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SYNTHESIS AND STEREOISOMERISM OF N-OXIDES OF THE DECAHYDROQUINOLINE SERIES

IV.* ESTABLISHMENT OF THE CONFIGURATION OF EPIMERIC N-OXIDES OF 4-SUBSTITUTED 1,2-DIMETHYLDECAHYDRO-4-QUINOLOLS BY PMR SPECTROSCOPY

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The orientation of the substituents attached to the nitrogen atom in epimeric N-oxides of 1,2-dimethyl-4-ethynyl (vinylethynyl, vinyl, acetyl) decahydro-4-quinolols was established by means of PMR spectroscopy with the aid of the dependence of the chemical shifts of the $3\text{-}H_a$ and $3\text{-}H_e$ protons on the orientation of the N→O bond and the effect of the diamagnetic anisotropy of the C–C and C–H bonds of the rings. It was found that the equatorial methyl group attached to the nitrogen atom resonates at weaker field than the axial methyl group. The quantitative ratio of the epimeric N-oxides in the mixtures was determined.

The present research was devoted to the determination by means of PMR spectroscopy of the orientation of the substituents attached to the nitrogen atom in epimeric N-oxides of 4-substituted 1,2-dimethyl-trans-decahydro-4-quinolols.

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*See [1] for communication III.

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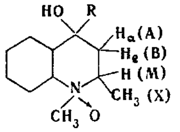

R = C≡CH, C≡C—CH=CH_2, CH=CH_2, $COCH_3$

Two epimeric N-oxides were obtained in the oxidation of 4-substituted 1,2-dimethyldecahydro-4-quinolols with hydrogen peroxide in methanol from amino alcohols that have an equatorial 2-CH_3 group, whereas only one N-oxide was obtained from amino alcohols with an axial 2-CH_3 group [2].

It is known [3] that in the series of cyclohexane derivatives polar substituents strongly deshield the axial proton in the case of 1,3-diaxial interaction, shifting its signal by 0.25-0.78 ppm.

In an investigation of N-oxides of substituted decahydroquinolines we found that in the case of an axial N→O bond the difference in the chemical shifts of the axially and equatorially oriented 3-H_a (A) and 3-H_e (B) protons changes markedly on passing from the base to the N-oxide, whereas in the case of an equatorial N→O bond this change is insignificant. As seen from Table 1, in one of the epimers of each pair of N-oxides the effect of the orientation of the N→O bond leads to a pronounced shift of the A proton to weak field and of the B proton to strong field as compared with the starting amino alcohol base. In contrast to this, the spectrum of the second epimer of the pair of N-oxides differs little from that of the base with respect to the relative position of the signals of the A and B protons. For example, in the spectrum of N-oxide VI (Fig. 1 and Table 1) the signal of the A proton is shifted to weak field by 0.66 ppm as compared with the spectrum of the starting vinylacetylenic amino alcohol (Fig. 3), whereas the signal of the B proton is shifted to strong field by 0.19 ppm. This sort of significant change in the chemical shifts of the A and B protons does not occur in the spectrum of epimeric N-

TABLE 1. Chemical Shifts (δ, ppm) and Spin–Spin Coupling Constants (J, Hz) of N-Oxides of Decahydroquinolols*

Compound	R	Substituent orientation			δ_{N-CH_3}	δ_X	δ_M	δ_A	δ_B	J_{MX}	J_{MA}	J_{MB}	J_{AB}	R_f	Yield, %
		1 CH_3	2 CH_3	4 OH											
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
I	C≡CH	1e	2e	4e	(2,32) 3,10 Δ—78	(1,18) 1,40 Δ−22	(2,60) 3,71 Δ−111	(1,60) 2,34 Δ−74	(2,0) 1,85 Δ+15	6,0	12,0	3,0	14,3	0,36	50
II		1a	2e	4e	(2,32) 2,86 Δ—54	(1,18) 1,45 Δ−27	(2,60) 3,62 Δ−102	(1,60) 1,89 Δ−29	(2,0) 2,21 Δ−21	6,0	12,0	3,0	15,0	0,55	50
III		1e	2e	4a	(2,30) 3,08 Δ—78	(1,15) 1,35 Δ−20	(2,60) 3,74 Δ−114	(1,75) 2,49 Δ−74	(2,01) 1,86 Δ−15	6,0	12,0	3,0	15,0	0,68	44
IV		1a	2e	4a	(2,30) 2,86 Δ—56	(1,15) 1,42 Δ−27	(2,60) 3,75 Δ−115	(1,75) 2,19 Δ−44	(2,01) 1,79 Δ+22	6,0	12,0	3,0	12,0	0,46	56
V		1e	2a	4a	(2,36) 3,10 Δ—74	(1,24) 1,60 Δ−36	(3,15) 3,49 Δ−34	(2,14) 2,87 Δ−73	(2,04) 1,94 Δ+10	7,5	6,0	2,3	15,0	0,47	100
VI	C≡C− −CH= =CH_2	1e	2e	4e	(2,28) 2,98 Δ—70	(1,18) 1,34 Δ−16	(2,50) 3,52 Δ−102	(1,62) 2,28 Δ−66	(1,98) 1,79 Δ+19	6,0	13,5	3,0	13,5	0,38	30
VII		1a	2e	4e	(2,28) 2,80 Δ—52	(1,18) 1,43 Δ−25	(2,50) 3,60 Δ−110	(1,62) 1,87 Δ−25	(1,98) 2,16 Δ−18	6,5	12,0	3,0	15,0	0,70	70
VIII		1e	2e	4a	(2,27) 2,98 Δ—71	(1,13) 1,28 Δ−15	(2,57) 3,64 Δ−107	(1,73) 2,38 Δ−65	(1,98) 1,76 Δ+22	6,0	12,0	3,0	13,5	0,64	50
IX		1a	2e	4a	(2,27) 2,78 Δ—51	(1,13) 1,38 Δ−25	(2,57) 3,66 Δ−109	(1,73) 2,12 Δ−39	(1,98) 2,18 Δ−20	6,5	12,0	3,0	15,0	0,41	50
X		1e	2a	4a	(2,26) 3,03 Δ—77	(1,20) 1,57 Δ−37	(3,02) 3,38 Δ−36	(2,17) 2,91 Δ−74	(1,95) 1,88 Δ+7	7,5	6,0	2,3	15,0	0,43	100

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
XI	$CH=CH_2$	1*e*	2*e*	4*e*	(2,32) 3,07 Δ—75	(1,14) 1,39 Δ−25	(2,44) 3,65 Δ−121	(1,74) 2,33 Δ−59	(1,76) 1,95 Δ−19	6.0	12,8	3.0	13.5	0,45	44
XII		1*a*	2*e*	4*e*	(2,32) 2.92 Δ—60	(1,14) 1,44 Δ−30	(2.44) 3.42 Δ−98	(1,74) 1,90 Δ−16	(1,76) 1,84 Δ−8	6.0				0.65	56
XIII		1*e*	2*e*	4*a*	(2,32) 3,06 Δ—76	(1,12) 1.34 Δ−22	(2,64) 3,74 Δ−110	(1,54) 2.26 Δ−72	(1,56) 1,36 Δ+29	6,0	12,0	3,0	15,0	0,63	46
XIV		1*a*	2*e*	4*a*	(2,32) 2,84 Δ—52	(1,12) 1,40 Δ−28	(2,64) 3,80 Δ−116	(1,54) 1,94 Δ−40	(1,56) 1,64 Δ−8	6,0	10,5	3,0	15,0	0,50	54
XV		1*e*	2*a*	4*a*	(2,36) 3,08 Δ—72	(1,28) 1,64 Δ−36	(3,10) 3,40 Δ−30	(2,04) 2,74 Δ−70	(1,56) 1,46 Δ+10	7,5	6,0	3,0	15,0	0,48	100
XVI	$COCH_3$	1*e*	2*e*	4*e*	(2,28) 3,01 Δ—73	(1,08) 1,28 Δ−20	(2,55) 3,55 Δ−100	(1,44) 2,11 Δ−67	(1,82) 1,64 Δ+18	6,0	12	3,0	15,0	0,67	40
XVII		1*a*	2*e*	4*e*	(2,28) 2,83 Δ−55	(1,08) 1,37 Δ−29	(2,55) 3,73 Δ—118	(1,44) 1,32 Δ−12	(1,82) 1,56 Δ−26	6,0	12	3,0	15,0	0,56	60
XVIII		1*e*	2*e*	4*a*	(2,32) 3,09 Δ−77	(1,14) 1,36 Δ−22	(2,64) 3,76 Δ−112	(1,79) 2,49 Δ−70	(1,47) 1,39 Δ+8	6,0	12	3,0	13,5	0,57	~50
XIX		1*a*	2*e*	4*a*	(2,32) 2,86 Δ—54	(1,14) 1,43 Δ−29	(2,64) 3,70 Δ−106	(1,79) 1,85 Δ−6	(1,47)	6,0	12		16,0	0,75	~50
XX		1*e*	2*a*	4*a*	(2,36) 3,13 Δ—77	(1,25) 1,62 Δ−37	(3,17) 3,56 Δ−39	(1,76) 3,04 Δ−128	(1,50) 1,42 Δ+8	7,5	6	2,3	13,5	0,51	100

*The PMR spectra of 0.25 M solutions of the compounds in CD_3OD were obtained with a JEOL PS-100 spectrometer. Tetramethylsilane was used as the internal standard. The δ values for the amino alcohol bases are presented in parentheses. The assignment of the signals was confirmed by double resonance. The Δ values are given in Hertz.

TABLE 2. r_i and θ_i Values

N—CH₃ (*a*)				N—CH₃ (*e*)			
$r^{(1)}C_2C_3—CH_3$	3,25Å	$\theta C_2C_3r^{(1)}$	78°28′	$r^{(2)}C_2C_3—CH_3$	3,55Å	$\theta C_2C_3r^{(2)}$	29°30′
$r^{(3)}C_9C_{10}—CH_3$	3,25Å	$\theta C_9C_{10}r^{(3)}$	78°28′	$r^{(4)}C_9C_{10}—CH_3$	3,55Å	$\theta C_9C_{10}r^{(4)}$	29°30′
$r^{(5)}C_6C_7—CH_3$	4,82Å	$\theta C_6C_7r^{(5)}$	52°15′	$r^{(6)}C_6C_7—CH_3$	5,02Å	$\theta C_6C_7r^{(6)}$	52°3′

oxide (Fig. 2). On the basis of this (also see [3]), an axial orientation of the N→O bond was assigned to N-oxide VI, and an equatorial orientation of the N→O bond was assigned to N-oxide VII. An axial orientation was also assigned to N-oxides I, III, VIII, XI, XIII, XVI, and XVIII on the same basis, whereas an equatorial orientation of the N→O bond was assigned to N-oxides II, IV, IX, XII, XIV, XVII, and XIX. A similar relationship has been observed for N-oxides of the tropane series [4].

To determine the orientation of the N→O bond in N-oxides V, X, XV, and XX with a 2a4a configuration, which do not have epimers with respect to the nitrogen atom, we compared their spectra with the spectra of epimeric pairs of N-oxides with a 2e4a or 2e4e configuration. This comparison showed that the change in the chemical shifts of the 3-H_a and 3-H_e protons on passing from the bases to N-oxides V, X, XV, and XX has the same character as observed in the case of N-oxides I, III, VI, VIII, XI, XIII, XVI, and XVIII, to the N→O bond in which an axial orientation was assigned. On the basis of this, an axial orientation was also assigned to the N→O bond in N-oxides V, X, XV, and XX.

The epimeric (with respect to the nitrogen atom) N-oxides can be categorized as two types with respect to the chemical shifts of the signals of the N-methyl groups: those with $\delta_{N\text{-}CH_3}$ values ranging from 2.98 to 3.10 ppm and those with $\delta_{N\text{-}CH_3}$ values ranging from 2.78 to 2.92 ppm. The data from the PMR spectra of the

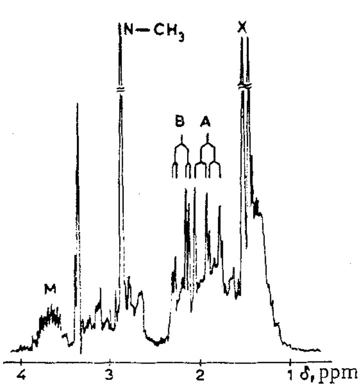

Fig. 1

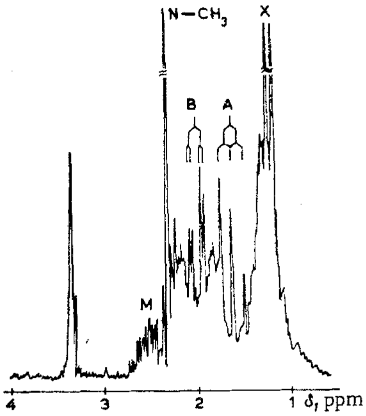

Fig. 2

Fig. 1. Fragment of the PMR spectrum of 1,2-dimethyl-4-vinylethynyldecahydro-4-quinolol N-oxide (VI) in CD_3OD.

Fig. 2. Fragment of the PMR spectrum of 1,2-dimethyl-4-vinylethynyldecahydro-4-quinolol N-oxide (VII) in CD_3OD.

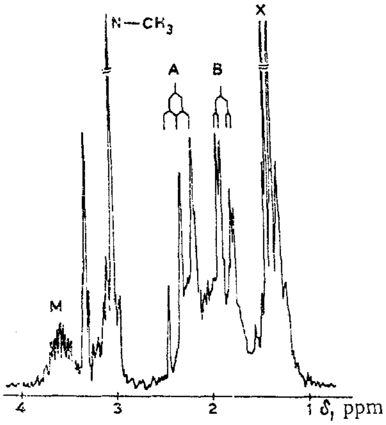

Fig. 3. Fragment of the PMR spectrum of 1,2-dimethyl-4-vinylethynyldecahydro-4-quinolol in CD_3OD.

bases of the investigated amino alcohols show that an a/e orientation of the 4-OH and 4-R groups has practically no effect on the chemical shifts of the 2-CH_3 and N-CH_3 groups (0.03-0.06 ppm). The donor–acceptor $N \rightarrow O$ bond has an identical effect on N–CH_3 in the case of an axially or equatorially oriented methyl group. Because of this, one may assume that the difference in the chemical shifts in the axial and equatorial N-methyl groups observed in the spectra of the N-oxides is evidently due mainly to the anisotropy of the C–C and C–H bonds of the rings, namely, the C_2-C_3, C_9-C_{10}, C_6-C_7, C_2-H_a, C_9-H_a, and C_7-H_a bonds. When the tensor of the magnetic susceptibility of the bond has axial symmetry, as is true in our case, the shielding effect ($\Delta\sigma_{ae}$) due to the magnetic anisotropy of the bonds can be calculated from the MacConnel equation [5]

$$\Delta\sigma_{ae} = \sum_i \frac{\Delta\chi_i}{3r_i^3}(1-3\cos^2\theta_i), \tag{1}$$

where $\Delta\chi_i$ is the molar magnetic susceptibility of the i-th bond, r is the distance from the i-th bond to the shieldable group, and θ_i is the angle between r and the direction of the i-th bond.

If the C–C and C–H bonds are equal to 1.54 and 1.09 Å, the valence angles have tetrahedral values, the induced dipole of the C–C bond is found in the middle of the C–H bond, and the dipole of the C–H bond is 0.77 Å away from the carbon atom, Eq. (1) can be reduced to Eq. (2), which is more convenient for the calculations:

$$\Delta\sigma_{ae} = \sum \frac{(-1)^i}{3}\,\frac{(1-3\cos^2\theta)}{r_i^3}\,(\Delta\chi_{C-C}-\Delta\chi_{C-H}). \tag{2}$$

Even i values in Eq. (2) correspond to r_i and θ_i up to an equatorial N−CH$_3$ bond, and odd i values correspond to r_i and θ_i up to axial N− CH$_3$ bond; $\Delta\chi_{C-C} - \Delta\chi_{C-H} = 4.2 \cdot 10^{-6}$ cm^3/mole. The r_i and θ_i values (Table 2) for the epimeric (with respect to the nitrogen atom) pair of N-oxides was found taking into account the fact that $l_{N-CH_3} = 1.83$ Å (the distance from the nitrogen atom to the center of rotation of the protons of the N-methyl group).

In accordance with the conditions of Eq. (2) the following will be true for the C−H bonds: the distance from the C−H dipole to the N−CH$_3$ (*a*) bond is equal to the distance from the C−C dipole to the N−CH$_3$ (e) bond, and vice versa; the same is also true for the θ_i angles. Substituting the r_i and θ_i values found in Eq. (2) and multiplying by the operating frequency of the spectrometer (100 MHz) for conversion to parts per million, we found that $\Delta\delta_{a(N\text{-}CH_2)} = 0.075$, $\Delta\delta_{e(N\text{-}CH_3)} = -0.82$, and $\Delta\delta_{ae(N\text{-}CH_3)} = 0.157$ ppm.

Thus the axial N-methyl group is shielded by the C−C and C−H bonds, whereas the equatorial N-methyl group is deshielded. This makes it possible to conclude that, of the two N−CH$_3$ signals corresponding to the epimeric N-oxides, the signal that resonates at stronger field should correspond to the axial epimer, whereas the signal resonating at weaker field should correspond to the equatorial N−CH$_3$ group.

The fact that the calculated difference in the chemical shifts of the N-methyl groups [$\Delta\delta_{ae(N\text{-}CH_3)} = 0.16$ ppm] lies in the experimentally found range (0.15-0.24 ppm) indicates that the decisive factor in the shielding of the methyl group attached to the nitrogen atom is the diamagnetic susceptibility of the C−C and C−H bonds of the rings.

The ratio of the stereiosimeric N-oxides in the epimeric mixtures was calculated from the areas of the signals of the N-methyl groups. The results attest to the absence of or low stereoselectivity of oxidation in most of the investigated examples. Appreciable predominance of the equatorial N-oxide in the mixture is observed only in the case of oxidation of the vinylacetylenic alcohol and the ketol that have an equatorial 2-CH$_3$ group and an axial 4-R substituent.

The chromatographic mobilities of the investigated N-oxides of 4-substituted 1,2-dimethyldecahydro-4-quinolols in a thin layer of Al$_2$O$_3$ is in agreement with the results of a determination of the orientation of the polar N→O and OH groups in these N-oxides by PMR spectroscopy and mass spectrometry [6]. Thus, for example, N-oxide I with an axial N→O bond and equatorial 4-OH substituent has a lower (0.36) R_f value than its epimer II (0.55) with an equatorial N→O bond. In the case of N-oxides I the two cis-oriented polar groups cause greater interaction with the sorbent and, as a consequence, are responsible for its lower chromatographic mobility. Less interaction with the sorbent and, consequently, greater chromatographic mobility are observed in the case of N-oxide II with a trans orientation of polar substituents. N-Oxides XVI and XVII constitute an exception to this rule. Here, one should take into account the presence of a strong hydrogen bond between the acetyl group and the 4-OH group, as a consequence of which the chromatographic mobility is determined only by the orientation of the N→O bond (see Table 1).

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