 20. The central effects of compounds *II* and *III* appear only in toxic doses (higher than D): An excitation effect in mice was observed which was manifested by the increase of motility and by convulsions and was followed by depression. With compound *XII* the central stimulation was observed after subcutaneous doses of 5–10 mg/kg already. Only compound *VI* brought about the discoordinating effect in the rotarod test in mice (ED_{50} = 20 mg/kg *i.v.*), a mild potentiation of the thiopental sleep in mice in a dose of 2·5 mg/kg *i.v.*, antinociceptive effect in the peritoneal test in mice (D_{50} = 0·3 mg/kg *s.c.*) and blocking of the reactivity of rats to a nociceptive stimulus in the peritoneal test (D_{50} = 0·64 mg/kg *s.c.*). On the other hand, the compound is inactive in other tests for analgesic activity (Haffner, D'Amour and Smith). It did not influence the reserpine hypothermia in mice but it mildly antagonized the ulcerogenic effect of reserpine in rats. All the four compounds had spasmolytic activity on the isolated rat duodenum in concentrations of 1–10 μg/ml towards the acetylcholine, as well as barium chloride contractions. Compounds *III* and *XII* in concentrations of 0·5–1·0% showed local anaesthetic effect in the test of infiltration anaesthesia in guinea-pigs. All the four compounds in doses D brought about brief and deep drop of blood pressure in normotensive anaesthetized rats. Compound *XII* in an oral dose of 100 mg/kg revealed an antitussic effect in guinea-pigs (the cough was generated by the citric acid aerosol).

The tested compounds revealed partly antimicrobial effects in the *in vitro* tests (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *II* 50, *III* 100; *Staphylococcus pyogenes aureus*, *III* 100; *Escherichia coli*, *III* 100; *Trichophyton mentagrophytes*, *II* 50, *III* 50, *VI* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in a Mettler FP-5 melting point recorder. The samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in KBr) with a Unicam SP 200G spectrophotometer, the ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the spectrometers MCH 1320 and/or Varian MAT 44S. The ^{13}C NMR spectra were 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 of ±0·08 ppm. The proton-coupled spectra were obtained using the "Gated decoupling" method (decoupler off during the acquisition). The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

Reaction of Dibenzo[*b,e*]thiepin-11(6*H*)-one with 4-Tolylsulfonylmethyl Isocyanide

Potassium (2·8 g) was dissolved in 20 ml tert-butyl alcohol, 20 ml dimethyl sulfoxide were added and the stirred mixture was treated at 10°C with a solution of 5·2 g dibenzo[*b,e*] thiepin-11(6*H*)-one[4–6] and 5·85 g 4-tolylsulfonylmethyl isocyanide[7] in 40 ml dimethyl sulfoxide, added dropwise. The mixture was stirred for 5·5 h at room temperature, allowed to stand overnight, poured

into water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue (3·75 g oil) was chromatographed on a column of 90 g silica gel. Elution with benzene gave 1·5 g (31%) 9,10-anthraquinone, m.p. 286 to 289°C (in a sealed capillary) after resublimation. For $C_{14}H_8O_2$ (208·2) calculated: 80·76% C, 3·87% H; found: 81·32% C, 4·01% H. Lit.[16], m.p. 285—286°C.

11-(2-Dimethylaminoethyl)-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*II*)

A) A solution of 13·4 g *I* (ref.[3]) in 60 ml dimethylformamide was stirred and treated under nitrogen with 1·8 g 80% NaH (suspension in oil). The mixture was stirred for 10 min, treated with 9·8 g 2-dimethylaminoethyl chloride and stirred for 15 min at 90°C. After cooling it was diluted with water and extracted with benzene. The extract was shaken with an excess of dilute hydrochloric acid, the aqueous acid layer was made alkaline with NH_4OH and the basic product was extracted again with benzene. Processing of the extract gave 13·9 g (80%) homogeneous oily *II*. Neutralization with oxalic acid dihydrate in a mixture of ethanol and ether gave the hydrogen oxalate hemihydrate, m.p. 172—176°C (ethanol). For $C_{21}H_{22}N_2O_4S + 0{\cdot}5\ H_2O$ (407·5) calculated: 61·90% C, 5·69% H, 6·87% N, 7·87% S; found: 62·50% C, 5·52% H, 6·66% N, 7·87% S.

B) A mixture of 4·85 g *I* (ref.[3]), 14·8 g 2-dimethylaminoethyl chloride, 0·3 g benzyltriethylammonium chloride and 20 g 50% NaOH was stirred for 6 h at 40—50°C, then diluted with water and extracted with benzene. The extract was shaken with dilute hydrochloric acid and separated in this way to basic and neutral products. The basic product *II* was released from the aqueous acid layer with NH_4OH and isolated by extraction with benzene; 3·6 g (58%) oil. Neutralization with oxalic acid gave the hydrogen oxalate hemihydrate melting at 172—176°C (ethanol), identical with the product obtained under *A*). The benzene layer, containing the neutral products, was evaporated *in vacuo* and the residue (1·5 g) gave by crystallization from benzene 0·10 g 9,10-anthraquinone melting at 280—283°C. Lit.[16], m.p. 285—286°C. The mother liquor was treated with light petroleum; standing and cooling led to crystallization of 0·30 g dibenzo[*b,e*]thiepin-11(6*H*)-one, m.p. 84—86°C (cyclohexane). The identity was confirmed by a direct comparison with an authentic sample[4] by TLC and the mixed-melting point method. Lit.[4], m.p. 86—87°C.

11-(3-Dimethylaminopropyl)-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*III*)

A) A suspension of 1·15 g 70% $NaNH_2$ in 10 ml benzene was stirred and treated dropwise at 5°C with a solution of 4·75 g *I* (ref.[3]) in 25 ml benzene. The mixture was stirred for 2h at 50°C, cooled to 2°C and treated over 5 min with a solution of 3·65 g 3-dimethylaminopropyl chloride in 20 ml ether. It was then heated under reflux for 5 h in a bath of 50°C, after cooling decomposed with 10 ml water and extracted with benzene. The basic product was transferred by shaking into excessive 3M-HCl, the aqueous layer was made alkaline with NH_4OH and the base isolated by extraction with benzene; 3·52 g (55%) homogeneous oily *III*. Neutralization with oxalic acid in a mixture of acetone and ether gave 3·0 g hydrogen oxalate, m.p. 161—163°C (ethanol–ether). Mass spectrum, *m/z* (%): 322 (M^+ corresponding to $C_{20}H_{22}N_2S$, 0·4%), 289 (0·9), 203 (1·2), 86 (9·2), 84 (2·0), 71 (2·4), 58 (100). For $C_{22}H_{24}N_2O_4S$ (412·5) calculated: 64·05% C, 5·86% H, 6·79% N, 7·77% S; found: 63·43% C, 5·73% H, 6·73% N, 7·70% S. The neutral product (2·52 g), which was obtained by evaporation of the organic layer, is a mixture containing according to TLC the starting *I*, dibenzo[*b,e*]thiepin-11(6*H*)-one[4] and some more polar components.

B) A mixture of 20 g 50% NaOH, 0·4 g benzyltriethylammonium chloride, 4·75 g *I* (ref.[3]) and 15 g 3-dimethylaminopropyl chloride was stirred for 8 h at 40—50°C, diluted with water

and extracted with benzene. Similar processing like under *A* gave 2·76 g (43%) oil *III* which afforded the hydrogen oxalate melting at 161—163°C (ethanol–ether), identical with that under *A*. The neutral product (2·5 g) was a mixture which did not contain the starting *I*.

11-(2-Dimethylaminoethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XI*)

A mixture of 3·6 g *II*, 4·0 g KOH and 6 ml ethanol was refluxed for 1 h, diluted with water and extracted with benzene. The aqueous layer was neutralized with acetic acid and extracted with chloroform. Evaporation of the extract gave 0·25 g (7%) 11-(2-dimethylaminoethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carboxylic acid (*X*), m.p. 242—428°C with decomposition (ethanol). Mass spectrum, *m*/*z* (%): 327 (M^+ corresponding to $C_{19}H_{21}NO_2S$, 6%), 282 (5·6), 237 (7·6), 223 (6·0), 211 (6·0), 205 (6·0), 178 (10), 73 (9·6), 59 (5·6), 58 [$CH_2{=}\overset{+}{N}(CH_3)_2$, 100], 46 (7·2), 45 (10·8). For $C_{19}H_{21}NO_2S$ (327·5) calculated: 69·69% C, 6·46% H, 4·28% N; found: 69·64% C, 6·61% H, 4·09% N.

The benzene extract was dried with K_2CO_3 and evaporated giving 2·2 g oily mixture which was chromatographed on a column of 150 g neutral Al_2O_3 (activity II). Benzene and then chloroform eluted 0·94 g (28%) oily *XI* which was neutralized with oxalic acid in ethanol and gave the hydrogen oxalate, m.p. 160—162°C (ethanol). Mass spectrum, *m*/*z* (%): 283 (M^+ corresponding to $C_{18}H_{21}NS$, 16·8%), 250 ($C_{18}H_{20}N$, 4·2), 238 (7·2), (237 (5·0), 223 (8·6), 210 ($C_{14}H_{10}S$, 8·6), 205 ($C_{16}H_{13}$, 18·4), 178 ($C_{14}H_{10}$, 14·8), 73 (16·0), 58 [$CH_2{=}\overset{+}{N}(CH_3)_2$, 100], 46 (15·6), 46 (15·6), 45 (28·8). For $C_{20}H_{23}NO_4S$ (373·5) calculated: 64·32% C, 6·21% H, 3·75% N, 8·58% S; found: 63·98% C, 6·39% H, 3·36% N, 7·98% S. Lit.[23] described a different synthesis of *XI* which was characterized as hydrochloride.

11-(1-Iminopropyl)-11-(2-dimethylaminoethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XII*)

The Grignard reagent was prepared from 1·21 g Mg and 5·5 g ethyl bromide in 20 ml ether. The stirred solution was cooled with ice and treated dropwise with a solution of 6·2 g *II* in 60 ml benzene. The mixture was stirred for 5·5 h at room temperature, allowed to stand overnight, decomposed with 100 ml 1 : 1 dilute hydrochloric acid, heated for 1·5 h to 100°C, diluted with water and the solution was washed with chloroform. It was then made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 6·2 g (91%) oily *XII* which was neutralized with maleic acid in ether; 8·3 g bis(hydrogen maleate), m.p. 162·5—164°C (acetone–ethanol–ether). Mass spectrum, *m*/*z* (%): 338 (M^+ corresponding to $C_{21}H_{26}N_2S$), 267 ($C_{20}H_{13}N$, 32·8), 179 (18), 178 ($C_{14}H_{10}$, 39·2), 59 (24·8), 58 ($CH_2{=}\overset{(+)}{N}(CH_3)_2$, 100], 45 (26·8). For $C_{29}H_{34}N_2O_8S$ (570·7) calculated: 61·04% C, 6·01% H, 4·91% N, 5·62% S; found: 60·99% C, 6·25% H, 4·78% N, 5·51% S.

A sample of the pure maleate was decomposed with NH_4OH, the oily base was isolated by extraction with ether and used for recording the spectra. IR spectrum (Nujol): 740 (4 adjacent Ar—H), 1 490, 1 584, 1 596, 3 015 (Ar), 1 630 (C=N), 2 733, 2 783 (N—CH_3), 3 200 cm^{-1} (NH). ^1H NMR spectrum: δ 6·90—7·50 (m, 8 H, ArH), 4·28 and 3·80 (ABq, J = 13·0 Hz at 60°C, 2 H, $ArCH_2S$), 2·25 (s, 6 H, CH_3NCH_3), 2·00—3·00 (m, 6 H, remaining 3 CH_2), 1·10 (t, 3 H, CH_3 in ethyl).

11-(2-Bromoethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*IV*)

A solution of 19·3 g *I* (ref.[3]) in 90 ml dimethylformamide was treated under nitrogen with 2·8 g 80% NaH (suspension in oil), the mixture was stirred for 20 min, treated with 27 g 1,2-dibromo-

ethane and stirred for 1 h at 65°C. It was then poured into water and extracted with benzene. The extract was dried with $MgSO_4$, evaporated and the residue was chromatographed on a column of 300 g silica gel. Benzene eluted 5·82 g (21%) almost homogeneous oily *IV* which was characterized only by the ^{1}H NMR spectrum: δ 6·80–7·80 (m, 8 H, ArH), 4·32 and 4·11 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·40–3·70 (m, 4 H, CH_2CH_2Br). The elution with benzene was continued and gave 1·6 g starting *I* (ref.[3]) which was followed by 0·90 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[4]. The identification of these compounds was based on comparison of their R_f values with those of the authentic substances (TLC).

Continued elution with benzene gave 3·65 g (18%) mixture of stereoisomers of 11,11′-ethylenebis(6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-carbonitrile) (*XIII*), m.p. 90–120°C (benzene–ethanol). IR spectrum: 750 (4 adjacent Ar—H), 1 585, 3 050 (Ar), 2 225 cm^{-1} (R—CN). Mass spectrum, m/z: 500 (M^+ corresponding to $C_{32}H_{24}N_2S_2$, 4·5%), 264, 237, 236, 204, 203. ^{1}H NMR spectrum: δ 6·70–7·90 (m, 16 H, ArH), 2·50–4·80 (m, 8 H, 4 CH_2). For $C_{32}H_{24}N_2S_2$ (500·7) calculated: 76·76% C, 4·83% H, 5·60% N, 12·81% S; found: 76·54% C, 5·18% H, 5·10% N, 12·23% S.

11-(3-Bromopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*V*)

A similar reaction of 14·25 g *I* (ref.[3]), 2·0 g 80% NaH and 18·2 g 1,3-dibromopropane in 60 ml dimethylformamide gave a crude product which was chromatographed on 300 g silica gel. Benzene eluted first 14·85 g (69%) homogeneous *V* which crystallized from a mixture of ether and hexane, m.p. 109–111°C. IR spectrum: 747, 750 (4 adjacent Ar—H), 1 482, 1 586, 3 020 (Ar), 2 218 cm^{-1} (R—CN). ^{1}H NMR spectrum: δ 7·00–8·00 (m, 8 H, ArH), 4·48 and 4·02 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·40 (bt, 2 H, CH_2Br), 2·60–3·20 (m, 2 H, NC—C—CH_2), *c.* 2·00 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{18}H_{16}BrNS$ (358·3) calculated: 60·34% C, 4·50% H, 22·30% Br, 3·91% N, 8·95% S; found: 60·59% C, 4·60% H, 22·43% Br, 3·78% N, 9·06% S.

Continued elution with benzene gave 0·45 g starting *I* and after 0·72 g mixture there were eluted 0·86 g stereoisomer A of 11,11′-trimethylenebis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile) (*XIV*-A), m.p. 164–168°C (benzene–cyclohexane). IR spectrum (Nujol): 753, 764 (4 adjacent Ar—H), 1 467, 1 490, 1 583, 3 020, 3 060 (Ar), 2215 cm^{-1} (R—CN). ^{1}H NMR spectrum: δ 6·90–7·80 (m, 16 H, ArH), 4·15 (m, 4 H, 2 $ArCH_2S$), 2·90 (m, 4 H, 2 NC—C—CH_2), 1·60 (m, 2 H, CH_2 in the middle of trimethylene). For $C_{33}H_{26}N_2S_2$ (514·7) calculated: 77·01% C, 5·09% H, 5·44% N, 12·46% S; found: 77·36% C, 5·46% H, 4·97% N, 12·13% S.

The preceding fraction was immediately followed by 0·63 g stereoisomer B of 11,11′-trimethylenebis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile) (*XIV*-B), m.p. 82–89°C (ethanol–benzene). ^{1}H NMR spectrum: δ 6·90–7·80 (m, 16 H, ArH), *c.* 4·20 (m, 4 H, 2 $ArCH_2S$), 2·90 (m, 4 H, 2 NC—C—CH_2), 1·60 (m, 2 H, CH_2 in the middle of trimethylene). For $C_{33}H_{26}N_2S_2$ (514·7) calculated: 77·01% C, 5·09% H, 5·44% N, 12·46% S; found: 77·86% C, 5·36% H, 5·31% N, 12·17% S.

11-[3-(4-Methylpiperazino)propyl]-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*VI*)

A mixture of 7·17 g *V* and 10 ml 1-methylpiperazine was heated under reflux for 7 h to 140°C. After cooling it was diluted with water and extracted with benzene. The basic product was extracted from the benzene solution into an excess of dilute hydrochloric acid, the obtained aqueous solution of the hydrochloride was made alkaline with 20% NaOH and the base was extracted with benzene. Processing of the extract gave 5·2 g (69%) oily *VI* which was neutralized with 4·0 g maleic acid in a mixture of acetone and ether; 7·6 g bis(hydrogen maleate), m.p. 170–172°C (ethanol). For $C_{31}H_{35}N_3O_8S$ (609·7) calculated: 61·07% C, 5·79% H, 6·89% N, 5·26% S; found: 60·46% C, 5·81% H, 6·61% N, 5·40% S.

11-(3-Chloropropyl)-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*VII*)

A) A mixture of 1·2 g 70% $NaNH_2$, 40 ml benzene and 4·75 g *I* (ref.[3]) was heated for 1 h to 50°C, treated with 4·0 g 3-(tetrahydro-2-pyranyloxy)propyl chloride[25] at 10°C and refluxed for 6 h. After cooling the mixture was decomposed with 20 ml water, the benzene layer was washed with water, dried with K_2CO_3 and evaporated. The residue was chromatographed on 250 g silica gel. A mixture of benzene and light petroleum eluted first 0·12 g starting *I* (m.p. 130°C; lit.[3], m.p. 137—139°C), which was followed by 1·57 g dibenzo[*b,e*]thiepin-11(6*H*)-one (m.p. 82—86°C; lit.[4], m.p. 86—87°C). Benzene alone eluted then 2·26 g starting chloride and chloroform eluted 2·3 g (30%) homogeneous oil whose further processing showed it to be the desired 11-[3-(tetrahydro-2-pyranyloxy)propyl]-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*VIII*).

B) A mixture of 4·75 g *I* (ref.[3]), 12·2 g 3-(tetrahydro-2-pyranyloxy)propyl chloride[25], 0·3 g benzyltriethylammonium chloride, 10 g NaOH in 6 ml water and 10 ml tetrahydrofuran was stirred under reflux for 6·5 h at 50°C. After cooling it was diluted with water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The resulting mixture was chromatographed on 200 g silica gel. A mixture of benzene and light petroleum eluted 1·52 g dibenzo[*b,e*]thiepin-11(6*H*)-one, m.p. 85—86·5°C (lit.[4], m.p. 86—87°C). Benzene eluted then 8·6 g starting chloride and, finally, elution with chloroform gave 1·02 g (13%) homogeneous *VIII*, identical with the product obtained under A (comparison of the R_F values by TLC)

C) A solution of 3·2 g *VIII* in 50 ml methanol was treated with 3 drops hydrochloric acid and refluxed for 1·5 h. Methanol was evaporated under reduced pressure, the residue was dissolved in benzene, the solution was washed with water, dried with K_2CO_3 and evaporated *in vacuo*. The residue (2·55 g) was dissolved in 30 ml benzene, the solution was treated with 2 ml $SOCl_2$ and the mixture refluxed for 3 h. After standing overnight it was evaporated *in vacuo*, the residue was dissolved in ether, the solution was washed with water, dried with $MgSO_4$ and evaporated; 2·60 g (98%) *VII*, m.p. 106—107·5°C (ether–light petroleum). IR spectrum (Nujol): 750, 756 (4 adjacent Ar—H), 1 490, 1 589, 3 048 (Ar), 2 233 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00 to 8·00 (m, 8 H, ArH), 4·54 and 4·12 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·60 (bt, 2 H, CH_2Cl), 2·60—3·40 (m, 2 H, NC—C—CH_2), 1·95 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{18}H_{16}ClNS$ (313·9) calculated: 68·88% C, 5·14% H, 11·30% Cl, 4·46% N, 10·22% S; found: 68·25% C, 5·16% H, 11·22% Cl, 4·36% N, 10·03% S.

11-Vinyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*IX*)

A) A mixture of 4·75 g *I* (ref.[3]), 13 g 1,2-dibromoethane, 0·3 g benzyltriethylammonium chloride and 20 g 50% NaOH was stirred for 6 h at 40—50°C, it was diluted with water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue was chromatographed on 200 g silica gel. A mixture of benzene and light petroleum eluted first 1·97 g (37%) crystalline *IX*, m.p. 98·5—99·5°C (cyclohexane). Mass spectrum, *m/z* (%): 264 (M + 1, 14), 263 (M^+ corresponding to $C_{17}H_{13}NS$, 64·8%), 262 (22·4), 248 (22·4), 236 (32), 235 (24), 221 (24·4), 204 (72), 203 (100), 178 (16·4), 159 (16), 104 (66·8). UV spectrum: λ_{max} 266 nm (log ε 3·92). IR spectrum: 753, 765, 777 (4 adjacent Ar—H), 935 (C=C of vinyl), 1 471, 1 490, 1 562, 1 588, 3 013, 3 043, 3 075 (Ar), 2 237 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·80 (m, 2 H, 1,10-H_2), 6·90—7·30 (m, 6 H, remaining ArH), 6·35 (dd, J = 16·0; 10·0 Hz, 1 H, CH of vinyl), 5·51 and 5·10 (2 d, J = 10·0 and 16·0 Hz, 1 + 1 H, CH_2 of vinyl), 4·81 and 3·50 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$). ^{13}C NMR spectrum (C^2HCl_3): 136·0; 134·1; 133·1; 130·5 (4 aromatic quaternary carbons), 119·9 (CN), 56·1 ($C_{(11)}$), 133·7 (CH of vinyl), 130·3; 130·1; 129·6; 129·1; 128·7; 128·5; 127·3; 123·5 (8 aromatic methine carbons), 120·5 (CH_2 of vinyl),

33·9 ppm ($C_{(6)}$). For $C_{17}H_{13}NS$ (263·3) calculated: 77·55% C, 4·98% H, 5·32% N, 12·15% S; found: 77·33% C, 4·92% H, 5·10% N, 12·34% S.

Continued elution with the same mixture of solvent yielded 0·59 g (11%) crystalline compound to which the structure of 1a,11b-dihydro-1*H*,7*H*-dibenzo[*b*,*f*]cycloropa[*d*]thiocin-11b-carbonitrile (*XVI*) was assigned, m.p. 196—197°C (benzene–cyclohexane). Mass spectrum, *m*/*z* (%): 264 (M + 1, 20·8), 263 (M^+ corresponding to $C_{17}H_{13}NS$, 87·2%), 236 (17·6), 235 (32), 234 (14), 230 (13·2), 135 (18·4), 115 (18·8), 104 (100). UV spectrum: λ_{max} 253 nm (log ε 3·95), infl. 262 nm (3·89). IR spectrum: 731, 765 (4 adjacent Ar—H), 1 465, 1 477, 1 498, 1 564, 1 592, 3 013, 3 050 (Ar), 2 237 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·98—7·69 (m, 8 H, ArH), 3·36 and 3·24 (ABq, J = 16·6 Hz, 2 H, $ArCH_2S$), 4·36 (t, J = 2·93 Hz, 1 H, 1a-H), 2·84 (m, 2 H, 1,1-H_2). ^{13}C NMR spectrum (C^2HCl_3): 136·3 ($C_{(5a)}$), 131·0; 130·6; 130·1 (remaining 3 aromatic quaternary carbons), 124·0 (CN), 35·7 (C-11b), 129·5; 129·4; 128·8; 128·6; 127·9; 127·6 (2 C); 125·4 (8 aromatic methine carbons), 37·0 ($C_{(1a)}$), 44·7 ($C_{(7)}$), 33·7 ($C_{(1)}$). For $C_{17}H_{13}NS$ (263·3) calculated: 77·55% C, 4·98% H, 5·32% N, 12·15% S; found: 77·47% C, 5·05% H, 5·02% N, 12·12% S.

B) A mixture of 4·75 g *I* (ref.[3]), 9·4 g 1,2-dibromoethane, 15 ml pyridine, 0·15 g benzyltriethylammonium chloride and 10 ml 50% NaOH was stirred for 5·5 h at 50°C and processed similarly like under *A*. The chromatography of the crude product on 200 g silica gel gave 1·11 g (21%) *IX*, m.p. 98·5—99·5°C (cyclohexane), and 0·54 g (10%) *XVI*, m.p. 196—197°C (benzene–hexane).

6,11-Ethano-6*H*,11*H*-dibenzo[*b*,*e*]thiepin-11-carbonitrile (*XV*)

A mixture of 4·75 g *I* (ref.[3]), 11·7 g 1,2-dibromoethane, 5·6 g K_2CO_3, 0·4 g benzyltriethylammonium chloride and 20 ml dimethyl sulfoxide was stirred and heated for 7 h to 100°C. After cooling it was diluted with water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$, filtered and evaporated. The residue was chromatographed on 200 g silica gel. Benzene eluted first 0·69 g starting *I*, m.p. 137—138°C (benzene–light petroleum) (lit.[3], m.p. 137—139°C), for which some spectra (not published until now, *cf*.[3,28]) were recorded for comparison. Mass spectrum, *m*/*z* (%): 237 (M^+ corresponding to $C_{15}H_{11}NS$, 60·8%), 236 (24), 226 (37), 204 (100), 203 (29), 197 (14), 193 (16), 177 (13), 165 (16), 105 (14), 104 (13), 99 (11), 98 (10). UV spectrum: λ_{max} 263 nm (log ε 4·01). ^{13}C NMR spectrum (C^2HCl_3): 134·6; 133·1; 132·6; 131·9 (4 aromatic quaternary carbons), 118·2 (CN), 130·0; 129·3; 129·2; 128·7; 126·6; 126·5; 125·7 (8 aromatic methine carbons), 39·6 ($C_{(11)}$), 33·8 ppm ($C_{(6)}$).

Continued elution with benzene gave 1·08 g (24% per conversion) homogeneous compound *XV* which crystallized from 96% ethanol as a hemihydrate, m.p. 120—125°C. Mass spectrum, *m*/*z* (%): 264 (M + 1, 65·6%), 263 (M^+ corresponding to $C_{17}H_{13}NS$, 8%), 237 (77·6), 236 (100), 225 (16), 222 (8), 221 (10), 209 (13), 205 (53), 204 (38). UV spectrum: λ_{max} 262·5 nm (log ε 3·92). IR spectrum: 730, 752 (4 adjacent Ar—H), 1 472, 1 490, 1 565, 1 690, 3 055 (Ar), 2 237 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·70—7·80 (m, 8 H, ArH), 2·50—4·60 (m, 5 H, $ArCHCH_2CH_2$). For $C_{17}H_{13}NS + 0{\cdot}5\ H_2O$ (272·4) calculated: 74·97% C, 5·18% H, 5·14% N, 11·77% S; found: 75·09% C, 5·19% H, 4·78% N, 11·80% S.

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