6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN-11-YL 3-QUINUCLIDINYL ETHERS: NEW POTENTIAL ANTIDEPRESSANTS AND ANTIHISTAMINE AGENTS

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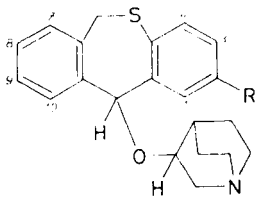
Reactions of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin and its 2-methyl derivative, and further of the methanesulfonates of 2-chloro- and 2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol with 3-quinuclidinol afforded the title ethers *I*—*IV*. The 2-methyl compound *II* (VÚFB-17 088) showed significant antihistamine activity and the 2-chloro compound *III* (VÚFB-17 089), having antireserpine and anticataleptic activity, proved a potential antidepressant agent.

1-Methyl-4-piperidinyl and 1-methylperhydroazepin-4-yl ethers derived from 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol were found to have significant antihistamine, antireserpine, and anticataleptic activity[1–3]. More recently we have completed the series by the corresponding 3-quinuclidinyl ethers *I*—*IV*; their synthesis and pharmacology are being described in the present paper.

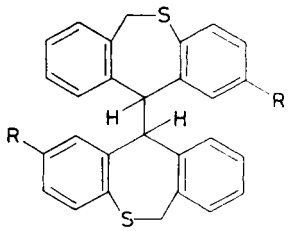


I, R = H *III*, R = Cl
II, R = CH_3 *IV*, R = Br

Compound *I* (mixture of two racemates similarly like *II*—*IV*) was obtained by reaction of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[3,4] with 3-quinuclidinol[5] in boiling dioxane in the presence of potassium carbonate. The resulting mixture was separated by extraction into aqueous tartaric acid to the basic and neutral components; the basic fraction was chromatographed and the seemingly homogeneous base *I* crystallized from ethanol. Its ^{1}H NMR spectrum does not display any sharp signal (even the skeletal H-11 appears as a broad singlet) and cannot thus be taken as a proof of homogeneity. The ether bond in *I* is cleaved easily by strong acids (hydrochloric, methanesulfonic) (cf. ref.[3]); the salts with maleic, fumaric,

and tartaric acids are stable but did not crystallize. 2,4,6-Trinitrobenzoate was prepared for characterization, and for pharmacoloigcal testing an aqueous solution of the hydrogen tartrate was used. Compound *II* was prepared similarly from 11-chloro-2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin[6]. The base crystallized easily and behaved like a homogeneous substance (constant melting point, sharp singlet of the $ArCH_3$ group in the ^1H NMR spectrum); it afforded easily a crystalline hydrogen maleate.

For preventing the losses on the basic products by their cleavage during the isolation into the aqueous acid layers, *III* and *IV* were prepared by a different way. 2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[7,8] and 2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[9] were treated with methanesulfonyl chloride in pyridine and the methanesulfonates formed were processed "in situ" by reactions with 3-quinuclidinol[5] in boiling pyridine. The crude products, mixtures of neutral and basic substances, were directly separated by chromatography on silica gel. The first to be eluted with benzene were highly melting inhomogeneous solids which are tentatively assigned to be the stereoisomeric mixtures of *V* and *VI* (cf. ref.[10]). The chloro compound could not be satisfactorily purified but in the case of the bromo compound, there is at least some evidence in favour of structure *VI*. The hypothesis that these compounds could be the corresponding bis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) ethers (cf. ref.[11]) seems to be excluded by the absence of ether bands (1 070 to 1 150 cm^{-1}) in the IR spectrum of our bromo compound. Further to be eluted with benzene were the starting 2-chloro- and 2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (unclear whether unreacted or reformed by cleavage of the product). The bases *III* and *IV* were eluted as the most polar products and were obtained in yields of 45–65%. They crystallized and behaved – especially *IV* – as homogeneous substances (constant melting point, ^1H NMR spectrum). For pharmacological testing they were transformed to maleates.



V, R = Cl
VI, R = Br

The ethers *I*–*IV* were pharmacologically tested in the form of salts; they were administered orally and the doses given (in mg/kg) were calculated per bases. Acute

toxicity in mice, LD_{50}: *I*, 165; *II*, 225; *III*, 166; *IV*, 221 (toxic symptoms in all cases were convulsions followed by paresis). Incoordinating activity in the rotarod test in mice, ED_{50}: *I*, 38·9 (60 min after the administration); *III*, 78·9 (30 min); *IV*, 49·7 (30 min). Influence on the locomotor activity of mice in the photo-cell method of Dews: *III*, in doses of 2 and 10 mg/kg without significant effect. Inhibition of the ulcerogenic effect of reserpine in rats: *I*, *II*, and *IV* had significant antireserpine effects in doses of 20 mg/kg; *III* was significantly active already at 5 mg/kg. Inhibition of the reserpine ptosis in mice: *III*, in the dose of 30 mg/kg antireserpine effect on the border of statistical significance. Antagonization of perphenazine catalepsy in rats: *III*, in the dose of 50 mg/kg anticataleptic effect in 90% of the animals; the dose of 20 mg/kg had only insignificant effect. The effect of serotonin in the test of rat paw oedema was not influenced by doses of 10 mg/kg of compounds *I*–*IV*. Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine in the rat hypothalamus: compounds *I*–*IV* were inactive in concentrations of 100 nmol l^{-1} in both lines. Antihistamine activity in the test of histamine aerosol in guinea pigs, PD_{50} : *I*, <1 (this dose protected 5 animals out of 8); *II*, 0·32; *III*, >1 (this dose protected 25% of the animals); *IV*, <1 (this dose protected 5 animals out of 8). Antihistamine activity in the test of histamine detoxication in guinea pigs, PD_{50} : *I*, >10 (this dose protected 38% of the animals); *II*, 3·3; *III*, >10 (protected only 1 animal out of 7); *IV*, >10 (protected 25% of the animals). Compounds *III* and *IV* did not reveal anticholinergic action in the test of methacholine lacrimation in rats. On the other hand, *III* in the dose of 10 mg/kg significantly inhibited the oxotremorine effects in mice (tremor and further cholinomimetic effects). In conclusion, *II* (VÚFB-17 088) showed the pharmacological profile of an antihistamine agent and *III* (VÚFB-17 089) displayed properties of a thymoleptic and potential antidepressant.

Antimicrobial tests in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml given unless they exceeded 128 μg/ml): *Streptococcus β-haemolyticus*. *I* 128, *II* 128, *III* 128, *IV* 128; *Streptococcus faecalis*, *I* 8, *II* 8, *III* 8, *IV* 128; *Staphylococcus pyogenes aureus*, *I* 2, *II* 2, *III* 4, *IV* 128; *Pseudomonas aeruginosa*, *I* 128, *II* 128, *III* 32, *IV* 128; *Escherichia coli*, *I* 8, *II* 16, *III* 8, *IV* 64; *Proteus vulgaris*, *I* 16, *II* 16, *III* 8, *IV* 128; *Trichophyton mentagrophytes*, *I* 50, *III* 50, *IV* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler block and they are 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. UV spectrum (in methanol, λ_{max} (log ε)) was recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, %) with a Varian MAT 44S spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel; preparative chromatography was carried out on columns of silica gel

(Merck 40). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)quinuclidine (*I*)

A solution of 4·5 g 3-quinuclidinol[5] in 65 ml dioxane was treated with 4·9 g K_2CO_3 and then slowly under stirring with 8·7 g 11-chloro-10,11-dihydrodibenzo[*b*,*e*]thiepin[3,4]. The mixture was refluxed for 1 h, a part of dioxane was evaporated in vacuo and the residue was distributed between water and benzene. The benzene layer was washed with water and the bases were extracted into a solution of 10 g tartaric acid in 100 ml water. The aqueous layer was made alkaline with NH_4OH and the bases were extracted with dichloromethane. Processing of the extract gave 6·8 g inhomogeneous base which was chromatographed on 60 g silica gel. Elution with a mixture of 90% chloroform, 5% chloroform saturated with NH_3 and 5% methanol gave 6·1 g (51%) homogeneous (TLC) *I* which crystallized from ethanol and after four recrystallizations from ethanol reached the constant m.p. 151—153°C. IR spectrum: 740, 750 (4 adjacent Ar—H); 1 056, 1 111 (R—O—R'); 1 480, 1 560, 1 593, 3 060, 3 075 (Ar). ^{1}H NMR spectrum: 1·00 to 2·20 bm, 5 H (CH_2CHCH_2 of quinuclidine); 2·50—3·20 bm, 6 H (3 NCH_2 of quinuclidine); 3·60 bs, 1 H (O—CH of quinuclidine); 4·00 bd and 4·52 bd, 1 + 1 H ($ArCH_2S$, ABq, J = 13·0); 5·65 bs, 1 H (Ar_2CH—O); 6·80—7·50 m, 8 H (8 ArH). For $C_{21}H_{33}NOS$ (337·5) calculated: 74·74% C, 6·87% H, 4·15% N, 9·50% S; found: 74·74% C, 6·96% H, 4·07% N, 9·71% S.

2,4,6-*Trinitrobenzoate*, m.p. 101—103°C (ethanol–ether). Mass spectrum: 337 (M^+, $C_{21}H_{23}$·NOS, 0·3), 226, 212, 197, 178, 165, 126, 98. For $C_{28}H_{26}N_4O_9S$ (594·6) calculated: 56·56% C, 4·41% H, 9·42% N, 5·39% S; found: 56·91% C, 4·69% H, 9·48% N, 5·64% S.

3-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)quinuclidine (*II*)

A similar reaction of 7·9 g 3-quinuclidinol[5] with 14·8 g 11-chloro-2-methyl-6,11-dihydrodibenzo-[*b*,*e*]thiepin[6] and 7·85 g K_2CO_3 in 120 ml dioxane at 90°C (2 h), similar processing and similar chromatography of the basic fraction (8·9 g, 45 g silica gel) gave 7·4 g (37%) of *II* which crystallized from 2-propanol or ethanol, constant m.p. 176—178°C after three recrystallizations. IR spectrum: 730, 768, 806, 878 (4 and 2 adjacent, and solitary Ar—H); 1 072 (R—O—R'); 1 487, 1 584, 1 593, 3 035, 3 070 (Ar). ^{1}H NMR spectrum: 1·00—3·20 m, 11 H (5 CH_2 and CH of quinuclidine); 2·28 s, 3 H ($ArCH_3$); 3·65 m, 1 H (O—CH of quinuclidine); 4·05 bd and 4·60 bd, 1 + 1 H ($ArCH_2S$, ABq, J = 13·0); 5·70 bs, 1 H (Ar_2CH—O); 6·70—7·50 m, 7 H (7 ArH). For $C_{22}H_{25}NOS$ (351·5) calculated: 75·17% C, 7·17% H, 3·99% N, 9·12% S; found: 75·00% C, 7·26% H, 3·76% N, 9·36% S.

Hydrogen maleate hemihydrate, m.p. 193—196°C (ethanol–ether). For $C_{26}H_{29}NO_5S$ + 0·5 H_2O (476·6) calculated: 65·52% C, 6·35% H, 2·94% N, 6·73% S; found: 65·67% C, 6·30% H, 2·74% N, 6·54% S.

3-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yloxy)quinuclidine (*III*)

A stirred solution of 12·5 g 2-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[7,8] in 75 ml pyridine was treated dropwise with 6·3 g methanesulfonyl chloride, the mixture was stirred for 1 h at 70°C, and for 2 h at room temperature. After standing overnight, 8·8 g 3-quinuclidinol[5] were added and the mixture was stirred and refluxed for 5 h. After cooling the mixture was diluted with 100 ml water and extracted with chloroform. The extract was washed with water and processed. The residue was chromatographed on a column of 180 g silica gel. Elution with benzene

gave in the first fraction 2·1 g solid (considered to be crude *V*) melting at 275—279°C (toluene) which was evidently contaminated by some polymeric material and its full purification was given up. The following benzene fractions recovered 1·4 g starting 2-chloro-6,11-dihydrodibenzo[*b,e*]-thiepin-11-ol (comparison by TLC). The desired product *III* (8·2 g, 46%) was eluted with a mixture of 93% chloroform, 5% chloroform saturated with NH_3 and 2% methanol. It crystallized from ethanol, m.p. 150—152°C. UV spectrum: 267 (4·05). IR spectrum: 770, 810, 871, 879 (4 and 2 adjacent, and solitary Ar—H); 1 030, 1 045, 1 060 (R—O—R'); 1 489, 1 572, 1 584, 1 600, 3 020, 3 038, 3 069 (Ar). ^{1}H NMR spectrum: 1·00—3·00 m, 11 H (5 CH_2 and CH of quinuclidine); 3·60 bm, 1 H (O—CH of quinuclidine); 4·30 vbs, 2 H ($ArCH_2S$); 5·80 bs, 1 H (Ar_2CH—O); 6·90—7·60 m, 7 H (7 ArH). For $C_{21}H_{22}ClNOS$ (371·9) calculated: 67·82% C, 5·96% H, 9·53% Cl, 3·77% N, 8·62% S; found: 67·85% C, 5·98% H, 9·66% Cl, 3·63% N, 8·84% S.

Hydrogen maleate, m.p. 177—180°C (ethanol–ether). For $C_{25}H_{26}ClNO_5S$ (488·0) calculated: 61·53% C, 5·37% H, 7·27% Cl, 2·87% N, 6·57% S; found: 61·44% C, 5·27% H, 7·40% Cl, 2·70% N, 6·79% S.

3-(2-Bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-yloxy)quinuclidine (*IV*)

Similar reaction of 15·4 g 2-bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol with 6·3 g methanesulfonyl chloride in 50 ml pyridine, followed by treatment with 8·9 g 3-quinuclidinol[5], and similar processing gave 20·1 g mixture of basic and neutral products which was chromatographed on 150 g silica gel. Benzene eluted first 4·4 g solid, tentatively considered as bis(2-bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl) (*VI*), m.p. 256—258°C (toluene). Mass spectrum: 578 (0·4), 544 (0·1), 375 (0·3), 320 (2·0), 305 (45), 291 (74), 290 (76), 289 (58), 275 (26), 256 (37), 227 (27), 210 (60), 178 (100), 165 (86), 152 (26), 91 (76), 89 (45), 63 (47). IR spectrum: 757, 804, 824 (4 and 2 adjacent Ar—H); 1 485, 1 550, 1 573, 3 028, 3 060 (Ar). For $C_{28}H_{20}Br_2S_2$ (580·4) calculated: 57·94% C, 3·47% H, 27·54% Br, 11·05% S; found: 57·26% C, 3·51% H, 26·80% Br, 10·70% S.

Continued elution with benzene recovered 2·7 g 2-bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (comparison by TLC). Elution with chloroform containing 5% chloroform saturated with NH_3 and 3% methanol afforded 13·6 g (65%) crude *IV* which was dissolved in 30 ml boiling toluene, the undissolved part was removed by filtration, and the filtrate gave by cooling 8·3 g crystalline *IV*, m.p. 157—160°C (ethanol). IR spectrum: 763, 769, 803, 879 (4 and 2 adjacent, and solitary Ar—H); 1 030, 1 050, 1 070 (R—O—R'); 1 483, 1 490, 1 570, 1 583, 3 038, 3 060, 3 075 (Ar). ^{1}H NMR spectrum: 1·00—2·20 m, 5 H (CH_2CHCH_2 of quinuclidine); 2·50—3·20 m, 6 H (3 NCH_2 of quinuclidine); 3·60 m, 1 H (O—CH of quinuclidine); 4·25 bs, 2 H ($ArCH_2S$); 5·65 s, 1 H (Ar_2CH—O); 6·85 d, 1 H (H-4, J = 9·0); 7·00—7·40 m, 5 H (H-3, 7, 8, 9, 10); 7·52 d, 1 H (H-1, J = 2·5). For $C_{21}H_{22}BrNOS$ (416·4) calculated: 60·58% C, 5·33% H, 19·19% Br, 3·36% N, 7·70% S; found: 60·75% C, 5·38% H, 19·50% Br, 3·20% N, 7·89% S.

Hydrogen maleate, m.p. 188—190°C (ethanol–ether). For $C_{25}H_{26}BrNO_5S$ (532·5) calculated: 56·39% C, 4·92% H, 15·01% Br, 2·63% N, 6·02% S; found: 56·40% C, 4·83% H, 14·96% Br, 2·43% N, 5·85% S.

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