STEREOCHEMISTRY OF THE OXIDATION AND ALKYLATION OF trans-1-ALKYL-4-ETHYNYLDECAHYDRO-4-QUINOLOLS

A. A. Akhrem, L. I. Ukhova,
N. F. Marchenko, G. P. Kukso,
and V. M. Gorul'ko

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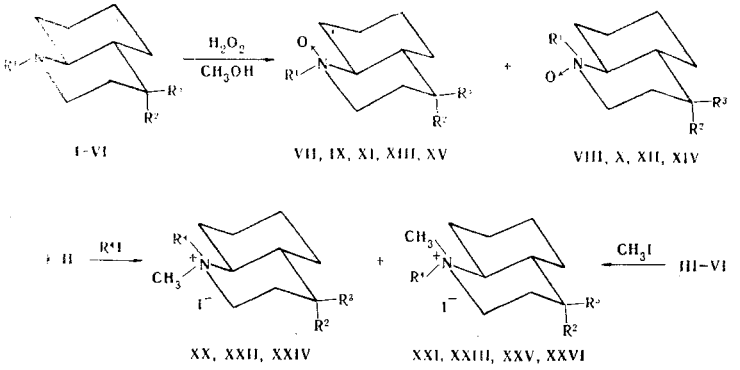
The stereochemistry of the oxidation and alkylation of the nitrogen atom of trans-1-alkyl-4-ethynyldecahydro-4-quinolols was investigated. The orientation of the substitutents attached to the nitrogen atom in the synthesized N-oxides and quaternary salts was determined on the basis of the PMR spectra and previously obtained data on the stereochemistry of the oxidation of 4-substituted 1,3-dimethyldecahydro-4-quinolols.

The stereochemistry of the quaternization of tertiary piperidine bases with alkyl halides has been studied in many papers (for example, see [1] and the literature cited therein). The oxidation of N-alkylpiperidines has been investigated to a lesser extent [2, 3]. The quaternization (alkylation [4] and cyanation [5]) of decahydroquinoline has also been discussed.

In a study of the stereochemistry of the oxidation of decahydroquinoline derivatives – stereoisomeric trans-1,2-dimethyldecahydro-4-quinolines and the tertiary alcohols obtained from them – with hydrogen peroxide in methanol we showed that the epimeric amino ketones undergo partial isomerization during oxidation, and each forms a mixture of three N-oxides corresponding to both amino ketones [6]. In contrast to amino ketones, the oxidation of 4-substituted trans-1,2-dimethyldecahydro-4-quinolols proceeds without isomerization, and each of the amino alcohols with an equatorial 2-CH_3 group forms two epimeric N-oxides, whereas amino alcohols with an axial 2-CH_3 group form only one N-oxide [7]. We also found that the oxidation of trans-1,2,2- and 1,2,9-trimethyl-4-ethynyldecahydro-4-quinolols with an axial methyl group in the 2 or 9 position, respectively, establishes preferred or selective incorporation of an oxygen atom from the axial region. In the oxidation of stereoisomeric 1-alkyl-2-methyl-4-ethynyldecahydro-4-quinolols one N-oxide is formed in each case, regardless of the orientation of the 2-CH_3 group [8]. In the present research we studied the oxidation of trans-1-alkyl-4-ethynyldecahydro-4-quinolols. For comparison with the oxidation, we also investigated the stereochemistry of their alkylation.



I, II, VII—X $R^1=CH_3$; III, XI, XII $R^1=C_2H_5$; V, XIII, XIV $R^1=n\text{-}C_3H_7$; VI, XV $R^1=i\text{-}C_3H_7$; I, III, V—VIII, XI—XV, XX, XXI, XXIV—XXVI $R^2=C\equiv CH$; II, IV, IX, X, XXII, XXIII $R^2=OH$; I, III, V—VIII, XI—XV, XX, XXI, XXIV—XXVI $R^3=OH$; II, IV, IX, X, XXII, XXIII $R^3=C\equiv CH$; I—IV, XX—XXIII $R^4=C_2H_5$; I, V, XXIV—XXV $R^4=n\text{-}C_3H_7$; I, VI, XXVI $R^4=i\text{-}C_3H_7$

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TABLE 1. Parameters of the PMR Spectra of N-Oxides of trans-1-Alkyl-4-ethynyldecahydro-4-quinolols

Starting base			N-Oxides			
compound	N–R¹	C≡CH orientation	compound	$\delta_{R^1(CH_3)}$, ppm	N–CH_3 (N–R^1) orientation	ratio, %
I	CH_3	*a*	VII	3,05	*e*	78
			VIII	3,01	*a*	22
II	CH_3	*e*	IX	3,02	*e*	79
			X	2,94	*a*	21
III	C_2H_5	*a*	XI	1,20	*e*	90
			XII	1,17	*a*	10
V	*n*-C_3H_7	*a*	XIII	0,88	*e*	95
			XIV	0,84	*a*	5
VI	*i*-C_3H_7	*a*	XV	1,26	*e*	100

TABLE 2. Parameters of the PMR Spectra of Quaternary Salts of trans-1-Alkyl-4-ethynyldecahydro-4-quinolols

Starting base			Quaternizing agent	Quaternization product				
compound	R¹	C≡CH orientation		compound	$\delta_{R^1(CH_3)}$, ppm	N–R^1 (N–CH_3) orientation	ratio in alkylation, %	ratio in methylation, %
I	CH_3	*a*	HCl	XVI	2,77	*e*	100	—
II	CH_3	*e*	HCl	XVII	2,77	*e*	100	—
I	CH_3	*a*	CH_3I	XVIII	2,95	*a*	—	—
					3,08	*e*		
II	CH_3	*e*	CH_3I	XIX	2,92	*a*	—	—
					3,03	*e*		
I	CH_3	*a*	C_2H_5I	XX	3,03	*a*	67	89
III	C_2H_5	*a*	CH_3I	XXI	3,07	*e*	33	11
II	CH_3	*e*	C_2H_5I	XXII	2,98	*e*	34	12
IV	C_2H_5	*e*	CH_3I	XXIII	2,93	*a*	66	88
I	CH_3	*a*	*n*-C_3H_7I	XXIV	2,97	*a*	70	65
V	*n*-C_3H_7	*a*	CH_3I	XXV	3,05	*e*	30	35
I	CH_3	*a*	*i*-C_3H_7I	XXVI	3,06	*a*	100	100
VI	*i*-C_3H_7	*a*	CH_3I					

The oxidation of 1-methyl-, 1-ethyl-, and 1-propyl-4-ethynyldecahydro-4-quinolols (I-III, V) gives in each case two epimeric N-oxides (Table 1). The alkylation of 1-methyl-substituted alcohols I and II with ethyl and propyl iodides, as in the methylation of 1-ethyl- and 1-propyl-substituted amino alcohols III-V, also proceeds with the formation of two isomers of the quaternary salts (Table 2). In contrast to this, only one isomer of the N-oxide or quaternary salt is formed in the oxidation and methylation of 1-isopropyl-substituted amino alcohol VI or in the alkylation of 1-methyl-substituted amino alcohol I with isopropyl iodide. In order to ascertain the stereospecificity of the quaternization of 1-alkyl-4-ethynyldecahydro-4-quinolols we obtained the PMR spectra of the individual N-oxides, quaternary salts, and hydrochlorides of 1-methyl-4-ethynyldecahydro-4-quinolols XVI and XVII (Tables 1 and 2). It is apparent from the PMR spectra that the protonation of amino alcohols I and II, which are epimeric with respect to the 4 position, proceeds strictly stereospecifically: In each case only one epimer of the hydrochloride is formed. Since the effective volume of the methyl group is greater than the volume of the hydrogen atom, one may assume its equatorial orientation in the case of hydrochlorides XVI and XVII; this is confirmed by the chemical shifts of the protons of the N-methyl groups [9-11].

The PMR spectra of 1-methyl-4-ethynyldecahydro-4-quinolol methiodides XVIII and XIX enable one to convince oneself that the chemical shifts of the protons of the axially and equatorially oriented methyl groups attached to the nitrogen atom are different.

In the determination of the orientation of the substituents attached to the nitrogen atom of the N-oxides of 1-alkyl-4-ethynyldecahydro-4-quinolols we proceeded from the fact that the protons of the equatorial methyl group attached to the nitrogen atom in the N-oxides of 4-substituted 1,2-dimethyldecahydro-4-quinolols [12] resonate at weaker field than the protons of the axial N-methyl group.

The orientation of the substituents attached to the nitrogen atom of N-ethyl- and N-propyl-substituted N-oxides was assigned on the basis of the chemical shifts of the protons of the methyl groups of these alkyl groups.

The thus-established orientation of the substituent attached to the nitrogen atom in the N-oxides of 1-alkyl-4-ethynyldecahydro-4-quinolols makes it possible to conclude that axial incorporation of the oxygen atom is preferred during oxidation of the base. Moreover, the larger the volume of the alkyl group of the starting

TABLE 3. 1-Alkyl-4-ethynyldecahydro-4-quinolol N-Oxides

Compound	mp, °C	Picrate mp, °C	R_f	Found, %			Empirical formula	Calc., %		
				C	H	N		C	H	N
VII	176—178	194—195	0,34	49,3	5,2	12,8	$C_{12}H_{19}NO_2 \cdot C_6H_3N_3O_7$	49,3	5,1	12,8
VIII	214—215	158—160	0,41	49,2	5,2	12,7	$C_{12}H_{19}NO_2 \cdot C_6H_3N_3O_7$	49,3	5,1	12,8
IX	194—195	199—201	0,53	49,4	5,0	12,7	$C_{12}H_{19}NO_2 \cdot C_6H_3N_3O_7$	49,3	5,1	12,8
X	245—246	158—159	0,16	49,2	4,9	12,7	$C_{12}H_{19}NO_2 \cdot C_6H_3N_3O_7$	49,3	5,1	12,8
XI	210—212	149—150	0,32	50,3	5,2	12,2	$C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$	50,4	5,3	12,4
XII	—	186—187	0,58	50,5	5,4	12,3	$C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$	50,4	5,3	12,4
XIII	207—209	189—190	0,28	51,7	5,5	11,5	$C_{14}H_{23}NO_2 \cdot C_6H_3N_3O_7$	51,9	5,6	11,3
XIV	—	—	0,67							
XV	204—205	185—186	0,40	51,6	5,5	11,4	$C_{14}H_{23}NO_2 \cdot C_6H_3N_3O_7$	51,9	5,6	11,3

TABLE 4. Quaternary Salts of trans-1-Alkyl-4-ethynyldecahydro-4-quinolols

Compound	mp, °C	R_f	Found, %				Empirical formula	Calculated, %			
			C	H	halogen	N		C	H	halogen	N
XVI	233—234	0,64	62,1	8,9	15,4	6,1	$C_{12}H_{19}NO \cdot HCl$	62,1	8,7	15,5	6,1
XVII	269—270	0,82	62,1	8,8	15,4	6,2	$C_{12}H_{19}NO \cdot HCl$	62,1	8,7	15,5	6,1
XVIII	215—217	—	46,5	6,4	37,2	4,1	$C_{13}H_{22}INO$	46,6	6,6	37,6	4,2
XIX	189—191	—	46,8	6,6	37,8	4,0	$C_{13}H_{22}INO$	46,6	6,6	37,6	4,2
XX	190—192	0,37	48,3	7,2	36,2	4,0	$C_{14}H_{24}INO$	48,2	6,9	36,4	4,0
XXI	191—192	0,54	48,5	6,8	36,1	4,0	$C_{14}H_{24}INO$	48,2	6,9	36,4	4,0
XXII	222—224	0,35	47,9	6,8	36,3	4,0	$C_{14}H_{24}INO$	48,2	6,9	36,4	4,0
XXIII	183—185	0,53	48,5	6,9	36,0	3,8	$C_{14}H_{24}INO$	48,2	6,9	36,4	4,0
XXIV	206—207	0,36	50,0	7,0	35,1	3,8	$C_{15}H_{26}INO$	49,7	7,1	34,9	3,9
XXV	220—222	0,61	50,0	7,1	35,2	3,7	$C_{15}H_{26}INO$	49,7	7,1	34,9	3,9
XXVI	198—200	0,41	49,8	7,1	34,9	3,7	$C_{15}H_{26}INO$	49,7	7,1	34,9	3,9

base, the more stereospecifically the oxidation proceeds (Table 1). As we see, the stereospecificity of the oxidation of trans-1-alkyl-4-ethynyldecahydro-4-quinolols is similar to that in the oxidation of trans-1,2-dimethyl-4-ethynyldecahydro-4-quinolols with an equatorial 2-CH_3 group, since two epimeric N-oxides are formed in both cases. However, the reaction proceeds more stereoselectively in the case of oxidation of trans-1-alkyl-4-ethynyldecahydro-4-quinolols.

The quaternization of 1-methyl-4-ethynyldecahydro-4-quinolols I and II with ethyl and propyl iodides takes place with preferred equatorial incorporation of the alkyl group, whereas the methylation of 1-ethyl- and 1-propyl-4-ethynyldecahydro-4-quinolols III-V proceeds with preferred axial incorporation of the methyl group.

It is apparent from the data in Table 2 that the epimer with an equatorial ethyl or propyl group and an axial methyl group attached to the nitrogen atom predominates in the products of the "forward" and "reverse" quaternization. These data also provide evidence that methylation takes place more stereoselectively than alkylation by substituents with a longer unbranched carbon chain.

As a consequence of the fact that the effective volume of the isopropyl group is considerably greater than the volume of the methyl group, an equatorial orientation of the isopropyl substituent in 1-isopropyl-4-ethynyl decahydro-4-quinolol methiodide XXVI was assumed.

The great similarity in the results obtained in the oxidation and alkylation of amino alcohols I and II, which are epimeric with respect to 4-C, indicates the absence of an effect of the configuration of the asymmetric center at 4-C on the stereochemistry of the quaternization reaction in this series.

EXPERIMENTAL

The oxidation of amino alcohols I-III, V, and VI was carried out with 30% H_2O_2 at a molar ratio of 1 :3 in methanol at room temperature. The alkylation of alcohols I and II was carried out with alkyl iodides at a molar ratio of 1 : 5 in acetone or methyl ethyl ketone at 80-90°. The methylation of amino alcohols III-VI was carried out with methyl iodide in ether at 5°. The trend of the oxidation and alkylation reactions was monitored by thin-layer chromatography (TLC) on Woelm aluminum oxide. An alcohol—acetone mixture (1 : 3) served as the solvent system for the chromatography of the N-oxides, whereas a chloroform—alcohol mixture (9 : 1) was the solvent system for chromatography of the quaternary salts. The individual oxidation and alkylation products were isolated by fractional crystallization from alcohol or alcohol—ether. The characteristics of the properties and the results of elementary analysis of the products are given in Tables 3 and 4.

The PMR spectra of the N-oxides and the quaternary salts were obtained from solutions in D_2O with a JEOL-PS-100 spectrometer at room temperature. The chemical shift of D_2O was 4.70 ppm.

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RESEARCH IN THE IMIDAZOLE SERIES

XCII.* REDUCTION OF SOME PYRROLO[1,2-a]IMIDAZOLE AND PYRROLO[1,2-a]BENZIMIDAZOLE DERIVATIVES

A. A. Druzhinina, P. M. Kochergin, R. M. Palei, and O. N. Minailova

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The reduction of pyrrolo[1,2-a]imidazole-2-one and pyrrolo[1,2-a]benzimidazole derivatives, which leads to the formation of 2,3-dihydropyrrolo[1,2-a]imidazole derivatives and derivatives of the previously unknown 1,2,3,3a-tetrahydropyrrolo[1,2-a]benzimidazole, was studied. A method was developed for the preparation of 5- and 7-amino derivatives of pyrrolo[1,2-a]-imidazole by reduction of the corresponding nitroso- and arylazo-substituted pyrrolo[1,2-a]-imidazoles.

Little study [2] has been devoted to the reduction of derivatives of polynuclear systems with a bridged nitrogen atom that include a pyrroloimidazole fragment. In developing research [3, 4] on the transformations of compounds of the pyrrolo[1,2-a]imidazole and pyrrolo[1,2-a]benzimidazole series we studied the reduction of some derivatives of these systems.

A method for the preparation of 2,3-dihydropyrrolo[1,2-a]imidazole derivatives from 1,2-dialkylimidazolines and α-halo ketones was proposed in [5]. In order to develop other methods for the synthesis of these compounds we carried out the reduction of pyrrolo[1,2-a]imidazol-2-ones (I, II) with lithium aluminum hydride

*See [1] for communication XCI.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. All-Union Scientific-Research Institute of the Technology of Blood Substitutes and Hormonal Preparations, Moscow 109004.

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