(6,11-DIHYDRODIBENZO[*b,e*]THIEPIN-11-YL)METHYLAMINE, (4-METHOXY-6,11-DIHYDRODIBENZO[*b,e*]THIEPIN-11-YL)-METHYLAMINE AND DERIVATIVES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Using the Curtius reaction, the acids *VIa* and *VIb* were transformed to the carbamates *IVa* and *IVb* which afforded by alkaline hydrolysis the primary amines *Ia* and *Ib*. The N-methyl derivatives *IIab* were obtained by reduction of the carbamates *IVab* with lithium aluminium hydride. The N,N-dimethyl derivatives *IIIab* resulted by methylation of the primary amines *Iab* with formaldehyde and formic acid. The synthesis of the acid *VIb* was carried out from phthalide and 2-methoxythiophenol in seven steps. The amines *Iab*–*IIIab* showed clear thymoleptic properties in the test of reserpine ptosis in mice and by inhibition of the perphenazine catalepsy in rats. The acid *VIb* has antiinflammatory activity.

The tertiary and secondary animes derived from 6,11-dihydrodibenzo[*b*, *e*]thiepin with a saturated or unsaturated three-membered amine side chain in position 11 are known by their antireserpine activity and found clinical use on the basis of their antidepressant efficacy[1–8]. The object of the present communication was the synthesis of the title compounds *Iab*–*IIIab* with a single methylene group between the position 11 of the skeleton and the amino group and a study of their pharmacological properties.

Our syntheses proceeded *via* 6,11-dihydrodibenzo[*b*, *e*]thiepin-11-acetic acids *VIab*, the first of which (*VIa*) has already been mentioned in patents[9,10] and its preparation has been described in one of the preceding papers of this series[11]. The 4-methoxy acid *VIb* was obtained by a seven-step synthesis starting from phthalide and 2-methoxythiophenol[12] and used methods similar to those described in our previous papers[2,3,5,11,13].

Heating a mixture of phthalide, 2-methoxythiophenol[12] and potassium carbonate to 125°C resulted in excellent yield in the acid *IX* which was cyclized with polyphosphoric acid in boiling toluene to 4-methoxydibenzo[*b*, *e*]thiepin-11(6*H*)-one (*X*). Reduction with sodium borohydride in boiling ethanol gave the alcohol *XI* which

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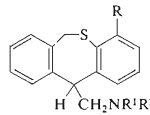
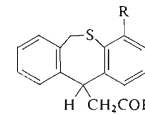
was treated with hydrogen chloride in tetrachloromethane in the presence of calcium chloride and afforded the chloro derivative *XII*. In the further step, diethyl malonate was first subjected to treatment with sodium hydride in benzene and then



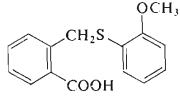


I, $R^1 = R^2 = H$
II, $R^1 = CH_3$, $R^2 = H$
III, $R^1 = R^2 = CH_3$
IV, $R^1 = COOC_2H_5$, $R^2 = H$
V, $R^1 = COCH_3$ $R^2 = H$

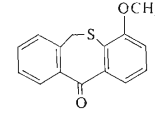
VI, $R^1 = OH$
VII, $R^1 = Cl$
VIII, $R^1 = NH_2$

In formulae *I*–*VIII*: *a*, R = H; *b*, $R = OCH_3$

alkylated with compound *XII*; the malonic ester *XIII* was obtained. The alkaline hydrolysis led to the acid *XIV* which was decarboxylated in an almost theoretical yield by heating with pyridine in the presence of piperidine and gave 4-methoxy-6,11-dihydrodibenzo[*b*, *e*]thiepin-11-acetic acid (*VIb*). Treatment with thionyl chloride in benzene resulted in the chloride *VIIb* which was transformed by a reaction with ammonia to the amide *VIIIb*.



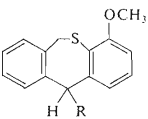
IX



X

The Curtius method[14] was used for transforming the acids *VIab* to the amines *Iab*. The acid chlorides *VIIab* were treated with sodium azide and converted to the corresponding acyl azides which were heated in crude state with ethanol and afforded under rearrangement the carbamates *IVab*. The primary amines *Iab* were obtained by hydrolysis with ethanolic potassium hydroxide. Reduction of the carbamates *IVab* with lithium aluminium hydride in ether gave the secondary amines *IIab* and methylation of the primary amines with formaldehyde and formic acid resulted in the tertiary amines *IIIab*. The primary amines *Iab* were acetylated with acetyl chloride in chloroform in the presence of sodium carbonate and gave the acetamido derivatives *Vab*; attempts at their cyclization by the Bischler–Napieralski reaction (with phosphoryl

chloride, mixture of phosphoryl chloride and phosphorus pentoxide, and polyphosphoric acid) did not lead to characterized products.



XI, R = OH *XIII*, R = $CH(COOC_2H_5)_2$
XII, R = Cl *XIV*, R = $CH(COOH)_2$

Compounds *Iab–IIIab* (in the form of salts described in the Experimental), *Vb VIb* and *VIIIb* were pharmacologically tested in the first line for the expected antireserpine and tranquillizing activity, further for anticonvulsant (*VIIIb*) and anti-inflammatory activity (*VIb*) and finally within a general screening program.

Acute toxicity in mice, LD_{50} (mg/kg): Orally, *IIa* 67, *IIb* 198, *Vb* > 2 500, *VIb* > > 1 000, *VIIIb* > 500; intravenously, *Ia* 20, *Ib* 15, *IIIa* 31·4, *IIIb* 38·4 (subtoxic doses elicit transient excitation followed by ataxia, convulsions and tremor). Doses used in the screening program, D (mg/kg): *i.v.*, *Ia* 4, *Ib* 3, *IIIa* 5; orally, *Vb* 300. Ataxia in the rotarod test in mice, ED_{50} (mg/kg): orally, *IIa* < 40 (ED_{70}), *IIb* > 40 (ED_{20}), *VIIIb* 193; *i.v.*, *Ia* and *Ib* inactive at the dose D, *IIIa* 5, *IIIb* 16·8. Thiopental potentiation: *Ia*, *Ib* and *Vb* inactive at the doses D; *IIab* and *IIIab* do not potentiate the thiopental sleeping time in mice significantly at doses equalling 20% of the LD_{50} given (the same way of administration). Influence in the locomotor activity of mice in the test of Dews: oral doses of 20 – 50 mg/kg *IIa* and *IIb* decrease mildly (without statistical significance) the locomotor activity; *i.v.* doses of 5 – 20 mg/kg of *IIIa* and *IIIb* decrease the locomotion clearly but still without statistical significance. Antireserpine activity: Compounds *Ia*, *Ib* and *IIIa* did not antagonize in doses D the reserpine hypothermia in mice; *IIIb* in doses of 2 and 4 mg/kg *i.p.* gave similar results. The antireserpine effect appeared in the test of ptosis in mice, ED (mg/kg) *i.p.*: *Ia* 4, *Ib* 3, *IIIa* 2·5. In oral doses of 50 mg/kg, compounds *IIa*, *IIb*, *IIIa* and *IIIb* did not antagonize the ulcerogenic effect of reserpine in rats. Anticataleptic activity (antagonization of the cataleptic activity of perphenazine in rats), PD_{50} (mg/kg) orally: *IIa* 10 – 30, *IIb* 100, *IIIa* 10 – 30, *IIIb* 100. Spasmolytic (parasympatholytic/musculotropic) effect; concentrations in μg/ml inhibiting the acetylcholine/barium chloride contractions of the isolated rat duodenum by 50% (atropine 0.05/papaverine 5): *Ia* 10/1 – 10, *Ib* inactive/10, *IIIa* 1 – 10/1 – 10. Local anaesthetic effect; a concentration bringing about a complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia (procaine, 1%): *Ia* 0·1 – 0·5%, *IIIa* 0·1 – 0·5%. Corneal anaesthesia; a concentration bringing about in 50% rabbits a complete anaesthesia of the

eye cornea (trimecaine, 1%): *Ia* 0·1 – 0·5%, *IIIa* 0·1 – 0·5%. Anticonvulsant effect: Compound *VIIIb* was practically inactive in an oral dose of 50 mg/kg towards the tonic-extensor convulsions of the hind extremities of mice brought about by electroshock. Antiinflammatory effect; oral dose in mg/kg/% of inhibition of Carrageenan edema of the rat paw: *VIb* 25/25$^+$ (statistically significant).

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Ia* 50, *Ib* 100, *IIa* 100, *Vb* 100, *VIb* 100; *Staphylococcus pyogenes aureus*, *Ia* 100; *Escherichia coli*, *Ia* 100; *Mycobacterium tuberculosis* H37Rv, *Ia* 12·5; *Ib* 25, *IIa* 25, *IIb* 100, *IIIa* 25, *IIIb* 100, *Vb* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) with a Unicam SP 200G spectrophotometer, the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MCH 1 320 spectrometer. The homogeneity of the compounds and composition of the reaction mixtures were checked by chromatography on thin layers of silica gel (Silufol).

2-(2-Methoxyphenylthiomethyl)benzoic Acid (*IX*)

A solution of 80 g phthalide in 75·4 g 2-methoxythiophenol[12] was heated to 110°C and treated over 2 min with 115 g K_2CO_3. The mixture was stirred for 5 min and heated to 125°C without stirring for 1 h. The melt was diluted with 750 ml hot water, the undissolved fraction was filtered off and the filtrate was acidified at 50°C with hydrochloric acid. After cooling to 10°C the crude product was filtered, washed with water and dried *in vacuo*; 128 g (87%), m.p. 116·5 – 120°C. Analytical sample, m.p. 120 – 122°C (aqueous ethanol). UV spectrum: λ_{max} 283 nm (log ε 3·82), infl. 228 nm (4·30), 250 nm (3·96). IR spectrum: 743 (4 adjacent Ar—H), 912, 1 302, *1 680*, 2 520, 2 640, 3 160 (COOH), 1 252, 1 278 ($ArOCH_3$), 1 577 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 12·00 (bs, 1 H, COOH), 8·05 (m, 1 H, 6-H), 7·00 – 7·50 (m, 5 H, 3,4,5,4′,5′-H_5), c. 6·80 (m, 2 H, 3′, 6′-H_2), 4·56 (s, 2 H, $ArCH_2S$), 3·88 (s, 3 H, OCH_3). For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·67% C, 5·14% H, 11·64% S; found: 65·13% C, 5·20% H, 11·57% S.

4-Methoxydibenzo[*b*,*e*]thiepin-11(6*H*)-one (*X*)

Polyphosphoric acid, prepared from 240 g P_2O_5 and 160 ml 85% H_3PO_4, was heated to 100°C and a solution of 54·8 g *IX* in 240 ml toluene was added. The mixture was stirred and refluxed for 2 h, decomposed with 600 g ice and water and extracted with toluene. The extract was washed with 5% NaOH and water, dried with K_2CO_3 and evaporated; 41·3 g (81%), m.p. 110 – 117°C. Analytical sample, m.p. 119·5 – 121°C (ethanol). UV spectrum: λ_{max} 240 nm (log ε 4·29), 285 nm (3·89), 364 nm (3·62), infl. 259 nm (4·13). IR spectrum: 708, 731, 760, 773, 800 (4 and 3 adjacent Ar—H), 1 259, 1 319 ($ArOCH_3$), 1 558, 1 592, 3 040 (Ar), 1 659 cm^{-1} (ArCOAr). ^{1}H NMR spectrum: δ 7·82 (q, J = 8·0; 2·0 Hz, 1 H, 1-H), 7·10 – 7·60 (m, 5 H, 2,7,8,9,10-H_5), 6·91 (q, J = 8·0; 2·0 Hz, 1 H, 3-H), 3·99 (s, 2 H, $ArCH_2S$), 3·89 (s, 3 H, OCH_3). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·28% C, 4·72% H, 12·51% S; found: 70·50% C, 4·81% H, 12·62% S.

4-Methoxy-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*XI*)

A stirred suspension of 137 g *X* in 1 650 ml ethanol was slowly treated at 45°C with 41 g $NaBH_4$ and the mixture was refluxed for 4 h. Ethanol was evaporated under reduced pressure, the residue diluted with water, the precipitated product was filtered, washed with water and dried: 127 g (92%), m.p. 166–167·5°C (ethanol). UV spectrum: λ_{max} 217·5 nm (log ε 4·28), 256 nm (3·96), 297 nm (3·50). IR spectrum: 689, 740, 793 (4 and 3 adjacent Ar—H), 1 045 (CHOH in a cycle), 1 250, 1 266 ($ArOCH_3$), 1 500, 1 570, 3 010, 3 043 (Ar), 3 245, 3 314 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·15–7·50 (m, 5 H, 1,7,8,9,10-H_5), 7·05 (t, J = 8·0 Hz, 1 H, 2-H), 6·80 (q, J = 8·0; 2·0 Hz ,1 H, 3-H), c. 6·12 [bs, 2 H, ArCH(OH)Ar], 4·58 and 4·30 (ABq, J = = 14·0 Hz, 2 H, $ArCH_2S$), 3·70 (s, 3 H, OCH_3). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·73% C, 5·46% H, 12·41% S; found: 69·59% C, 5·52% H, 12·52% S.

11-Chloro-4-methoxy-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XII*)

A suspension of 51·6 g *XI* and 60 g $CaCl_2$ in 1000 ml tetrachloromethane was saturated at room temperature for 1·5 h with hydrogen chloride. The mixture was then filtered and the filtrate evaporated. The residue crystallized from a mixture of 80 ml cyclohexane and 200 ml light petroleum; 52·0 g (94%), m.p. 98–105°C. Analytical sample, m.p. 102–105°C (toluene–cyclohexane–light petroleum). UV spectrum: λ_{max} 228 nm (log ε 4·45), 256 nm (3·99), 298 nm (3·60). IR spectrum: 708, 721, 771 (4 and 3 adjacent Ar—H), 1 080, 1 253 ($ArOCH_3$), 1 570, 1 593, 3 045 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60–7·40 (m, 7 H, Ar—H), 6·20 (s, 1 H, Ar_2CHCl), 5·50 and 3·70 (2 d, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·80 (s, 3 H, OCH_3). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·08% C, 4·73% H, 12·81% Cl, 11·58% S; found: 65·56% C, 4·73% H, 12·60% Cl, 11·48% S.

Diethyl (4-Methoxy-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)malonate (*XIII*)

A solution of 33·0 g diethyl malonate in 70 ml benzene was added dropwise over 40 min to a stirred suspension of 5·1 g 80% NaH in 560 ml benzene. The mixture was heated to 60°C and treated over 1 h with a solution of 47·2 g *XII* in 290 ml benzene. The mixture was refluxed for 3 h and allowed to stand overnight at room temperature. It was then washed with water, dried with $MgSO_4$ and evaporated. The residue was dissolved in 50 ml boiling methanol and allowed to crystallize; 49·5 g (72%), m.p. 95–102°C. Analytical sample, m.p. 102–104°C (ethanol). IR spectrum: 723, 750, 770 (4 and 3 adjacent Ar—H), 1 030, 1 050, 1 161, 1 250, 1 268 (C—O—R), 1 572 (Ar), 1 730, 1 760 cm^{-1} [$CH(COOR)_2$]. For $C_{22}H_{24}O_5S$ (400·5) calculated: 65·98% C, 6·04% H, 8·00% S; found: 65·90% C, 6·26% H, 7·87% S.

(4-Methoxy-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)malonic Acid (*XIV*)

A solution of 64·5 g *XIII* in 520 ml ethanol was treated with a solution of 260 g KOH in 260 ml water and the mixture was refluxed for 6·5 h. Ethanol was evaporated under reduced pressure, the residue was diluted with water, the solution washed with benzene, filtered with charcoal and the filtrate acidified with hydrochloric acid. The product was filtered at 10°C and crystallized from aqueous methanol; 43·4 g (79%), m.p. 145–148°C. Further crystallization from aqueous methanol was connected with a sudden rise of the melting point to 182–183°C, after drying 223–226°C. IR spectrum: 729, 750, 769 (4 and 3 adjacent Ar—H), 1179, 1 264, 1 270 ($ArOCH_3$, COOH), 1 475, 1 577 (Ar), 958, *1 715*, *1 750*, 2 680, 3 111 cm^{-1} (COOH). For $C_{18}H_{16}O_5S$ (344·4) calculated: 62·77% C, 4·68% H, 9·31% S; found: 63·13% C, 4·94% H, 9·73% S.

4-Methoxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-acetic Acid (*VIb*)

A mixture of 23·0 g *XIV*, 30 ml pyridine and 2·5 ml piperidine was heated under reflux for 2·5 h in a bath of 120°C. It was then poured into 120 ml 5M-HCl, the mixture was cooled with ice to 3°C, the product was filtered, washed with water and dried; 18·7 g (95%), m.p. 217–220°C. Analytical sample, m.p. 219·5–221·5°C (ethanol). IR spectrum: 705, 725, 758, 774, 804 (4 and 3 adjacent Ar—H), 1 046, 1 264 ($ArOCH_3$), 929, *1 703*, 2 548, 2 593, 2 660, 2 710, infl. 3 080 (R—COOH), 1 567 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·00 (bs, 1 H, COOH), 6·60–7·40 (m, 7 H, Ar—H), 5·00 (t, J = 8·0 Hz, 1 H, Ar_2CH), 4·80 and 3·90 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·64 (s, 3 H, OCH_3), 3·21 (d, J = 8·0 Hz, 2 H, CH_2CO). For $C_{17}H_{16}O_3S$ (300·4) calculated: 67·97% C, 5·37% H, 10·67% S; found: 67·79% C, 5·69% H, 10·82% S.

4-Methoxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-acetic Acid Chloride (*VIIb*)

A suspension of 30 g *VIb* in 150 ml benzene was treated with a solution of 29 g $SOCl_2$ in 50 ml benzene, the mixture was stirred for 2·5 h at 60–70°C and refluxed for 0·5 h. It was then evaporated under reduced pressure and the residue crystallized from a mixture of 50 ml benzene and 40 ml light petroleum; 28 g (88%), m.p. 108–112°C. IR spectrum: 720, 752, 762, 774, 787 (4 and 3 adjacent Ar—H), 1 040, 1 080, 1 260 ($ArOCH_3$), 1 500, 1 571, 3 045 (Ar), 1 798 cm^{-1} RCOCl). For $C_{17}H_{15}ClO_2S$ (318·8) calculated: 64·04% C, 4·72% H, 11·12% Cl, 10·06% S; found: 64·61% C, 4·90% H, 10·95% Cl, 10·16% S.

4-Methoxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-acetic Acid Amide (*VIIIb*)

A) A solution of 3·2 g crude *VIIb* in 20 ml benzene was slowly added to a saturated solution of NH_3 in 60 ml benzene and the mixture was stirred and saturated with NH_3 at room temperature for 0·5 h. After standing overnight the product was filtered, suspended in 60 ml water, filtered again, washed with water and dried; 3·0 g (99%), m.p. 195–200°C. Analytical sample, m.p. 202–204°C (aqueous ethanol). IR spectrum: 688, 723, 750, 766, 782 (4 and 3 adjacent Ar—H), 1 048, 1 268 ($ArOCH_3$), 1 576, 1 619, 1 690 ($RCONH_2$), 3 050 (Ar), 3 160, 3 210, 3 275, 3 410 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·52 (bs, 2 H, $CONH_2$), 6·60–7·40 (m, 7 H, Ar—H), 5·04 (t, J = 7·0 Hz, 1 H, Ar_2CH), 4·75 and 3·95 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·68 (s, 3 H, OCH_3), 3·01 (d, J = 7·0 Hz, 2 H, CH_2CO). For $C_{17}H_{17}NO_2S$ (299·4) calculated: 68·19% C, 5·72% H, 4·68% N, 10·71% S; found: 68·12% C, 5·91% H, 4·80% N, 10·63% S.

B) A solution of 3·2 g crude *VIIb* in 20 ml benzene was added dropwise under stirring to 75 ml conc. NH_4OH, the mixture was stirred for 1 h at room temperature, the solid product was filtered and crystallized from aqueous ethanol; 2·3 g (79%), m.p. 202–204°C.

Ethyl N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylmethyl)carbamate (*IVa*)

A solution of 14·5 g *VIIa* (ref.[11]) in 70 ml acetone was added dropwise over 1 h to a stirred solution of 4·9 g NaN_3 in 15 ml water at 15–18°C. The mixture was stirred for 1 h at room temperature, poured into 700 g ice and water, stirred for 45 min and filtered. The solid was suspended in 50 ml ethanol and filtered again; 14·8 g crude acid azide, m.p. 73–76°C with decomposition. It was refluxed with 150 ml ethanol under stirring for 3 h, 70 ml ethanol were distilled off, the residue was treated dropwise with 6·5 ml water and cooled overnight in a refrigerator; 12·7 g (81%), m.p. 114–121°C. Analytical sample, m.p. 122–125°C (ethanol). IR spectrum: 755 (4 adjacent Ar—H), 1 247, 1 268, 1 288 (COOR), 1 540, 1 688 (NHCOOR), 3 332, 3 340 cm^{-1} (NH). ^1H NMR spectrum: δ 6·70–7·30 (m, 8 H, Ar—H), 4·60 (bt, 1 H, NH), 3·70–4·60 (m, 7 H,

$ArCH_2S$, Ar_2CHCH_2, OCH_2), 1·11 (t, J = 7·0 Hz, 3 H, CH_3 in ethyl). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·97% C, 6·11% H, 4·47% N, 10·23% S; found: 69·04% C, 6·13% H, 4·21% N, 10·50% S.

Ethyl N-(4-Methoxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl-methyl)carbamate (*IVb*)

Similarly like in the preceding case, 3·2 g *VIIb* in 15 ml acetone was reacted with 0·98 g NaN_3 in 3 ml water and the acid azide obtained (3·1 g, m.p. 80—81°C with decomposition) was rearranged by refluxing with 30 ml ethanol; 2·45 g (72%) *IVb*, m.p. 158·5—160·5°C (ethanol). IR spectrum: 696, 724, 763, 773 (4 and 3 adjacent Ar—H), 1 039, 1 051, 1 080 ($ArOCH_3$), 1 266, *1 690*, *1 719* (NHCOOR), 1 475, 1 542, 1 553, 1 573, 3 060 (Ar), 3 285 cm^{-1} (NH). ^1H NMR spectrum: δ 6·50—7·30 (m, 7 H, Ar—H), 4·70 (bt, 1 H, Ar_2CH), 4·60 (t, 1 H, NH), 3·80—4·50 (m, 6 H, $ArCH_2S$, CH_2N, CH_2O), 3·73 (s, 3 H, OCH_3), 1·18 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl), For $C_{19}H_{21}NO_3S$ (343·4) calculated: 66·44% C, 6·16% H, 4·08% N, 9·34% S; found: 66·40% C, 6·29% H, 4·47% N, 9·41% S.

11-(Aminomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*Ia*)

A solution of 9·4 g *IVa* and 85 g KOH in 95 ml ethanol was refluxed for 3 h (bath of 110°C), diluted with 70 ml water and extracted with benzene. The benzene layer was extracted with 200 ml 1M-H_2SO_4, the solid sulfate was filtered off and combined with the aqueous layer. The suspension was made alkaline with 50 ml 5M-NaOH, the base extracted with benzene, the extract dried (K_2CO_3) and evaporated; 6·2 g (86%), m.p. 102—105°C. Analytical sample, m.p. 105·5—106·5°C (benzene–cyclohexane). IR spectrum: 752 (4 adjacent Ar—H), 1 488, 1 584, 3 028 (Ar), 1 620, 3 300, 3 360 cm^{-1} (NH_2). ^1H NMR spectrum: δ 6·70—7·30 (m, 8 H, Ar—H), 4·48 and 3·88 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·31 (t, J = 7·0 Hz, 1 H, Ar_2CH), 3·50 (d, J = 7·0 Hz, 2 H, CH_2N), 1·14 (s, 2 H, NH_2). For $C_{15}H_{15}NS$ (241·4) calculated: 74·64% C, 6·26% H, 5·80% N, 13·29% S; found: 75·04% C, 6·30% H, 5·71% N, 13·07% S.

Hydrochloride, m.p. 254—256°C with decomposition (ethanol). For $C_{15}H_{16}ClNS$ (277·8) calculated: 64·84% C, 5·80% H, 12·76% Cl, 5·04% N, 11·54% S; found: 64·56% C, 5·85% H, 12·54% Cl, 4·85% N, 11·70% S.

11-(Aminomethyl)-4-methoxy-6,11-dihydrodibenzo[*b,e*]thiepin (*Ib*)

IVb (2·05 g) was hydrolyzed with 17 g KOH in 18 ml ethanol similarly like in the preceding case and gave 1·15 g (62%) base *Ib* solvated with 0·5 molecule of benzene, m.p. 67—71°C (benzene). Mass spectrum, m/z: 271 (M^+ corresponding to $C_{16}H_{17}NOS$), 242, 241, 210, 209, 208, 194, 178, 165, 30. IR spectrum: 691, 756, 772 (4 and 3 adjacent Ar—H), 1 046, 1 062, 1 076, 1 255 ($ArOCH_3$), 1 490, 1 566 (Ar), 3 340, 3 420 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·60—7·40 (m, Ar—H), 4·70 and 3·96 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 4·48 (t, J = 7·0 Hz, 1 H, Ar_2CH), 3·68 (s, 3 H, OCH_3), 3·38 (bd, J = 7·0 Hz, 2 H, CH_2N), 2·20 (bs, 2 H, NH_2). For $C_{16}H_{17}NOS$ + + 0·5 C_6H_6 (310·4) calculated: 73·50% C, 6·49% H, 4·51% N, 10·33% S; found: 73·63% C, 6·73% H, 4·34% N, 10·28% S.

Hydrochloride, m.p. 255—257°C (aqueous ethanol). For $C_{16}H_{18}ClNOS$ (307·8) calculated: 62·42% C, 5·89% H, 11·52% Cl, 4·55% N, 10·42% S; found: 61·75% C, 5·80% H, 11·68% Cl, 4·35% N, 10·55% S.

Hemisulfate hemihydrate, m.p. 176—178°C (dimethylformamide–methanol). For $C_{16}H_{17}$. .$NOS + 0{\cdot}5\ H_2SO_4 + 0{\cdot}5\ H_2O$ (329·4) calculated: 58·33% C, 5·81% H, 4·25% N, 14·60% S; found: 58·38% C, 5·84% H, 4·07% N, 14·30% S.

Hydrogen oxalate, m.p. 150—154°C (ethanol–ether). For $C_{18}H_{19}NO_5S$ (361·4) calculated: 3·87% N, 8·87% S; found: 4·00% N, 8·57% S.

11-(Methylaminomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*IIa*)

A suspension of 4·6 g *IVa* in 200 ml ether was added dropwise to a stirred suspension of 3·4 g $LiAlH_4$ in 80 ml ether over 0·5 h and the mixture was refluxed for 8 h. After standing overnight it was decomposed by a slow addition of a mixture of 3·5 ml 20% NaOH and 12 ml water, the mixture was stirred for 30 min with 3·5 g K_2CO_3 and filtered. Evaporation of the filtrate gave 3·4 g (88%) oily base *IIa* which was transformed by treatment with HCl in a mixture of ethanol and ether to the hydrochloride, m.p. 243—244°C (ethanol–ether). Mass spectrum, *m/z*: 255 (M^+ corresponding to $C_{16}H_{17}NS$), 223 (M − S), 211 (M − CH_2NHCH_3), 208, 178, 44 (base peak, $CH_2{=}\overset{+}{=}NHCH_3$). For $C_{16}H_{18}ClNS$ (291·8) calculated: 65·84% C, 6·22% H, 12·15% Cl, 4·80% N, 10·99% S; found: 66·36% C, 6·11% H, 12·18% Cl, 4·79% N, 10·99% S.

4-Methoxy-11-(methylaminomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*IIb*)

IVb (7·55 g) was similarly reduced with 5·0 g $LiAlH_4$ in 370 ml ether and gave 5·0 g (80%) oily base which was transformed to the hydrochloride, m.p. 248—251°C (ethanol–ether). Mass spectrum, *m/z*: 285 (M^+ corresponding to $C_{17}H_{19}NOS$), 242, 214, 213, 165, 44 (base peak). For $C_{17}H_{20}ClNOS$ (321·9) calculated: 63·43% C, 6·26% H, 11·02% Cl, 4·35% N, 9·96% S; found: 63·69% C, 6·45% H, 11·05% Cl, 4·15% N, 10·07% S.

11-(Dimethylaminomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*IIIa*)

A mixture of 7·3 g *Ia*, 11·6 g formic acid, 17·2 ml 32% formaldehyde and 16 ml water was stirred and refluxed for 16 h. After cooling, the mixture was made alkaline with 5M-NaOH and extracted with chloroform. Evaporation of the extract gave the crude base which was dissolved in 15 ml ethanol and the solution was neutralized with a solution of HCl in ether. Standing and cooling gave 7·2 g (78%) hydrochloride, m.p. 216—217°C (ethanol). Mass spectrum, *m/z*: 269 (M^+ corresponding to $C_{17}H_{19}NS$), 223, 178, 165, 58 (base peak, $CH_2{=}\overset{(+)}{N}[CH_3]_2$). For $C_{17}H_{20}ClNS$ (305·9) calculated: 66·75% C, 6·59% H, 11·59% Cl, 4·58% N, 10·48% S; found: 66·76% C, 6·64% H, 11·83% Cl, 4·48% N, 10·51% S.

4-Methoxy-11-(dimethylaminomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*IIIb*)

Ib (2·7 g) was methylated similarly like in the preceding case with a boiling mixture of 3·7 g formic acid and 6 ml 30% formaldehyde in 6 ml water. The base crystallized from ethanol and melted at 124—125°C. IR spectrum: 763, 788, 793 (4 and 3 adjacent Ar—H), 1 080, 1 245, 1 253 ($ArOCH_3$), 1 500, 1 565, 2 980, 3 000, 3 035 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·50—7·30 (m, 7 H, Ar—H), 5·50 (m, 1 H, Ar_2CH), 4·42 and 4·05 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·72 (s, 3 H, OCH_3), c. 3·12 (m, 2 H, CH_2N), 2·25 (s, 6 H, CH_3NCH_3). For $C_{18}H_{21}NOS$ (299·4) calculated: 72·20% C, 7·07% H, 4·68% N, 10·71% S; found: 72·44% C, 7·32% H, 5·00% N, 10·68% S.

Hydrochloride. m.p. 213—215°C (ethanol). For $C_{18}H_{22}ClNOS$ (335·9) calculated: 64·36% C, 6·60% H, 10·56% Cl, 4·17% N, 9·55% S; found: 64·66% C, 6·75% H, 10·60% Cl, 3·94% N, 9·85% S.

N-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylmethyl)acetamide (*Va*)

A mixture of 9·5 g *Ia*, 35 g Na_2CO_3 and 150 ml benzene was stirred and treated dropwise over 20 min with a solution of 10·0 g acetyl chloride in 10 ml benzene. It was refluxed for 2 h, cooled to 50°C, treated with 5·0 g acetyl chloride in 6 ml benzene and the refluxing was continued for further 2·5 h. After cooling the solid was filtered off, dissolved in 200 ml water and extracted with benzene. The extract was combined with the original benzene filtrate, the solution was washed with water and 2·5M-HCl, dried with $MgSO_4$ and evaporated; 10·8 g (99%), m.p. 135—142°C (softening at 85—95°C). Analytical sample, m.p. 144·5—146·5°C (methanol), IR spectrum: 745, 750 (4 adjacent Ar—H), 1553, 1645 (RNHCOR), 1 600, 3 000, 3 035 (Ar), 3 225 cm^{-1} (NH). ^1H NMR spectrum: δ 6·70—7·30 (m, 8 H, Ar—H), 5·71 (bt, 1 H, NH), 4·59 (t, J = 7·0 Hz, 1 H, Ar_2CH), 4·48 and 3·88 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), c. 4·12 (m, 2 H, CH_2N), 1·81 (s, 3 H, $COCH_3$). For $C_{17}H_{17}NOS$ (283·4) calculated: 72·05% C, 6·05% H, 4·94% N, 11·31% S; found: 72·02% C, 6·13% H, 4·84% N, 11·22% S.

N-(4-Methoxy-6,11-dihydrodibenzo[*b,e*]thiepin-11-ylmethyl)-acetamide (*Vb*)

Ib (3·25 g) was similarly acetylated with 4·7 g acetyl chloride in 70 ml benzene in the presence of 12·7 g Na_2CO_3 and gave 2·5 g (67%) *Vb*, m.p. 201—204°C. Analytical sample, m.p. 204—204·5°C (methanol). IR spectrum: 700, 719, 759, 771 (4 and 3 adjacent Ar—H), 1 043, 1 052, 1 077, 1 259, 1 269 ($ArOCH_3$), 1 570, 1 633 (RNHCOR), 3 245 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SO.C^2H_3$): δ 7·90 (bt, J = 7·0 Hz, 1 H, NH), 6·60—7·30 (m, 7 H, Ar—H), 4·70 (t, J = 7·0 Hz, 1 H, Ar_2CH), 4·58 and 3·98 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·92 (t, J = 7·0 Hz, 2 H, CH_2N), 3·68 (s, 3 H, OCH_3), 1·71 (s, 3 H, $COCH_3$). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·97% C, 6·11% H, 4·47% N, 10·23% S; found: 68·54% C, 6·34% H, 4·27% N, 10·30% S.

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