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SYNTHESIS OF 3a,4,6,7,11b,12-HEXAHYDRO-3a-METHYL-7-PHENYLBENZO[a]FURO[2,3-g]QUINOLIZINES

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By alkylation of stereoisomeric 7a-methyl-2-oxo-5-phenylfuro-[2,3-c]piperidines with phenacyl bromide and subsequent reduction of the keto group by sodium borohydride, amino alcohols were obtained; heating of these products in 70% sulfuric acid affords 3a,4,6,7,11b,12-hexahydro-3a-methyl-7-phenylbenzo[a]furo[2,3-g]quinolizines. It was found that the cis-quinolizidine, upon heating to 150°C in acetic acid, is isomerized to the trans-quinolizidine.

Compounds containing a 7-phenylbenzo[a]quinolizine fragment are of interest as potential analgesics [1] and psychotropic preparations [2, 3]. Such compounds had been synthesized previously by the interaction of 3,4-dihydro-4-phenylisoquinoline and its polycyclic analogs with methyl vinyl ketone [1, 3] and by intramolecular cyclization of phenacylpyridines [4] and of amides obtained from 5-hydroxy- and 5-oxocarboxylic acids and 2,2-diphenylethylamine and its analogs [3, 5].

We had previously developed a method for the synthesis of benzo[a]furo[2,3-g]quinolizines by heating N-allyl-, methallyl-, and (2-hydroxyethyl)-substituted 2-oxofuro[2,3-c]piperidines in a strongly acidic medium [6-8], and we established biological activity for some of the synthesized compounds [6]. It was of interest to use this scheme to obtain 7-phenylbenzo[a]furo[2,3-g]quinolizines. The use of N-(2-hydroxy-2-phenylethyl)-2-oxofuro[2,3-c]piperidines in the cyclization, by analogy with the known scheme for the synthesis of 7-arylpyrazino[2,1-a]isoquinolines [9], should ensure that the cyclization process would proceed smoothly. Thus, by the alkylation of 2-oxofuro[2,3-c]piperidines I,II by phenacyl bromide, we obtained the lactones III,IV, which were reduced by sodium borohydride to the alcohols V,VI and subsequently heated in 70% sulfuric acid, upon which they were converted to the quinolizines VII,VIII. The reduction of the carbonyl group in the ketones III,IV is stereoselective. On the basis of the integral intensities of the signals from protons bonded to the carbinol center, it was established that the ratio of isomers in the alcohol V was 9:1 [respectively, 4,67 ppm (dd, 10.5 and 3.5 Hz) and 4.28 ppm (dd, $J_{AX} + J_{BX} = 13.0$ Hz)], and for the alcohol VI the ratio of isomers was 2:1 [respectively, 4.71 ppm (dd, 10.0 and 3.0 Hz) and 4.89 ppm (dd, 9.0 and 4.5 Hz)]. The configurations of the isomers were not analyzed. (See scheme at the top of the next page.)

The stereochemistry of reduction of the carbonyl group is apparently governed by 1,4-asymmetric induction. The selectivity is higher for the ketone III, since the phenyl substituent on the piperidine ring has an equatorial orientation and provides better shielding of one of the sides of the carbonyl group, which in turn suggests a certain conformational stability of the phenacyl substituent. The formation of isoquinolines from optically active N-benzyl-N-(2-hydroxy-2-phenylethyl)amines ordinarily proceeds with a greater degree of racemization [10]. The cyclization of the alcohols V,VI proceeds with preferential formation of the quinolizines VII,VIII with an equatorial position of the substituent on $C_{(7)}$. We had noted this sort of

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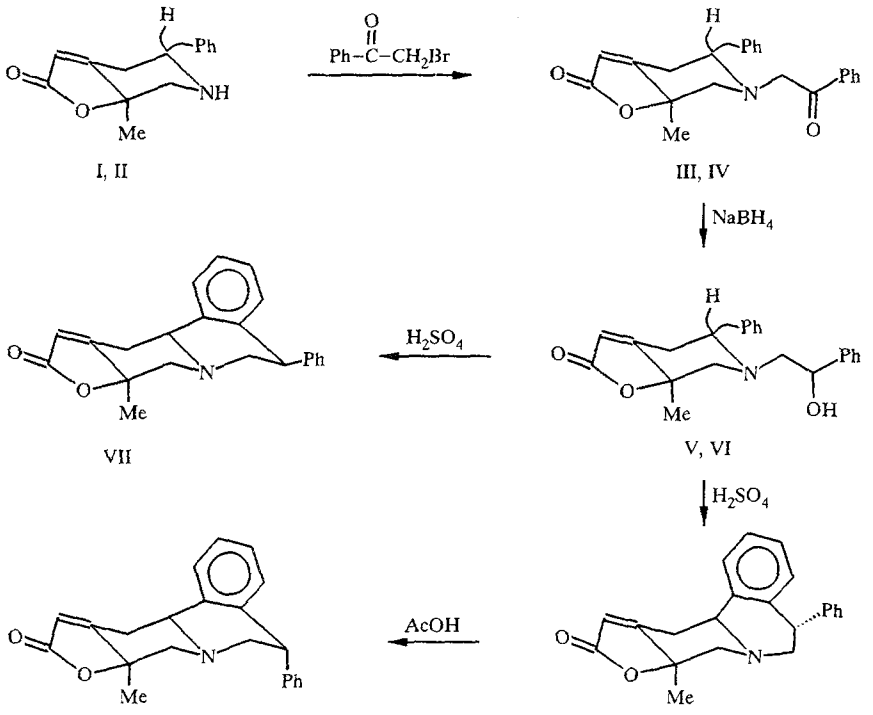
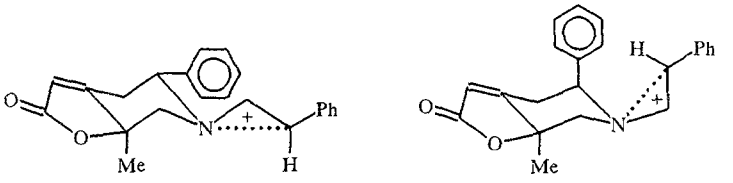


I, III, V) 5e–pH; II, IV, VI) 5a–Ph

relationship previously [6], and it has also been noted by other investigators [9, 11]. The relationship can be explained on the basis of adequate conformational rigidity of the heterocycle as a result of two factors: the orientation of the substituent on the nitrogen atom in the carbocation that is formed, and steric hindrance that arises as the cation center approaches the benzene ring. Compounds V,VI can each form four different carbocations, of which A and B have the advantage in cyclization.



Spectroscopic data and elemental analyses confirm the composition and structure of compounds III-VIII, and are in good agreement with previous results on 7-methylbenzo[a]furo[2,3-g]quinolizines [6]. Thus, the presence of Bohlman bands in the 2700-2850 cm^{-1} interval in the IR spectrum of compound VII, as well as the splitting of the PMR signal from the proton on $C_{(11b)}$ in the form of a quadruplet with SSCC 10.0 and 3.0 Hz, indicates trans-linking of rings B and C; the absence of Bohlman bands in the IR spectrum of compound VIII, along with the splitting of the PMR signal from the proton on $C_{(11b)}$ in the form of a quadruplet with SSCC 7.5 and 1.0 Hz, indicates cis-linkage of the B and C rings. The splitting of the signal from the proton on $C_{(7)}$ in the PMR spectra of compounds VII,VIII in the form of a quadruplet with large total values of the SSCC (17 and 18 Hz, respectively) indicates axial orientation of this hydrogen atom.

It is known that benzo[a]quinolizines with cis-linkage of rings B and C, when they are boiled in propionic acid, may undergo isomerization to the thermodynamically more stable benzo[a]quinolizines with trans-B/C linkage [12]. We found that upon heating the cis-quinolizine VIII in acetic acid, the trans-quinolizine IX was obtained, differing from compound VII in the orientation of the phenyl substituent on $C_{(7)}$.

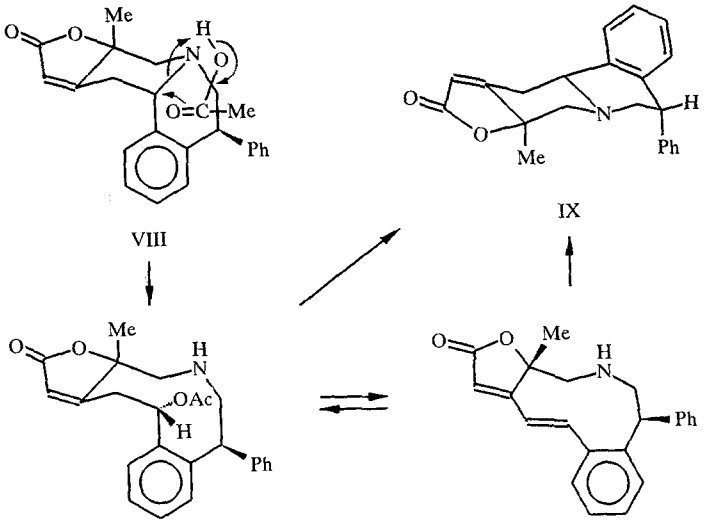
The trans-B/C linkage in the quinolizine IX is confirmed by the presence of Bohlman bands in the IR spectrum in the 2700-2850 cm^{-1} interval, and also by the values of the SSCC (11.5 and 2.5 Hz) of the proton on $C_{(11b)}$. The signal from the

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
III	$C_{22}H_{21}NO_3$	122...123	1755, 1690, 1655	82
IV	$C_{22}H_{21}NO_3$	132...133	1755, 1690, 1650	66
V	$C_{22}H_{23}NO_3$	159...160	3615, 3500, 1780, 1650	90
VI	$C_{22}H_{23}NO_3$	Oil	3620, 3500, 1780, 1650	100
VII	$C_{22}H_{21}NO_2$	146...147	2805, 2760, 2750, 1780, 1650	60
VIII	$C_{22}H_{21}NO_2$	196...197	1780, 1650	69
IX	$C_{22}H_{21}NO_2$	152...153	2815, 2770, 1760, 1655	65

proton on $C_{(7)}$ in the form of a broad singlet confirms the axial orientation of the phenyl substituent on ring B. Attention should be directed to the shielding of the methyl group on $C_{(3a)}$ by this phenyl substituent.

In the isomerization of the cis-lactone VIII to the trans-lactone IX, we believe that the most probable path is rupture of the $C_{(11b)}$-N bond [13] with the formation of an intermediate macroring [14]



However, attempts to fix the intermediate macroring in the form of an acetamide by performing the reaction in the presence of acetic anhydride did not give any positive results. This can evidently be attributed to the higher rates of the cyclization reaction in comparison with the rate of acetylation of the intermediate macroring.

EXPERIMENTAL

IR spectra of solutions of the substances in CCl_4 were taken in a Specord IR-75 instrument. PMR spectra in $CDCl_3$ were obtained in a Bruker WM-360 instrument, with HMDS internal standard. The course of the reaction and the purity of the products were monitored by TLC on Silufol plates with 2:1 ether–hexane as the eluent. The 2-oxofuro[2,3-c]piperidines I,II were obtained in accordance with [2].

Elemental analyses for C, H, and N were consistent with the calculated contents.

7a(a)-Methyl-2-oxo-6-phenacyl-5-phenylfuro[2,3-c]piperidine (III,IV). A 0.01-mole quantity of the lactone I, II and 0.011 mole of phenacyl bromide were dissolved in 15 ml of acetonitrile; then 0.011 mole of diisopropylethylamine was added and the mixture was held at 25°C until the original compound I, II had disappeared as indicated by TLC. Then 100 ml of ether was added, and the reaction mixture was washed with water, dried with sodium sulfate, and passed through a thin layer of silica gel, Grade L 40/100. After evaporating the solvent, the residue was crystallized from a 2:1 toluene–hexane mixture.

7a(a)-Methyl-2-oxo-6-(2-hydroxy-2-phenylethyl)-5-phenylfuro[2,3-c]piperidine (V,VI). To a solution of 5 mmoles of compound III,IV in 30 ml of methanol, sodium borohydride was added in portions until the original ketone III,IV disappeared, as indicated by TLC. The reaction mixture was neutralized with acetic acid, the methanol was driven off, the

residue was dissolved in ether and washed with water, the organic layer was dried with sodium sulfate, and the solvent was evaporated.

3a,4,6,7,11b,12-Hexahydro-3a(a)-methyl-2-oxo-7(e)-phenylbenzo[a]furo[2,3-g]quinolizine (VII, VIII). A 4-mmole quantity of compound V,VI was dissolved in 6 ml of 70% sulfuric acid and held for 10 min at 50°C; the reaction mixture was diluted with 100 ml of water, neutralized with sodium hydroxide solution, and extracted with ether. The organic solution was dried with sodium sulfate, the solvent was evaporated, and the residue was crystallized from a 2:1 toluene–hexane mixture. PMR spectrum of VII, δ, ppm: 1.65 (s, 3a-CH_3); 2.33 (d, 4-H_a; 10.5 Hz); 2.48 (ddd, 12-H_a; 13.0, 10.0; 1.5 Hz); 2.72 (t, 6-H_a; 11.0 Hz); 3.07 (dd, 6-H_e; 11.0; 6.0 Hz); 3.25 (d, 4-H_e; 10.5 Hz); 3.43 (dd, 12-H_e; 13.0; 3.0 Hz); 3.47 (dd, 11b-H_a; 10.0; 3.0 Hz); 4.38 (dd, 7-H_a; 11.0; 6.0 Hz); 5.85 (d, 1-H; 1.5 Hz); 6.80-7.37 mp (m, 9-arom.). PMR spectrum of VIII, δ, ppm: 1.68 (s, 3a-CH_3); 2.71 (d, 4-H_a; 10.5 Hz); 3.00 (ddd 12-H_a; 13.0; 7.5; 1.5 Hz); 3.11 (d, 4-H_e; 10.5 Hz); 3.30-3.37 (m, 6-CH_2); 3.53 (dd, 12-H_e; 13.0; 1.0 Hz); 4.31 (dd, 7-H_a; $J_{AX} + J_{BX} = 18.0$ Hz); 4.70 dd, 11b-H_e; 7.5; 1.0 Hz); 5.68 (d, 1-H; 1.5 Hz); 6.83-7.35 mp (m, 9-H_{arom}).

3a,4,6,7,11b(a),12-Hexahydro-3a(a)-methyl-2-oxo-7(a)-phenylbenzo[a]furo[2,3-g]quinolizine (IX). A 2-mmole quantity of compound VIII was dissolved in 5 ml of acetic acid and heated in a sealed ampul for 5 h at 150°C. The reaction mixture was cooled and diluted with 50 ml of water, then neutralized with 20% sodium hydroxide solution. The product that was released was extracted with ether and dried with sodium sulfate, after which the solvent was evaporated. The residue was crystallized from a 2:1 toluene–hexane mixture. PMR spectrum, δ, ppm: 1.38 (s, 3a-CH_3); 2.30 and 3.00 (2d, 4-CH_2; 11.0 Hz); 11.0 Hz); 2.51 (br.t, 12-H_a; 11.5 Hz); 2.93 and 3.35 (2br.d, 6-CH_2; 11.5 Hz); 3.15 dd, 12-H_e; 11.5; 2.5 Hz); 3.45 (dd, 11b-H_a); 11.5; 2.5 Hz); 4.1 (br.s, 7-H_e); 5.81 (br.s, 1-H); 7.00-7.27 mp (m, 9-H_{arom}).

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