SYNTHESIS AND SOME CHEMICAL PROPERTIES OF PIPERIDINE-4-SPIRO-2'-OXIRANES

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The reaction of 5e-aryl-3-hydroxy-3-methylpiperidin-4-ones with diazomethane yielded piperidine-4-spiro-2'-oxiranes. It was shown that the reaction takes place stereospecifically with formation of 4a-O-spiroepoxides. Some chemical properties of the synthesized piperidine-4-spiro-2'-oxiranes were investigated.

The development of methods of synthesis of compounds of the hydroxypiperidine series, which includes many natural physiologically active derivatives [1, 2], is of definite interest.

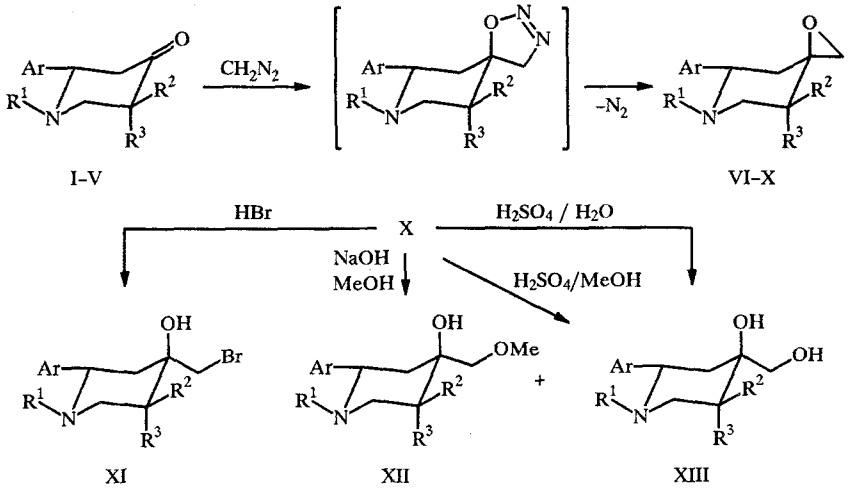
Spirocyclic epoxides based on 3-hydroxypiperidin-4-ones were synthesized in the present study, and the stereochemistry of the methylenation reaction and some chemical properties of the epoxides obtained were investigated. These epoxides can play the role of convenient precursors of different piperidine hydroxy and amino derivatives.

Diazomethane as a neutral reagent with respect to acid—base properties was used as the methylenation agent, since 3-hydroxypiperidin-4-ones can undergo rearrangements with constriction of the piperidine ring in acid and basic media [3].

The reaction of stereoisomeric 3*a*- and 3*e*-hydroxypiperidin-4-ones I-V with diazomethane results in the formation of adducts at the carbonyl group — spirocyclic oxadiazolines. Their existence has been recorded chromatographically, but these products could not be isolated in pure form due to spontaneous conversion into the corresponding spiroepoxides VI-X.

3*e*-Hydroxypiperidin-4-ones react with diazomethane much more slowly than their 3*a*-hydroxy analogs. After holding compound I with diazomethane for 48 h, the yield of epoxide VI is only 10% (75% of the starting substance). When the reaction time is increased to 300 h (in the case of compound II), the yield of the corresponding epoxide VII is 36%, but the initial substance cannot be separated.

3*a*-Hydroxypiperidin-4-ones III-V react with diazomethane for 18-24 h, forming corresponding epoxides VIII-X with an almost quantitative yield. This difference in the reactivity could be due to the presence of an intramolecular hydrogen bond between the hydroxyl group hydrogen atom and the carbonyl oxygen in the molecules of 3*e*-hydroxypiperidin-4-ones. However, piperidone Ia trimethylsilyl ether does not react with diazomethane in general, which suggests that the observed difference in the behavior of the diastereomers is probably due to the steric accessibility of the carbonyl group.



I, VI Ar = Ph, $R^1 = R^3 = Me$, $R^2 = OH$; II, VII Ar = PhCH = CH, $R^1 = R^2 = Me$, $R^2 = OH$; III, VIII Ar = Ph, $R^1 = R^2 = Me$, $R^3 = OH$; IV, IX Ar = 4-$MeOC_6H_4$, $R^1 = R^2 = Me$, $R^3 = OH$; V, X—XIII Ar = =Ph, $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = OH$

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TABLE 1. Properties of Compounds VI-XIII

Compound	Empirical formula	mp, °C	Yield, %	Compound	Empirical formula	mp, °C	Yield, %
VI	$C_{14}H_{19}NO_2$	95...97	10	X	$C_{20}H_{23}NO_2$	123...124	92
VII	$C_{16}H_{21}NO_2$	60...61	35	XI	$C20H_{24}BrNO_2$	130...131	87
VIII*	$C_{14}H_{19}NO_2$	—	82	XII	$C21H_{27}NO_3$	139...140	85**
IX	$C_{15}H_{21}NO_3$	58...59	83	XIII	$C20H_{25}NO_3$	158...160	74

*Separated as an oil.

**Yield with method A.

A hydroxyl group absorption band (3490-3500 cm^{-1}) is observed in the IR spectra of substances VI-X, and the characteristic band at 1720 cm^{-1} belonging to the carbonyl group is absent. The PMR spectra contain signals of aromatic protons in the 7-7.5 ppm region, the signal of 3-methyl group protons in the form of a singlet, and signals of piperidine and epoxide ring protons, and the latter appear as two doublets with a spin-spin coupling constant (SSCC) of 3.8-4.8 Hz.

The configuration of products VI-X is such that the epoxide ring oxygen occupies an axial position. In the PMR spectra of the epoxides, the H-5 proton signal is shifted by 1.5-1.8 ppm to the stronger field on average in comparison to the signal of piperidones I-V, which indicates the shielding effect of the oxygen atom unshared electron pairs on this proton, to which the synclinal position with respect to the equatorial hydrogen atom at $C_{(5)}$ should probably be assigned.

No compound with equatorial orientation of the epoxide ring oxygen could be isolated in any of the cases investigated, which indicates the stereospecificity of the reaction. No products of the side reaction of ring expansion, which takes place in the reaction of tetrahydrothiopyran-4-ones with diazomethane, were also detected in the reaction mixture [5].

Spirocyclic epoxide X was added to the reaction with nucleophilic and electrophilic reagents. In the reaction of compound X with hydrobromic acid, bromohydrin XI, whose PMR spectrum contains signals of bromomethyl group protons forming two doublets with a SSCC of 11.3 Hz, is formed as the only product. The reaction of epoxide X with sodium hydroxide in methanol yields compound XII, whose structure is confirmed by both the PMR spectrum and by back synthesis from bromohydrin XI. Addition of water to epoxide X catalyzed by sulfuric acid yields a triol of the structure of XIII. The structure of compound XIII was demonstrated spectrally and by oxidation into piperidone I with iodic acid.

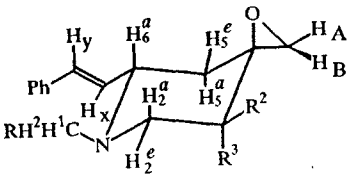
When epoxide X was boiled in methanol with sulfuric acid and the reaction mixture was subsequently neutralized with sodium hydrocarbonate, a mixture of compounds XII and XIII was separated in the ratio of 1:2. Obtaining triol XIII was unexpected, since direct opening of the epoxide ring by water is excluded in the given conditions. The formation of product XIII is probably due to primary addition of methyl sulfate or sulfuric acid and hydrolysis of the ester formed to triol in the stage of its separation as a base.

EXPERIMENTAL

The PMR spectra of solutions of the substances in $CDCl_3$ or acetone-d_6 were obtained on Bruker WM-360 (360 MHz) and Varian BS-567A (100 MHz) with TMS as the internal standard. The IR spectra of 0.1 mole of solutions of the substances in CCl_4 were recorded on a Specord IR-75 spectrometer. The reaction mixture was analyzed by thin-layer chromatography on Silufol plates or an unattached layer of silica gel. The starting piperidin-4-ones were obtained with the methods described in [4, 6], and diazomethane was prepared by alkaline decomposition of N-nitrosomethylurea [7]. The yields of the compounds, melting points, and spectral characteristics are reported in Tables 1 and 2.

1-R^1-3-hydroxy-3-methyl-5*e*-arylpiperidine-4-spiro-2′-oxiranes (VI-X). A. Here 50 ml of an ether solution of diazomethane prepared from 0.03 mole of N-nitrosomethylurea was added to a solution of 0.01 mole of piperidone III-V in 50 ml of ether and left at room temperature in the dark for 18-24 h, closing the flask with a Bunsen valve; the solution was then evaporated, the residue was crystallized from hexane—carbon tetrachloride mixture 5:1, and epoxides IX and X were obtained. Compound VIII was isolated as an oil which was purified after dissolving in hexane while heating and filtering through a 1 cm thick layer of aluminum oxide.

TABLE 2. PMR Spectra of Compounds VI-XIII*



Compound	Chemical shift, ppm											J, SSCC, Hz							
	H^1H^2C	R^2	R^3	Ar	H_2^e	H_2^a	H_5^e	H_5^a	H_6^a	H_A,H_B	H_X,H_Y	H_2^e,H_2^a	H_5^e,H_5^a	H_5^e,H_6^a	H_5^a,H_6^a	H_A,H_B	H_X,H_Y	H_X,H_6	H^1H^2R
VI	2,00	2,20	1,56	7,30	2,85	2,25	1,42	2,35	3,12	2,56, 3,05	—	11,4	14,4	3,4	12,0	4,8	—	—	—
VII	2,21	—	1,41	7,42	2,74	2,12	1,30	2,18	2,78	2,53, 2,98	6,05, 6,63	10,8	15,2	4,2	11,2	4,4	16,2	8,6	—
VIII	2,01	1,00	3,77	7,27	2,68	2,49	1,21	2,55	3,10	2,45, 2,92	—	12,0	15,0	3,6	11,8	4,0	—	—	—
IX[a]	2,00	0,98	3,74	6,82, 7,19	2,68	2,46	1,20	2,53	3,14	2,45, 2,93	—	11,8	14,3	3,1	12,0	4,0	—	—	—
X	2,98, 3,81	0,93	3,63	7,28	2,73	2,37	1,35	2,67	3,57	2,51, 2,97	—	11,5	14,5	3,2	11,5	3,8	—	—	13,1
XI	2,95, 3,78	1,12	2,03	7,27	2,65	2,51	2,02	1,92	3,55	3,76, 3,79	—	11,8	14,5	3,7	11,3	11,3	—	—	14,0
XII[b]	2,94, 3,75	1,09	2,64	7,23	2,60	2,45	1,80	1,92	3,59	3,24, 3,64	—	12,0	14,4	3,6	11,8	9,1	—	—	13,7
XIII	2,98, 3,77	1,12	2,16	7,26	2,59	2,47	1,72	2,16	3,60	3,66	—	11,4	14,6	3,5	12,4	—	—	—	13,0

*The spectra of compounds VI-X were recorded in $CDCl_3$, and those of compounds XI-XIII were recorded in acetone-d_6;
[a]signal of methoxy group in IX at 3.74 ppm, [b] signal of methoxy group in XII at 3.32 ppm.

B. For compound I, the reaction was conducted similar to method A, but the reaction mixture was chromatographed in a column containing aluminum oxide (ether—hexane eluent, 1:2), separating the unreacted piperidone I and epoxide VI.

C. For compound II, the reaction and treatment of the reaction mixture were conducted with method B, but the reaction time was increased to 300 h. Epoxide VII was separated as an oil which crystallized on standing.

1-Benzyl-4*e*-bromomethyl-3*a*,4*a*-dihydroxy-3*e*-methyl-5*e*-phenylpiperidine (XI, $C_{20}H_{24}O_2NBr$). Here 1 ml of 47% hydrobromic acid (8 mmole) was added to a solution of 2.5 mmole of epoxide X in 10 ml of 1,4-dioxane. The reaction mixture was poured into 50 ml of 5% sodium hydrocarbonate solution after 3 h and extracted with ether (3 × 30 ml). The ether extracts were washed with water, dried over magnesium sulfate, evaporated dry, and the residue was crystallized from hexane, isolating bromohydrin XI.

1-Benzyl-3*a*,4*a*-dihydroxy-3*e*-methyl-4*e*-methoxymethyl-5*e*-phenylpiperidine (XII, $C_{21}H_{27}O_3N$). A. Here 1 ml of a 20% solution of sodium hydroxide in methanol was added to a solution of 2.5 mmole of epoxide X in 40 ml of methanol. The mixture was boiled with a reflux condenser for 3 h, the methanol was distilled off, and the residue was crystallized from hexane, yielding compound XII.

B. Then 1 ml of a 20% solution of sodium hydroxide in methanol was added to a solution of 1 mmole of bromohydrin XI in 20 ml of methanol and boiled for 1 h with a reflux condenser. The reaction mixture was filtered and evaporated dry. The residue was dissolved in 20 ml of ether and washed with water (2 × 10 ml). The ether solution was dried over magnesium sulfate and the ether was distilled off, yielding crystalline compound XII.

1-Benzyl-4*e*-hydroxymethyl-3*a*,4*a*-dihydroxy-3*e*-methyl-5*e*-phenylpiperidine (XIII, $C_{20}H_{25}O_3N$). Here 2.5 mmole of epoxide X was dissolved in 20 ml of a 10% solution of sulfuric acid and held at room temperature for 24 h. The reaction mixture was neutralized with a 5% solution of sodium hydrocarbonate (100 ml) and extracted with ether (4 × 50 ml). The ether extracts were dried over magnesium sulfate and evaporated, yielding crystalline compound XIII.

Reaction of 1-benzyl-4*e*-hydroxymethyl-3*a*,4*a*-dihydroxy-3*e*-methyl-5*e*-phenylpiperidine (XIII) with iodic acid. Here 0.5 mmole of compound XIII was dissolved in 10 ml of chloroform, and 1.5 mmole of iodic acid in 20 ml of water and 0.01 g of triethylbenzylammonium chloride were added. The mixture was stirred at room temperature for 3 h, neutralized with 10 ml of a 5% solution of sodium hydrocarbonate, and the organic phase was separated. The chloroform layer was dried over magnesium sulfate and evaporated, and the residue was crystallized from hexane. The product did not differ from piperidone I in chromatographic mobility and did not cause depression of the melting point when mixed with a known pure sample of compound I.

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