SYNTHESIS OF BENZO[a]FURO[2,3-g]QUINOLINZINES FROM 2-METHYL-2-CINNAMOYLOXIRANE

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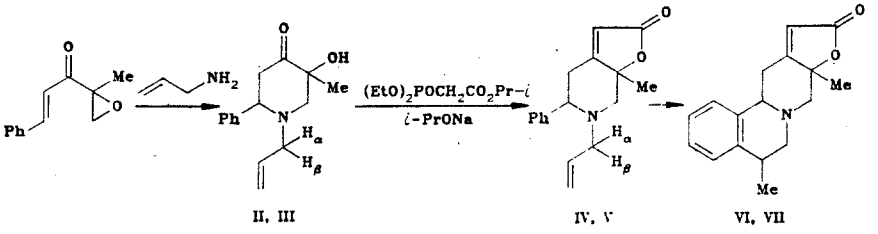
Stereoisomeric 1e-allyl-3-hydroxy-3-methyl-6e-phenyl-4-piperidones were obtained by reaction of 2-methyl-2-cinnamoyloxirane with allylamine. Their PO-olefinization and subsequent heating in 96% H_2SO_4 leads to 3a,4,6,7,11b,12-hexahydro-3a,7-dimethyl-2-oxobenzo[a]furo[2,3-g]quinolizines.

Interest in the chemistry of benzo[a]furoquinolizines is due to the similarity of their structure to that of natural and related active compounds [1-3]. The only method until recently for constructing the benzo[a]furo[2,3-g]quinolizine skeleton is by reductive photocyclization of enamides of the isoquinoline series [3].

We have proposed a new path of synthesis of compounds of this type [4], based on the readily available cinnamoyloxirane I. Thus, in the reaction of compound I with allylamine, stereoisomeric piperidones II, III were obtained, which were converted according to the Witting-Horner reaction into lactones IV, V. On heating in 96% H_2SO_4 the latter cyclized into quinolizidines VI, VII.



II, III IV, V VI, VII

II 3e-OH, 3a-Me, 6e-Ph; III 3a-OH, 3e-Me, 6e-Ph; IV 5e-Ph; V 5a-Ph; VI 11b(α)-H, 3a(β) and 7(α)-Me; VII 11b(β)-H, 3a(β) and 7(β)-Me

The structure of all the synthesized compounds was confirmed by the data of elemental analysis, IR, PMR, NMR and mass spectra (Tables 1 and 2). The structure of 1e-allyl-3-hydroxy-4-piperidones II, III conforms well with the literature data [5, 6]. The frequency values of the absorption maxima in the IR spectra, corresponding to the C=C and C=O bonds of lactones IV-VII, are characteristic of unsaturated γ-lactones. The chair-conformation of the six-membered rings in compounds II-VII and the relative orientation of their substituents follow from the spin-spin coupling constants in the PMR spectra (Table 1) [8]. The types of coupling of rings B and C in quinolizidines VI, VII is also confirmed by the presence or absence of Bohlmann bands in the IR spectra in the 2700...2850 cm^{-1} region [9]. The proposed conformation of compound VI with an α-orientation of the 11b-H atom conforms with the presence of these absorption bands, and also with the value of the chemical shift of the proton under consideration in the PMR spectrum [10]. In the IR spectrum of quinolidizine VII, the Bohlmann bands are absent, and in the case of a chair-conformation of the piperidine ring, the cis-B/C coupling appears to be the only one possible. The shift to the strong field of most of the carbon atoms signals of the quinolizidine fragment in the ^{13}C NMR spectra (Table 2) during the cis/B/C coupling, which is noted for benzo[a]quinolizidines VI, VII, is significant [11].

To investigate the pharmacological activity, we studied the acute toxicity, the neurotropic and analgesic properties of methanesulfonate VI and hydrochloride VII in tests on white mice.

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TABLE 1. Characteristics of Compounds II-VII

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (SSCC, Hz)	M	Yield, %
II	$C_{15}H_{19}NO_2$	45...46	1645, 1720, 3505	1,63 (s, 3-CH_3); 2,24 (d, 2-H_a; 11,3); 2,52 (d.d, 5-H_e; 13,5; 3,5); 2,55 (d.d, H_α; 14,0; 7,0); 2,83 (d.d., 5-H_a; 13,5; 11,5); 3,16 (d.d.t, H_β, 14,0; 4,5; 2,0; 2,0); 3,27 (d, 2-H_e; 11,3); 3,47 (d.d, 6-H_a; 11,5; 3,5); 3,83 (s, OH); 5,05...5,16 (m, C=CH_2); 5,66...5,86 (m, CH=C); 7,23...7,40 (m, 5H arom.)	245	81
III	$C_{15}H_{19}NO_2$	Oil	1645, 1715 sh., 1730, 3495	1,28 (s, 3-CH_3); 2,37 (d, 2-H_a; 12,0); 2,48 (d.d, 5-H_e; 14,5; 4,0); 2,75 (d.d, H_α; 14,5; 7,5); 3,04 (d.d, 5-H_a; 14,5; 10,5); 3,09 (d, 2-H_e; 12,0); 3,12 (d.d.t, H_β; 14,5; 4,5; 2,0; 2,0); 3,59 (d.d, 6-H_a; 10,5; 4,0); 3,40...3,72 (OH); 5,02...5,13 (m, C=CH_2); 5,65...5,84 (m, CH=C); 7,17...7,37 (m, 5H arom.)	245	80
IV	$C_{17}H_{19}NO_2$	80...81	1655, 1765, 1775 sh.	1,68 (s, 7a-CH_3); 2,07 (d, 7-H_a; 10,8); 2,57 (d.d.d, 4-H_a; 13,5; 10,8; 1,8); 2,59 (d.d, H_α; 14,0; 7,5); 2,84 (d.d, 4-H_e; 13,5; 3,5); 3,13 (d.d.t, H_β; 14,0; 4,5; 2,0; 2,0); 3,20 (d.d, 5-H_a; 10,8; 3,5); 3,43 (d, 7-H_e; 10,8); 5,03...5,12 (m, C=CH_2); 5,62...5,85 (m, CH=C); 5,68 (d, 3-H; 1,8); 7,26...7,40 m. d. (m, 5H, arom.)	269	65
V	$C_{17}H_{19}NO_2$	67...67,5	1650, 1770	1,68 (s, 7a-CH_3); 2,71 (d, 7-H_a; 11,0); 2,84 (d.d, H_α; 14,2; 7,0); 2,98 (d, 7-H_e; 11,0); 3,02 (d.d, 4-H_e; 14,0; 1,5); 3,09 (d.d.d, 4-H_a, 14,0; 7,1; 1,8); 3,26 (d.d.t, H_β; 14,2; 5,8; 1,6; 1,6); 4,29 (d.d, 5-H_e; 7,1; 1,5); 5,10...5,20 (m, C=CH_2); 5,72...5,82 (m, CH=C); 5,81 (d, 3-H; 1,8); 7,12...7,19 (m, 2H arom.); 7,24...7,38 (m, 3H arom.)	269	62
VI	$C_{17}H_{19}NO_2$	106...107	1655, 1768, 1780 sh, 2765, 2805	1,27 (d, 7-CH_3; 7,0); 1,61 (s, 3a-CH_3); 2,33 (d, 4-H_a; 10,8); 2,35 (t, 6-H_a; 11,5); 2,51 (d.d.d, 12-H_a; 12,5; 10,5; 1,8); 2,98 (d.d, 6-H_e; 11,5; 5,2); 3,20...3,28 (m, 7-H_a); 3,29 (d, 4-H_e; 10,8); 3,33 (d.d, 11b-H_a; 10,5; 3,0); 3,40 (d.d, 12-H_e; 12,5; 3,0); 5,81 (d, 1-H; 1,8); 7,16...7,41 (m, 4H arom.)	269	63
VII	$C_{17}H_{19}NO_2$	129...130	1658, 1770, 1780 sh.	1,20 (d, 7-CH_3; 6,3); 1,65 (s, 3a-CH_3); 2,57 (d, 4-H_a; 10,5); 2,96 (t, 6-H_a; 11,5); 2,97 (d, 4-H_e; 10,5); 2,98 (d.d.d, 12-H_a; 13,5; 5,6; 1,8); 2,96...3,04 (m, 7-H_a); 3,17 (d.d, 6-H_e; 11,5; 5,2); 3,46 (d.d, 12-H_e; 13,5; 1,6); 4,49 (d.d, 11b-H_e; 5,6; 1,6); 5,61 (d, 1-H; 1,8); 7,08...7,27 (m, 4H arom.)	269	70

TABLE 2. Chemical Shifts in ^{13}C NMR Spectra of Compounds VI and VII

Compound	δ, ppm											
	$C_{(1)}$	$C_{(2)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(6)}$	$C_{(7)}$	$C_{(7a)}$–$C_{(11a)}$	$C_{(11b)}$	$C_{(12)}$	$C_{(12a)}$	3a-CH_3	7-CH_3
VI	112,62	172,10	84,18	66,69	59,61	32,99	124,68; 126,03; 126,64; 126,87; 135,91; 139,68	64,29	34,07	173,41	22,20	17,82
VII	114,12	172,03	84,27	58,80	58,32	26,56	124,88; 126,12; 127,07; 127,69; 132,52; 139,57	58,58	28,64	170,54	22,18	19,31

The acute toxicity index (LD_{50}) on intravenous administration of the above salts was equal to 181.4 and 114.6 mg/kg, respectively, i.e., in accordance with the accepted classification these compounds can be classed as slightly toxic.

When administered to the mice in doses comprising 20% of LD_{50} these compounds manifest a distinct general neurotropic action: they suppress the orienting reaction; increase the survival time of test animals after the administration of strychnine and corazole; intensify the reserpine hypothermia; prolong the analgesic effect of morphine, although by themselves they do not alter the threshold of pain sensitivity to a temperature dependent irritant.

Thus, a preparative method has been developed for the synthesis of benzo[a]furo[2,3-g] quinolizines, which are of definite interest for the synthesis of new biologically active compounds.

EXPERIMENTAL

The IR spectra of solutions of the compounds in C_2Cl_4 were run on a UR-20 spectrophotometer. The PMR and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker WM-360 spectrometer, using HMDS as internal standard. The mass spectra were recorded on a Varian MAT-311 mass-spectrometer at 70 eV. The characteristics of compounds II-VII are given in Table 1. The data of the elemental analysis of the compounds obtained agree with the calculated values.

1e-Allyl-3a-hydroxy-3a-methyl-6e-phenyl-4-piperidone (II). A 50.0 g portion (0.27 mole) of cinnamoyloxirane I was dissolved in 300 ml of dioxane, and 50 ml of water and 30 g (0.52 mole) of allylamine were successively added. The reaction mixture was allowed to stand for 24 h at 18....20°C, and then was evaporated. The residue was dissolved in 200 ml of 10% HCl, and the solution was allowed to stand overnight. The aqueous solution was then filtered and the filtrate was made alkaline with $NaHCO_3$. The precipitate that separated out was extracted with ether, the ether solution was dried over Na_2SO_4, evaporated, and the residue was crystallized from pentane.

1e-Allyl-3a-hydroxy-3e-methyl-6e-phenyl-4-piperidone (III). An 8 g portion (0.21 mole) of allylamine was added at 150...160°C to a solution of 18 g (0.096 mole) of cinnamoyloxirane I in 50 ml of benzene. The reaction mixture was allowed to stand at the above temperature for 2 h and was then treated as described in the preceding experiment.

6e-Allyl-8a-methyl-2-oxo-5-phenylfuro[2,3-c]piperidine (IV, V). A 28.6 g portion (0.12 mole) of isopropyl diethylphosphonoacetate was added to a solution of sodium isopropylate, prepared by dissolution of 2.53 g (0.11 mole) of sodium in 250 ml of isopropanol, and then while cooling the mixture with tap water, 21.9 g (0.1 mole) of piperidone II, III was added. The mixture was stirred to the complete dissolution of piperidone; it was then acidified with acetic acid, the solvent was evaporated, and the residue was dissolved in ether and washed with a saturated solution of $NaHCO_3$ and water. After evaporation of the solvent, the residue was dissolved in 100 ml of isopropanol, 16.4 g (0.20 mole) of sodium isopropylate was added, and the mixture was allowed to stand for 5 h at 20...25°C. The mixture was then acidified with acetic acid, the solvent was evaporated, and the residue was dissolved in ether. The ether solution was washed with a saturated solution of $NaHCO_3$ and water, dried over Na_2SO_4, evaporated and the residue was crystallized from isopropanol.

3a,4,6,7,11b,12-Hexahydro-3a,7-dimethyl-2-oxobenzo[a]furo[2,3-g]quinolizines (VI, VII). A mixture of 1 g (3.8 mmole) of lactone IV, V and 2 ml of 96% H_2SO_4 was allowed to stand for 2 h 30 min at 110...115°C. It was then diluted with water (30 ml), and allowed to stand for another hour at the same temperature. The solution was cooled, made alkaline with Na_2CO_3, extracted with ether, and the extract was dried over Na_2SO_4. The solvent was evaporated, and the residue was crystallized from isopropanol.

3a,4,6,7,11b(α),12-Hexahydro-3a(β),7(α)-dimethyl-2-oxobenzo[a]-furo[2,3-g]quinolizine methanesulfonate (IV·CH_3SO_3H, $C_{17}H_{19}NO_2 \cdot CH_4O_3S$). A 1.06 g portion (11 mmoles) of methanesulfonic acid was added to a solution of 2.69 g (10 mmoles) of lactone IV in 10 ml of acetone. The precipitated salt was filtered and washed with cold acetone. Yield, 3.2 g (88%) of methanesulfonate, mp 193...194°C.

3a,4,6,7,11b(β),12-Hexahydro-3a(β),7(β)-dimethyl-2-oxobenzo[a]-furo[2,3-g]quinolizine hydrochloride (V·HCl, $C_{17}H_{19}NO_2 \cdot HCl$). Dry HCl was passed through a solution of 2.69 g (10 mmoles) of lactone V in 20 ml of ether to pH 4...5. The precipitated hydrochloride was recrystallized from isopropanol. Yield 2.8 g (91%) of the salt, mp 208-210°C.

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