

N-SUBSTITUTED DERIVATIVES OF 6,11-DIHYDRODIBENZO[*b, e*]-THIEPIN-11-AMINE AND RELATED COMPOUNDS; SYNTHESIS AND PHARMACOLOGICAL SCREENING

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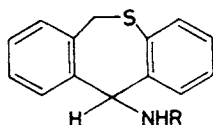
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Reactions of N-(6,11-dihydrodibenzo[*b, e*]thiepin-11-yl)chloroacetamide (*II*) with dimethylamine, morpholine, and 2-(1-piperaziny)ethanol afforded the amino amides *III*–*V*. Substitution reactions of 11-chloro-6,11-dihydrodibenzo[*b, e*]thiepin with ethylenediamine and N,N-dimethylethylenediamine gave the diamines *VI* and *VII*. 6,11-Dihydrodibenzo[*b, e*]thiepin-11-amine (*I*) was treated with ethyl chloroacetate and ethyl 2-bromopropionate to give the amino esters *X* and *XI* which were transformed on the one hand to the acids *VIII* and *IX*, and to the amides *XII* and *XIII* on the other. (6,11-Dihydrodibenzo[*b, e*]thiepin-11-yl)methylamine (*XVIa*) and (10,11-dihydro-5*H*-dibenzo[*a, d*]cycloheptene-5-yl)methylamine (*XVIIb*) were transformed via the chloroacetamides *XVIIa* and *XVIIb* to the (4-methyl-1-piperaziny)acetamides *XVa* and *XVb*. Compound *V* showed local anaesthetic and antiarrhythmic activity, the diamine *VII* had antihistamine and antiserpine effects, the amide *XII* was found to be an anticonvulsant, and the piperazines *XVa* and *XVb* inhibited effectively the formation of the indomethacin-induced gastric ulcers in rats.

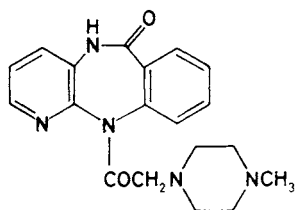
In connection with the preparation of a series of carbamates and ureas, derived from 6,11-dihydrodibenzo[*b, e*]thiepin-11-amine (*I*), as potential anticonvulsant agents, we carried out an efficient synthesis of *I* (ref.¹) which has now been used as starting material for the synthesis of some N-substituted derivatives as further potential neurotropic and cardiovascular agents. In the first line, the N-(aminoacyl) derivatives *III*–*V* were prepared via the known chloroacetamide *II* (ref.²). Reactions of *II* with potassium iodide in boiling acetone (cf. ref.³) and the following treatment with an excess of dimethylamine gave *III* in theoretical yield. The base was characterized by spectra and converted to the hydrochloride. The substitution reaction of *II* with an excess of morpholine was carried out in boiling toluene; *IV* was obtained and characterized similarly like in the case of *III*. Reaction of *II* with excessive 2-(1-piperaziny)ethanol in boiling chloroform gave the oily base *V* which was converted to the bis(hydrogen maleate).

As analogues of the antiulcer and antisecretory agent pirenzepine (*XIV*) (ref.⁴), *XVa* and *XVb* were prepared. The starting (6,11-dihydrodibenzo[*b, e*]thiepin-11-yl)-methylamine (*XVIa*) (ref.⁵) has now been obtained by reduction of 6,11-dihydrodi-

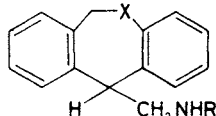


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| I, R = H | VIII, R = CH ₂ COOH |
| II, R = COCH ₂ Cl | IX, R = $\begin{array}{c} \text{—CHCOOH} \\ \\ \text{CH}_3 \end{array}$ |
| III, R = COCH ₂ N(CH ₃) ₂ | X, R = CH ₂ COOC ₂ H ₅ |
| IV, R = COCH ₂ N $\begin{array}{c} \text{O} \\ \text{O} \end{array}$ | XI, R = $\begin{array}{c} \text{—CHCOOC}_2\text{H}_5 \\ \\ \text{CH}_3 \end{array}$ |
| V, R = COCH ₂ N $\begin{array}{c} \text{O} \\ \text{O} \end{array}$ NCH ₂ CH ₂ OH | XII, R = CH ₂ CONH ₂ |
| VI, R = CH ₂ CH ₂ NH ₂ | XIII, R = $\begin{array}{c} \text{—CHCONH}_2 \\ \\ \text{CH}_3 \end{array}$ |
| VII, R = CH ₂ CH ₂ N(CH ₃) ₂ | |

benzo[*b,e*]thiepin-11-carbonitrile⁶ with aluminium hydride (from lithium aluminium hydride and aluminium chloride) in a mixture of ether and tetrahydrofuran. The analogous (10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-yl)methylamine (*XVIb*) was prepared similarly: 5-Chloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene⁷ was treated with trimethylsilyl cyanide⁸ in dichloromethane in the presence of stannic chloride (analogy of cyanation of tertiary alkyl chlorides^{9,10}) and gave 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-carbonitrile (for different procedures of preparation, cf. refs^{11,12}). Its reduction to *XVIb* according to Humber¹³ used aluminium hydride. Both amines *XVIa* and *XVIb* were treated with chloroacetyl chloride in benzene in the presence of *N,N*-dimethylacetamide at 50°C (method¹⁴) which resulted in *XVIIa* and *XVIIb*. The final substitution reactions of *XVIIa* and *XVIIb* with 1-methylpiperazine were carried out in boiling chloroform and gave *XVa* and *XVb* which were converted to dihydrochlorides.



XIV



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| XV, R = COCH ₂ N $\begin{array}{c} \text{O} \\ \text{O} \end{array}$ NCH ₃ |
| XVI, R = H |
| XVII, R = COCH ₂ Cl |

In formulae XV - XVII: *a*, X = S *b*, X = CH₂

Reactions of 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin¹⁵ with ethylenediamine and *N,N*-dimethylethylenediamine in boiling chloroform gave the diamines *VI* and *VII*; oily bases were converted to salts. (Benzhydrylamino)acetic acid and its substitution derivatives were described as anti-inflammatory agents¹⁶. We have now prepared two similar 6,11-dihydrodibenzo[*b,e*]thiepin derivatives *VIII* and *IX* as their cyclic analogues. The amine *I* was reacted in boiling toluene with an excess of ethyl chloroacetate or ethyl 2-bromopropionate in the presence of potassium carbonate or sodium carbonate. The reactions proceeded very slowly and requested rather long reaction time (30–45 h); they afforded *X* and *XI* in reasonable yields. Hydrolysis of *X* and *XI* to the acids *VIII* and *IX* was carried out with sodium hydroxide in boiling aqueous methanol. The acid *IX* was obtained as a 2 : 1 solvate with ethanol and its identity was confirmed by the mass spectrum. Some acids of the type of *VIII*, especially with a longer alkylene chain between NH and COOH, were described^{17–19} as stimulant, antidepressant, antihistamine, analgesic, and antitussive agents²⁰. Our esters *X* and *XI* were transformed to the amides *XII* and *XIII* by heating with liquid ammonia in methanol to 135°C.

The compounds prepared were pharmacologically tested, mostly in the form of salts, described in the Experimental. Acute toxicity in mice, LD₅₀ (in mg/kg) on oral administration: *VI*, 1 000; *VII*, 238; *VIII*, >1 000; *IX*, >1 000; *X*, >1 000; *XI*, >1 000; *XII*, >1 000; *XIII*, 940; *XVa*, 152; *XVb*, 612; LD₅₀ (mg/kg) on i.v. administration: *III*, 40; *IV*, 40; *V*, 100; *VI*, 25. Doses (D in mg/kg) used in the general pharmacological screening: *III*, 8 i.v.; *IV*, 8 i.v.; *V*, 20 i.v.; *VI*, 200 p.o.; *VII*, 100 p.o. Compound *III* was considered an analogue of the antidepressant agent hydrothiadene²¹ and was, therefore, tested for antireserpine activity (ptosis and hypothermia in mice): proved inactive at the dose D. In concentrations of 0.1–0.5% it showed activity in the test of corneal anaesthesia in rabbits (more active than trimecaine). In concentrations of 1–10 µg/ml it had spasmolytic activity on the isolated rat duodenum towards contractions elicited by acetylcholine as well as by barium chloride. Approximately same spasmolytic activity was shown by *IV*. This compound showed also anticonvulsant effects against pentetrazole in mice (ED = 10–40 mg/kg orally). Compound *V* in the concentration of 0.1–0.5% had local anaesthetic effect in the test of infiltration anaesthesia in guinea-pigs. In doses of 10–20 mg/kg i.v. it brought about antiarrhythmic effect in rats (these doses prolonged with statistical significance the latency of ventricular extrasystoles elicited with aconitine; intensity of the effect between those of quinidine and procainamide). In the test following the prolongation of the refractory phase of the electrically stimulated rabbit heart atria, the antiarrhythmic concentration was $2.3 \cdot 10^{-5} \text{ mol l}^{-1}$ (for comparison the effective concentrations (in mol l⁻¹) of some standard antiarrhythmic agents are given: trimecaine, $1 \cdot 10^{-7}$; metipranolol, $1.6 \cdot 10^{-5}$; propranolol, $2.6 \cdot 10^{-5}$; quinidine, $4.7 \cdot 10^{-5}$; procainamide, $3.0 \cdot 10^{-4}$). It is necessary to note that our colleagues² found effective antiarrhythmics in the series of analogous sulfones with

special emphasis on 11-(diethylaminoacetamido)-6,11-dihydrodibenzo[*b,e*]thiepin 5,5-dioxide hydrogen fumarate (VÚFB-14 524) (refs^{22,23}).

The diamines *VI* and *VII* showed some antireserpine and antihistamine effects: *VI* antagonized significantly the reserpine-induced ptosis and hypothermia in mice at the dose *D*; *VII* at 10 mg/kg orally inhibited significantly the reserpine hypothermia in mice but at the dose of 50 mg/kg did not significantly influence the ulcerogenic effect of reserpine in rats. Antihistamine activity: *VII* in the oral dose of 2 mg/kg protected 10% and in the dose of 10 mg/kg 90% of the guinea-pigs from the lethal effect of a standard dose of histamine, administered intrajugularly. In the test of histamine aerosol in guinea-pigs, the oral dose of 10 mg/kg protected 80% of the animals and 2 mg/kg 40% from the bronchospasm. *VI* at the dose *D* increased the motor activity in mice (stimulant effect). *VII* elicited ataxia in the rotarod test in mice; ED₅₀ = 43 mg/kg orally (maximum in 30 min after the administration). This compound showed also a mild mydriatic effect in mice (oral doses of 50 to 100 mg/kg).

Compounds *VIII*–*XII* were tested for anti-inflammatory activity using three types of oedema in female rats (carrageenan, adjuvant, and kaolin oedema) and ibuprofen as the standard. They were administered in oral doses of 100 and 200 mg/kg and the inhibition of the oedema was registered. Only the amide *XII* showed significant inhibition of the adjuvant oedema in the dose of 200 mg/kg (there was also some inhibition of the other two types of oedema but this was not significant) (ibuprofen had significant effects at 100 mg/kg in all three oedema types). Compounds *VIII*, *IX*, and *X* had weak and insignificant activity at 200 mg/kg in the carrageenan oedema.

The amides *XII* and *XIII* were tested as potential anticonvulsant agents in mice (oral administration). In the electroshock test, *XII* had full anticonvulsant effect (in 100% animals) in the dose of 100 mg/kg (the dose of 10 mg/kg was inactive), PD₅₀ = 43 mg/kg; *XIII*, PD₅₀ = 204 mg/kg. In the test of pentetrazole convulsions, *XII* had the PD₅₀ = 50 mg/kg; *XIII* was inactive still at 800 mg/kg. *XIII* had mild incoordinating effect in the rotarod test in mice, ED₅₀ = 275 mg/kg.

Methylpiperazinoacetamides *XVa* and *XVb* were tested as potential antiulcer agents (for methods, cf. ref.²⁴). The indomethacin-induced gastric lesions in rats were used as the model. Both compounds inhibited the formation of these lesions very effectively (ED₅₀ in mg/kg orally): *XVa*, 21.4; *XVb*, 41.2 (for pirenzepine (*XIV*), used as the standard, ED₅₀ = 32.7 mg/kg). On the other hand, their anticholinergic activity, assessed by means of the mouse mydriasis test, is weak. In the oral dose of 100 mg/kg, *XVa* was active in 90% animals, but in the dose of 50 mg/kg in 10% only. Compound *XVb* in the oral dose of 100 mg/kg was active only in 10% animals (10 mg/kg of *XIV* were active in 100% animals).

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at suitably elevated temperature. The IR spectra (mostly in Nujol, ν in cm^{-1}) were recorded with Unicam SP 200G and Perkin-Elmer 298 spectrophotometers, 1H NMR spectra (in C^2HCl_3 , δ , J in Hz) with a Tesla BS 487C (80 MHz) spectrometer (unless stated otherwise), and the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers (m/z and % given). The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

10,11-Dihydro-5H-dibenzo[*a,d*]cycloheptene-5-carbonitrile

Trimethylsilyl cyanide⁸ (11.3 g) was added to a solution of 21.1 g 5-chloro-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene⁷ in 150 ml dichloromethane and the stirred mixture was treated very slowly with 6.0 g $SnCl_4$. The mixture was stirred for 10 h at room temperature, diluted with 150 ml dichloromethane, and decomposed with 200 ml water. After shaking the organic layer was separated, the aqueous layer was extracted with dichloromethane, the combined organic layers were washed with 5% $NaHCO_3$, dried, and evaporated. The residue gave by crystallization from benzene 18.3 g (91%) product, m.p. 88.5–89.5°C (tetrachloromethane–hexane). IR spectrum: 760 (4 adjacent Ar–H); 1 488, 1 572, 1 600, 3 020, 3 060, 3 080 (Ar); 2 245 (R–CN). 1H NMR spectrum: 3.18 s, 4 H ($ArCH_2CH_2Ar$); 5.39 s, 1 H (Ar_2CHCN); 6.90–7.50 m, 8 H (8 ArH). Refs^{11,12}, m.p. 91–92 and 85–87°C, respectively.

(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)methylamine (*XVIa*)

A stirred solution of 3.40 g $LiAlH_4$ in 190 ml tetrahydrofuran was slowly treated with a solution of 8.85 g $AlCl_3$ in 100 ml ether in the nitrogen atmosphere, the mixture was stirred for 10 min, 10.5 g 6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile⁶ in 100 ml tetrahydrofuran were added, and the mixture was refluxed for 11 h. After cooling it was decomposed with stirring by a slow addition of 5 ml water, 5 ml 15% NaOH, and 15 ml water, stirred for 30 min, the solid was filtered off, and the filtrate was evaporated. The residue crystallized from a small amount of a mixture of benzene and cyclohexane; 9.90 g (93%), m.p. 103.5–106°C. Ref.⁵, m.p. 105.5 to 106.5°C.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylmethyl)chloroacetamide (*XVIIa*)

A stirred solution of 11.2 g *XVIa* and 6.06 g *N,N*-dimethylacetamide in 120 ml benzene was treated over 30 min with a solution of 7.86 g chloroacetyl chloride in 30 ml benzene. The mixture was stirred for 40 min at 50°C, after cooling diluted with benzene, the solution was washed with water, dried, and evaporated. The oily residue (13.4 g, 91%) was used for further work. For characterization, it was crystallized from a mixture of benzene and hexane; m.p. 108 to 111.5°C (benzene). IR spectrum (KBr): 749, 754 (4 adjacent Ar–H); 1 545, 1 642, 1 670 (RCONHR-); 3 255, 3 330 (NH). 1H NMR spectrum: 3.90 bs, 2 H ($COCH_2Cl$); c. 4.20 m, 2 H (CH_2N); 4.50 m, 1 H (Ar_2CH); 6.50 bs, 1 H (NH); 6.90–7.40 m, 8 H (8 ArH). For $C_{17}H_{16}ClNOS$ (317.8) calculated: 64.24% C, 5.07% H, 11.15% Cl, 4.41% N, 10.09% S; found: 64.02% C, 5.05% H, 11.15% Cl, 4.50% N, 10.01% S.

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-ylmethyl)chloroacetamide (*XVIIb*)

A solution of 6.21 g LiAlH_4 in 300 ml ether was stirred and treated slowly under nitrogen with a solution of 16.5 g AlCl_3 in 300 ml ether. The mixture was stirred for 10 min and treated over 30 min with a solution of 18.0 g 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-carbonitrile in 300 ml ether. The stirring at room temperature was continued for 10 min and the mixture was refluxed for 6 h. After cooling it was decomposed by addition of 25 ml water which were followed by 100 ml 25% H_2SO_4 . The mixture was filtered, the aqueous layer was separated, made alkaline with 20% NaOH , and the product was isolated by extraction with a mixture of benzene and chloroform. Evaporation of the extract gave 17.8 g crude *XVIIb* which was dissolved in 180 ml benzene, 9.7 g *N,N*-dimethylacetamide were added, and the mixture was stirred and treated dropwise with a solution of 12.6 g chloroacetyl chloride in 5 ml benzene. It was stirred for 1 h at 50–60°C, benzene was evaporated in vacuo, the residue was dissolved in 600 ml chloroform, the solution was washed with water and saturated NaHCO_3 , dried, and evaporated. The residue crystallized from benzene; 20.5 g (83% calculated per the starting nitrile), m.p. 135–137.5°C (benzene). IR spectrum: 750, 767 (4 adjacent Ar—H); 1492, 3018, 3055 (Ar); 1527, 1649 (RCONHR·); 3290 (NH). ^1H NMR spectrum: 2.80–3.50 m, 4 H (ArCH₂CH₂Ar); 3.85 m, 2 H (CH₂N); 3.93 s, 2 H (COCH₂Cl); 4.20 m, 1 H (Ar₂CH); 6.48 bs, 1 H (NH); 7.15 s, 8 H (8 ArH). For $\text{C}_{18}\text{H}_{18}\text{ClNO}$ (299.8) calculated: 72.11% C, 6.05% H, 11.83% Cl, 4.67% N; found: 71.87% C, 6.07% H, 12.16% Cl, 4.91% N.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)dimethylaminoacetamide (*III*)

A mixture of 2.0 g *II* (ref.²), 70 ml acetone, and 1.2 g KI was stirred and refluxed for 2 h. After cooling to room temperature, it was treated under stirring with 9.6 g liquid dimethylamine, introduced to the bottom of the reaction flask. The mixture was stirred for 6 h at 25–30°C and refluxed for 2 h, the volatile components were evaporated in vacuo, the residue (3.6 g) was dissolved in 50 ml chloroform, the solution was washed with water, and shaken with 5 ml 2*M*- H_2SO_4 . The precipitated sulfate was filtered, combined with the aqueous layer of the filtrate, made alkaline with NH_4OH , and extracted with chloroform. Processing of the extract gave 2.07 g (theoretical) *III*, m.p. 140–141°C (benzene–light petroleum). IR spectrum: 751 (4 adjacent Ar—H); 1540, 1651 (RCONHR·); 2775, 2822 (N—CH₃); 3030, 3063 (Ar); 3292 (NH). ^1H NMR spectrum: 2.62 s, 6 H (N(CH₃)₂); 3.00 s, 2 H (COCH₂N); 4.12 d, 1 H and 4.42 d, 1 H (ArCH₂S, $J = 16.0$; 16.0); 6.49 d, 1 H (Ar₂CHN, $J = 9.0$); 6.90–7.50 m, 8 H (8 ArH); 8.75 bd, 1 H (CONH, $J = 9.0$). For $\text{C}_{18}\text{H}_{20}\text{N}_2\text{OS}$ (312.4) calculated: 69.19% C, 6.45% H, 8.97% N, 10.26% S; found: 69.60% C, 6.61% H, 8.88% N, 9.89% S.

Hydrochloride, m.p. 170–171°C (water). For $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{OS}$ (348.9) calculated: 61.96% C, 6.06% H, 10.16% Cl, 8.03% N, 9.19% S; found: 61.75% C, 6.25% H, 10.20% Cl, 7.76% N, 9.29% S.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-2-(4-morpholinyl)acetamide (*IV*)

A mixture of 4.5 g *II* (ref.²), 30 ml toluene, and 6.5 g morpholine was stirred and refluxed for 2.5 h. After cooling it was diluted with 30 ml benzene, washed several times with water, and shaken with an excess of 5*M*- HCl . The oily hydrochloride was combined with the aqueous acid layer, the mixture was made alkaline with NH_4OH , and the product was isolated by extraction with benzene. Processing of the extract gave 4.5 g (85%) residue which crystallized from a mixture of benzene and light petroleum, m.p. 135–141°C. Analytical sample, m.p. 137–139°C (benzene–light petroleum). IR spectrum: 766 (4 adjacent Ar—H); 1495, 1663 (RCONHR·); 3030 (Ar);

3.290 (NH). ^1H NMR spectrum: 2.42 m, 4 H (CH_2NCH_2 of morpholine); 3.01 s, 2 H (COCH_2N); 3.70 m, 4 H (CH_2OCH_2 of morpholine); 4.08 d, 1 H and 4.38 d, 1 H (ABq, ArCH_2S , $J = 16.0$); 6.40 d, 1 H (Ar_2CHN); 7.00–7.50 m, 8 H (8 ArH); 8.98 bd, 1 H (CONH , $J = 10.0$). For $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (354.5) calculated: 67.76% C, 6.26% H, 7.90% N, 9.05% S; found: 67.57% C, 6.03% H, 7.81% N, 9.08% S.

Hydrochloride, m.p. 198–199°C (ethanol–ether). For $\text{C}_{20}\text{H}_{23}\text{ClN}_2\text{O}_2\text{S}$ (390.9) calculated: 61.44% C, 5.93% H, 9.07% Cl, 7.17% N, 8.20% S; found: 61.03% C, 6.21% H, 8.92% Cl, 7.18% N, 8.37% S.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-2-(4-(2-hydroxyethyl)-1-piperazinyl)acetamide (*V*)

A mixture of 3.03 g *II* (ref.²), 10 ml chloroform, and 5.3 g 2-(1-piperazinyl)ethanol was stirred and refluxed for 2.5 h, cooled, diluted with 50 ml chloroform, washed several times with water, and extracted with 50 ml 2*M*- H_2SO_4 . After heating to 45°C, the aqueous layer was separated, made alkaline with NH_4OH , and the product was extracted with chloroform. Processing the extract gave 3.7 g (93%) crude *V* which was dissolved in 15 ml acetone and the solution was neutralized with 2.4 g maleic acid in 5 ml ethanol; 5.8 g bis(hydrogen maleate), m.p. 86–89°C (acetone–ethanol–ether). For $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_3\text{S}$ (629.7) calculated: 57.22% C, 5.60% H, 6.67% N, 5.09% S; found: 56.83% C, 5.49% H, 6.68% N, 4.98% S.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylmethyl)-2-(4-methyl-1-piperazinyl)acetamide (*XVa*)

A mixture of 14.8 g *XVIIa*, 30 ml chloroform, and 10.2 g 1-methylpiperazine was stirred and refluxed for 5 h. After cooling it was diluted with 250 ml chloroform, washed several times with water, dried, and evaporated; 16.4 g (92%) oily *XVa*. Neutralization with HCl in ethanol gave the dihydrochloride (17.5 g) which crystallized from aqueous ethanol as the monohydrate, m.p. 165.5–170°C. Mass spectrum: 381 (M^+ , $\text{C}_{22}\text{H}_{27}\text{N}_3\text{OS}$, 2.5), 348 (1), 339 (1), 315 (2), 225 (7), 211 (3), 191 (3), 178 (9), 170 (11), 141 (10), 113 (100), 70 (85). For $\text{C}_{22}\text{H}_{29}\text{Cl}_2\text{N}_3\text{OS} + \text{H}_2\text{O}$ (472.5) calculated: 55.92% C, 6.61% H, 15.01% Cl, 8.89% N, 6.79% S; found: 55.91% C, 6.41% H, 15.07% Cl, 8.96% N, 6.94% S.

Treatment of a sample of this salt with NH_4OH and extraction with ether gave the homogeneous oily base which was used for recording the ^1H NMR spectrum (Tesla BS 567A, 100 MHz): 2.23 s and 2.23 bm, 7 H (NCH_3 and the adjacent CH_2NCH_2 of piperazine); 2.30 bm, 4 H ($\text{CH}_2\text{N}^1\text{CH}_2$ of piperazine); 2.97 s, 2 H (COCH_2N); 4.00–4.80 m, 5 H (ArCH_2S , remaining CH_2N and Ar_2CH); 7.28 bm, 8 H (8 ArH).

N-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-ylmethyl)-2-(4-methyl-1-piperazinyl)acetamide (*XVb*)

A mixture of 18.6 g *XVIIIb*, 100 ml chloroform, and 13.7 g 1-methylpiperazine was stirred and refluxed for 2.5 h. Similar processing like in the preceding case gave the oily base *XVb* which crystallized from ethanol; 19.0 g (84%), m.p. 148–149.5°C. IR spectrum: 753, 760 (4 adjacent Ar-H); 1517, 1650 (RCONHR); 1501, 1600, 3020, 3050 (Ar); 2760, 2780 (N-CH_3); 3225, 3253 (NH). ^1H NMR spectrum: 2.18 s, 3 H (NCH_3); c. 2.30 bm, 8 H (4 CH_2N of piperazine); 2.90 s, 2 H (COCH_2N); 3.00–3.50 m, 4 H ($\text{ArCH}_2\text{CH}_2\text{Ar}$); 3.88 m, 2 H (remaining CH_2N); 4.25 m, 1 H (Ar_2CH); c. 7.15 bm, 8 H (8 ArH). For $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}$ (363.5) calculated: 75.99% C, 8.04% H, 11.56% N; found: 76.03% C, 8.05% H, 11.58% N.

Dihydrochloride, m.p. 187–189°C (aqueous ethanol). For $\text{C}_{23}\text{H}_{31}\text{Cl}_2\text{N}_3\text{O}$ (436.4) calculated: 63.30% C, 7.16% H, 16.25% Cl, 9.63% N; found: 62.92% C, 7.07% H, 16.21% Cl, 9.21% N.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)ethylenediamine (*VI*)

A mixture of 6.15 g 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin¹⁵, 6 ml chloroform, and 12 g ethylenediamine was stirred and refluxed for 8 h. After cooling it was diluted with 70 ml chloroform, washed with water, and extracted three times with 30 ml 2.5M-HCl. The aqueous layer was filtered with charcoal, made alkaline with NH₄OH, and the base *VI* was isolated by extraction with chloroform; 5.9 g (87%) oil. Neutralization with maleic acid in ethanol gave the bis(hydrogen maleate), m.p. 154–156°C (ethanol). Mass spectrum: 270 (M⁺, C₁₆H₁₈N₂S, 1.7), 226 (19.2), 211 (60), 210 (80), 179 (24), 178 (81.6), 72 (92.8), 65 (38.8), 55 (88.4), 54 (36.8), 47 (100), 45 (47.6). For C₂₄H₂₆N₂O₈S (502.5) calculated: 57.36% C, 5.22% H, 5.58% N, 6.38% S; found: 57.33% C, 5.21% H, 5.47% N, 6.35% S.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-N',N'-dimethylethylenediamine (*VII*)

A mixture of 4.92 g 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin¹⁵, 12.5 ml chloroform, and 1.8 g N,N-dimethylethylenediamine was stirred and refluxed for 14 h. Processing like in the preceding case gave directly the solid dihydrochloride (4.0 g, 60%) which crystallized from ethanol as the hemihydrate, m.p. 168.5–169.5°C. For C₁₈H₂₄Cl₂N₂S + 0.5 H₂O (380.4) calculated: 56.83% C, 6.62% H, 18.64% Cl, 7.37% N, 8.43% S; found: 56.93% C, 6.45% H, 18.66% Cl, 7.21% N, 8.38% S.

Ethyl 2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)acetate (*X*)

A mixture of 7.04 g *I* (ref.¹), 70 ml toluene, 26 g K₂CO₃, and 20.2 g ethyl chloroacetate was stirred and refluxed for 32 h. After cooling it was diluted with toluene, the solid was filtered off, and washed with toluene. The filtrate was washed with water, filtered with charcoal, dried, and evaporated. The residue was crystallized from 13 ml ethanol; 6.7 g (69%) *X*, m.p. 95–99°C. Analytical sample, m.p. 99–101°C (ethanol). IR spectrum: 752 (4 adjacent Ar—H); 1 198, 1 224, 1 728 (RCOOR'); 3 295 (NH). ¹H NMR spectrum: 1.31 t, 3 H (CH₃ of ethyl, *J* = 7.0); 2.20 bs, 1 H (NH); 3.41 s, 2 H (CH₂CO); 4.28 q, 2 H (OCH₂, *J* = 7.0); 5.10 and 4.20, two flat bands, 1 + 1 H (ArCH₂S); 5.18 s, 1 H (Ar₂CH); 7.00–7.50 m, 8 H (8 ArH). For C₁₈H₁₉NO₂S (313.4) calculated: 68.98% C, 6.11% H, 4.47% N, 10.23% S; found: 69.14% C, 6.14% H, 4.55% N, 10.20% S.

Hydrochloride, m.p. 145–146°C with decomposition (ethanol–ether). For C₁₈H₂₀ClNO₂S (349.9) calculated: 61.79% C, 5.76% H, 10.13% Cl, 4.00% N, 9.17% S; found: 61.33% C, 5.74% H, 9.87% Cl, 4.03% N, 9.01% S.

Ethyl 2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)propionate (*XI*)

A stirred mixture of 4.54 g *I* (ref.¹), 60 ml toluene, 10.1 g Na₂CO₃, and 10.85 g ethyl 2-bromopropionate was refluxed for 46 h and was similarly processed (cf. *X*); 6.5 g (99%) oily *XI*. Hydrochloride, m.p. 148.5–150.5°C (ethanol–ether). For C₁₉H₂₂ClNO₂S (363.9) calculated: 62.71% C, 6.09% H, 9.74% Cl, 3.85% N, 8.81% S; found: 62.72% C, 6.03% H, 9.67% Cl, 3.74% N, 8.85% S.

2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)acetic Acid (*VIII*)

A mixture of 5.3 g *X*, 17.5 ml 10% NaOH, and 17.5 ml methanol was stirred and refluxed for 1.5 h. Methanol was distilled off, the residue was diluted with 25 ml water, filtered with charcoal, and the filtrate was washed with ether. At 40°C the solution was neutralized with 2.5M-CH₃COOH

to pH 6–6.5. After cooling the product was filtered, washed with water, and dried; 2.9 g (60%), m.p. 104–108°C. Analytical sample, m.p. 105–106°C (aqueous ethanol). IR spectrum: 750 (4 adjacent Ar—H); 918, 1 220, 1 392, infl. 3 100 (COOH); 1 632, 1 720 (COO⁻); 2 560 (NH₂⁺); 3 060 (Ar). For C₁₆H₁₅NO₂S (285.4) calculated: 67.33% C, 5.30% H, 4.91% N, 11.24% S; found: 66.69% C, 5.45% H, 5.23% N, 11.01% S.

2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)propionic Acid (*IX*)

A similar reaction of 5.45 g *XI* with 17.5 ml 5M-NaOH in 17.5 ml methanol gave 4.1 g (91%) *IX* which crystallized from ethanol as a 2 : 1 solvate with ethanol, m.p. 192.5°C. Mass spectrum: 299 (M⁺, C₁₇H₁₇NO₂S, 5.6), 284, 266, 254, 226 (C₁₄H₁₃NS, 12), 210 (C₁₄H₁₆S, 100), 178 (C₁₄H₁₀, 50.4), 165 (C₁₃H₉, 12). For C₁₇H₁₇NO₂S + 0.5 C₂H₆O (322.4) calculated: 67.05% C, 6.25% H, 4.35% N, 9.95% S; found: 67.09% C, 5.79% H, 4.58% N, 10.20% S.

2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)acetamide (*XII*)

A mixture of 6.7 g *X*, 30 ml methanol, and 40 ml liquid NH₃ was heated in an autoclave for 4 h to 135°C. It was then diluted with 50 ml methanol, filtered with charcoal, and evaporated; 5.7 g (94%), m.p. 99–103°C (benzene). IR spectrum: 745 (4 adjacent Ar—H); 1 633 (RCONH₂); 3 200, 3 400 (NH₂). For C₁₆H₁₆N₂OS (284.4) calculated: 67.57% C, 5.67% H, 9.85% N, 11.28% S; found: 67.04% C, 5.81% H, 9.41% N, 11.12% S.

2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylamino)propionamide (*XIII*)

A similar reaction of 3.6 g *XI*. HCl with 50 ml liquid NH₃ in 20 ml methanol gave 2.3 g (78%) *XIII* which was crystallized from a mixture of benzene, ethanol, and light petroleum, m.p. 102–105°C, after drying at 78°C m.p. 80–82°C. IR spectrum (KBr): 750 (4 adjacent Ar—H); 1 600, 3 018 (Ar); 1 690 (CONH₂); 3 145, 3 265, 3 390, 3 400, 3 520 (NH, NH₂). ¹H NMR spectrum: 1.30 d, 3 H (C—CH₃); 3.10 q, 1 H (N—CH—CO); 5.00 flat band, 2 H (ArCH₂S); 6.10 and 6.60, flat bands, 3 H (NH and NH₂); 6.90–7.40 m, 8 H (8 ArH). For C₁₇H₁₈N₂OS (298.4) calculated: 68.42% C, 6.08% H, 9.39% N, 10.75% S; found: 67.82% C, 6.25% H, 9.28% N, 10.57% S.

The substance melting at 102–105°C was identified as 3 : 1 solvate with benzene. ¹H NMR spectrum: 7.00–7.30 m, 8 H (8 ArH); 7.28 s, 2 H (1/3 C₆H₆). For C₁₇H₁₈N₂OS + 1/3 C₆H₆ calculated: 70.34% C, 6.21% H, 8.63% N, 9.89% S; found: 70.11% C, 6.26% H, 8.61% N, 9.38% S.

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REFERENCES

1. Valenta V., Bartošová M., Protiva M.: Collect. Czech. Chem. Commun. 45, 517 (1980).
2. Rajšner M., Mikšík F., Trčka V., Helfert J.: Czech. 210,369 (Appl. 01. 10. 80); Chem. Abstr. 101, 54944 (1984).
3. Conant J. B., Kirner W. R.: J. Am. Chem. Soc. 46, 232 (1924).
4. Kitagawa H., Kurahashi K., Fuhiiwara M., Kohei H.: Arzneim.-Forsch. 28, 2122 (1978).

5. Valenta V., Metyš J., Protiva M.: *Collect. Czech. Chem. Commun.* **47**, 984 (1982).
6. Šindelář K., Buděšínský M., Vaněk T., Holubek J., Svátek E., Matoušová O., Rees Ch. V., Protiva M.: *Collect. Czech. Chem. Commun.* **52**, 2281 (1987).
7. Mychajlyszyn V., Protiva M.: *Collect. Czech. Chem. Commun.* **24**, 3955 (1959).
8. Reetz M. T., Chatziiosifidis I.: *Synthesis* **1982**, 330.
9. Reetz M. T., Chatziiosifidis I.: *Angew. Chem.* **93**, 1075 (1981).
10. Reetz M. T., Chatziiosifidis I., Künzer H., Müller-Starke H.: *Tetrahedron* **39**, 961 (1983).
11. Davis M. A., Winthrop S. O., Stewart J., Sunahara F. A., Herr F.: *J. Med. Chem.* **6**, 251 (1983).
12. Van Der Stel C., Haasjes A., Tersteegje H. M., Nauta W. Th.: *Rec. Trav. Chim. Pays-Bas* **84**, 1466 (1965).
13. Humber L. G., Davis M. A., Thomas R. A., Otsen R., Watson J. R.: *J. Heterocycl. Chem.* **3**, 247 (1966).
14. Weisz I., Ötvös L.: *Arch. Pharm.* **318**, 766 (1985).
15. Seidlová V., Rajšner M., Adlerová E., Protiva M.: *Monatsh. Chem.* **96**, 650 (1965).
16. Nagatomi H., Ando K., Kawasaki M., Yasui B., Miki Y., Takemura S.: *Chem. Pharm. Bull.* **27**, 1021 (1979).
17. Malen Ch., Danree B., Poignant J. C. (Science Union et Cie. Société Française de Recherche Médicale): *Ger. Offen.* 2,011,806 (Br. Appl. 27.03.69); *Chem. Abstr.* **74**, 13024 (1971).
18. Malen Ch., Danree B., Poignant J. C. (Science Union et Cie. — Société Française de Recherche Médicale): *Ger. Offen.* 2,065,636 (Br. Appl. 27.03.69); *Chem. Abstr.* **83**, 9833 (1975).
19. Science Union et Cie. — Société Française de Recherche Médicale: *Japan.* 78 05,661 (Appl. 07.03.72); *Chem. Abstr.* **89**, 43155j (1978).
20. Malen Ch. E., Poignant J.-C.: *Experientia* **28**, 811 (1972).
21. Protiva M.: *Pharm. Ind.* **32**, 923 (1970).
22. Helfert J., Černoch Z.: *Cesk. Fysiol.* **34**, 427 (1985).
23. Peterková M., Matoušová O., Ryska M., Koruna I., Schlanger K., Rejholec V.: *Cesk. Farm.* **34**, 370 (1985).
24. Hulinská H., Taufmann P., Frycová H., Protiva M.: *Collect. Czech. Chem. Commun.* **53**, (1988).

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