SYNTHESIS OF 3-(6,11-DIHYDRODIBENZO[*b,e*]THIEPIN-11-YLIDENE)-PROPANOIC ACID AND RELATED COMPOUNDS

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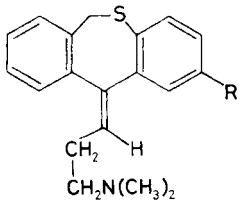
The alcohol *XIa*, obtained by reaction of dibenzo[*b,e*]thiepin-11(6*H*)-one with vinylmagnesium bromide, was transformed by treatment with hydrogen bromide in acetic acid to the bromo compound *XIIa* which was converted *via* the nitrile *XIIIa* to the title acid *VIIIa*. The pure (*E*)-isomer was prepared and correlated *via* the dimethylamide *XVIIIa* with (*E*)-prothiadene (*Ia*). Similar procedures in the 2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin and 10,11-dihydrodibenzo-[*a,d*]cycloheptene series afforded the acids *VIIIb* and *IV*. The acids *VIIIab* were oxidized with hydrogen peroxide to the sulfoxides *IXab* and to the sulfones *Xab*. The acid *IV* is the suggested metabolite of the antidepressant amitriptyline (*II*) and the acids *VIIIab*—*Xab* are potential metabolites of the antidepressant prothiadene (*Ia*) and the antihistamine agent methiadene (*Ib*). The amides *VII* and *XVIab* were prepared from the acids *via* the acid chlorides. The (*Z*)-isomer of prothiadene (*XXII*) was prepared from dibenzo[*b,e*]thiepin-11(6*H*)-one by the Wittig reaction. The acids *IV*, *VIIIab* and *IXab* showed some antiinflammatory activity.

(*E*)-N,N-Dimethyl-3-(6,11-dihydrodibenzo[*b,e*]thiepin-11-ylidene)propylamine (*Ia*) hydrochloride (prothiadene, dosulepin, dothiepin) (refs[1-5]) continues its way to become a worldwide used antidepressant agent[6-10]. For this reason we continue our studies of the fate of this drug in living organisms by preparing potential metabolites. Until now the following compounds were prepared: S-oxide, monodemethyl analogue (northiadene), northiadene S-oxide, didemethyl analogue, S,S-dioxide, northiadene S,S-dioxide and 2-hydroxy derivative of prothiadene; the first four of them were identified as metabolites[11]. The more recent investigations of the metabolism of prothiadene (*Ia*) (refs[12-17]) improved the methods of identification and determination of the known metabolites but hardly enhance the number of the recognized metabolites. By means of high-performance liquid chromatography, there was detected in human serum samples a substance which is not identical with any known prothiadene metabolite and represents probably a new one[13]; its identity remains unknown. The major polar metablite in rate urine was identified as a glucuronic acid conjugate and the aglycone of *m/z* 312 was tentatively designated as "a hydroxylated prothiadene" (ref.[14]); it was probably not directly compared with our 2-hydroxy compound[11]. The recent contribution[18] announces the isolation of two conjugated metabolites from human urine which were identified as a quaternary

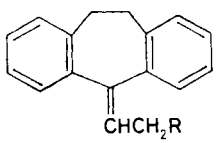
ammonium-linked glucuronide of prothiadene and a tertiary N-glucuronide of northiadene. It is to be expected that the set of identified prothiadene metabolites remains rather incomplete.



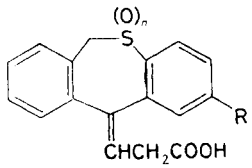
I

In formulae *I*, *VIII*–*XVIII*: *a*, R = H
b, R = CH_3

Facino *et al.*[19] announced the presence of an acid metabolite in urine of rabbits treated with amitriptyline (*II*) or nortriptyline (*III*) (in the latter case the formation of the acid metabolite was three times higher than in the former case). The metabolite was isolated in small amounts by thin-layer chromatography and formula *IV* was attributed to it. It was suggested that the oxidative deamination of the amitriptyline (*II*) side chain, starting with the partial demethylation to nortriptyline (*III*), proceeds further to the acid *IV* and represents a minor metabolic pathway for the degradation of *II* and *III*. Because the correctness of this hypothesis is very likely, it is surprising that the mentioned paper[19] is the only one in this line and that there are no reports on the synthesis of the acid *IV*. The structural analogy between amitriptyline (*II*) and prothiadene (*Ia*) is very close and, therefore, the same metabolic pathway must be considered for *Ia*. Its hypothetical products could then be the acid *VIIIa* and its S-oxidated derivatives *IXa* and *Xa*. The main object of this paper is the synthesis of the acids *VIIIa*–*Xa*. Similar acids *VIIIb*–*Xb*, derived from the antihistamine agent methiadene (*Ib*) (refs[1,3,20–22]), were included and also the synthesis of the amitriptyline-derived acid *IV* is being described.



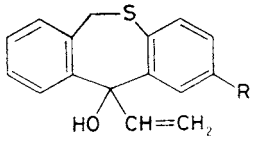
II, R = $CH_2N(CH_3)_2$
III, R = CH_2NHCH_3
IV, R = COOH
V, R = CN
VI, R = COCl
VII, R = $CONH_2$



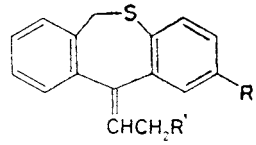
VIII, *n* = 0
IX, *n* = 1
X, *n* = 2

The first two steps of the synthesis of the acid *VIIIa* were carried out similarly like the analogous transformations in the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclo-

heptene series[23]. Vinyl bromide[24] was reacted with magnesium in tetrahydrofuran and the resulting Grignard ragent was subjected to treatment with dibenzo[*b*,*e*]-thiepin-11(6*H*)-one[2]; 11-vinyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*XIa*) resulted in a very good yield. Its reaction with hydrogen bromide in acetic acid proceeded under allylic rearrangement and afforded 11-(2-bromoethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIIa*). The following substitution reaction with potassium cyanide was carried out in a mixture of aqueous ethanol and tetrahydrofuran without heating and gave the nitrile *XIIIa*. Hydrolysis with a boiling solution of potassium hydroxide in aqueous ethanol afforded a mixture of geometrical isomers of *VIIIa*. Crystallization from benzene led to the homogeneous prevailing isomer to which on the basis of the IR and ^{1}H NMR spectra the (*E*)*trans*-configuration was assigned (corresponding to prothiadene (*Ia*)). Chromatography of the mother liquors on silica gel gave a different material with constant melting point, in which the IR spectrum indicated the prevailing presence of the (*Z*)*cis*-isomer. According to the ^{1}H NMR spectrum we are dealing here with a 1 : 1 mixture of the (*E*)- and (*Z*)-isomers of the acid *VIIIa*.



XI

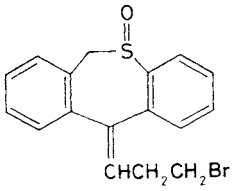


XII, R' = Br
XIII, R' = CN
XIV, R' = CH_2I

XV, R' = COCl
XVI, R' = $CONH_2$
XVII, R' = $COOC_2H_5$
XVIII, R' = $CON(CH_3)_2$

The successful preparation of the acid *VIIIa* was preceded by some unsuccessful or less successful synthetic attempts. In the first one we tried to use the Stobbe reaction[25]. While benzophenone reacts easily with diethyl succinate in the presence of sodium hydride[26], and affords the wanted product, our attempts to use dibenzo-[*b*,*e*]thiepin-11(6*H*)-one[2] as the ketone component under various conditions[25-27] led only to mixtures from which we did not succeed to isolate the wanted ester acid (the only characterized and crystalline product was identified as diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate[28]). The second attempt was directed to the oxidation of 11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin[11] to the corresponding aldehyde with pyridine N-oxide[29] in chloroform (for analogy, *cf.*[30,31]). A new product was isolated but identified by analysis and spectra as 11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin S-oxide (*XIX*); the only reaction was thus the shift of the oxygen atom from the nitrogen atom of the reagent to the sulfur atom of the substrate. For enhancing the reactivity of the halogen atom, the atom

of bromine in the starting compound was substituted by iodine by the Conant–Finkelstein reaction[32] (treatment with sodium iodide in boiling acetone) and the 11-(3-iodopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIVa*) was obtained. For avoiding the just encountered N—O to S—O exchange, dimethyl sulfoxide was used as the oxidation agent (analogy[33,34]); the crude product obtained did not give, however, by oxidation with silver oxide (*cf.*[35]) the wanted acid *VIIIa*. The last attempt used the Wittig reaction[36]: 2-carboxyethyltriphenylphosphonium chloride[37] was reacted in a mixture of tetrahydrofuran and dimethyl sulfoxide with sodium hydride and then with dibenzo[*b*,*e*]thiepin-11(6*H*)-one[2] (analogy[38]). Processing of the mixture and repeated crystallization of the crude acid obtained gave the acid *VIIIa* having the same melting point like the (*E*)-isomer. This is somewhat surprising because the Wittig reaction with tricyclic ketones like dibenzo[*b*,*e*]thiepin-11(6*H*)-one results normally in the (*Z*)-isomers as main product[39,40] (*cf.* also the preparation of the (*Z*)-isomer of prothiadene, described in this article).



XIX

The *trans*-acid ((*E*)-*VIIIa*) was oxidized with hydrogen peroxide in acetic acid at room temperature. After 60 min the reaction was complete and the product crystallized; it was identified as the S-oxide *IXa* (band at 1 010 cm^{-1} in the IR spectrum and the polarographic reduction). According to the ^1H NMR spectrum, the product is homogeneous, and the IR spectrum indicates (*E*)-configuration. Similar oxidation of the acid (*E*)-*VIIIa* with an excess of hydrogen peroxide in boiling acetic acid resulted in the sulfone *Xa* (in the IR spectrum bands between 1 123 and 1 309 cm^{-1}). It is also homogeneous and *trans*-configuration is again indicated by the IR spectrum. Both S-oxidated acids (*IXa*, *Xa*) are potential metabolites of prothiadene (*Ia*), the sulfoxide (*E*)-*IXa* being more likely.

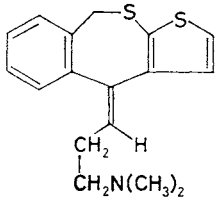
The acid (*E*)-*VIIIa* was transformed by treatment with thionyl chloride in boiling benzene to the acid chloride *XVa* which was subjected to reaction with a saturated solution of ammonia in chloroform; the amide (*E*)-*XVIa* was the product. A reaction of the chloride *XVa* with a mixture of ethanol and chloroform led to the ethyl ester (*E*)-*XVIIa*. Both compounds were crystalline and were characterized by spectra. Treatment of the acid chloride *XVa* with dimethylamine in benzene gave an oily product which was chromatographed on silica gel; the completely homogeneous dimethylamide *XVIIIa* was obtained in a high yield (analyzed as the chromato-

graphed oily product). Its reduction with lithium aluminium hydride in boiling ether gave the basic product in an almost theoretical yield; the hydrochloride was found to be identical with the authentic (*E*)-prothiadene (*Ia*) hydrochloride[5]. The conversion of the acid *VIIIa* to this product may be considered a correlation with a compound of established configuration on the double bond and thus a further proof of the (*E*)-configuration of the prevailing component of the acid *VIIIa*, obtained by the synthesis just described.

In the 2-methyl series, 2-methyldibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,20] was the starting compound, the synthesis of the acid *VIIIb* used similar reactions and proceeded *via* the tertiary alcohol *XIb*, the bromide *XIIb* and the nitrile *XIIIb*. The homogeneous acid *VIIIb*, obtained from the crude product by repeated crystallization, is considered the (*E*)-isomer *per analogiam* with the acid *VIIIa*. Oxidation of the acid *VIIIb* with hydrogen peroxide in acetic acid under analogous conditions like in series *a* gave the well characterized sulfoxide *IXb*, and the sulfone *XVb* crystallizing either from toluene or from ethanol as solvates with different melting points. The product obtained by crystallization from ethanol is considered a hemihydrate. Similarly like in series *a*, the acid *VIIIb* was transformed *via* the acid chloride *XVb* to the amide *XVIb*. Most of the compounds were characterized by spectra.

In the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene series, the 5-(2-bromoethylidene) derivative was known[23]. It was transformed to the nitrile *V* by reaction with potassium cyanide in dimethylformamide at room temperature. Alkaline hydrolysis afforded the acid *IV* whose mass, UV, IR and ^{1}H NMR spectra were recorded. The well characterized substance is thus available for comparison with the acid metabolite of amitriptyline (*II*) and nortriptyline (*III*) (*cf.*[19]). Similarly, like in the two preceding series, the acid *IV* was transformed *via* the acid chloride *VI* to the amide *VII*.

The attempt to prepare a similar potential acid metabolite of the antihistamine agent dithiadene, *i.e.* (*E*)-4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XX*) (refs[40–43]), failed in the second synthetic step. Thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[42] reacted with vinylmagnesium bromide in a mixture of



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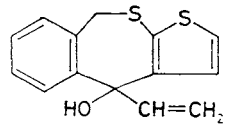
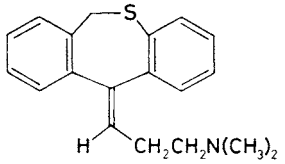


XXI

tetrahydrofuran and benzene and gave in a yield of 50% *XXI*. Its reaction with hydrogen bromide in acetic acid resulted, however, in a bromine-free amorphous and high-melting product which did not give the mass spectrum even after heating to 320°C. The work in this series was discontinued.

Because of the need of larger amounts of homogeneous (*Z*)- and (*E*)-isomers of prothiadene (*XXII* and *Ia*) and due to the fact that the present method for their preparation *via* the corresponding N-monodemethyl analogues[5] is not sufficiently efficient, we have now prepared the (*Z*)-isomer *XXII* using the Wittig method[36] in analogy to the procedure described for the synthesis of N,N-dimethyl-3-(6,11-dihydrodibenz[*b*,*e*]oxepin-11-ylidene)propylamine[39]. 3-Dimethylaminopropylidene triphenylphosphorane was generated by reaction of 3-dimethylaminopropyltriphenylphosphonium bromide hydrobromide[39] with n-butyllithium in a mixture of tetrahydrofuran and hexane and subjected *in situ* to treatment with dibenzo[*b*,*e*]thiepin-11(6*H*)-one[2]. Processing gave the crude base which was chromatographed on silica gel affording about 50% of the almost homogeneous compound *XXII*. Crystallization of the maleate gave a product containing exclusively the (*Z*)-compound (*cf.*[44,45]). *Via* the crystalline base[5] the hydrochloride of *XXII* was prepared[5]. For preparing the (*E*)-isomer *Ia*, the homogeneous (*E*)-N-methyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine[5] is a good starting material. It was not necessary to transform this compound to prothiadene (*Ia*) in two steps, *i.e.* formylation with chloral and the following reduction of the N-formyl compound with lithium aluminium hydride[5]. Reductive methylation with formaldehyde and formic acid in boiling water was used; the base thus obtained was transformed to the hydrochloride containing 99·6% of the (*E*)-isomer. Crystallization of the maleate is very efficient for removing the last traces of the (*Z*)-isomer.



XXII

The acids *IV*, *VIIIab*, *IXab* and *Xa* were tested for antiinflammatory and analgetic activity (methods, *cf.*[46,47]) in comparison with ibuprofen[48], used as the standard. The amides *VII* and *XVIab* were tested for anticonvulsant activity. Oral administration was used in all cases and the doses are given in mg/kg. In testing for the acute toxicity in female mice, compounds *IV*, *VII* and *XVIb* proved nontoxic in the dose of 500 mg/kg, and compounds *VIIIab*, *IXa*, *Xa* and *XVIa* were nontoxic in the dose of 1 000 mg/kg; ibuprofen in the dose of 1 000 mg/kg elicited the perishing of 10%

of the animals. For testing the antiinflammatory activity, three types of oedema in female rats were used, the tested compounds were administered in the dose of 100 mg/kg and the results are expressed as % of inhibition of the oedema ($^+$ means statistical significance). Carrageenan oedema: *IV*, 39$^+$; *VIIIa*, 16$^+$; *VIIIb*, 18$^+$; *IXa*, 26$^+$; *IXb*, 26$^+$; ibuprofen, 45$^+$. Adjuvant oedema: *VIIIa*, 33$^+$; *VIIIb*, 11; *IXa*, 32$^+$; *Xa*, 4; ibuprofen, 56$^+$. Kaolin oedema: *IV*, 10; ibuprofen, 55$^+$. For assesing the analgetic activity, the test of inhibition of the writhing syndrome in male mice[47] was used (the reaction was elicited by intraperitoneal injection of 0·7% acetic acid), ED_{50} (numbers in parentheses mean the number of animals protected from the nociceptive reaction and the number of animals in the group): *IV*, >100 (0/6); *VIIIa*, >200 (2/6); *VIIIb*, 200; *IXa*, >200 (1/6), *Xa*, >200 (2/6); ibuprofen, 194 mg/kg. The testing for anticonvulsant activity used the electroshock and pentetrazole seizures in mice[49]. In the doses given, the compounds were inactive in these tests. Electroshock: *VII*, 50; *XVIa*, 10; *XVIb*, 50; pentetrazole: *XVIb*, 50. Compound *XVIa* in high doses showed indication of central depressant action but in the dose of 50 mg/kg was inactive in the rotarod test in mice. In conclusion, the compounds tested had very low toxicity, were less active than ibuprofen in the inhibition of carrageenan oedema in rats, only compound *VIIIb* had analgetic activity comparable with that of ibuprofen, and the amides in the doses used were inactive as anticonvulsants.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa at room temperature or at 77°C. UV spectra (mostly in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (mostly 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 homogeneity of the compounds and the composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with Na_2SO_4, $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure in rotating evaporators.

11-(3-Bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5-Oxide (*XIX*)

A solution of 4·60 g 11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin[11] in 50 ml chloroform was added dropwise over 20 min to a stirred solution of 2·65 g pyridine N-oxide[29] in 50 ml chloroform at 40–50°C. The mixture was refluxed with stirring for 5 h; the starting compound was completely consumed (TLC). Under stirring and cooling the mixture was slowly treated with 80 ml 1M H_2SO_4 and stirred for 10 min. The separated chloroform layer was washed with water, solution of Na_2CO_3, and water, was dried and evaporated. The residue crystallized from benzene: 2·5 g (52%), m.p. 149–152°C. Analytical sample, m.p. 151–152°C (benzene). IR spectrum: 756, 766, 778 (4 adjacent Ar—H), 1 028, 1 037 (Ar—SO—R), 1 483, 1 555, 3 030, 3 045, 3 055 cm^{-1} (Ar). Polarographic reduction in 0·25M H_2SO_4 (towards a saturated calomel electrode) showed the reduction wave at $E_{1/2}$ −0·70 V corresponding to the sulfoxide. ^{1}H NMR

spectrum (at 60°C): δ 7·75 (m, 1 H, 4-H), 7·00—7·50 (m, 7 H, remaining ArH), 6·03 (t, J = 7·0 Hz, 1 H, C=CH), 4·69 and 4·38 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2SO$), 3·40 (t, J = 7·0 Hz, 2 H, CH_2Br), 2·62 (q, J = 7·0 Hz, 2 H, CH_2 in the middle of the propylidene chain). For $C_{17}H_{15}BrOS$ (347·3) calculated: 58·80% C, 4·35% H, 23·01% Br, 9·23% S; found: 58·63% C, 4·42% H, 23·30% Br, 9·23% S.

11-(3-Iodopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIVa*)

A solution of 6·6 g 11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin[11] in 150 ml acetone was added dropwise over 30 min to a stirred solution of 6·30 g NaI in 100 ml acetone and the mixture was stirred and refluxed for 20 h. After cooling, the solid was filtered off, the filtrate was evaporated *in vacuo*, and the residue distributed between chloroform and water. The organic layer was dried, evaporated, and the residue was crystallized from acetone; 5·80 g (77%), m.p. 150—154°C. Analytical sample, m.p. 153—154°C (acetone). UV spectrum: λ_{max} 232·5 nm (log ε 4·37), 305 nm (3·42), infl. 267 nm (3·95). IR spectrum: 730, 750, 761 (4 adjacent Ar—H), 1 481, 1 583, 3 040 (Ar), 1 630 cm^{-1} (conjugated C=C). ^1H NMR spectrum: δ 6·90—7·50 (m, 8 H, ArH), 5·88 (t, J = 7·0 Hz, 1 H, C=CH), 5·00 and 3·35 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·20 (t, J = 7·0 Hz, 2 H, CH_2I), 2·60 (m, 2 H, CH_2 in the middle of propylidene). For $C_{17}H_{15}IS$ (378·3) calculated: 53·98% C, 4·00% H, 33·54% I, 8·48% S; found: 54·47% C, 3·98% H, 33·26% I, 8·66% S.

11-Vinyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*XIa*)

Mg (23·9 g) under 30 ml tetrahydrofuran was activated with a grain of iodine and with 1·5 ml 1,2-dibromoethane and after the reaction was over, 10% of a solution of 104 g vinyl bromide[24] in 400 ml tetrahydrofuran was added (dry ice–ethanol condenser, nitrogen atmosphere). The reaction started immediately and the remaining part of the vinyl bromide solution was added dropwise under stirring at such a rate as to maintain the temperature of 58—62°C. The addition required about 1·5 h, the mixture was refluxed for 30 min in the bath of 65°C and cooled to 40°C. The dry ice condenser was substituted by a normal reflux condenser and over 1 h solution of 113·2 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[2] in 400 ml tetrahydrofuran was added dropwise under stirring (30—35°C). The mixture was allowed to stand overnight in a refrigerator and then decomposed under cooling (ice and NaCl) with a solution of 100 g NH_4Cl in 500 ml water. Benzene (500 ml) was added and the mixture was filtered, the aqueous layer was extracted with benzene and the benzene solutions were combined, dried, and evaporated. The residue was crystallized from a mixture of 230 ml benzene and 500 ml light petroleum; 116·1 g (91%) (including the product from the mother liquor), m.p. 129—132°C. Analytical sample, m.p. 130 to 132°C (benzene–hexane). UV spectrum: λ_{max} 261 nm (log ε 3·95). IR spectrum: 755, 765 (4 adjacent Ar—H), 940, 1 025 ($CH=CH_2$), 1 128 (R_3C-OH), 1 484, 1 563, 1 590, 3 060, 3 085 (Ar), 1 625 (C=C), 3 520 cm^{-1} (OH). ^1H NMR spectrum: δ 7·80 and 7·10 (2 m, 2 + 6 H, ArH), 6·48 (dd, J = 10·0; 17·0 Hz, 1 H, CH=), 5·34 (dd, J = 1·0; 10·0 Hz) and 5·08 (dd, J = 1·0; 17·0 Hz) (1 + 1 H, $=CH_2$), 4·88 and 3·53 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·18 (s, 1 H, OH). For $C_{16}H_{14}OS$ (254·4) calculated: 75·56% C, 5·55% H, 12·61% S; found: 75·74% C, 5·58% H, 12·43% S.

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

Grignard reagent was prepared similarly from 26·5 g Mg and 115 g vinyl bromide[24] in 230 ml tetrahydrofuran and was reacted with a solution of 133 g 2-methyldibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,20] in 400 ml tetrahydrofuran. Similar processing gave 73·3 g (50%) *XIb*, m.p. 144—146°C

(ethanol). IR spectrum: 761, 815, 891 (4 and 2 adjacent, and solitary Ar—H), 939, 971, 1 626 ($R_2C{=}CH_2$), 1 158, 1 162 ($R_3C{-}OH$), 1 486, 3 020, 3 050 (Ar), 3 430 cm^{-1} (OH). ^1H NMR spectrum: δ 7·80 (m, 1 H, 7-H), 7·68 (bs, 1 H, 1-H), 7·15 (m, 3 H, 8,9,10-H_3), 7·00 (d, J = 8·5 Hz, 1 H, 4-H), 6·85 (dd, J = 8·5; 2·0 Hz, 1 H, 3-H), 6·48 (dd, J = 17·0; 10·0 Hz, 1 H, CH=), 5·38 (dd, J = 10·0; 1·0 Hz) and 5·10 (dd, J = 17·0; 1·0 Hz) (1 + 1 H, $=CH_2$), 4·85 and 3·58 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·25 (s, 3 H, CH_3), 2·16 (s, 1 H, OH). For $C_{17}H_{16}OS$ (268·4) calculated: 76·08% C, 6·01% H, 11·95% S; found: 75·84% C, 6·12% H, 11·77% S.

4-Vinyl-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*XXI*)

Grignard reagent, prepared from 10·0 g Mg and 43·0 g vinyl bromide[24] in 200 ml tetrahydrofuran, was reacted similarly like in preceding cases with a solution of 40·0 g thieno[2,3-*c*]-2--benzothiepin-4(9*H*)-one[42] in 250 ml benzene. Similar processing gave 22·4 g (50%) *XXI*, m.p. 100—103°C (benzene–hexane). ^1H NMR spectrum: δ 7·70 (m, 1 H, 5-H), 7·25 (d, J = 5·5 Hz, 1 H, 2-H), 7·15 (m, 3 H, 6,7,8-H_3), 6·92 (d, J = 5·5 Hz, 1 H, 3-H), 6·25 (dd, J = 10·5; 18·0 Hz, 1 H, CH=), 5·21 (bd, J = 10·5 Hz) and 5·03 (bd, J = 18·0 Hz) (1 + 1 H, $=CH_2$), 4·70 and 3·70 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·45 (s, 1 H, OH). For $C_{14}H_{12}OS_2$ (260·4) calculated: 64·52% C, 4·65% H, 24·63% S; found: 64·21% C, 4·81% H, 24·20% S.

11-(2-Bromoethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIIa*)

A suspension of 31·8 g *XIa* in 370 ml acetic acid was stirred and treated at 15°C with 240 ml 15% solution of HBr in acetic acid over 30 min. The mixture was stirred at 15°C for 30 min, evaporated *in vacuo* and the rest of acetic acid was removed by addition of 100 ml xylene and evaporation *in vacuo*, which was repeated once more. The residue was crystallized from a mixture of 30 ml benzene and 70 ml hexane; 37·2 g (94%) *XIIa* (the second product obtained by processing of the mother liquor included), m.p. 109—111°C. Analytical sample, m.p. 112—113°C (cyclohexane). UV spectrum: λ_{max} 233 nm (log ε 4·31), 270 nm (3·87), 310 nm (3·41). IR spectrum (CS_2): 719, 727, 747, 763 (4 adjacent Ar—H; this part of the spectrum indicates the prevailing presence of the (*E*)-isomer), 2 920, 2 960 (CH_2), 3 020, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80—7·40 (m, 8 H, ArH), 6·15 (t, J = 8·0 Hz, 1 H, C=CH), 4·80 and 3·32 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·84 (m, 2 H, CH_2Br). For $C_{16}H_{13}BrS$ (317·3) calculated: 60·57% C, 4·13% H, 25·19% Br, 10·11% S; found: 60·91% C, 4·09% H, 25·10% Br, 10·03% S.

11-(2-Bromoethylidene)-2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIIb*)

A similar reaction of 30·0 g *XIb* in 330 ml acetic acid with 220 ml 15% HBr in acetic acid gave 27·5 g (74%) *XIIb*, m.p. 134—136°C (toluene–hexane). UV spectrum: λ_{max} 232 nm (log ε 4·33), 262 nm (3·92), 313 nm (3·39). IR spectrum: 765, 772, 800, 806, 865, 875, 884 (4 and 2 adjacent, and solitary Ar—H), 1 485, 1 572, 1 599, 3 005, 3 020, 3 040, 3 065 (Ar), 1 625 cm^{-1} (Ar—C=C). ^1H NMR spectrum: δ 6·80—7·40 (m, 7 H, ArH), 6·20 (t, J = 9·0 Hz, 1 H, C=CH), 4·80 and 3·35 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·88 (m, CH_2Br), 2·25 (s, 3 H, $ArCH_3$). For $C_{17}H_{15}BrS$ (331·3) calculated: 61·64% C, 4·56% H, 24·12% Br, 9·68% S; found: 61·71% C, 4·69% H, 24·38% Br, 9·74% S.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionitrile (*XIIIa*)

A stirred solution of 38·2 g *XIIa* in a mixture of 110 ml tetrahyrofuran and 80 ml ethanol was treated dropwise with a solution of 11·8 g KCN in 20 ml water. The temperature rose spontaneously to 40°C, and the mixture was stirred for 1·5 h at room temperature. It was evaporated

in vacuo, the residue was diluted with 200 ml water, and the mixture was extracted with dichloromethane. The extract was washed with water, dried and evaporated. The crude product was dissolved in 150 ml benzene, the solution was filtered through a layer of 30 g silica gel which was washed with 100 ml benzene. The filtrate was evaporated and the residue crystallized from a mixture of 40 ml hexane; 25·4 g (80%) *XIIIa*, m.p. 118–120°C. Analytical sample, m.p. 120 to 121°C (benzene–hexane). UV spectrum: λ_{max} 231 nm (log ε 4·32), 258 nm (3·93), 206 nm (3·50). IR spectrum (CS_2): 719, 728, 747, 764 (4 adjacent Ar—H; this part of the spectrum indicates the prevailing presence of the (*E*)-isomer), 2 250 (R—CN), 2 920, 2 960 (CH_2), 3 020, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90–7·40 (m, 8 H, ArH), 5·88 (t, J = 8·0 Hz, 1 H, C=CH), 4·75 and 3·45 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·95 (d, J = 8·0 Hz, 2 H, CH_2CN). For $C_{17}H_{13}NS$ (263·4) calculated: 77·53% C, 4·98% H, 5·32% N, 12·17% S; found: 77·87% C, 4·78% H, 5·14% N, 12·19% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionitrile (*XIIIb*)

A stirred solution of 27·5 g *XIIb* in 700 ml dimethylformamide was treated at 0–5°C with 14·0 g KCN, added in small portions. The mixture was stirred for 4 h under cooling (0–5°C) and 14 h at room temperature. It was then diluted with 500 ml water and extracted with toluene. The extract was dried and evaporated, and the residue was crystallized from toluene; 18·0 g (79%) *XIIIb*, m.p. 132–135°C. Analytical sample, m.p. 137–140°C (toluene–hexane). UV spectrum: λ_{max} 232 nm (log ε 4·33), 262 nm (3·92), 315 nm (3·40). IR spectrum: 761, 812, 880 (4 and 2 adjacent and solitary Ar—H), 1 484, 1 600, 3 020, 3 068 (Ar), 1 640 (Ar—C=C), 2 245 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·80–7·50 (m, 7 H, ArH), 5·95 (t, J = 7·0 Hz, 1 H, C=CH), 4·78 and 3·40 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·00 (d, J = 7·0 Hz, 2 H, CH_2CN), 2·28 (s, 3 H, $ArCH_3$). For $C_{18}H_{15}NS$ (277·4) calculated: 77·94% C, 5·45% H, 5·05% N, 11·56% S; found: 77·80% C, 5·68% H, 4·90% N, 11·56% S.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)propionitrile (*V*)

A solution of 33 g 5-(2-bromoethyliden)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (m.p. 108–109°C) (ref.[23]) in 700 ml dimethylformamide was stirred and treated at 5–10°C with 21·5 g KCN, added over 30 min in small portions. The mixture was stirred for 2 h at 5–10°C, for 24 h at room temperature, and heated to 60°C. After cooling the mixture was diluted with 750 ml water and extracted with toluene. Processing of the extract and crystallization of the crude product from toluene gave 20·5 g (76%) *V*, m.p. 139–140°C. Analytical sample, m.p. 144–147°C (toluene). UV spectrum: λ_{max} 239 nm (log ε 4·10). IR spectrum (KBr): 763, 779 (4 adjacent Ar—H), 1 484, 1 600, 3 025, 3 060, 3 090 (Ar), 1 635 (Ar—C=C), 2 245 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·18 (m, 8 H, ArH), 5·82 (t, J = 8·0 Hz, 1 H, C=CH), 3·12 (d, 2 H, CH_2CN), 2·50–3·50 (m, 4 H, $ArCH_2CH_2Ar$). For $C_{18}H_{15}N$ (245·3) calculated: 88·13% C, 6·16% H, 5·71% N; found: 88·18% C, 6·37% H, 5·49% N.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid (*VIIIa*)

A) A suspension of 26·8 g *XIIIa* in 80 ml ethanol was treated with a solution of 28 g KOH in 28 ml water and the mixture was refluxed for 3·5 h, cooled, diluted with 350 ml water, and washed with benzene. The aqueous solution was acidified with 150 ml 15% hydrochloric acid and extracted with dichloromethane. The extract was dried and evaporated. The residue was crystallized from 95 ml benzene; 22·0 g (78%) mixture of (*E*)- and (*Z*)-*VIIIa*, m.p. 150–170°C. Two further crystallizations from benzene afforded 11·5 g (41%) of constantly melting (*E*)-*VIIIa*,

m.p. 174—175°C. UV spectrum (diethyl ether): λ_{max} 230 nm (log ε 4·39), 260·5 nm (3·98), 303·5 nm (3·37). IR spectrum (CS_2): 722, 732, 747, 765 (4 adjacent Ar—H; this part of the spectrum resembles the corresponding part of the spectrum of *I*, and, therefore, the (*E*)-configuration is very likely), 923, 1 220, 1 287, 1 706, 2 540, 2 640, 2 720, infl. 3 200 (COOH), 3 020, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·25 (bs, 1 H, COOH), 6·80—7·40 (m, 8 H, ArH), 6·00 (t, J = = 7·0 Hz, 1 H, C=CH), 4·84 and 3·30 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·00 (d, J = = 7·0 Hz, 2 H, CH_2CO). For $C_{17}H_{14}O_2S$ (282·4) calculated: 72·31% C, 5·00% H, 11·36% S; found: 72·23% C, 5·02% H, 11·25% S.

The mother liquors were evaporated and the residue (8·6 g) was chromatographed on a column of 250 g silica gel. The elution was with benzene, benzene with 10% chloroform and 1 : 1 benzene--chloroform. From the middle fraction there was obtained 0·8 g substance melting at 137—141°C. Crystallization from a mixture of benzene and hexane gave a constantly melting product, m.p. 139—141°C, which was considered to be (*Z*)-*VIIIa*. ^1H NMR spectrum showed the product to be a 1 : 1 mixture of (*E*)- and (*Z*)-*VIIIa*. UV spectrum (diethyl ether): λ_{max} 230·5 nm (log ε 4·39), 258 nm (3·96), 304·5 nm (3·33). IR spectrum (CS_2): 747, 766 (4 adjacent Ar—H; resembles the spectrum of *XXII* and, therefore (*Z*)-*VIIIa* should be an important component), 925, 1 220, 1 384, 1 708, 2 540, 2 630, 2 720, infl. 3 200 (COOH), 3 020, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·00 (bs, 1 H, COOH), 6·80—7·30 (m, 8 H, ArH), 6·00 (t, J = 7·0 Hz, 0·5 C=CH of the (*E*)-isomer), 5·75 (t, J = 7·0 Hz, 0·5 C=CH of the (*Z*)-isomer), 4·84 and 3·30 (ABq, J = 13·0 Hz, 0·5 + 0·5 H of $ArCH_2S$ of the (*E*)-isomer), 4·80 (bd) and 3·41 (bd) (ABq, J = 13·0 Hz, 0·5 + 0·5 H of $ArCH_2S$ of the (*Z*)-isomer), 3·30 (d, J = 7·0 Hz, 1 H of CH_2CO of the (*Z*)-isomer), 3·00 (d, J = 7·0 Hz, 1 H of CH_2CO of the (*E*)-isomer). For $C_{17}H_{14}O_2S$ (282·4) calculated: 72·31% C, 5·00% H, 11·36% S; found: 71·87% C, 5·15% H, 11·30% S.

B) A solution of 5·6 g 2-carboxyethyltriphenylphosphorium chloride[37] in a mixture of 30 ml tetrahydrofuran and 30 ml dimethyl sulfoxide was added to a stirred suspension of 2·0 g 80% NaH (in oil) in 10 ml tetrahydrofuran (nitrogen atmosphere). This was followed by a solution of 3·4 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[2] in 30 ml tetrahydrofuran and 30 ml dimethyl sulfoxide, which was added over 1·5 h under external cooling. The mixture was stirred and cooled for 7 h, allowed to stand overnight in a refrigerator, diluted with 100 ml ether, and decomposed under stirring by treatment with 150 ml 10% NaOH (pH 9—10). The aqueous layer was separated, acidified with 1 : 1 dilute hydrochloric acid and extracted with ether. Processing of the extract gave 3·2 g crude product which was crystallized from benzene; 2·1 g (50%), m.p. 165—175°C. Further crystallization from ethanol gave the product melting at 172—174°C which corresponds to (*E*)-*VIIIa* (*cf.* under *A*).

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid (*VIIIb*)

XIIIb (30·0 g) was hydrolyzed with 31 g KOH in a mixture of 100 ml ethanol and 35 ml water similarly like in the preceding case under *A*. The refluxing of the mixture was prolonged to 6 h. Processing gave 19·5 g (61%) mixture of (*E*)-*VIIIb* and (*Z*)-*VIIIb*, m.p. 167—175°C. Repeated crystallization from toluene gave the homogeneous major component which is considered to be the (*E*)-isomer, m.p. 176—179°C. UV spectrum: λ_{max} 231 nm (log ε 4·37), 261 nm (4·00), 311 nm (3·67). IR spectrum: 761, 809, 881 (4 and 2 adjacent, and solitary Ar—H), 940, 1 218, 1 713, 2 620, 2 725, infl. 3 100 cm^{-1} (COOH). ^1H NMR spectrum: δ 11·40 (bs, 1 H, COOH), 6·80 to 7·40 (m, 7 H, ArH), 6·10 (t, J = 7·0 Hz, 1 H, C=CH), 4·88 and 3·38 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·08 (d, J = 7·0 Hz, 2 H, CH_2CO), 2·29 (s, 3 H, $ArCH_3$). For $C_{18}H_{16}O_2S$ (296·4) calculated: 72·95% C, 5·44% H, 10·82% S; found: 72·98% C, 5·61% H, 10·96% S.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)propionic Acid (*IV*)

A mixture of 14·0 g *V*, 50 ml ethanol, 14·5 g KOH and 17 ml water was refluxed for 3 h and processed similarly like in the preceding cases. There were obtained 10·2 g (66%) product melting at 123–127°C. Analytical sample, m.p. 131–133°C (toluene). Mass spectrum, *m/z* (%): 264 (M^+ corresponding to $C_{18}H_{16}O_2$, 30%), 219 (21), 205 (100), 204 (40), 203 (43), 202 (37), 191 (50), 91 (47), UV spectrum: λ_{max} 237 nm (log ε 4·12). IR spectrum: 756, 773 (4 adjacent Ar—H), 932, 1 223, 1 700, 2 540, 2 620, 2 735, infl. 3 100 (COOH), 1 484, 1 595, 3 000, 3 020, 3 050, 3 090 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·70 (bs, 1 H, COOH), 6·90–7·40 (m, 8 H, ArH), 6·00 (t, *J* = 8·0 Hz, 1 H, C=CH), 3·18 (d, 2 H, CH_2CO), 2·50–3·50 (bm, 4 H, $ArCH_2CH_2Ar$). For $C_{18}H_{16}O_2$ (264·3) calculated: 81·79% C, 6·10% H; found: 81·59% C, 6·12% H.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid S-Oxide (*IXa*)

(*E*)-*VIIIa* (1·4 g) was dissolved in 15 ml acetic acid at 60°C, the solution was cooled to 20°C and treated with 0·57 g 30% H_2O_2. After 60 min standing at room temperature, the product crystallized. The mixture was allowed to stand overnight, filtered, the product was washed with 10 ml ethanol and 40 ml hexane, and dried *in vacuo*; 1·3 g (88%), m.p. 228–229°C. Analytical sample, m.p. 228–230°C (aqueous ethanol). UV spectrum: inflexes at 240 nm (log ε 4·12) and 271 nm (3·63). IR spectrum: 741, 759, 777 (4 adjacent Ar—H; the intensity of these bands indicates the (*E*)-configuration), 900, 1 182, 1 721, 2 480, 2 560, 2 670, infl. 3 150 (COOH), 1 010 (Ar—SO), 3 030, 3 070 cm^{-1} (Ar). Polarographic reduction (saturated calomel electrode) in 0·25M H_2SO_4 in 20% ethanol proceeded at $E_{1/2}$ −0·63 V (SO). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·00–8·00 (8 H, ArH), 6·20 (t, *J* = 7·0 Hz, 1 H, C=CH), 4·50 (bs, 2 H, $ArCH_2S$), 3·00 (d, *J* = 7·0 Hz, 2 H, CH_2CO). For $C_{17}H_{14}O_3S$ (298·4) calculated: 68·44% C, 4·73% H, 10·75% S; found: 68·09% C, 4·88% H, 10 72% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid S-Oxide (*IXb*)

Similar oxidation of 1·1 g *VIIIb* with 0·3 ml 30% H_2O_2 in 15 ml acetic acid gave 1·05 g (90%) *IXb*, m.p. 211–214°C (aqueous ethanol). UV spectrum: infl. at 245 nm (log ε 4·07). IR spectrum: 762, 818, 869 (4 and 2 adjacent, and solitary Ar—H), 900, 1 182, 1 718, 2 480, 2 560, 2 674 (COOH), 1 010 (Ar—SO), 1 590, 3 020, 3 060 cm^{-1} (Ar). Polarographic reduction (saturated calomel electrode) in 0·1M HCl in 10% ethanol proceeded at $E_{1/2}$ −0·635 V (SO). For $C_{18}H_{16}O_3S$ (312·4) calculated: 69·22% C, 5·16% H, 10·26% S; found: 68·79% C, 5·22% H, 10·05% S.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid S,S-Dioxide (*Xa*)

(*E*)-*VIIIa* (0·7 g) was dissolved in 6·5 ml acetic acid at 60°C, the solution was cooled to 20°C and treated with 0·8 g 30% H_2O_2. The mixture was stirred, refluxed for 3 h and evaporated *in vacuo*. The residue was triturated with 5 ml benzene and crystallized; 0·7 g (89%), m.p. 197 to 199°C (ethanol–benzene). UV spectrum: inflexes at 236 nm (log ε 4·07) and 275 nm (3·35). IR spectrum: 719, 747, 757, 776, 779, 797 (4 adjacent Ar—H; the relative intensities of the bands at 776 and 747 cm^{-1}, when compared with the spectrum of *Ia*, indicate the (*E*)-configuration), 920, 1 230, 1 700, 2 530, 2 615, 2 640, 2 725, infl. 3 150 (COOH), 1 123, 1 150, 1 300, 1 309 cm^{-1} (SO_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·00–8·00 (m, 8 H, ArH), 6·21 (t, *J* = 7·0 Hz, 1 H, C=CH), 5·11 and 4·72 (ABq, *J* = 13·0 Hz, 1 + 1 H, $ArCH_2SO_2$), 3·00 (d, *J* = 7·0 Hz, 2 H, CH_2CO). For $C_{17}H_{14}O_4S$ (314·4) calculated: 64·95% C, 4·49% H, 10·20% S; found: 64·42% C, 4·60% H, 10·27% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionic Acid S,S-Dioxide (*Xb*)

Similar oxidation of 1·0 g *VIIIb* in 25 ml acetic acid with 0·5 ml 30% H_2O_2 gave a crude product which crystallized from ethanol as the hemihydrate, m.p. 194–198°C. For $C_{18}H_{16}O_4S + 0{\cdot}5\ H_2O$ (337·4) calculated: 64·08% C, 5·08% H; found: 64·00% C, 4·95% H.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionyl Chloride (*XVa*)

A suspension of 2·85 g (*E*)-*VIIIa* in 10 ml benzene was stirred and treated over 10 min with a solution of 1·5 g $SOCl_2$ in 2 ml benzene, added dropwise. The mixture was refluxed for 3 h and evaporated *in vacuo*. The residue was dissolved in a boiling mixture of 1 ml benzene and 3 ml hexane, the product crystallized by cooling; 2·9 g (97%), m.p. 72–76°C. UV spectrum: λ_{max} 230 nm (log ε 4·40), 305 nm (3·41), infl. 261 nm (3·95). IR spectrum: 730, 757, 767 (4 adjacent Ar—H), 1 489, 1 554, 1 588, 3 020, 3 065 (Ar), 1 798 cm^{-1} (RCOCl); in CS_2: 730, 737, 750, 768 cm^{-1} (the bands at 730, 750 and 768 cm^{-1} correspond to the (*E*)-isomer; the weak band at 737 cm^{-1} indicates the possibility of the presence of a small amount of the (*Z*)-isomer). ^1H NMR spectrum: δ 6·90–7·40 (m, 8 H, ArH), 6·00 (t, J = 7·0 Hz, 1 H, C=CH), 4·83 and 3·33 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·50 (d, J = 7·0 Hz, 2 H, CH_2CO). For $C_{17}H_{13}ClOS$ (300·8) calculated: 67·88% C, 4·36% H, 11·79% Cl, 10·66% S; found: 68·32% C, 4·56% H, 11·50% Cl, 10·99% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionyl Chloride (*XVb*)

A similar reaction of 6·5 g *VIIIb* with 3·6 g $SOCl_2$ in 35 ml benzene gave 6·45 g (94%) product melting at 108–110°C (toluene–hexane). UV spectrum: λ_{max} 228 nm (log ε 4·38), 260 nm (3·96), 309 nm (3·39). IR spectrum: 765, 814, 839, 895 (4 and 2 adjacent, and solitary Ar—H), 1 598, 3 025, 3 075 (Ar), 1 795 cm^{-1} (RCOCl). For $C_{18}H_{15}ClOS$ (314·8) calculated: 68·67% C, 4·80% H, 11·26% Cl, 10·18% S; found: 68·64% C, 4·68% H, 11·05% Cl, 9·94% S.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)propionyl Chloride (*VI*)

A suspension of 6·0 g *IV* in 30 ml benzene was stirred and treated at 50°C with a solution of 3·75 g $SOCl_2$ in 7 ml benzene, added dropwise over 20 min. The mixture was refluxed for 5 h and processed similarly like in the preceding experiments. Crystallization of the crude product from a mixture of 5 ml benzene and 10 ml hexane gave 5·3 g (83%) *VI*, m.p. 69–73°C. Analytical sample, m.p. 74–76°C (benzene–hexane). UV spectrum: λ_{max} 238 nm (log ε 4·14). IR spectrum: 738, 762, 778 (4 adjacent Ar—H), 1 485, 1 600, 3 000, 3 015, 3 060, 3 070 (Ar), 1 790 cm^{-1} (RCOCl). For $C_{18}H_{15}ClO$ (282·8) calculated: 76·46% C, 5·35% H, 12·54% Cl; found: 76·08% C, 5·32% H, 12·18% Cl.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionamide (*XVIa*)

A solution of 7·5 g *XVa* in 30 ml chloroform was slowly added to a stirred solution of 6·0 g NH_3 in 20 ml chloroform at the temperature bellow 10°C. The mixture was kept at this temperature for 1 h and at room temperature for 3 h. It was then washed with water, dried and evaporated. The residue was crystallized from ethanol; 4·5 g (64%), m.p. 181–184°C. UV spectrum: λ_{max} 231 nm (log ε 4·37), 304·5 nm (3·45), infl. 260 nm (3·97). IR spectrum: 739, 753, 770 (4 adjacent Ar—H), 1 487, 1 610, 3 025, 3 055, 3 070 (Ar), 1 621 (Ar—C=C), 1 660 ($CONH_2$), 3 170, 3 285, 3 425 cm^{-1} (NH_2); in CS_2: 734, 748, 768 cm^{-1} (these bands indicate the prevalency of the (*E*)-isomer). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·70–7·50 (m, 10 H, ArH and $CONH_2$),

6·09 (t, J = 7·0 Hz, 1 H, C=CH), 4·80 and 3·62 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·80 (m, 2 H, CH_2CO). For $C_{17}H_{15}NO_5$ (281·4) calculated: 72·57% C, 5·37% H, 4·98% N, 11·39% S; found: 72·81% C, 5·62% H, 4·77% N, 11·55% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionamide (*XVIb*)

Similar reaction of 6·5 g *XVb* and 6·5 g NH_3 in 55 ml chloroform gave 3·5 g (57%) *XVIb*, m.p. 210–211°C (methanol). IR spectrum (KBr): 760, 801, 888 (4 and 2 adjacent, and solitary Ar—H), 1 619, 1 648 ($CONH_2$), 2 850, 2 920 (C—H), 3 400 cm^{-1} (NH_2). ^1H NMR spectrum (C^2H_3.SOC^2H_3): δ 6·80–7 50 (m, 7 H, ArH), 6 05 (t, J = 7·0 Hz, 1 H, C=CH), 4·80 and 3·60 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·80 (m, 2 H, CH_2CO), 2·24 (s, 3 H, $ArCH_3$). For $C_{18}H_{17}$.NOS (295·4) calculated: 73 19% C, 5·80% H, 4·74% N, 10·85% S; found: 72·67% C, 5·71% H, 4·73% N, 10·65% S.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)propionamide (*VII*)

Similar reaction of 5·3 g *VI* with 4·5 g NH_3 in 40 ml chloroform gave 2·3 g (47%) *VII*, m.p. 148–150°C (ethanol). UV spectrum: λ_{max} 237 nm (log ε 4·15). IR spectrum: 744, 761, 778 (4 adjacent Ar—H), 1 481, 1 610, 3 055 (Ar), 1 650 ($CONH_2$), 3 110, 3 280, 3 410 cm^{-1} (NH_2). ^1H NMR spectrum: δ 7·10 (m, 8 H, ArH), 6·10 and 5·50 (2 bs, 1 + 1 H, $CONH_2$), 6·00 (t, J = = 7·0 Hz, 1 H, C=CH), 3·10 (bs, 4 H, $ArCH_2CH_2Ar$), 3·00 (d, J = 7·0 Hz, 2 H, CH_2CO). For $C_{18}H_{17}NO$ (263·3) calculated: 82·10% C, 6·51% H, 5·32% N; found: 81·97% C, 6·96% H, 5·15% N.

Ethyl 3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionate (*XVIIa*)

A stirred solution of 8·0 g *XVa* in 50 ml chloroform was cooled and treated dropwise with 10 ml ethanol. The mixture was stirred for 2 h at room temperature, washed with water, dried and evaporated. The residue was crystallized from ethanol; 8·0 g (97%) *XVIIa*, m.p. 92–94°C. Mass spectrum, m/z (%): 310 (M^+ corresponding to $C_{19}H_{18}O_2S$, 20%), 237 (15), 235 (16), 223 (100), 203 (60). UV spectrum: λ_{max} 230 nm (log ε 4·45), infl. at 256 nm (4·00) and 302 nm (3·49). IR spectrum: 760, 771 (4 adjacent Ar—H), 1 189, 1 725 (RCOOR'), 1 489, 1 586 cm^{-1} (Ar); in CS_2: 732, 751, 769 cm^{-1} (corresponds to the (*E*)-isomer). ^1H NMR spectrum: δ 6·90–7·40 (m, 8 H, ArH), 6·10 (t, J = 7·0 Hz, 1 H, C=CH), 4·90 and 3·32 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 4·12 (q, J = 7·0 Hz, 2 H, CH_2O), 3·00 (d, J = 7·0 Hz, 2 H, CH_2CO), 1·22 (t, J = = 7·0 Hz, 3 H, CH_3). For $C_{19}H_{18}O_2S$ (310·4) calculated: 72·57% C, 5·85% H, 10·33% S; found: 73·03% C, 5·81% H, 10·28% S.

N,N-Dimethyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propionamide (*XVIIIa*)

A solution of 2·9 g *XVa* in 10 ml benzene was added dropwise over 10 min to a stirred and cooled (0–5°C) solution of 4·5 g dimethylamine in 20 ml benzene. The mixture was stirred for 10 min, refluxed for 10 min, cooled, washed with 50 ml water, 25 ml 2% hydrochloric acid, 25 ml 2% $NaHCO_3$ and water, dried, and evaporated. The residue (3·2 g) was chromatographed on 25 g silica gel. Benzene eluted the impurities and chloroform eluted 3·0 g (100%) of the oily product (homogenous according to TLC). This product was used for the reduction. However, the elemental analysis was not satisfactory. For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N, 10·36% S; found: 74·72% C, 6·42% H, 4·05% N, 9·82% S.

(*E*)-N,N-Dimethyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (*I*)

A) A solution of 2·6 g *XVIIIa* in 15 ml ether was added over 15 min to a stirred suspension of 0·5 g $LiAlH_4$ in 20 ml ether and the mixture was refluxed for 4 h. After cooling, the mixture was decomposed by successive addition of 0·5 ml water, 0·5 ml 15% NaOH and 1·5 ml water. The solid was filtered off, washed with ether, the filtrate was dried and evaporated. The residue (2·5 g) was dissolved in 100 ml ethanol, the solution was acidified with a solution of HCl in ether, and 35 ml ether were added. The precipitated hydrochloride was filtered, washed with ether, and dried *in vacuo*; 2·4 g (86%), m.p. 224–227°C. Crystallization from a mixture of ethanol and ether raised the melting point to 225–229°C (ref.[5], m.p. 226–227°C). A sample of the hydrochloride was treated with NH_4OH and the base was extracted with dichloromethane. Processing of the extract gave the base melting at 52–54°C (ref.[5], m.p. 53–54°C).

B) (*E*)-N-Methyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine[5] (5·8 g) was suspended in 11 ml water, 5·3 ml 85% formic acid were added and the mixture was heated as to get a clear solution. 35% Formaldehyde (3·0 ml) was added and the mixture was refluxed for 18 h. It was diluted with 40 ml water, made alkaline under cooling with 40% NaOH, and the base was extracted with benzene. Processing of the extract gave 5·7 g (94%) oily base which is homogeneous ^{1}H NMR spectrum: δ 6·80–7·40 (m, 8 H, ArH), 5·92 (bt, J = 6·0 Hz, 1 H, C=CH), 4·95 (bd) and 3·34 (bd) (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·20 (m, 4 H, NCH_2CH_2), 2·14 (s, 6 H, $N(CH_3)_2$). By treatment with HCl in ethanol–ether, the base was transformed to the hydrochloride which crystallized from a mixture of 25 ml ethanol and 8 ml ether; 5·3 g, m.p. 227–229°C. The compound is identical with the hydrochloride, obtained under *A*, and according to gas chromatography, it contains 99·5% (*E*)-isomer.

Hydrogen maleate, m.p. 136–138°C (ethanol). For $C_{23}H_{25}NO_4S$ (411·5) calculated: 67·13% C, 6·12% H, 3·40% N, 7·79% S; found: 67·49% C, 6·24% H, 3·46% N, 7·88% S.

(*Z*)-N,N-Dimethyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (*XXII*)

A suspension of 357 g 3-dimethylaminopropyltriphenylphosphonium bromide hydrobromide[39] in 1 l tetrahydrofuran was stirred under nitrogen and treated under cooling (20–28°C) over 30 min with 92·8 g n-butyllithium in hexane (a 10% solution), added dropwise. The mixture was stirred for 30 min at 25°C, heated for 15 min to 55°C, cooled to 20°C, and treated over 30 min with a solution of 132 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[2] in 300 ml tetrahydrofuran; the temperature was maintained at 23–28°C. The mixture was stirred for 10 h at room temperature, decomposed with 150 ml water (stirring and cooling) and 1 l 5% hydrochloric acid, diluted with 750 ml water, and washed with toluene. The aqueous acid layer was made alkaline with 1·25 l NH_4OH and the bases were extracted with dichloromethane. The extract was washed with water, allowed to stand overnight with K_2CO_3 and charcoal, filtered, and evaporated. The residue (231 g) was dissolved in a 1 : 3 mixture of chloroform and benzene and chromatographed on a column of 1·7 kg silica gel. Elution with 1 : 1 chloroform–benzene, chloroform with 20% benzene, and finally chloroform with 2% methanol and 5% chloroform saturated with NH_3 gave an inhomogeneous product which was crystallized from a mixture of 200 ml benzene and 50 ml heptane; 85 g (49%) almost pure *XXII*, m.p. 87·5–92°C. For further purification the base was transformed to the hydrogen maleate which was recrystallized from ethanol to the constant melting point 153–155°C. For $C_{23}H_{25}NO_4S$ (411·5) calculated: 67·13% C, 6·12% H, 3·40% N, 7·79% S; found: 67·07% C, 5·92% H, 3·31% N, 7·94% S.

This salt was decomposed with NH_4OH and the pure base was obtained by extraction with ether, m.p. 91–92·5°C (heptane) (ref.[5], m.p. 91–93°C). The hydrochloride, obtained from this base, melted at 215–217°C (ethanol–ether) (ref.[5], m.p. 214–216°C); according to gas chromato-

graphy 100% of the (*Z*)-isomer. ^{1}H NMR spectrum of the base: δ 6·90—7·30 (m, 8 H, ArH), 5·63 (bm, 1 H, C=CH), 4·85 (vbd) and 3·40 (vbd) (ABq, 1 + 1 H, $ArCH_2S$), 2·40 (m, 4 H, NCH_2CH_2), 2·19 (s, 6 H, $N(CH_3)_2$). Following argumentation was used for the interpretation of the ^{1}H NMR spectra of *Ia* and *XXII* (and also of the isomeric *VIIIa*) (*cf.*[40,50]). The position of substituents on the exocyclic double bond influences the rate of inversion of the protons of the CH_2 group in position 6. In (*E*)-isomers, the bulky side chains interact with this CH_2 group and decrease the rate of the inversion. The barriers of inversion and the coalescence temperatures are higher with the (*E*)-isomers and lower with the (*Z*)-isomers. From the temperature-dependent spectra, the following barriers were calculated: *Ia*, 72 588 J/mol (coalescence temperature about 80°C); *XXII*, 68 266 J/mol (coalescence temperature about 60°C). At room temperature the CH_2 group of the (*E*)-isomer appears as a system of two doublets while in the case of the (*Z*)--isomer (with a higher rate of inversion) it appears as two flat signals. The second point enabling the differentiation of the isomers are the signals of the olefinic protons. In (*Z*)-isomers, these protons are more shielded by the aromatic ring C than the corresponding protons of the (*E*)-isomers by the aromatic ring A.

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