REACTION OF 6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN-11-CARBONITRILE WITH 1,2-DIBROMOETHANE, A REINVESTIGATION. FORMATION OF 11,12-DIHYDRO-6*H*-6,12-METHANODIBENZO[*b*,*f*]THIOCIN--12-CARBONITRILE

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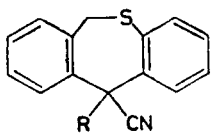
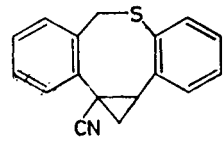
Reinvestigation of the minor product of reaction of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*I*) with 1,2-dibromoethane in the presence of tetrabutylammonium bromide or benzyltriethylammonium chloride and 50% sodium hydroxide by means of ^{1}H and ^{13}C NMR spectroscopy led to the formula *XI* named in the title, which was confirmed by X-ray crystallographic analysis. The product of a similar reaction, carried out in dimethyl sulfoxide in the presence of potassium carbonate at 100°C was identified as the stereoisomeric mixture of 11,11′-ethylenebis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitriles) (*XII*) which was separated to the components by preparative HPLC. The title compound *XI* was oxidized to the sulfoxide *XIII* and the sulfone *XIV*, and was transformed by reduction and the following methylation to amines *XV* and *XVI*. The reduction of the vinyl nitrile *III* with lithium aluminium hydride is complicated on the one hand by allylic rearrangement, and with cyanide anion abstraction on the other, the products being (*E*,*Z*)-mixture of 3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)-propylamines (*XVII*) and 11-vinyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*). The amine *XVI* is devoid of thymoleptic activity.

Some time ago[1] the alkylation reaction of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11--carbonitrile (*I*) with 1,2-dibromoethane was investigated with the aim at preparing the corresponding 11-(2-bromoethyl) compound *II*. This reaction carried out by making use of sodium hydride as the anion forming agent in dimethylformamide at 65°C gave, indeed, the desired product *II* but the yield was low (21%). For this reason, conditions of the phase-transfer catalysis[2–5] were used. The first modification of this procedure consisted in treatment of the nitrile *I* with excessive 1,2-dibromoethane in the presence of benzyltriethylammonium chloride and 50% sodium hydroxide solution at 40–50°C (in the presence or absence of pyridine). The second modification used solid potassium carbonate instead of the sodium hydroxide solution, dimethyl sulfoxide as the reaction medium and 100°C as the reaction

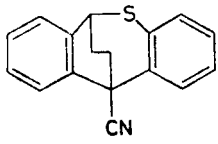
temperature. In both cases mixtures were obtained which were separated by chromatography on silica gel. The desired bromoethyl compound *II* was not obtained at all. In the first case, two crystalline products $C_{17}H_{13}NS$ were isolated and the major one (m.p. 98·5–99·5°C, 37%) was identified as the 11-vinyl nitrile *III*. The minor product (m.p. 196–197°C, 11%) was tentatively assigned to be the cyclopropa-annelated nitrile *V*. In the second case, only one solid product was obtained whose mass spectrum indicated also the elemental composition $C_{17}H_{13}NS$. This led to the tentative assignment of the structure *VI*. The compound, however, was amorphous (m.p. 120–125°C), its analysis characterized it as a hemihydrate, and in its ^{1}H NMR spectrum (80 MHz) the aliphatic protons afforded an unresolved multiplet at 2·50–4·60. Since a reasonable idea about the mode of formation of compound *V* under the given conditions was lacking and the experimental facts supporting the formula *VI* were weak, serious doubts about the correctness of both formulae arose. On the basis of some mechanistic reasoning, the new formula *VII* was suggested for the compound melting at 196–197°C, instead of the published formula *V* (ref.[1]). It was clear that a reinvestigation of the case was needed.



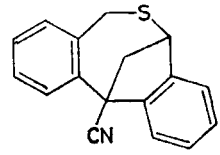
I, R = H
II, R = CH_2CH_2Br
III, R = $CH{=}CH_2$
IV, R = $CH(Br)-CH_3$



V



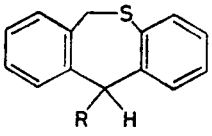
VI



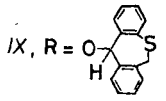
VII

In the first line, a new method for preparing the starting nitrile *I* was elaborated; the existing methods[6,7] have been little efficient. The new method consists in treatment of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[6] with trimethylsilyl cyanide[8] in dichloromethane in the presence of stannic chloride (analogy of cyanation of tertiary alkyl chlorides[9,10]); a simple processing gave the nitrile *I* in a yield of 86%. In a larger batch, processing of the mother liquor after the crystallization of compound *I* from ethanol gave 4% of a higher melting substance which was identified

as the amide *VIII* (*cf.*[11]). An attempt at a direct one-step conversion of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[12] into the nitrile *I* by treatment with sodium cyanide and chlorotrimethylsilane in a mixture of acetonitrile and dimethylformamide in the presence of a catalytic amount of sodium iodide (method[13]) resulted in the known[6,14] bis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) ether (*IX*) as the only crystalline product. Small differences in the melting points in comparison with samples of the ether *IX*, prepared previously[6,14], are to be explained by the fact that we are dealing here with stereoisomeric mixtures differing in their composition.



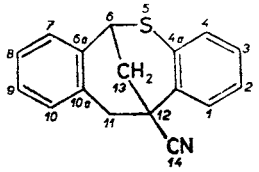
VIII, R = $CONH_2$



X, R = $CH{=}CH_2$

The further step was the alkylation of the nitrile *I* with 1,2-dibromoethane in the presence of benzyltriethylammonium chloride and 50% aqueous sodium hydroxide at 40–60°C in 5–7 times greater batches than previously described[1]. The substitution of benzyltriethylammonium chloride with tetrabutylammonium bromide did not affect the course of the reaction. The obtained mixtures were chromatographed on silica gel and the first product to be eluted with a mixture of benzene and light petroleum was the vinyl nitrile *III*, obtained in yields of about 30%. This was followed by the critical substance melting at 192–195°C, obtained this time in somewhat lower yields (about 8%) than previously[1]. For confirming or rejecting the suggested structures *V* and *VII*, a complete reinvestigation of the spectra was undertaken. The mass spectrum confirmed the elemental composition $C_{17}H_{13}NS$. The ^1H NMR spectrum (200 MHz) showed, in addition to the eight aromatic protons, the presence of one methine group (δ 4·38 dd) in the neighbourhood of methylene group (δ 2·90 ddd and δ 2·80 dd) and further isolated methylene group (δ 3·16 d and δ 3·33 dd). The given chemical shifts and especially geminal coupling constants of CH_2 groups (−13·2 Hz and −16·4 Hz, resp.) practically exclude the structure *V* with a cyclopropane ring (experimentally determined values range from −9·1 to −0·5 Hz, ref.[15]). From the inspection of Dreiding models it follows that also structure *VII* with rigid skeleton can hardly explain the observed values of vicinal couplings J = 4·8 and 2·4 Hz in fragment —CH—CH_2— (model of *VII* shows the torsion angles about 30° and 90°) and long-range coupling (2·0 Hz) between the hydrogens

of two present CH_2 groups. These facts led us to the suggestion of structure *XI*, which fits all the ^1H NMR parameters. Additional arguments in favour of structure *XI* were provided by the proton-coupled ^{13}C NMR spectrum. For the alternative structures *VII* and *XI* it is possible to estimate the numbers of expected geminal and vicinal coupling constants $J(C, H)$ for aliphatic carbon atoms —CH_2— and —CH_2—CH—. While for the structure *VII* their numbers are different (two, one resp. five couplings), there is the same number of three couplings for each in *XI*. The observed fine structure of signals at δ 44·62 ($J \approx 5{\cdot}0$; 4·5 and 4·5 Hz), δ 33·56 ($J \approx 6{\cdot}0$; 3·5 and 1·5 Hz) and δ 37·00 (poorly resolved multiplet with $\sum J \approx 11$ Hz) is in full agreement only with structure *XI*. The results of these ^1H and ^{13}C NMR studies is thus the unequivocal rejection of structure *V* and is in clear disagreement with the alternative formula *VII*. On the other hand, the data obtained lead to the rather unexpected structure of 11,12-dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-carbonitrile (*XI*).



XI

The final proof of the correctness of formula *XI* was obtained from X-ray crystallographic analysis. The perspective view of compound *XI* is given in Fig. 1. Full details of the crystallographic analysis will be published elsewhere[16]. The coupling constants of aliphatic protons in *XI* indicate the close similarity of its conformation in the solution and crystal. Torsion angles H6—C6—C13—H13A (−68·7°) and H6—C6—C13—H13B (56·9°) correspond very well with the observed values $J(6, 13A) = 2{\cdot}4$ Hz and $J(6, 13B) = 4{\cdot}8$ Hz, giving approximate torsion angles −73° and 57° by using a Karplus-type equation[17]. Also the long-range coupling $J(11A, 13A) = 2{\cdot}0$ Hz, indicating nearly planar zig-zag arrangement of fragment H11A—C11—C12—C13—H13A in solution is well documented by torsion angles H11A—C11—C12—C13 (174·7°) and C11—C12—C13—H13A (172·3°) in crystal[16].

Reasoning about the possible mode of formation of compound *XI* as the minor product of the reaction described, resulted in the following hypothesis (Scheme 1). The 11-(2-bromoethyl) compound *II* has, anyway, to be assumed as the primary product and the precursor of the vinyl compound *III*, *i.e.* the main reaction product, formed by the base-catalyzed elimination of hydrogen bromide. Compound *II* can form the benzylic carbanion *A*, which is somewhat stabilized by the adjacent sulfur atom. Displacement of the bromine atom by this highly reactive carbanion gives the tetracyclic structure *VI* which looks stable and could already have been the

product but the presence of the base effects its transformation to a further carbanion *B*. This tertiary carbanion could undergo ring opening (Grob fragmentation style[18,19]) (*cf.* arows in *B*) to give a low equilibrium concentration of the primary carbanion *C*. This carbanion is highly reactive and can undergo an intramolecular nucleophilic aromatic substitution (arrows in *C*) to give the much more stable carbanion *D*. Alternatively, and perhaps more likely, the carbanion *B* could rearrange directly to *D* without the intervention of *C* as a discrete intermediate. Molecular models show that carbanion *D* is well set up to cyclize as shown to give the final carbanion *E*, which, on protonation, gives the product *XI*. Another possibility, which also should be considered, is the formation of the sulfonium cation *F* from *II*, its further transformation to the sulfur ylide *G* (*cf.*[20]) which undergoes the Stevens rearrangement[21] to give *VI*. Formation of the minor product *XI* involves an interesting cascade of carbanions whose stabilities depend on the precise structural relationship of the aromatic rings, the sulfur atom, and the cyanide group. The key molecular rearrangement thus arises in a rather unusual intramolecular nucleophilic aromatic substitution reaction $B \rightarrow D$. It is interesting to note that in this mechanism the two (separated) methylene groups in positions 11 and 13 of the molecule *XI* are derived from the dibromoethane, and this could be tested by appropriate labelling experiments.

The alkylation experiment in which potassium carbonate in dimethyl sulfoxide was used instead of the 50% sodium hydroxide solution[1] was also repeated. Chromatography of the mixture obtained gave a moderate yield of an amorphous solid

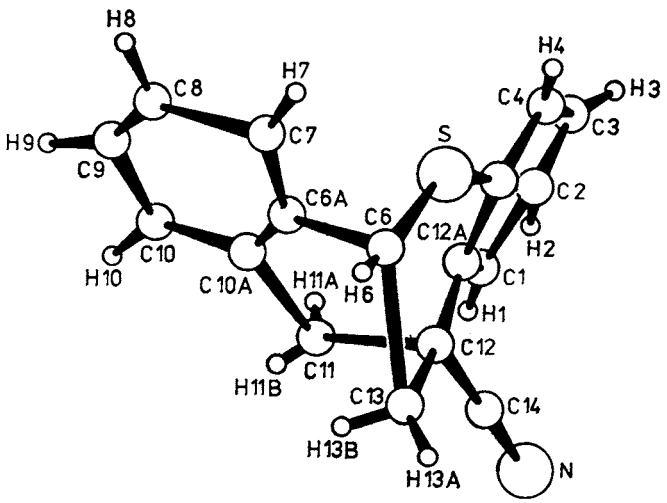
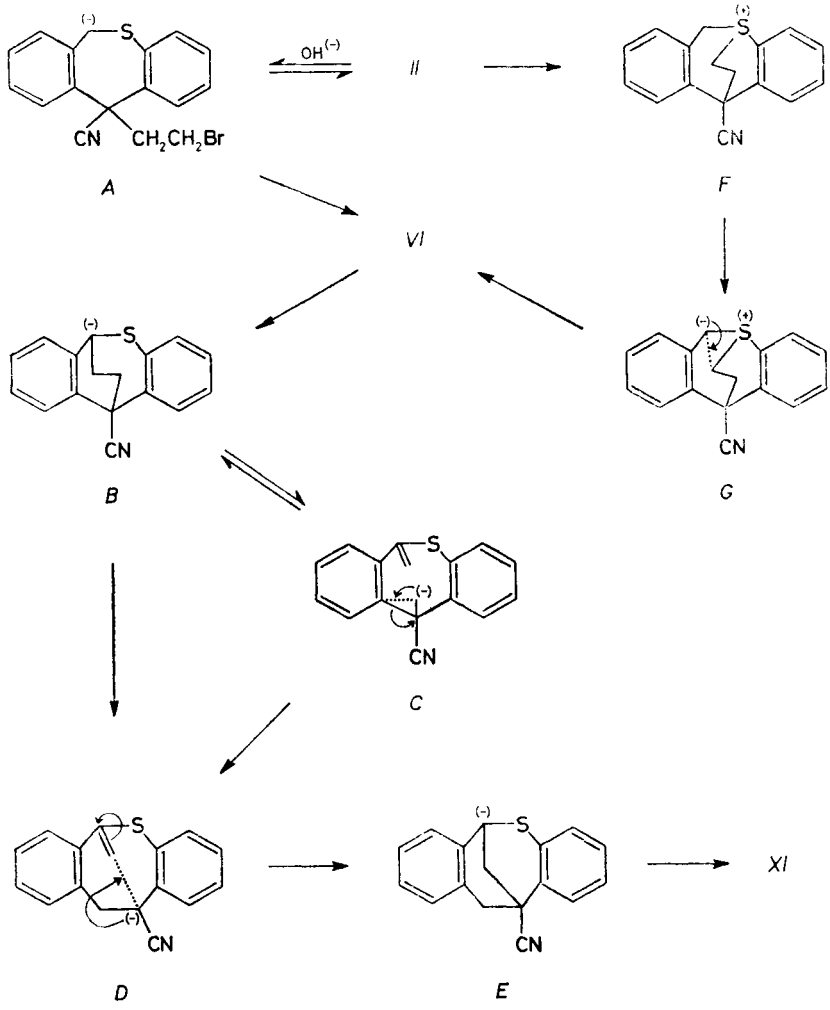


FIG. 1
Perspective view of molecule *XI*

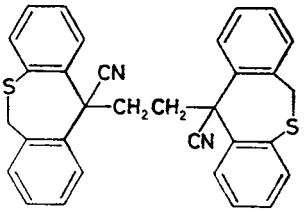


SCHEME 1

which was found identical with the previously reported[1] stereoisomeric mixture of 11,11'-ethylenebis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitriles) (*XII*). It succeeded to separate this mixture by preparative HPLC on silica gel and to characterize both isomers (*XIIa*, *XIIb*) by means of mass and ^{1}H NMR spectra. Formula *VI*, suggested previously[1] for this compound, has to be withdrawn, being evidently wrong.

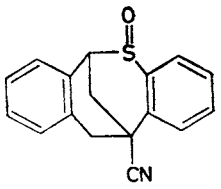
Compound *XI* and *III* were used as starting materials for some chemical transformations having the purpose of further characterization of these compounds on the one hand, and of searching after new biologically active substances in this area on

the other. Oxidation of compound *XI* with an excess of hydrogen peroxide in acetic acid at room temperature gave two products: The main one, lower melting and better soluble substance, and the higher melting and less soluble minor product.

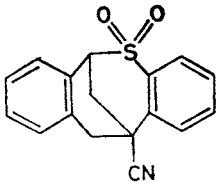


XII

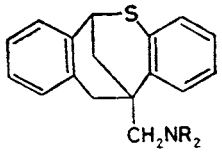
The first was characterized to be the sulfoxide *XIII* (mass and NMR spectra; the S—O band at 1 050 cm^{-1} in the IR spectrum) and the other as the sulfone *XIV* (mass and NMR spectra; the SO_2 bands at 1 127 and 1 300 cm^{-1} in the IR spectrum). Reduction of the nitrile *XI* with aluminium hydride, prepared *in situ* by the reaction of lithium aluminium hydride with aluminium chloride in ether (method[22,23]), gave the primary amine *XV* which was isolated and purified in the form of the hydrogen maleate. The mass spectrum confirmed the elemental composition and the released oily base was used for recording the ^1H NMR spectrum. Methylation of the primary amine *XV* by the Eschweiler–Clarke method[24,25] resulted in the tertiary amine *XVI*. In this case, the base was crystalline and its structure was corroborated by the spectra; it afforded a hydrogen maleate which was used for the biological testing.



XIII



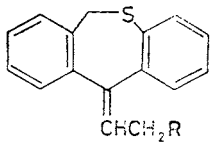
XIV



XV, R = H
XVI, R = CH_3

The vinyl nitrile *III* was reduced with lithium aluminium hydride in ether and the basic product was transformed to the maleate in a mixture of ether and ethanol. The mass spectrum indicated the expected composition $C_{17}H_{17}NS$ (*i.e.* +4 H) but the ^1H NMR spectrum of the released base suggested for the product the unexpected formula *XVII* (*cf.*[7]). Lithium aluminium hydride must have acted first as the allylic rearrangement reagent (*cf.*[26]) and only then reduce the primarily formed rearranged nitrile *XVIII* (*cf.*[27]). The double signal of the =CH— proton (triplets at δ 5·85

and 5·58) in the product *XVII* characterized it as a mixture of (*E*)- and (*Z*)-isomers with the approximate ratio of 60 : 40. The previously and differently prepared compound *XVII* (ref.[7]) was the homogeneous (*E*)-isomer (only one triplet at δ 5·90 corresponding to =CH—). Rearrangements of the allylic nitriles of the present type do not seem to be frequent phenomena (*cf.*[28,29]). In addition to the rather little amount of the basic product *XVII*, there was an important neutral oily product characterized by the ^{1}H NMR spectrum as 11-vinyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*). It is considered to be the result of a simple nucleophilic displacement of the nitrile group in *III* with the hydride anion.



XVII, R = CH_2NH_2
XVIII, R = CN

The last experiment to be carried out was the addition of hydrogen bromide to the vinyl nitrile *III* by boiling a solution of compound *III* in dioxane with 48% hydrobromic acid. A rather high-melting substance was obtained in a good yield which is little soluble in benzene and ether, and soluble in chloroform. Its mass spectrum indicated the expected composition $C_{17}H_{14}BrNS$ but the analysis corresponded to the hemihydrate. In the IR spectra (in KBr or chloroform) there was a typical nitrile band at 2 250 (or 2 255) cm^{-1}. The expected 11-(1-bromoethyl) nitrile *IV* should be a mixture of two racemates. But obtaining the homogeneous, high-melting solid in high yield and its NMR spectra unequivocally indicate that we are dealing here only with one racemate. High stereospecificity of the bromide anion attack in this case is probably due to the dissymmetry of the molecule of *III* and its prefered conformation. The ^{1}H and ^{13}C NMR spectra are in full agreement with the expected structure *IV*. This product easily regenerates the starting vinyl nitrile *III*; this was first found in an attempt at a nucleophilic substitution reaction by refluxing with 1-methylpiperazine in chloroform (the recovery is almost quantitative) but only shaking of the chloroform solution with the dilute aqueous ammonia leads to the same result.

The amine *XVI* could be considered a potential antidepressant and was, therefore, pharmacologically tested in that line. In the animal tests it was administered orally in the form of the hydrogen maleate; the doses given were calculated *per* base. Acute toxicity in mice, LD_{50} = 185 mg/kg. In concentrations of 100 nmol l^{-1} it did influence the binding neither of 4 nmol l^{-1} [^{3}H]imipramine, nor 4 nmol l^{-1} [^{3}H]-desipramine in the hypothalamus of the rat brain. In the photo-cell test of Dews,

it did not influence in the dose of 10 mg/kg the spontaneous locomotor activity of mice, evaluated in the intervals of 1 and 3 h after the administration. In the dose of 25 mg/kg it had no significant effect towards the reserpine ptosis in mice and in the dose of 50 mg/kg it did not influence significantly the formation of gastric ulcers in rats, elicited with reserpine. In conclusion, compound *XVI* did not show properties of a possible antidepressant agent. In microbiological testing *in vitro* it showed in concentrations of 50 μg/ml inhibiting activity towards *Trichophyton mentagrophytes* and *Aspergillus niger*.

EXPERIMENTAL

The melting points 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. The UV spectra were recorded in methanol on Unicam SP 8 000 spectrophotometer. Infrared spectra (mostly in Nujol) were taken on Perkin–Elmer PE 298 or PE 580 instruments. The NMR spectra were measured in C^2HCl_3 (unless stated otherwise) on a FT-NMR spectrometer Varian XL-200 (^1H at 200 MHz; ^{13}C at 50·3 MHz) and a CW-NMR spectrometer Tesla BS 487 C (^1H at 80 MHz). Mass spectra were measured on Varian MAT 311, MAT 44S, MCH 1 320, and/or AEI MS 902 instruments. The homogeneity of the compounds was tested by thin-layer chromatography on silica gel (Silufol). Preparative HPLC was carried out on an apparatus consisting of a Consta-Metric I pump (LDC, U.S.A.), a Knauer injection valve (Knauer, F.R.G.) and UVM-4 detector (VD ČSAV, Czechoslovakia).

6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*I*)

A solution of 60·0 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[6] in 500 ml dichloromethane was treated with 29·0 g trimethylsilyl cyanide[8], and then slowly under stirring with 6·5 ml $SnCl_4$. The mixture was stirred for 30 min and allowed to stand for 3 days at room temperature. It was then poured into water, the organic layer was washed with 5% $NaHCO_3$, and evaporated. The solid crude product obtained (57·8 g, m.p. 129—131°C) was recrystallized from ethanol; 49·6 g (86%), m.p. 137—137·5°C (change of the crystal form at 130—132°C). Refs[6,7], m.p. 130—132°C and 137—139°C, respectively.

In a larger batch, 160 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[6], 80 g trimethylsilyl cyanide[8], and 18 ml $SnCl_4$ in 1 l dichloromethane gave similarly 107 g (70%) *I*, m.p. 133·5—136°C. Evaporation of the ethanolic mother liquor and repeated crystallization of the residue from ethanol and ethanol–benzene gave 6·3 g (4%) 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carboxamide (*VIII*), m.p. 178—179°C (the analysis in agreement with the empirical formula $C_{15}H_{13}NOS$). Ref.[11], m.p. 179—180°C.

Bis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) Ether (*IX*)

A mixture of 4·6 g 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[12], 1·0 g NaCN, 25 mg NaI, 4·4 g chlorotrimethylsilane, 40 ml acetonitrile, and 40 ml dimethylformamide was stirred and heated for 7 h to 60°C. After standing overnight, it was poured into water and extracted with ether. The extract was dried with $MgSO_4$ and evaporated. The residue was dissolved in a mixture of benzene and light petroleum and chromatographed on a column of 150 g silica gel. One of the first fractions, eluted with the indicated mixture of solvents, was the homogeneous product,

showed to be *IX*, 2·20 g (48%), m.p. 186—192°C. Mass spectrum, *m/z* (%): 438 (M^+, $C_{28}H_{22}OS_2$), 227 ($C_{14}H_{11}OS$, 70), 211 ($C_{14}H_{11}S$, 57), 210 ($C_{14}H_{10}S$, 100), 197 ($C_{13}H_9S$), 194 ($C_{14}H_{10}O$, 34), 179 (34), 178 ($C_{14}H_{10}$, 84), 91 (43). IR spectrum (KBr): 745 (4 adjacent Ar—H), 1 056, 1 078, 1 124 (R—O—R), 1 563, 1 586, 3 020, 3 060 cm^{-1} (Ar). The analysis is in agreement with the mass spectrum. Refs[6,14], m.p. 204—206°C and 191—192°C, respectively.

11,12-Dihydro-6*H*-6,12-methanodibenzo[*b,f*]thiocin-12-carbonitrile (*XI*)

A mixture of 31·7 g *I*, 90 g 1,2-dibromoethane, and 3·0 g tetrabutylammonium bromide was homogenized by stirring and heating to 70°C, after cooling to 40°C 100 g 50% aqueous NaOH were added, and the mixture was stirred for 6·5 h at 50—55°C. It was then distributed between benzene and water, the benzene layer was washed with water, dried, and evaporated under reduced pressure. The residue (48·3 g) was chromatographed on a column of 240 g SiO_2. In the first benzene–light petroleum fractions 11·0 g (31%) 11-vinyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*III*), m.p. 96—99°C (cyclohexane), were eluted. Ref.[1], m.p. 98·5—99·5°C.

Continued elution with a mixture of benzene and light petroleum gave 2·7 g (8%) homogeneous *XI*, m.p. 192—195°C (benzene–light petroleum). Mass spectrum, *m/z* (%): 263 (M^+, $C_{17}H_{13}NS$, 70), 262 ($C_{17}H_{12}NS$, 22·5), 247 ($C_{17}H_{11}S$, 5), 235 ($C_{16}H_{11}S$, 22), 230 (10), 221 ($C_{15}H_9S$, 8), 202 ($C_{16}H_{10}$, 11), 172 ($C_{10}H_6NS$, 6), 154 ($C_{11}H_8N$, 7), 135 (C_8H_7S, 25), 127 (11), 115 (21), 104 (C_8H_8, 100), 91 (10), 78 (12). ^{1}H NMR spectrum (200 MHz): 2·80 dd, 1 H (H-13, J(13, 13′) = = 13·2; J(13, 6) = 4·8), 2·90 ddd, 1 H (H-13′, J(13′, 13) = 13·2; J(13′, 6) = 2·4; J(13′, 11) = = 2·0), 3·33 dd, 1 H (H-11, J(11, 11′) = 16·4; J(11, 13′) = 2·0), 3·61 d, 1 H (H-11′, J(11′, 11) = = 16·4), 4·38 dd, 1 H (H-6, J(6, 13) = 4·8; J(6, 13′) = 2·4), 6·89—7·71 m, 8 H (Ar—H). ^{13}C NMR spectrum (50·3 MHz): 33·56 t (C-13), 35·65 s (C-12), 37·00 d (C-6), 44·62 t (C-11), 123·95 s (C-14), 125·38 d, 127·46 d, 127·54 d, 127·83 d, 128·60 d, 128·74 d, 129·32 d, 129·47 d (8 aromatic —CH=), 129·99 s, 130·53 s, 130·88 s, 136·25 s (4 aromatic —C=).

11,11′-Ethylenebis(6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitriles) (*XII*)

A mixture of 9·5 g *I*, 23·4 g 1,2-dibromoethane, 11·2 g K_2CO_3, 0·8 g benzyltriethylammonium chloride, and 40 ml dimethyl sulfoxide was stirred and heated for 7 h to 100°C. After cooling it was distributed between benzene and water, the mixture was filtered, the benzene layer of the filtrate was washed with water, dried, and evaporated. The residue (9·7 g) was chromatographed on a column of 200 g silica gel. In the first benzene eluates, a part of the starting *I* was recovered (0·57 g, m.p. 133—135°C). Further elution with benzene led to 2·36 g (24%) amorphous solid, precipitating from cyclohexane or ethanol and melting at 110—115°C. It is the mixture of two diastereoisomers *XII* for which ref.[1] gave the m.p. 90—120°C. With preparative HPLC (stainless steel column 8 × 250 mm packed with Separon Si VSK (5 μm), mobile phase heptane–6% ethyl acetate, flow rate 4 ml/min, UV detection at 262 nm) the both diastereoisomers *XIIa* and *XIIb* were isolated (c. 2 mg of each). Mass spectra (nearly identical for *XIIa* and *XIIb*), *m/z* (%): 500 (M^+, $C_{32}H_{24}N_2S_2$, 13), 264 ($C_{17}H_{14}NS$, 64), 237 ($C_{15}H_{11}NS$, 59), 236 ($C_{15}H_{10}NS$, 100), 204 ($C_{15}H_{10}N$, 29), 203 ($C_{15}H_9N$, 49). ^{1}H NMR spectrum of *XIIa* (200 MHz, T = 50°C): 2·66 ddd, 1 H (J = 14·4; 6·0; 3·0), 2·79 ddd, 1 H (J = 14·4; 10·0; 3·0), 2·92 ddd, 1 H (J = 13·5; 6·0; 3·0) and 3·38 ddd, 1 H (J = 13·5; 10·0; 3·0, —CH_2—CH_2—), 3·85 bd, 1 H (J = 15·2), 4·64 bd, 1 H (J = 15·2), 4·13 vbd, 1 H ($J \approx$ 15·2) and 4·53 vbd, 1 H ($J \approx$ 15·2) — 2 CH_2S, 6·89—7·78 m, 8 H (Ar—H). ^{1}H NMR spectrum of *XIIb* (200 MHz, T = 50°C): 2·72—2·85 m, 3 H and 3·42 m, 1 H (—CH_2—CH_2—), 3·80 d, 1 H (J = 15·0), 3·96 d, 1 H (J = 15·0), 3·86 bd, 1 H ($J \approx$ 15·2) and 4·04 bd, 1 H ($J \approx$ 15·2) — 2 CH_2S, 7·00—7·78 m, 8 H (Ar—H).

11,12-Dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-carbonitrile 5-Oxide (*XIII*)

A solution of 1·1 g *XI* in 50 ml acetic acid was treated with 1·0 ml 30% H_2O_2 and the mixture was allowed to stand for 4 days at room temperature. After partial evaporation *in vacuo*, the residue was diluted with water, and the precipitated solid was filtered; 1·07 g, m.p. 224–255°C. Crystallization from a mixture of benzene and ethanol led first to 0·22 g (18%) insoluble substance which was shown to be the not completely homogeneous 11,12-dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-carbonitrile 5,5-dioxide (*XIV*), m.p. 275–283°C (ethanol–chloroform). Mass spectrum, *m/z* (%): 295 (M^+, $C_{17}H_{13}NO_2S$, 7), 252 ($C_{15}H_{12}OS$, 15), 235 ($C_{16}H_{11}S$, 75), 127 ($C_{10}H_7$, 15), 115 (C_9H_7, 100). IR spectrum: 766 (4 adjacent Ar—H), 1 127, 1 300 (SO_2), 1 487, 1 490, 1 570, 1 580, 1 593, 3 065 (Ar), 2 240 cm^{-1} (R—CN). ^1H NMR spectrum (200 MHz): 2·97 dd, 1 H (H-13, *J*(13, 13′) = 14·5; *J*(13, 6) = 5·4), 3·27 dd, 1 H (H-11, *J*(11, 11′) = 16·7; *J*(11, 13′) = 2·4), 3·75 d, 1 H (H-11′, *J*(11′, 11) = 16·7), 3·78 ddd, 1 H (H-13′, *J*(13′, 13) = 14·5; *J*(13′, 11) = 2·4; *J*(13′, 6) = 1·9), 4·46 dd, 1 H (H-6, *J*(6, 13) = 5·4; *J*(6, 13′) = 1·9), 6·94 to 7·85 m, 8 H (Ar—H). ^{13}C NMR spectrum (50·3 MHz): 31·54 t (C-13), 35·92 s (C-12), 43·31 t (C-11), 57·49 d (C-6), 121·88 s (C-14), 125·26 s, 131·11 s, 133·42 s, 137·91 s (4 aromatic —C=), 124·86 d, 127·71 d, 128·55 d, 129·06 d, 129·97 d, 130·42 d, 132·69 d, 133·69 d (8 aromatic —CH=). The NMR spectra of *XIV* proved the presence of 25% *XIII* as admixture. For $C_{17}H_{13}NO_2S$ (295·3) calculated: 69·14% C, 4·44% H, 4·74% N, 10·84% S; found: 69·81% C, 4·43% H, 4·80% N, 11·00% S.

From the benzene–ethanol solution there crystallized 0·81 g (69%) *XIII*, m.p. 217–219°C and after resolidification 228–230°C (benzene–ethanol–light petroleum). Mass spectrum, *m/z* (%): 279 (M^+, $C_{17}H_{13}NOS$, 1·3), 262 ($C_{17}H_{12}NS$, 3), 252 ($C_{15}H_{12}OS$, 5·4), 235 ($C_{16}H_{11}S$, 100), 127 ($C_{10}H_7$, 5·3), 115 (C_9H_7, 10). IR spectrum: 760, 769 (4 adjacent Ar—H), 1 050 (R—S=O), 1 502, 1 570, 1 582 (Ar), 2 225 cm^{-1} (R—CN). ^1H NMR spectrum (200 MHz): 2·63 dd, 1 H (H-13, *J*(13, 13′) = 14·3; *J*(13, 6) = 5·0), 3·18 dd, 1 H (H-11, *J*(11, 11′) = 16·4; *J*(11, 13′) = = 2·2), 3·70 d, 1 H (H-11′, *J*(11′, 11) = 16·4), 3·70 ddd, 1 H (H-13′, *J*(13′, 13) = 14·3; *J*(13′, 11) = = 2·2; *J*(13′, 6) = 1·8), 4·52 dd, 1 H (H-6, *J*(6, 13) = 5·0; *J*(6, 13′) = 1·8), 6·93–7·85 m, 8 H (Ar—H). ^{13}C NMR spectrum (50·3 MHz): 23·08 t (C-13), 35·64 s (C-12), 43·04 t (C-11), 53·97 d (C-6), 122·43 s (C-14), 125·81 s, 131·80 s, 133·32 s, 134·61 s (4 aromatic —C=), 127·56 d, 129·18 d, 129·32 d, 129·51 d, 129·98 d, 130·27 d, 133·21 d, 133·43 d (8 aromatic —CH=). For $C_{17}H_{13}NOS$ (279·4) calculated: 73·09% C, 4·69% H, 5·01% N, 11·48% S; found: 72·81% C, 4·76% H, 4·86% N, 11·41% S.

11,12-Dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-ylmethylamine (*XV*)

A solution of 1·6 g $AlCl_3$ in 10 ml ether was added dropwise to a stirred solution of 0·6 g $LiAlH_4$ in 10 ml ether in nitrogen atmosphere and a solution of 2·1 g *XI* in 30 ml tetrahydrofuran was added over 15 min. The mixture was refluxed for 5 h, cooled, decomposed by a slow addition of 2 ml water and 5 ml 20% NaOH, the precipitated solid was filtered off, extracted with boiling benzene, the extract was combined with the organic layer, and the solution was evaporated. The residue (2·1 g) was dissolved in ether and the solution was neutralized with a solution of 0·95 g maleic acid in ether; 2·6 g (85%) hydrogen maleate, m.p. 172–174°C (ethanol). Mass spectrum, *m/z* (composition): 267 (M^+, $C_{17}H_{17}NS$), 250 ($C_{17}H_{14}S$), 235 ($C_{16}H_{11}S$), 204 ($C_{16}H_{12}$), 104 (C_8H_8). For $C_{21}H_{21}NO_4S$ (383·5) calculated: 65·78% C, 5·52% H, 3·65% N, 8·36% S; found: 65·90% C, 5·58% H, 3·61% N, 8·57% S.

A sample of the hydrogen maleate was decomposed with NH_4OH and the homogeneous oily base was isolated by extraction with ether. ^1H NMR spectrum (80 MHz): 1·06 s, 2 H (NH_2), 2·14 dd, 1 H (H-13, *J*(13, 13′) = 14·0; *J*(13, 6) = 5·0), 2·74 dd, 1 H (H-13′, *J*(13′, 13) = 14·0;

J(13', 6) = 2·0), 2·86 s, 2 H (CH_2N), 2·80 d, 1 H (H-11, J(11, 11') = 13·0), 3·43 d, 1 H (H-11', J(11', 11) = 13·0), 4·34 dd, 1 H (H-6, J(6, 13) = 5·0; J(6, 13') = 2·0), 6·80—7·60 m, 8 H (Ar—H).

N,N-Dimethyl-11,12-dihydro-6*H*-6,12-methanodibenzo[*b*,*f*]thiocin-12-ylmethylamine (*XVI*)

A mixture of 2·15 g *XV*, 2·5 ml 98% formic acid, and 2·0 ml 40% formaldehyde was heated for 7 h under reflux to 100°C. After cooling it was distributed between 10% NaOH and benzene, the benzene layer was washed with water, dried with K_2CO_3, and evaporated *in vacuo*. The crystalline residue (2·3 g, 97%), m.p. 119—123°C, is the almost homogeneous base *XVI*. Analytical sample, m.p. 122—124°C (cyclohexane). Mass spectrum, *m/z* (%): 295 (M^+, $C_{19}H_{21}NS$, 2), 250 ($C_{17}H_{14}S$, 2·5), 234 ($C_{16}H_{10}S$, 1), 202 ($C_{16}H_{10}$, 2), 58 (C_3H_8N, $CH_2{=}N(CH_3)_2$, 100). UV spectrum: λ_{max} 253 nm (log ε 3·93), infl. 261 nm (3·88). IR spectrum: 732, 749, 760 (4 adjacent Ar—H), 1 493, 1 590, 3 050 (Ar), 2 720, 2 760, 2 810 cm^{-1} (N—CH_3). ^{1}H NMR spectrum (80 MHz): 2·20 s, 6 H ($N(CH_3)_2$), 2·40 dd, 1 H (H-13, J(13, 13') = 14·0; J(13, 6) = 5·0), 2·80 dd, 1 H (H-13', J(13', 13) = 14·0; J(13', 6) = 2·0), 2·82 s, 2 H (CH_2N), 2·75 d, 1 H (H-11, J(11, 11') = = 13·0), 3·18 d, 1 H (H-11', J(11', 11) = 13·0), 4·34 dd, 1 H (H-6, J(6, 13) = 5·0; J(6, 13') = = 2·0), 6·80—7·60 m, 8 H (Ar—H). For $C_{19}H_{21}NS$ (295·5) calculated: 77·24% C, 7·16% H, 4·74% N, 10·85% S; found: 77·23% C, 7·20% H, 4·71% N, 11·03% S.

Hydrogen maleate, m.p. 158—159°C (ethanol–ether). For $C_{23}H_{25}NO_4S$ (411·5) calculated: 67·13% C, 6·12% H, 3·40% N, 7·79% S; found: 66·79% C, 6·22% H, 3·86% N, 8·24% S.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yliden)propylamine (*XVII*)

A solution of 5·3 g *III* in 100 ml ether was added dropwise over 20 min to a stirred solution of 2·8 g $LiAlH_4$ in 50 ml ether, and the mixture was refluxed for 5·5 h under N_2. After cooling, the stirred mixture was decomposed by a slow addition of 5 ml water and 15 ml 20% NaOH, the solid was filtered off, washed with ether, and the filtrate was evaporated. The residue (3·8 g) was neutralized with 1·3 g oxalic acid dihydrate in ether; 0·5 g (7%) *XVII* hydrogen oxalate, m.p. 203—204·5°C (ethanol). Mass spectrum, *m/z* (composition): 267 (M^+, $C_{17}H_{17}NS$), 238 ($C_{16}H_{14}S$), 223 ($C_{15}H_{11}S$), 221 ($C_{15}H_9S$), 204 ($C_{16}H_{12}$). For $C_{19}H_{19}NO_4S$ (357·4) calculated: 63·85% C, 5·36% H, 3·92% N, 8·97% S; found: 63·70% C, 5·53% H, 4·04% N, 9·36% S.

The oily base *XVII* was released from the oxalate and used for recording the ^{1}H NMR spectrum which characterized the substance as a mixture of (*E*)- and (*Z*)-isomers (approximately 60 : 40). ^{1}H NMR spectrum (80 MHz): 1·10 bs, 2 H (NH_2), 2·08 m, 1 H and 2·30 m, 1 H (C—CH_2—C), 2·65 m, 2 H (CH_2N), 3·28 d, 1 H (H-6, J(6, 6') = 13·0), 4·85 d, 1 H (H-6', J(6', 6) = 13·0), 5·58 t and 5·85 t, 1 H (=CH— in (*E*)- and (*Z*)-form, resp., J = 7·0), 6·80 to 7·30 m, 8 H (Ar—H).

The ethereal filtrate after the hydrogen oxalate was evaporated and the residue was distributed between light petroleum and water. Processing of the organic layer gave 3·0 g (63%) almost homogeneous oil which was identified as 11-vinyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*). ^{1}H NMR spectrum (80 MHz): 3·59 d, 1 H (H-6, J(6, 6') = 13·0), 4·88 d, 1 H (H-6', J(6', 6) = 13·0), 4·60—5·20 m, 2 H (=CH_2), 5·60—6·50 m, 2 H (Ar_2CH and CH=), 6·80—7·30 m, 8 H (Ar—H).

11-(1-Bromoethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*IV*)

A solution of 5·0 g *III* in 50 ml dioxane was treated with 50 ml 48% HBr and the mixture was refluxed for 5·5 h. The solvent was evaporated and the residue was distributed between water and chloroform (proved insoluble in benzene and ether). The chloroform solution was diluted with benzene which led to crystallization of 5·55 g (85%) homogeneous substance melting at

177—181°C. Crystallization from a mixture of ethanol and ether changed only slightly the melting point to 177—183°C. Mass spectrum, *m/z* (composition): 344 (M^+, $C_{17}H_{14}BrNS$), 264 ($C_{17}H_{14}$.NS), 249 ($C_{16}H_{11}NS$), 236 ($C_{15}H_{10}NS$, base peak), 222 ($C_{15}H_{10}N$), 204 ($C_{12}H_{14}NS$). UV spectrum: λ_{max} 270 nm (log ε 3·31), inflexes at 265 nm (3·25) and 277 nm (3·22). IR spectrum (KBr): 759, 784 (4 adjacent Ar—H), 1 464, 1 494, 1 581 (Ar), 2 250 cm^{-1} (R—CN); in $CHCl_3$: 2 255 cm^{-1} (R—CN). ^1H NMR spectrum (200 MHz, C^2HCl_3 + 10% $C^2H_3O^2H$): 1·86 d, 3 H (CH_3, J = 6·9), 5·05 s, 2 H (CH_2S), 5·21 q, 1 H (CHBr, J = 6·9), 7·20—7·80 m, 7 H (Ar—H), 8·48 m, 1 H (Ar—H). ^1H NMR spectrum (80 MHz, $C^2H_3SOC^2H_3$): 1·65 d, 3 H (CH_3, J = 7·0), 4·88 d, 1 H (H-6, J(6, 6′) = 13·0), 5·30 d, 1 H (H-6′, J(6′, 6) = 13·0), 5·51 q, 1 H (CHBr, J = 7·0), 7·10—7·80 m, 7 H (Ar—H), 8·48 m, 1 H (Ar—H). For $C_{17}H_{14}BrNS$ + 1/2 H_2O (353·3) calculated: 57·79% C, 4·28% H, 22·62% Br, 3·96% N, 9·08% S; found: 57·82% C, 4·19% H, 23·08% Br, 4·08% N, 9·12% S.

A mixture of 3·0 g *IV* hemihydrate, 10 ml 1-methylpiperazine, and 10 ml chloroform was refluxed for 8 h and the neutral product was isolated by the conventional procedure; 2·2 g (96%) crude *III*, after crystallization from cyclohexane 1·6 g homogeneous *III* melting at 97·5—98·5°C. The same product was obtained by distributing *IV* hemihydrate between dilute NH_4OH and chloroform.

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