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SYNTHESIS OF 3-HYDROXY-3-METHYL-7-PHENYLBENZO[*a*]QUINOLIZIN-2-ONES

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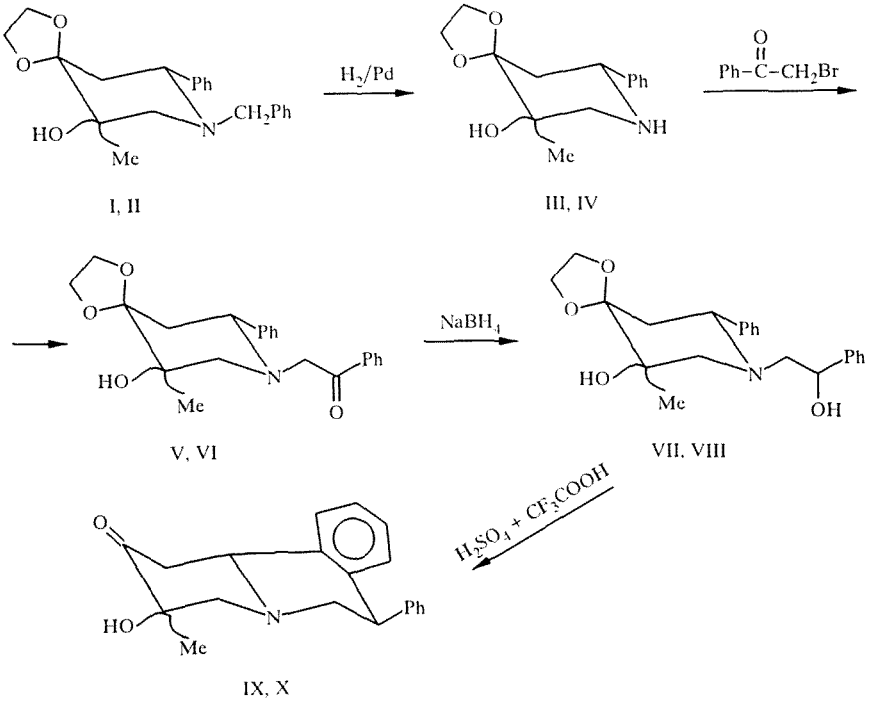
Amino alcohols were prepared by debenzylation of 1-benzyl-3-hydroxy-3-methyl-6(e)-phenyl-4-piperidone ethylene ketals, alkylation with phenacyl bromide, and subsequent reduction of the carbonyl group, and holding the alcohol in a mixture of sulfuric and trifluoroacetic acids yields 3-hydroxy-3-methyl-7(e)-phenylbenzo[a]quinolizin-2-ones. The possibility of recyclization of the latter while boiling in a mixture of acetic anhydride and acetic acid by α-ketol rearrangement or rupture of the C—N bond was demonstrated.

Benzo[*a*]quinolizin-2-ones are of great interest for synthesis of biologically active natural compounds and their analogs [1]. A method of preparation of 3-hydroxy-7-phenylbenzo[*a*]quinolizin-2-ones which can be used in the search for new analgesics [2] was developed in the present study.

N-acetonyl(phenacyl)-substituted 2-arylpyridines are cyclized in acid medium with the formation of benzo[*a*]quinolizinium salts [3]. An attempt to cyclize 1-(2-oxoalkyl)-3(*e*)-hydroxy-6(*e*)-phenyl-4-piperidones unexpectedly resulted in the formation of products of tandem acetylation — 1-aza-5,7-dioxatricyclo[4.3.1.$0^{4,8}$]decane derivatives [4]. N-substituted 2-aryl-4-piperidone ethylene ketals can be used for synthesis of benzo[*a*]quinolizin-2-ones by closing of ring B with



I, III, V, VII, IX 3(*e*)-OH; II, IV, VI, VIII, X 3(*a*)-OH

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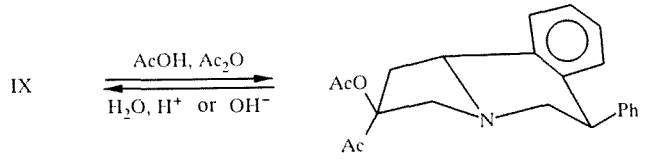
formation of a $C_{(7)}$—$C_{(7a)}$ bond [5]. We obtained substances V and VI by debenzylation of ethylene ketals I and II and subsequent alkylation of compounds III and IV with phenacyl bromide. Attempts to conduct intramolecular cyclization of V and VI in different conditions (sulfuric acid, boron trifluoride etherate, aluminum chloride in nitrobenzene, or methylene chloride) were unsuccessful. In all cases, complex mixtures of products were formed according to the TLC data. The ease of intramolecular cyclization of N-benzyl-N-(2-hydroxy-2-phenylethyl)amines [6] led to their use for constructing a benzo[*a*]quinolizine system of products of reduction of N-phenacyl carbonyl in 2-oxo-5-phenylfuro[2,3-*c*]piperidine derivatives [7]. In consideration of the lability of the α-ketol group, the softest conditions of cyclization of compounds VII and VIII were selected. Benzo[*a*]quinolizines IX and X — the products of intramolecular cyclization with simultaneous removal of the shielding group — were obtained by holding VII and VIII in a mixture of sulfuric and trifluoroacetic acids at room temperature and subsequent treatment.

The structure of compounds IX and X was confirmed by the data from elemental analysis, the IR and PMR spectra (Table 1). The position of the bands of stretching vibrations of O—H and C=O bonds correspond to the published data for 3-hydroxy-4-piperidones [8]. The existence of Bollman bands in the 2700-2850 cm^{-1} region indicates *trans*-B/C coupling and axial orientation of the hydrogen at $C_{(11b)}$. The observed SSCC between protons at $C_{(1)}$ and $C_{(11b)}$ confirm this finding. The values of the SSCC (11.5 and 5.5 Hz) of the proton at $C_{(7)}$ with the protons at $C_{(6)}$ support its pseudo-axial orientation.

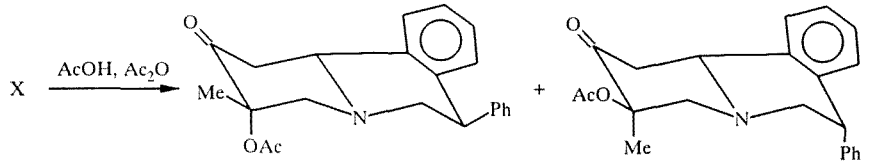
It was interesting to obtain systems similar to IX, X with a 7(*a*)-phenyl group. We previously isomerized *cis*-7(*e*)-phenylbenzo[*a*]furo[2,3-*g*]quinolizines by boiling in acetic acid [7]. The study of the behavior of compounds IX and X in similar conditions showed that difficult-to-separate mixtures of products are formed. When compound IX is boiled in acetic acid in the presence of acetic anhydride, pyrrolo[2,1-*a*]isoquinoline XI — the product of α-ketol rearrangement — was obtained. In hydrolysis of compound XI in both acid and in basic medium, initial compound IX was formed.



XI

The structure of compound XI is primarily confirmed by the appearance of the signal of an acetyl methyl group at 2.15 ppm in the PMR spectrum. The SSCC of the methine protons indicate their pseudo-axial orientation. The configuration of the $C_{(2)}$ atom was assigned according to [9].

When compound X was heated in acetic acid in the presence of acetic anhydride, a mixture of two acetates XIIa and XII in the ratio of 70:30 was obtained. According to the data in the PMR spectrum, acetate XIIa is the product of acetylation of starting ketol X, and acetate XIIb is the product of its isomerization. Actually, the signal of the proton at $C_{(7)}$ of acetate XII is observed at 4.38 ppm in the form of a quadruplet with SSCC of 11.0 and 3.5 Hz, which indicates its axial orientation.



XII a XIIb

The signal of the proton at $C_{(7)}$ in the 4.12 ppm region in compound XIIb is in the shape of a broadened singlet, which supports its pseudo-axial orientation. The signals of the protons at $C_{(11b)}$ in the PMR spectrum of a mixture of acetates XIIa, b are observed at 3.75 and 3.98 ppm in the form of two quadruplets with vicinal SSCC of 11.5 and 3.5 Hz, which indicates its axial orientation. The almost identical chemical shift of signals of the methyl groups at $C_{(3)}$ in compounds XIIa, b (1.41 and 1.40 ppm) and the significant difference in the chemical shifts of these signals in compounds IX and X could be due to shielding of the methyl group by the phenyl substituent in the case of acetate XIIb, from which their mutual *cis*-position follows. The mechanism of isomerization of compound X remains open to discussion. We can hypothesize that the reaction includes the stage of breaking of the $C_{(11b)}$—N bond with formation of a microring.

TABLE 1. Characteristics of Compounds III-XII

Compound	Empirical formula	mp, °C	IR spectrum ν, cm^{-1}	Yield, %
III	$C_{14}H_{19}NO_3$	118...119	3345, 3575	90
IV	$C_{14}H_{19}NO_3$	121...122	3340, 3480, 3590	91
V	$C_{22}H_{25}NO_4$	145...146	1690, 3575	94
VI	$C_{22}H_{25}NO_4$	187...188	1700, 3480	82
VII	$C_{22}H_{27}NO_4$	140...141	3465, 3575	95
VIII	$C_{22}H_{27}NO_4$	Oil	3430, 3590	96
IX	$C_{20}H_{21}NO_2$	183...184	1720, 2760, 2805, 3500	53
X	$C_{20}H_{21}NO_2$	138...139	1720, 2755, 2810, 3480	55
XI	$C_{22}H_{23}NO_3$	152...153	1725, 1745, 2800	81
XII.a,b	$C_{22}H_{23}NO_3$	114...115	1720, 1745, 2730, 2800, 3415	82

EXPERIMENTAL

The IR spectra of solutions of the substances in CCl_4 ($c = 10^{-3}$ M, $l = 1$ cm) were made on a Specord IR-75. The PMR spectra in $CDCl_3$ were made on a Bruker WM-360 spectrometer with HMDS as the internal standard. The course of the reactions and purity of the products were monitored by TLC on Silufol UV-254 plates, development with iodine vapors. Compounds I and II were obtained by the method in [8].

The data from elemental analysis for C, H, and N in the compounds obtained corresponded to the calculated data.

3-Hydroxy-3-methyl-6(*e*)-phenyl-4-piperidone Ethylene Ketal (III, IV). Here 15 ml of acetic acid and 1.0 g of 10% $Pd/BaSO_4$ were added to a solution of 0.05 mole of ketal I, II in 200 m of methanol. The reaction mixture was stirred in an atmosphere of hydrogen until absorption stopped. The catalyst was filtered off and the methanol was distilled off. The residue was dissolved in 30 ml of water and alkalized with 20% sodium hydroxide solution to pH 9. The product was extracted with methylene chloride (3 × 150 ml). The organic layer was separated, dried with sodium sulfate, and evaporated. The product was crystallized from toluene—hexane mixture, 3:1.

3-Hydroxy-3-methyl-1-phenacyl-6(*e*)-phenyl-4-piperidone Ethylene Ketal (V, VI). A mixture of 0.03 mole of ketal III, IV, 0.03 mole of phenacyl bromide, and 0.06 mole of potash in 150 ml of acetonitrile and 50 ml of water was stirred at 18-20°C until the initial ketal had disappeared according to TLC data. After addition of 300 m of ether, the organic layer was separated, carefully washed with water, dried with sodium sulfate, and evaporated. Compounds V, VI were crystallized respectively from toluene—hexane, 2:1, and ether—hexane, 3:1.

3-Hydroxy-1-(2-hydroxy-2-phenylethyl)-3-methyl-6(*e*)-phenyl-4-piperidone Ethylene Ketal (VII, VIII). Sodium borohydride was added by portions to a solution of 5 mmole of compound V, VI in 30 ml of methanol until the starting compound had disappeared according to TLC data. The reaction mixture was neutralized with acetic acid, the methanol was distilled off, the residue was dissolved in ether, and the organic layer was washed with water, dried with sodium sulfate, and evaporated. Compound VII was crystallized from toluene—hexane, 3:1.

1,3,4,6,7(*a*),11b(*a*)-Hexahydro-3-hydroxy-3-methyl-7(*e*)-phenylbenzo[*a*]quinolizin-2-one (IX, X). Here 5 mmole of compound VII, VIII was dissolved in 6 m of trifluoroacetic acid, 6 ml of 90% sulfuric acid was added and held at 18-20°C for 5 and 110 min, respectively. The reaction mixture was poured into 200 ml of water and neutralized with 20% sodium hydroxide solution. The product separated was extracted with ether, and the organic layer was separated, dried with sodium sulfate, and evaporated.

Compound IX was crystallized from isopropyl alcohol—hexane, 3:1. PMR spectrum ($CDCl_3$): 1.57 (s, 3-CH_3); 2.49 (d, 4-H_a, 11.5 Hz); 2.69 (t, 6-H_a, 11.5 Hz); 2.75 (d.d, 1-H_a, 14.8, 11.5 Hz); 3.10 (d, 4-H_e, 11.5 Hz); 3.12 (d.d, 1-H_e, 14.0, 4.0 Hz); 3.14 (d.d, 6-H_e, 11.5, 5.5 Hz); 3.71 (d.d, 11b-H_a, 11.5, 4.0 Hz); 3.86 (s, OH); 4.42 (d.d, 7-H_a, 11.5, 5.5 Hz); 6.80-7.36 (m, 9-H_{arom}).

Compound X was crystallized from toluene—hexane, 1:1. PMR spectrum ($CDCl_3$): 1.29 (s, 3-CH_3); 2.58 (d, 4-H_a, 12.0 Hz); 2.82 (t, 6-H_a, 11.5 Hz); 2.95-3.03 (m, 3H); 3.13 (d.d, 6-H_3, 11.5, 5.5 Hz); 3.80 (d.d, 11b-H_a, $^1J + {}^2J = 14.0$ Hz); 4.15 (s, OH); 4.45 (d.d, 7-H_e, 11.5, 5.5 Hz); 6.80-7.33 (m, H_{arom}).

1,2,3,5,6(β),10b(α)-Hexahydro-2(β)-acetyl-3(α)-acetoxy-6(α)-phenylpyrrolo[2,1-*a*]-isoquinoline (XI). A solution of 3 mmole of compound IX in 6 ml of acetic acid and 3 ml of acetic anhydride was boiled with a reflux condenser for 1 h.

The reaction mixture was evaporated, diluted with 50 ml of water, alkalized to pH 9 with 20% sodium hydroxide solution, and the precipitated product was extracted with ether. The organic layer was separated, dried with sodium sulfate, evaporated, and the residue was crystallized from hexane. PMR spectrum ($CDCl_3$): 2.15 (c, CH_3); 2.21 (c, CH_3); 2.15-2.21 (m, 1H); 2.58-2.70 (m, 3H); 3.40 (d.d,5-H_e, 11.5, 6.5 Hz); 3.85 (d. d, 10b-H_a, 10.0, 6.0 Hz); 3.88 (d, 3-H, 12.0 Hz); 4.38 (d.d, 6-H_a, 10.0, 6.5 Hz); 6.80-7.32 (m, 9-H_{arom}).

1,3,4,6,7,11b(*a*)-Hexahydro-3-acetoxy-3-methyl-7-phenylbenzo[*a*]quinolizin-2-one (XIIa, b) was prepared similar to XI. It was crystallized from alcohol—hexane, 1:2.

REFERENCES

1. F. D. Popp and R. F. Watts, Heterocycles, **6**, 1189 (1977).
2. B. E. Maryanoff, D. F. McComsey, R. J. Taylor, and J. F. Gardocki, J. Med. Chem., **24**, 79 (1981).
3. C. K. Bradsher and L. E. Beavers, J. Am. Chem. Soc., **77**, 453 (1955).
4. G. V. Pshenichnyi, Vu Din' Khoang, V. A. Mashenkov, and L. S. Stanishevskii, Khim. Geterotsikl. Soedin., No. 5, 704 (1989).
5. M. Rubiralta, A. Diez, A. Balet, and J. Bosch, Tetrahedron, **43**, 3021 (1987).
6. S. J. Coote, S. G. Davies, D. Middlemiss, and A. Naylor, J. Chem. Soc., Perkin Trans. 1, No. 12, 2223 (1989).
7. Vu Din' Khoang, G. V. Pshenichnyi, V. A. Mashenkov, and L. S. Stanishevskii, Khim. Geterotsikl. Soedin., No. 12, 1679 (1993).
8. L. S. Stanishevskii, I. G. Tishchenko, and A. M. Zvonok, Khim. Geterotsikl. Soedin., No. 5, 670 (1975).
9. L. S. Stanishevskii, I. G. Tishchenko, and A. Ya. Guzikov, Zh. Org. Khim., **7**, 2612 (1971).