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OXIRANYL β-AMINOVINYL KETONES.
6.* SYNTHESIS OF N-SUBSTITUTED *cis*-10-HYDROXY-$\Delta^{2,3}$-OCTAHYDRO-4-QUINOLINONES

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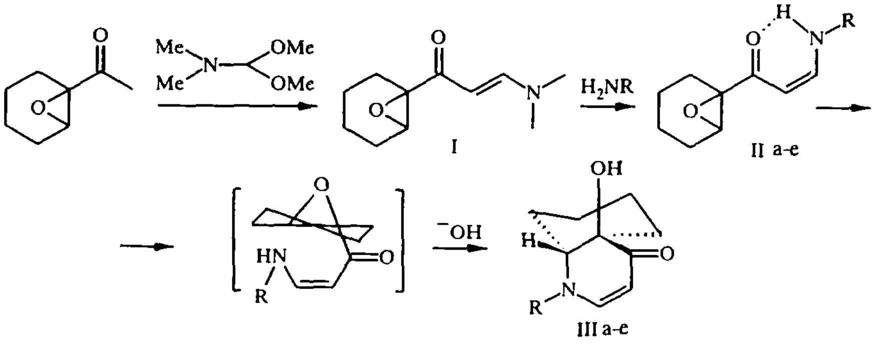
A method was developed for the synthesis of cis-*10-hydroxy-1-methyl(aryl)-$\Delta^{2,3}$-octahydro-4-quinolinones by the cyclization of 1-[*cis*-3-N-methyl(aryl)aminoacryloyl]-1,2-epoxycyclohexanes.*

Octahydro- and decahydro-4-quinolinones form the structural basis of a series of neuroleptics and alkaloids of interest as biologically active substances [2, 3]. Decahydro-4-quinolinones are synthesized by the condensation of aromatic aldehydes with 1-acetylcyclohexene followed by the reaction of the obtained divinyl ketones with primary amines [4]. This gives mixtures of *cis*- and *trans*-fused decahydro-4-quinolinones. A method for the synthesis of *cis*-10-hydroxydecahydro-4-quinolinone by the cyclization of 1-(*trans*-3-phenylacryloyl)-1,2-epoxycyclohexane with methylamine has been described [5]. *cis*-Fusion of the alicycle and heterocycle takes place as a result of *trans*-opening of the epoxy ring by the amine.

In the present work, we studied the possibility of using the above-mentioned method of ring closure to construct the hydrogenated quinoline system of *cis*-$\Delta^{2,3}$-octahydro-4-quinolinones from the corresponding epoxyaminoenones.

To obtain the initial epoxyaminoenones we reacted 1-acetyl-1,2-epoxycyclohexane with DMFA dimethyl acetal. As a result, we obtained a 71% yield of dimethylaminoepoxyenone (I), the transamination of which with methylamine, aniline, *p*-toluidine, *p*-anisidine, and *p*-bromoaniline gave the respective epoxyaminovinyl ketones (IIa-e) containing a secondary amino group with yields of 63-92%. The latter were cyclized to the octahydroquinolones (IIIa-d) by the action of tetrabutylammonium hydroxide.



II, III a R = Me; b R = Ph; c R = p-MeC_6H_4; d R = p-$MeOC_6H_4$; e R = p-BrC_6H_4

In the aminovinyl ketone, according to the spin–spin coupling constants (12.5 Hz) of the protons of the double bond (Table 2), the aminoenone fragment has the *trans* configuration, and in the case of compounds (IIa-e) the spin–spin coupling constant amounts to 8.5 Hz, which is typical of *cis*-aminoenones [6]. The enones (IIa-e) are in the s-*cis* conformation, as demonstrated by the presence in their IR spectra of a very broad absorption band for the N–H bond, participating in intramolecular interaction with the carbonyl group, at 3133-3147 cm^{-1}.

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*For Communication 5, see [1].

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TABLE 1. Spectral Data for Compounds (I, IIa-e, IIIa-e)

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, spin—spin coupling constant (*J*), Hz
I	1647, 1553, 1416, 1367, 1100, 920, 867	1,00...2,43 (9H, m, $4CH_2$ and 2-H); 2,90 [6H, s, 3′-$N(CH_3)_2$]; 5,13 (1H, d, J = 12,5, 2′-H); 7,50 (1H, d, $J_{3'2'}$ = 12,5, 3′-H)
IIa	3145, 1644, 1595, 1560, 1220, 927, 860	0,90...2,20 (8H, m, $4CH_2$); 2,90 (3H, d, J = 7,0, 3′-NCH_3); 3,07 (1H, m, 2-H); 5,17 (1H, d, $J_{2'3'}$ = 7,0, 2′-H); 6,7 (1H, d. d, $J_{3'2'}$ = 7,0, $J_{3',NH}$ = 13,0, 3′-H); 9,80 (1H, br.s, NH)
IIb	3406, 3247, 1632, 1595, 1557, 1275, 1117, 999, 819, 680	1,00...2,80 (8H, m, $4CH_2$); 3,06 (1H, m, 2-H); 3,11 (1H, d, $J_{2'3'}$ = 7,6, 2′-H); 6,90...7,60 (6H, m, C_6H_5 and 3′-H); 11,68 (1H, d, $J_{3'NH}$ = 11,4, NH)
IIc	3147, 1640, 1593, 1553, 1477, 1280, 1220, 1120, 1000, 927, 867, 809, 727	1,02...2,01 (8H, m, $4CH_2$); 2,27 (3H, s, $C\underline{H}_3$—C_6H_4); 3,02 (1H, br.s, 2-H); 5,40 (1H, d, $J_{2'3'}$ = 8,40, 2′-H); 6,67...7,07 (4H, m, C_6H_4); 7,07 (1H, dd, $J_{3'2'}$ = 8,4, $J_{3'NH}$ = 11,4, 3′-H); 11,71 (1H, d., $J_{NH3'}$ = 12,0, NH)
IId	3107, 1632, 1593, 1560, 1480, 1280, 1200, 1120, 1033, 1000, 927, 867, 837, 717	0,98...2,00 (8H, m, $4CH_2$); 2,91 (1H, br.s, 2-H); 3,65 (3H, s, CH_3O); 5,30 (1H, d, $J_{2'3'}$ = 2′-H); 6,50...6,97 (4H, m, C_6H_4); 7,07 (1H, dd, $J_{2'3'}$ = 7,1, $J_{3'NH}$ = 12,0, 3′H); 11,6 (1H, d, $J_{NH3'}$ = 12,0, NH)
IIe	3120, 1636, 1593, 1553, 1473, 1280, 1227, 1120, 1073, 1000, 927, 867, 817	0,90...2,12 (8H, m, $4CH_2$); 3,00 (1H, m, 2-H); 5,45 (1H, d, $J_{2'3'}$ = 8,6, 2′-H); 6,60...7,60 (5H, m, C_6H_4 and 3′-H); 11,60 (1H, d, $J_{NH3'}$ = 12,0, NH)
IIIa	3553, 3435, 1640, 1587, 1233, 1147, 1068	1,00...2,12 (8H, m, $4CH_2$); 3,02 (4H, s, 1-CH_3 and 10-OH); 3,23 (1H, dd, J_{98} = 3,4, $J_{98'}$ = 3,2, 9-H); 4,95 (1H, d, J_{32} = 7,2, 3-H); 6,99 (1H, d, J_{23} = 7,2, 2-H)
IIIb	3560, 3435, 1637, 1573, 1488, 1234, 1164, 1035, 793, 688	1,13...2,16 (8H, m, $4CH_2$); 3,28 (1H, br.s, 10-OH); 3,90 (1H, dd, J_{98} = 4,1, $J_{98'}$ = 4,4, 9-H); 5,13 (1H, d, J_{32} = 7,1, 3-H); 7,00...7,50 (6H, m, C_6H_5, 2-H)
IIIc	3567, 3427, 1640, 1582, 1516, 1240, 1173, 1040, 827	1,20...2,14 (8H, m, $4CH_2$); 2,31 (3H, s, $C\underline{H}_3C_6H_4$); 3,35 (1H, br.s, 10-OH); 3,87 (1H, d.d, J_{98} = 4,0, $J_{98'}$ = 4,2, 9-H); 5,08 (1H, d, J_{32} = 7,5, 3-H); 7,00...7,34 (5H, m, C_6H_4 and 2-H)
IIId	3566, 3440, 1640, 1580, 1514, 1220, 1040, 833	1,10...2,20 (8H, m, $4CH_2$); 3,51 (1H, br.s, 10-OH); 3,73 (3H, s, CH_3O); 3,79 (1H, t, J_{98} = 4,0, 9-H); 5,07 (1H, d. J_{32} = 7,3, 3-H); 6,80...7,30 (5H, m, C_6H_4 and 2-H)
IIIe	3551, 3420, 1635, 1505, 1240, 1160, 1026, 828	0,90...2,00 (8H, m, $4CH_2$); 2,77 (1H, br.s, 10-OH); 4,08 (1H, t, J_{98} = 5,6, 9-H); 6,82...7,60 (5H, m, C_6H_4, 2-H)

The cyclization of the aminovinyl ketones (IIa-e) takes place according to the Fürst–Plattner rule [7] through diaxial opening of the epoxy ring. Here, the hydroxyl group in the quinolones (IIIa-e) must occupy the axial position in the cyclohexane fragment, while the hydrogen atom at position 9 is in the equatorial position.

The signal of the 9-H proton of the quinolones (IIIa-e) takes the form of a triplet or two almost merging doublets with spin–spin coupling constant 3.2-4.4 Hz and lies in the range of 3.22-4.08 ppm, which is typical of the protons in a *cis*-fused bicyclic system.

The accuracy of the established configuration of the quinolones (III) is also confirmed by the spin–spin coupling constant, calculated by means of the Karplus equation [8] from the dihedral angles between the hydrogen atoms at positions 8 and 9. The angles were determined as a result of calculation of the geometry of compounds (IIIa-e) by molecular mechanics. The vicinal spin–spin coupling constants amount to 3.01-3.20 Hz between the equatorial protons and 3.88-3.59 Hz between the axial and equatorial protons. The calculated spin–spin coupling constants were close to the experimental values. For comparison with the obtained spin–spin coupling constants of the quinolones, the analogous constants were calculated for the stereoisomers of the quinolone (IIIa), in which the proton at $C_{(9)}$ occupies the axial position, while the hydroxyl group is either axial or equatorial. Here it was found that the spin–spin coupling constants of the protons amount to 11.64 and 11.77 Hz for diaxial coupling and 3.68 and 3.87 Hz respectively in the case of axial–equatorial coupling.

During calculation of the structures of the quinolones (IIIa-e) with an axial hydroxyl group it was established that a strong intramolecular hydrogen bond can form between the hydroxyl and carbonyl groups. Investigation of the IR spectra of dilute solutions of the quinolones (IIIa-e) showed the presence of a strong comparatively narrow absorption band in the form of a Gaussian curve in the region of 3440-3450 cm^{-1}, characteristic of the vibrations of the O–H bond participating in a strong intramolecular hydrogen bond.

TABLE 2. Characteristics of Compounds (I, IIa-e, IIIa-e)

Com-pound	Molecular formula	$\frac{\text{Found, \%}}{\text{Calculated, \%}}$			mp, °C	Yield, %
		C	H	N		
I	$C_{11}H_{17}NO_2$	$\frac{67,41}{67,66}$	$\frac{8,56}{8,78}$	$\frac{7,29}{7,17}$	36...37	71
IIa	$C_{10}H_{15}NO_2$	$\frac{66,34}{66,27}$	$\frac{8,09}{8,34}$	$\frac{7,91}{7,73}$	75...76	63
IIb	$C_{15}H_{17}NO_2$	$\frac{74,27}{74,05}$	$\frac{7,23}{7,04}$	$\frac{5,92}{5,76}$	88...89	78
IIc	$C_{16}H_{19}NO_2$	$\frac{74,45}{74,68}$	$\frac{7,55}{7,44}$	$\frac{5,68}{5,44}$	86...87	85
IId	$C_{16}H_{19}NO_3$	$\frac{70,19}{70,31}$	$\frac{7,26}{7,01}$	$\frac{5,24}{5,12}$	70...71	92
IIe	$C_{15}H_{16}BrNO_2$*	$\frac{56,12}{55,91}$	$\frac{5,24}{5,00}$	$\frac{4,56}{4,35}$	110...111	90
IIIa	$C_{10}H_{15}NO_2$	$\frac{66,52}{66,27}$	$\frac{8,24}{8,34}$	$\frac{7,85}{7,73}$	150...151	72
IIIb	$C_{15}H_{17}NO_2$	$\frac{74,29}{74,05}$	$\frac{6,93}{7,04}$	$\frac{5,87}{5,76}$	146...147	84
IIIc	$C_{16}H_{19}NO_2$	$\frac{74,41}{74,68}$	$\frac{7,57}{7,44}$	$\frac{5,68}{5,44}$	150...152	85
IIId	$C_{16}H_{19}NO_3$	$\frac{70,09}{70,31}$	$\frac{7,26}{7,01}$	$\frac{5,40}{5,12}$	148...149	70
IIIe	$C_{15}H_{16}BrNO_2$†	$\frac{56,27}{55,91}$	$\frac{5,23}{5,00}$	$\frac{4,55}{4,35}$	205...206	81

*Found %: Br 24.62. Calculated %: Br 24.81.

†Found %: Br 24.56. Calculated %: Br 24.81.

EXPERIMENTAL

The IR spectra of 0.15 M solutions of compounds (IIa-e, IIIa-e) and millimolar solutions of the quinolones (IIIa-e) with absorbing layers of 0.15 and 10.0 mm respectively were recorded in chloroform on a Specord IR-75 spectrophotometer. The PMR spectra were recorded in deuterochloroform on Tesla BS-467 and Bruker AC-200 spectrometers at 60 and 200 MHz respectively. The chemical shifts were measured on the δ scale with reference to HMDS. The reaction was monitored on Silufol plates. The eluant was acetone–hexane, and the developers were iodine vapor and 4% potassium permanganate solution.

The characteristics of compounds (II) and (IIIa-e) are given in Tables 1 and 2.

1-(*cis*-3-N,N-Dimethylaminoacryloyl)-1,2-epoxycyclohexane (I). Methanol was slowly distilled from a solution of 14 g (0.1 mole) of acetylcyclohexene oxide [9] and 17 g (0.15 mole) of DMFA dimethyl acetal in 50 ml of toluene over 28 h so that the temperature of the boiling mixture did not rise above 70°C. The toluene was then removed on a rotary evaporator, and the product (I) was isolated by vacuum distillation of the residue.

1-(*cis*-3-N-Methylaminoacryloyl)-1,2-epoxycyclohexane (IIa). A solution of 3 g (16.2 mmole) of the aminoenol (I) in a mixture of 15 ml of 30 mole % aqueous methylamine and 5 ml of dioxane was kept at room temperature for 3 days. The water and dioxane were then distilled on a rotary evaporator, and the product (IIa) was isolated by crystallization of the residue from ether.

1-(*cis*-3-N-Arylaminoacryloyl)-1,2-epoxycyclohexanes (IIb-e). We dissolved 5.4 mmole of the aminoenone (I) in a solution of 6 mmole of the arylamine in the smallest amount of 20% acetic acid. The reaction mixture was kept at room temperature for 24 h and was then diluted with water (~10 ml). The crystals of the product (II) were filtered off and crystallized from ethanol.

1-N-Methyl(aryl)-*cis*-10-hydroxy-$\Delta^{2,3}$-octahydro-4-quinolinones (IIIa-e). A solution of 50 mmole of the aminoenone (IIa-e) and 0.1 g of tetrabutylammonium hydroxide in 5 ml of dioxane was heated to 50°C and kept for 30 min. The end of the reaction was determined by TLC with 2:3 acetone–hexane as eluant. The reaction mixture was diluted with ten times the amount of water and extracted with ether, and the extract was dried with sodium sulfate. The ether was distilled, the residue was crystallized from a 3:1 mixture of heptane and isopropyl alcohol, and the product (III) was isolated.

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