POTENTIAL ANTIDEPRESSANTS: SYNTHESIS OF TWO 4-(AMINOALKOXY)DIBENZO[*b,e*]THIEPIN-11(6*H*)-ONES

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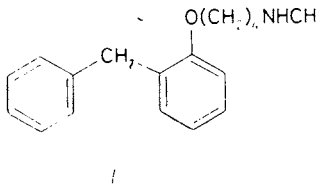
Heating of 4-methoxydibenzo[*b,e*]thiepin-11(6*H*)-one with pyridine hydrochloride to 225 to 235°C effected demethylation and gave *IV*. Its sodium salt reacted with 3-dimethylaminopropyl chloride in ethanol and afforded the 4-(3-dimethylaminopropoxy) compound *II*. The isomeric ether *III* was prepared via the 4-(4-bromobutoxy) compound *V*. Hydrochloride of *II* (VÚFB-17 033) inhibited mildly the binding of [^{3}H]desipramine in rat hypothalamus, had antireserpine activity in rats, mild anticonvulsant effect, and antihypoxic effect in the test of nitrogen anoxia in mice.

In a preceding communication[1] we have described a series of thioxanthone and xanthone analogues of the experimental antidepressant and cerebral activator "bifemelane" (*I*) (ref.[2]). Proceeding further along this line we have designed and synthesized compounds *II* and *III*, derived from the thioxanthones by enlargement of the central ring.



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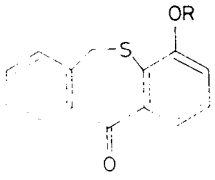

II, R = $(CH_2)_3N(CH_3)_2$
III, R = $(CH_2)_4NHCH$
IV, R = H
V, R = $(CH_2)_4Br$

4-Methoxydibenzo[*b,e*]thiepin-11(6*H*)-one[3] has been chosen as the starting compound for the synthesis of *II* and *III*. Its heating with pyridine hydrochloride to 225–235°C afforded in a good yield *IV* whose identity was confirmed by spectra. A solution of sodium ethoxide in ethanol was used to release the base from 3-dimethylaminopropyl chloride hydrochloride and to form the sodium salt from *IV*,

and reaction of these two compounds in boiling ethanol afforded *II*, which was transformed to the hydrochloride. Reaction of the potassium salt of *IV* with 1,4-dibromobutane in boiling methanol gave *V* which was reacted with methylamine in aqueous ethanol at room temperature. The secondary amine *III* was obtainld in a high yield and was transformed to the hydrochloride. The structures of *II*, *III*, and *V* were corroborated by spectra.

Compounds *II* and *III* were tested pharmacologically in the form of hydrochlorides; the doses given (in mg/kg) were calculated per bases. In the tests the compounds were administered orally. The tests used were oriented towards the expected antidepressant and cerebral activating properties. Acute toxicity in mice, LD_{50} in mg/kg; *II*, 473 (toxic symptoms: sedation, clonic convulsions); *III*, 718 (sedation, dyspnea, convulsions). Discoordinating effects in the rotarod test in mice, ED_{50} in mg/kg: *III*, c. 200. Anticonvulsant effect in the electroshock test in mice, PD_{50} in mg/kg: *II*, 100; *III*, inactive at 100 mg/kg. Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine in rat hypothalamus, IC_{50} in nmol l^{-1}: *II*, >100, 1 119; *III*, >100, >100. Antireserpine effect in rats (inhibition of the reserpine-elicited gastric ulcer formation): *II*, significant effect at 50 mg/kg (administered simultaneously with reserpine); *III*, inactive at 50 mg/kg. Potentiation of yohimbine toxicity in mice: *III*, inactive at 100 mg/kg. Antihypoxic action in the test of nitrogen anoxia in mice: *II*, the dose of 200 mg/kg prolonged the time of survival by 100% (in comparison with the control); *III*, at 200 mg/kg without effect. In conclusion: Compound *II* (VÚFB-17 033) showed indications of potential antidepressant and cerebral activating properties while *III* was inactive.

The compounds were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml, unless they exceed 100 μg/ml, are given): *Streptococcus β-haemolyticus*, *III* 50; *Streptococcus faecalis*, *III* 50; *Staphylococcus pyogenes aureus*, *II* 50, *III* 25; *Pseudomonas aeruginosa*, *III* 50; *Proteus vulgaris*, *II* 50.

EXPERIMENTAL

The melting points were determined in 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 a suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm (log ε)) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol, ν in cm^{-1}) with Perkin–Elmer 298 spectrophotometer, and ^{1}H NMR spectra (in $CDCl_3$ unless stated otherwise, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

4-Hydroxydibenzo[*b*,*e*]thiepin-11(6*H*)-one (*IV*)

A mixture of 29·7 g 4-methoxydibenzo[*b*,*e*]thiepin-11(6*H*)-one[3] and 89 g pyridine hydrochloride was heated under stirring for 45 min in a bath having the temperature of 225–235°C. After

cooling to 60°C the mixture was diluted with 400 g of water and ice and after 1 h standing the solid product was filtered. It was dissolved in 500 ml boiling ethanol, the solution was filtered with active carbon, and the filtrate was evaporated. The residue was crystallized from 250 ml ethanol; 24·7 g (88%) of *IV*, m.p. 180–185°C. Analytical sample, m.p. 186–189°C (methanol). UV spectrum: 237 (4·21), 260 (4·02), 288 (3·83), 359 (3·48). IR spectrum: 713, 730, 762, 774, 805 (3 and 4 adjacent Ar—H); 1 150 (ArOH); 1 557, 1 570, 1 598 (Ar); 1 623 (ArCOAr'); 3 165 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 4·12 s, 2 H (2 H-6); 7·00 dd, 1 H (H-3, J = 8·0; 2·5); 7·15 t, 1 H (H-2, J = 8·0); 7·30–7·70 m, 5 H (H-1,7,8,9,10). For $C_{14}H_{10}O_2S$ (242·3) calculated: 69·40% C, 4·16% H, 13·23% S; found: 69·72% C, 4·12% H, 13·45% S.

4-(3-Dimethylaminopropoxy)dibenzo[*b*,*e*]thiepin-11(6*H*)-one (*II*)

3-Dimethylaminopropyl chloride hydrochloride (6·4 g) was added to a solution of sodium ethoxide, prepared from 1·9 g Na and 80 ml ethanol. The mixture was stirred for 10 min and treated with 7·3 g *IV*; it was then refluxed for 11 h. After cooling the crystallized NaCl was filtered off, washed with benzene and thanol, the filtrate was acidified with hydrochloric acid, and evaporated in vacuo. The residue was distributed between water and benzene, the aqueous solution was made alkaline with NH_4OH, and the base was extracted with benzene. Drying (K_2CO_3) and evaporation in vacuo gave 8·6 g (88%) of crude *II* which crystallized on standing, m.p. 63–65°C (cyclohexane). UV spectrum: 237 (4·27), infl. 254 (4·13), 275 (3·87), 358 (3·59). IR spectrum: 660, 732, 777, 808 (3 and 4 adjacent Ar–H); 1 254 (Ar–O–R); 1 585, 3 070 (Ar); 1 647 (ArCOAr'); 2 750, 2 810 (N–CH_3). ^{1}H NMR spectrum: 1·95 m, 2 H (CH_2 in position 2 of propane); 2·18 s, 6 H ($N(CH_3)_2$); 2·45 t, 2 H (CH_2N, J = 7·0); 3·95 s, 2 H (2 H-6); 4·00 t, 2 H (CH_2O, J = 7·0); 6·88 dd, 1 H (H-3, J = 8·5; 2·0); 7·10 t, 1 H (H-2, J = 8·5); 7·30 m, 4 H (H-1,7,8,9); 7·75 bd, 1 H (H-10, J = 8·5). For $C_{19}H_{21}NO_2S$ (327·4) calculated: 69·69% C, 6·47% H, 4·28% N, 9·79% S; found: 70·00% C, 6·59% H, 4·24% N, 9·95% S.

Hydrochloride, m.p. 172–175°C (ethanol–ether). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·95% C, 6·17% H, 9·93% Cl, 3·93% N, 8·65% S.

4-(4-Bromobutoxy)dibenzo[*b*,*e*]thiepin-11(6*H*)-one (*V*)

A solution of 2·6 g KOH and 9·7 g *IV* in 100 ml methanol was treated with 17·6 g 1,4-dibromobutane and the mixture was refluxed with stirring for 10·5 h. The solvent was evaporated in vacuo, the residue was distributed between water and benzene, the benzene layer was washed with 10% NaOH and water, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was crystallized from a mixture of benzene and light petroleum; 10·1 g (67%) of *V*, m.p. 121–124°C. Analytical sample, m.p. 123–126°C (benzene–light petroleum). UV spectrum: 239 (4·24), infl. 256 (4·10), 285 (3·80), 364 (3·54). IR spectrum: 662, 734, 772 (3 and 4 adjacent Ar–H); 1 257 (Ar–O–R); 1 551, 1 584, 1 599, 3 055 (Ar); 1 643 (ArCOAr'). ^{1}H NMR spectrum: 2·00 m, 4 H (CH_2CH_2 in positions 2 and 3 of the butane chain); 3·45 t, 2 H (CH_2Br, J = 7·0); 3·95 s, 2 H (2 H-6); 4·00 t, 2 H (CH_2O, J = 7·0); 6·85 dd, 1 H (H-3, J = 8·5; 2·0); 7·12 t, 1 H (H-2, J = 8·5); c. 7·40 m, 4 H (H-1,7,8,9); 7·75 bd, 1 H (H-10, J = 8·5). For $C_{18}H_{17}BrO_2S$ (377·3) calculated: 57·30% C, 4·54% H, 21·18% Br, 8·50% S; found: 57·86% C, 4·56% H, 21·43% Br, 8·68% S.

4-(4-Methylaminobutoxy)dibenzo[*b*,*e*]thiepin-11(6*H*)-one (*III*)

A solution of 10·1 g *V* in 450 ml ethanol was treated with 105 ml 41% aqueous methylamine and the mixture was stirred for 7 h at room temperature. After standing overnight, further 95 ml methylamine solution were added and the stirring was continued for 8 h. Ethanol was

evaporated under reduced pressure, the residue was treated with 10% NaOH, and the product was extracted with benzene. The extract was washed with 10% NaOH and water and the base was extracted by shaking into 3M-HCl. The acid aqueous layer was made alkaline with NH_4OH and the released base was isolated by extraction with chloroform. Processing of the extract gave 7·0 g (80%) of *III*, m.p. 73–78°C. Analytical sample, m.p. 75–78°C (cyclohexane–hexane). UV spectrum: 248 (4·26), infl. 264 (4·13), 293·5 (3·86), 360 (3·58). IR spectrum: 718, 730, 770 (3 and 4 adjacent Ar—H); 1 251 (Ar—O—R); 1 555, 1 586, 1 598, 3 040 (Ar); 1 640 (ArCOAr'); 2 790 (N—CH_3); 3 301 (NH). ^{1}H NMR spectrum: 1·43 s, 1 H (NH); 1·75 m, 4 H (CH_2CH_2 in positions 2 and 3 of the butane chain); 2·40 s, 3 H (CH_3N); 2·59 t, 2 H (CH_2N, J = 7·0); 3·92 s, 2 H (2 H-6); 4·00 t, 2 H (CH_2O, J = 7·0); 6·85 dd, 1 H (H-3, J = 8·5; 2·0); 7·00–7·50 m, 5 H (H-1,2,7,8,9); 7·75 bd, 1 H (H-10). For $C_{19}H_{21}NO_2S$ (327·4) calculated: 69·69% C, 6·47% H, 4·28% N, 9·79% S; found: 69·43% C, 6·57% H, 4·48% N, 9·77% S.

Hydrochloride, m.p. 215–218°C (methanol). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·79% C, 6·14% H, 9·68% Cl, 3·74% N, 9·04% S.

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