SYNTHESIS OF SPIRO OXIRANE DERIVATIVES OF THE DECAHYDROQUINOLINE SERIES

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It was established that 1-methyl-, 1-ethyl-, 1,2-dimethyl-, and 1,2,2-trimethyl-4-oxiranyl-trans-decahydro-4-quinolols undergo isomerization under the influence of aqueous or alcohol solutions of sodium hydroxide, barium hydroxide, and thiourea with migration of the oxide ring to give the corresponding spiro epoxy compounds. A comparison of the IR spectra of the spiro epoxy compounds with the spectra of alternative products, viz., the corresponding keto alcohols, showed that keto alcohols are not formed under the given reaction conditions. The indicated conclusions are confirmed by the IR, PMR, and mass spectra.

Owing to the facile opening of the oxirane ring under the influence of various reagents, epoxy compounds are of interest as intermediates in the synthesis of diverse functionally substituted derivatives. In order to obtain new derivatives of the decahydroquinoline series that contain various functions in the side chain and are potential biologically active compounds we investigated the transformations of epoxy alcohols of this series, which have become accessible owing to a recently developed method [1]. In the present communication we present the results of a study of the behavior of epoxy alcohols of the decahydroquinoline series under the influence of several bases.

It is known [2, 3] that a hydroxy group attached to the carbon atom adjacent to the oxirane ring can participate in an intramolecular nucleophilic rearrangement that consists in opening of the epoxide ring that is already present and the formation of a new epoxide ring. This phenomenon has been called epoxide migration. As regards the site of opening of the epoxide ring under base catalysis conditions, it evidently should be primarily determined by the relative magnitudes of the positive charges on its carbon atom. Because of the negative inductive effect of the alcohol grouping, the greatest positive charge in epoxy alcohols should be localized on the α-carbon atom (with respect to the alcohol group) of the oxide ring, which is the primary site of attack by the alkoxide anion.

In the investigation of the behavior of stereoisomeric 1-methyl-, 1-ethyl-, 1,2-dimethyl- and 1,2,2-trimethyl-4-oxiranyl-trans-decahydro-4-quinolols (I-VIII) under the influence of aqueous or alcohol solutions of sodium hydroxide, barium hydroxide, and thiourea we established that these epoxy alcohols undergo isomerization to give the corresponding spiro epoxy compounds IX-XVI — products of migration of the oxide ring (Table 1). The alternative products of isomerization of epoxy derivatives I-VIII, viz., keto alcohols XVII-XXIV or aldehydo alcohols, are not formed under the conditions described. This is confirmed by the absence in the IR spectra of IX-XVI of an absorption band at 1700 cm^{-1}.

For comparison with spiro derivatives IX-XVI, keto alcohols XVII-XXIV were synthesized by another method, viz., by hydration of the corresponding acetylenic alcohols in the presence of mercuric sulfate by the method in [4]. Only one band of an associated hydroxy group at 3473-3480 cm^{-1} and a symmetrical band of a carbonyl group at 1704-1706 cm^{-1} are observed in the IR spectra of dilute solutions of the synthesized ketols XVIII, XX, and XXII-XXIV, which have an equatorial acetyl group. A split band of stretching vibrations of associated (3472-3475 cm^{-1}) and free (3610-3614 cm^{-1}) hydroxy groups are observed in the spectra of ketols XVII, XIX, and XXI, which have an axially oriented acetyl group. These data are in agreement with the principles established in [6]. The PMR spectra of the synthesized ketols also confirm their structures: The methyl protons of the acetyl group give a singlet at 2.14-2.19 ppm (Table 2).

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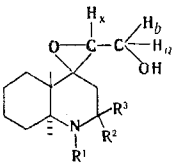
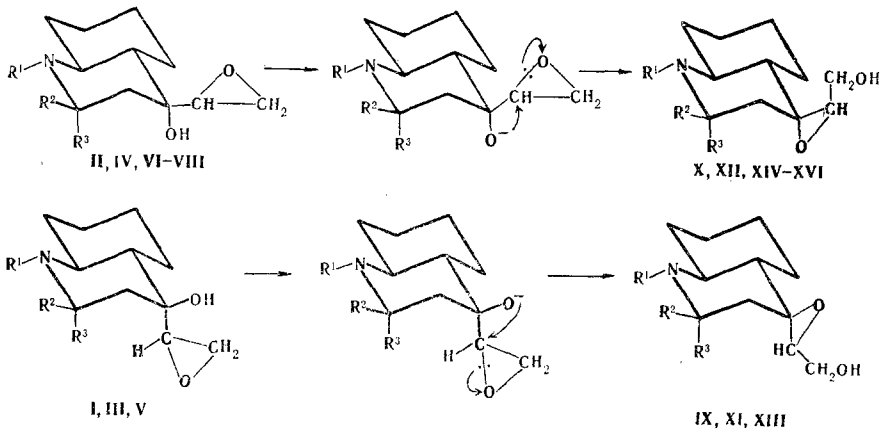
TABLE 1. Spiro Epoxy Derivatives of the Decahydroquinoline Series (IX-XVI)



Compound	R¹	R²	R³	mp, °C	δ, ppm			J, Hz			Found, %			Empirical formula	Calc., %		
					H_a	H_b	H_x	J_{AB}	J_{AX}	J_{BX}	C	H	N		C	H	N
IX	CH_3	H	H	118—119	3,69	3,87	3,19	11,5	6,3	4,5	68,4	10,3	6,6	$C_{12}H_{21}NO_2$	68,2	10,0	6,6
X	CH_3	H	H	116—117	3,72	3,83	3,29	10,5	5,6	4,9	68,3	10,0	6,4	$C_{12}H_{21}NO_2$	68,2	10,0	6,6
XI	C_2H_5	H	H	91—92	3,72	3,87	3,20	11,5	6,3	4,5	69,1	10,1	6,3	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XII	C_2H_5	H	H	133—134	3,68	3,82	3,31	10,6	5,8	4,9	69,5	10,3	6,1	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XIII	CH_3	CH_3	H	126—128	3,69	3,87	3,20	11,5	6,2	4,5	69,3	10,3	6,2	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XIV	CH_3	CH_3	H	150—152	3,67	3,80	3,26	10,6	5,7	4,9	69,5	10,0	6,1	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XV	CH_3	H	CH_3	128—130	3,71	3,78	3,13	10,6	6,0	4,9	69,3	10,0	6,1	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XVI	CH_3	CH_3	CH_3	152—153	3,63	3,75	3,13	10,6	6,0	5,0	70,2	10,2	5,8	$C_{14}H_{25}NO_2$	70,3	10,5	5,9

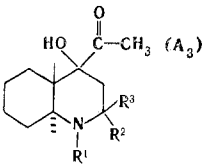


I, II, IX, X $R^1=CH_3$, $R^2=R^3=H$; III, IV, XI, XII $R^1=C_2H_5$, $R^2=R^3=H$; V, VI, XIII, XIV $R^1=R^2=CH_3$, $R^3=H$; VII, XV $R^1=R^3=CH_3$, $R^2=H$; VIII, XVI $R^1=R^2=CH_3$

The attacking hydroxy group in the cyclohexane system should have a trans orientation with respect to the epoxide oxygen atom [2]. Since opening of the epoxide ring is nucleophilic substitution at a carbon atom that takes place with inversion, the entering group of atoms should attack the carbon atom at a point that is opposite the oxygen atom of the epoxide ring. The hydroxy group should be present as the free anion; after migration, the new hydroxy group will have a trans orientation with respect to the new epoxide ring in a position suitable for nucleophilic attack. Migration of the epoxide bridge should therefore be a reversible reaction. In our case the isomerization of epoxy alcohols I-VIII proceeds virtually completely to give the most substituted and, probably, thermodynamically more favorable spiro epoxy compounds IX-XVI; migration of the epoxide ring takes place with the same ease in both epoxy alcohols with an axial hydroxy group (II, IV, VI, VII, and VIII) and their epimers with an equatorial hydroxy group (I, III, and V).

The structures of the synthesized spiro epoxy compounds were proved by a combination of spectral and chemical methods of investigation. A comparative study of the esterification of starting epoxides I-VIII and their isomerization products IX-XVI showed that IX-XVI are converted completely to the corresponding O-acetates XXV-XXXII under the influence of acetic anhydride at room temperature in 2-6 h, whereas I-VIII, which have a tertiary hydroxy group, remain unchanged under these conditions. This proves the presence of a primary hydroxy group in isomerization products IX-XVI (Table 3).

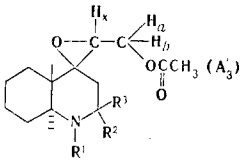
TABLE 2. 4-Acetyl-Substituted Alkyldecahydro-4-quinolols



Compound	R¹	R²	R³	mp, °C	Configuration of 4-OH	Vibrational frequencies, cm⁻¹			δ, ppm		Found, %			Empirical formula	Calc., %		
						νC=O	free νOH	assoc. νOH	N–R¹[a]	A₃	C	H	N		C	H	N
XVII	CH_3	H	H	152—153	*e*	1702—1716	3614	3475	2,28	2,16	68.2	10,0	6,8	$C_{12}H_{21}NO_2$	68,2	10,0	6,6
XVIII	CH_3	H	H	77—78	*a*	1704	—	3480	2,27	2,19	68,5	10,0	6,7	$C_{12}H_{21}NO_2$	68,2	10,0	6,6
XIX	C_2H_5	H	H	131—132	*e*	1700—1714	3610	3472	1,01	2,14	69,4	10,3	6,2	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XX	C_2H_5	H	H	70—71	*a*	1705	—	3480	1,03	2,17	69,6	10,4	6,2	$C_{13}H_{23}NO_2$	69,3	10,3	6,2
XXI[b]	CH_3	CH_3	H	139—140	*e*	1700—1715	3612	3475	2,26	2,17	—	—	—	- -	—	—	—
XXII[b]	CH_3	CH_3	H	112—113	*a*	1706	—	3480	2,26	2,19	—	—	—	—	—	—	—
XXIII[b]	CH_3	H	CH_3	63—64	*a*	1706	—	3475	2,30	2,19	—	—	—	—	—	—	—
XXIV	CH_3	CH_3	CH_3	104—105	*a*	1705	—	3473	2,22	2,19	70,4	10,6	6,0	$C_{14}H_{25}NO_2$	70,3	10,5	5,9

[a]The chemical shift of the signal of the methyl group of R^1 is presented. [b]The synthesis of XXI-XXIII is described in [4, 5].

TABLE 3. O-Acetates of Spiro Epoxy Derivatives of the Decahydroquinoline Series



Compound	R¹	R²	R³	mp, °C	δ, ppm					*J*, Hz			Found, %			Empirical formula	Calc., %		
					N–R¹	A'₃	A	B	X	J_{AX}	J_{BX}	J_{AB}	C	H	N		C	H	N
XXV	CH_3	H	H	178—180[a]	2,28	2,11	4,03	4,39	3,20	6,8	4,5	12	61,1	8,4	4,9	$C_{16}H_{27}NO_5$	61,3	8,7	4,5
XXVI	CH_3	H	H	46—47	2,41	2,20	4,23	4,53	3,46	7,2	4,5	12	66,5	9,5	5,8	$C_{14}H_{23}NO_3$	66,4	9,2	5,5
XXVII	C_2H_5	H	H	162—164[b]	1,0[c]	2,13	4,05	4,39	3,21	7,5	4,5	12	51,8	5,7	11,6	$C_{21}H_{28}N_4O_{10}$	52,1	5,9	11,7
XXVIII	C_2H_5	H	H	140—142[b]	1,04[c]	2,20	4,23	4,54	3,47	7,5	4,5	12	52,0	5,8	11,4	$C_{21}H_{28}N_4O_{10}$	52,1	5,9	11,7
XXIX	CH_3	CH_3	H	67—68	2,39	2,21	4,23	4,60	3,37	6,8	4,2	12	67,1	9,4	5,3	$C_{15}H_{25}NO_3$	67,4	9,4	5,2
XXX	CH_3	CH_3	H	88—90	2,31	2,11	4,05	4,32	3,29	6,8	4,5	12	67,3	9,2	5,2	$C_{15}H_{25}NO_3$	67,4	9,4	5,2
XXXI	CH_3	H	CH_3	165—166[a]	2,34	2,08	4,00	4,32	3,17	7,1	4,5	12	62,1	9,0	4,4	$C_{17}H_{29}NO_5$	62,4	8,9	4,3
XXXII	CH_3	CH_3	CH_3	191—192[a]	2,27	2,11	4,00	4,30	3,19	7,3	4,2	12	63,4	8,9	4,3	$C_{18}H_{31}NO_5$	63,3	9,2	4,1

[a]The melting points and elementary compositions of the acetate salts of the esters are presented. [b]The melting points and elementary compositions of the picrates are presented. [c]The chemical shift of the methyl group of the ethyl grouping (R^1) is presented.

In the IR spectra spiro epoxy compounds IX-XVI the band due to the stretching vibrations of the C–H bond of the epoxide ring lies at 3015-3040 cm^{-1} [8]. An intense doublet band of hydroxy groups (3635 and 3615 cm^{-1}) due to the existence of two conformers and a weak band at 3550 cm^{-1} due to the intramolecular bond of the hydroxy group with the epoxide oxygen atom are characteristic for dilute solutions of the spiro epoxy compounds. The absorption band of a hydroxy group at 3100-3600 cm^{-1} is absent in the IR spectra of the acetates of the spiro epoxy compounds (XXV-XXXII), but absorption bands of an ester group are observed at 1230-1250 cm^{-1} and 1740-1750 cm^{-1}.

The protons of the methylene group of the side chain are nonequivalent in the PMR spectra of spiro epoxy alcohols IX-XVI and spiro epoxy acetates XXV-XXXII; this is due to the fact that they are adjacent to an asymmetric carbon atom. In this case the nonequivalence of the methylene protons may be the result of retarded rotation or unequal populations of the various conformations or may be a consequence of incomplete averaging of the chemical and magnetic environments of the two methylene protons. The CH_2 and CH protons of the side chain of spiro epoxy compounds IX-XVI, as well as acetates XXV-XXXII, therefore form an ABX system of protons, and the splitting that is characteristic for this system [9] is present in the

TABLE 4. Mass Spectra of Spiro Epoxy Compounds IX-XVI

Compound	m/z values (relative intensities of the ion peaks in percent relative to the maximum peak)[a]
IX	211 (15), 180 (100), 166 (16), 137 (14), 124 (16), 67 (14), 55 (13), 44 (50), 42 (29), 41 (20)
X	211 (11), 180 (100), 166 (11), 137 (22), 124 (13), 119 (12), 67 (14), 44 (48), 42 (27), 41 (18)
XI	225 (17), 210 (16), 195 (16), 194 (100), 180 (22), 138 (17), 137 (14), 58 (33), 42 (21), 41 (24)
XII	225 (12), 210 (11), 195 (16), 194 (100), 180 (16), 138 (14), 137 (18), 58 (33), 42 (15), 41 (21)
XIII	225 (9), 210 (27), 194 (100), 180 (11), 164 (13), 150 (12), 137 (19), 98 (13), 67 (14), 58 (58)
XIV	225 (7), 210 (11), 195 (11), 194 (100), 180 (7), 150 (8), 137 (15), 119 (10), 98 (10), 58 (41)
XV	225 (12), 210 (30), 195 (16), 194 (100), 180 (11), 150 (9), 137 (21), 119 (12), 67 (12), 58 (56)
XVI	239 (8), 224 (100), 208 (83), 194 (15), 164 (14), 137 (17), 72 (59), 56 (41), 42 (29), 41 (28)

[a]The most intense peaks in the mass spectrum of each compound are presented.

PMR spectra of these compounds. The chemical shifts and spin–spin coupling constants (SSCC) of the indicated protons for IX-XVI and XXV-XXXII are presented in Tables 1 and 3, respectively. The introduction of an electron-acceptor acetoxy group gives rise to a paramagnetic shift of the methylene protons (AB) of spiro epoxy acetates XXV-XXXII as compared with spiro epoxy alcohols IX-XVI of 0.4-0.6 ppm. The previous orientation of the substituents of the piperidine ring was confirmed by means of double homonuclear resonance, and, consequently, isomerization products IX-XVI are actually spiro oxirane derivatives of decahydroquinoline rather than products of expansion of the piperidine ring.

The molecular-ion peaks ($[M^+]$) in the mass spectra of spiro epoxy derivatives IX and X (m/z 211), XI-XV (m/z 225), and XVI (m/z 239) constitute evidence that these compounds are structural isomers of starting epoxy alcohols I-VIII. However, in contrast to epoxy compounds I-VIII, the mass spectra of which contain intense $[M - C_2H_3O]^+$ ion peaks due to cleavage of the epoxide group, the presence of intense peaks of $[M - CH_3O]^+$ ions, which are formed as a result of detachment of a hydroxymethyl group, is characteristic for the mass spectra of spiro epoxy alcohols IX-XVI. The mass spectra of the epimeric (with respect to the C_2 atom) of epoxy alcohols XIV and XV also differ with respect to the intensities of the peaks of the $[M - CH_3]^+$ ions, which are due to detachment of a methyl group from the 2 position: The $I_{[M-CH_3]^+}/I_{[M]^+}$ value is greater for XV than for XIV. This confirms the axial orientation of the indicated substituent in the first compound and the equatorial orientation in the second compound [10].

EXPERIMENTAL

General Method for the Synthesis of Spiro Oxirane Derivatives of the Decahydroquinoline Series (IX-XVI). A) A 5.3-ml (2.6 mmole) sample of a 0.5 N solution of sodium hydroxide was added to a solution of 0.01 mole of the epoxy alcohol in 50 ml of water, and the reaction mixture was maintained at 20°C for 1-1.5 h. The course of the reaction was monitored by means of thin-layer chromatography (TLC) on 70 × 25 mm plates with Woelm Al_2O_3 (neutral) in a chloroform–ethanol (10:1) system. At the end of the reaction, the product was extracted with chloroform, and the extract was dried over magnesium sulfate. The solvent was removed at reduced pressure, and the crude product was purified by crystallization: IX-XI from hexane, and XII-XVI from hexane–ethyl acetate (5:1).

B) A 0.01 mole-sample of thiourea was added to a solution of 0.01 mole of epoxy alcohol in 50 ml of water and the mixture left to stand at room temperature for 2 h. The treatment of the product of the reaction and the precipitate was conducted by the method described in A.

C) A 0.01-mole sample of barium hydroxide was added to a solution of 0.01 mole of the epoxy alcohol in 100 ml of ethanol, and the mixture was heated at 70-80°C for 3-4 h. The solvent was then removed, and the product was isolated by the method described in A.

The yields of isomerization products IX-XVI obtained by methods A-C ranged from 85 to 90%.

The IR spectra of solutions ($5 \cdot 10^{-3}$ mole/liter) of IX-XXIV in CCl_4 and of KBr pellets or films of spiro acetates XXV-XXXII were recorded with a UR-20 spectrometer. The PMR spec-

tra of solutions of IX-XVI and XXV-XXXII in $CDCl_3$ and of XVII-XXIV in CD_3OD were recorded with a Jeol JNK-PS-100 spectrometer (100 MHz) relative to tetramethylsilane. The mass spectra were recorded with an LKB-2091 spectrometer equipped with a system for direct introduction of the samples into the ion source at a vaporization temperature of 200°C and an ionizing-electron energy of 70 eV.

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EPOXIDATION OF UNSATURATED ALCOHOLS OF THE DECAHYDROQUINOLINE SERIES

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The epoxy derivatives of stereoisomeric 1-alkyl-, 1,2-dimethyl-, and 1,2,2-trimethyl-4-vinyl-trans-decahydroquinolols were synthesized by oxidation with performic acid in formic acid solution. The compounds were characterized by their PMR and mass spectra. An analysis of the spectral data made it possible to conclude that the synthesized compounds and the starting vinyl alcohols have the same configurations.

The epoxidation of unsaturated compounds that contain an allylic hydroxy group and a heteroatom in the ring has not been adequately studied. There are only a few communications that deal with the oxidation of olefinic alcohols of the pyran, thiopyran, piperidine [1, 2], and decahydroquinoline [3, 4] series. In addition, owing to their high reactivities, epoxy alcohols are of great interest as intermediates in the synthesis of diverse functionally substituted derivatives that possibly have biological activity. The aim of the present research was to study the oxidation of some 4-vinyldecahydro-4-quinolols and to find the optimum conditions for the preparation of epoxy alcohols of this series.

An analysis of the literature data [5, 6] shows that a convenient method for the preparation of epoxy compounds without involvement of the nitrogen atom, which is sensitive to electrophilic oxidation by peracids, is oxidation with performic acid in formic acid solution, which sharply reduces the nucleophilicity of the nitrogen atom (epoxidation *in situ*). In this method formic acid is both the solvent and the oxygen atom carrier, while performic acid is formed as an intermediate. Although formic acid opens the epoxide ring at a much greater rate than other acids, the high rates of formation and consumption of performic acid prevent its rapid decomposition with the loss of an active oxygen atom. The mechanism of epoxidation by peracids includes a spiran transition state [7].

We investigated the oxidation by performic acid of stereoisomeric 1-alkyl-, 1,2-dimethyl-, and 1,2,2-trimethyl-4-vinyl-trans-decahydro-4-quinolols (I-VIII), the synthesis of which was previously described in [8-10]. As a result of varying the ratio and concentrations of the

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