SYNTHESIS AND STEREOISOMERISM OF N-OXIDES OF THE DECAHYDROQUINOLINE SERIES

III.* EPIMERIZATION OF THE C_2 CENTER IN ISOMERIC 1,2-DIMETHYL-trans-DECAHYDRO-4-QUINOLONES DURING THE PREPARATION OF THE N-OXIDES

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The results of the oxidation of a number of 4-substituted 1,2-dimethyldecahydro-4-quinolones with hydrogen peroxide in methanol are in conformity with the results obtained by us earlier and confirm that the stereochemistry of the oxidation of nitrogen depends on the configuration of the methyl substituent in the 2 position of the decahydroquinoline ring. Under these conditions, the epimeric 1,2-dimethyl-trans-decahydro-4-quinolones undergo partial interisomerization at the 2 position to give a mixture of three N-oxides that correspond to both amino ketones. The oxidation of the corresponding ketals proceeds like the oxidation of amino alcohols without epimerization. It is thereby shown that the epimerization of the C_2 center during the formation of the N-oxides from epimeric 1,2-dimethyl-trans-decahydro-4-quinolones occurs with the participation of the carbonyl group.

In developing our research on the stereochemistry of the epoxidation of decahydroquinoline derivatives, in the present communication we set forth the results of the oxidation of 1,2-dimethyl-4-ethynyl- (I) and -4-vinyldecahydro-4-quinolones (VI) of the 2e4e configurational series,† three stereoisomeric 1,2-dimethyl-4-acetyldecahydro-4-quinolones (2e4*a*, 2e4e, and 2*a*4e – XIV, XIX, and XXIV, respectively), and two epimeric (with respect to the 2 position) 1,2-dimethyl-trans-decahydro-4-quinolones (XXVII, XXXII) with hydrogen peroxide in methanol.

A mixture of N-oxides II and III, from which individual picrates IV and V were isolated, was obtained in the oxidation of acetylenic alcohol I (2e4e) with hydrogen peroxide in methanol. Under the same conditions, two N-oxides (VII and VIII), which were identified through picrates IX and X, are also formed from vinyl alcohol VI. Oxidation of alcohol VI with 2 mole of peracetic acid in chloroform gave epoxide N-oxide XI, which was isolated and identified through picrate XII, and the presence of N-oxide VIII was detected qualitatively by thin-layer chromatography (TLC). Oxidation of alcohol VI with performic acid gave epoxide XIII, and an epoxide N-oxide identical to XI was synthesized from the latter by oxidation with hydrogen peroxide. Compound XI was also obtained by oxidation of N-oxide VII with peracetic acid.

Oxidation of keto alcohol XIV (2e4*a*) with hydrogen peroxide in methanol gave a mixture of isomeric N-oxides XV and XVI, which could be separated by fractional crystallization. Keto alcohol XIX (2e4e) under similar conditions also forms a mixture of two isomeric N-oxides XX and XXI, which were separated as picrates XXII and XXIII.

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*See [1, 2] for communications I and II.

† The symbols 2*a* or 2e indicate axial or equatorial orientations of the methyl group in the 2 position; 4*a* or 4e designate axial or equatorial orientations of the 4-R substituent.

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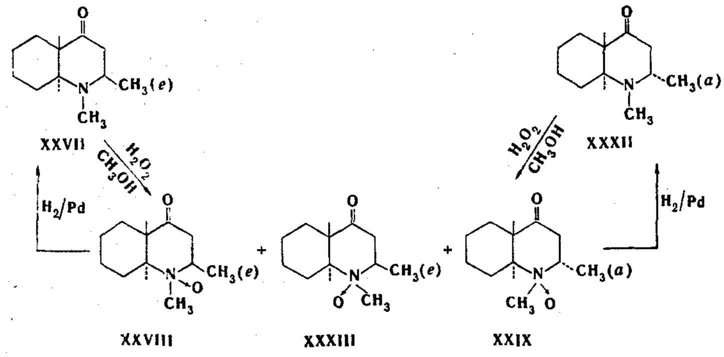
Keto alcohol XXIV (2*a*4e) behaves differently on oxidation with hydrogen peroxide in methanol and gives only one N-oxide (XXV).

The above results are in conformity with the results that we previously obtained and confirm the effect of the orientation of the methyl substituent in the 2 position of the decahydroquinoline ring on the stereochemistry of the oxidation of the nitrogen atom.

In contrast to amino alcohols, which retain their configuration during oxidation, as attested to by the reduction of the N-oxides obtained to the starting amino alcohols, epimeric amino ketones XXVII (2e) and XXXII (2*a*) undergo partial interisomerization at the 2 position on oxidation with hydrogen peroxide in methanol to each give a mixture of three N-oxides that correspond to both amino ketones. In both cases, picrate XXX, which corresponds to N-oxide XXVIII, and picrate XXXI, which corresponds to N-oxide XXIX, were isolated as a result of separation of the mixture of N-oxides.

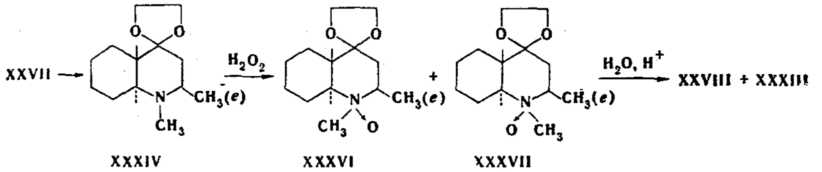
To relate the N-oxides to the starting amino ketones, the latter were regenerated by catalytic hydrogenation of the N-oxides. Amino ketone XXVII was obtained from N-oxide XXVIII, while amino ketone XXXII was obtained from N-oxide XXIX, which was used in the hydrogenation as the picrate. On the basis of the evident predominance of N-oxide XXVIII over N-oxide XXIX in the products of the oxidation of the amino ketones, it can be concluded that amino ketone XXVII, which has an equatorial methyl group, and the N-oxide formed from it (XXVIII) are much more stable under the oxidation conditions than ketone XXXII, which has an axial methyl group, and its N-oxide (XXIX). In addition to N-oxides XXVIII and XXIX, a third reaction product (XXXIII) was detected by TLC. On the basis of data on the stereochemistry of the oxidation of amino alcohols, it can be assumed that XXXIII was formed in the oxidation of ketone XXVII and is an epimer of N-oxide XXVIII with respect to the nitrogen atom.

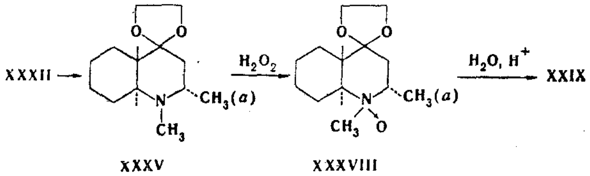


It might have been assumed that the carbonyl group participates in the epimerization of ketones XXVII and XXXII. To verify this assumption, the corresponding ethylene ketals (XXXIV and XXXV) were oxidized under the conditions of the oxidation of the ketones. The oxidation of ketal XXXIV (2e) gave two of its N-oxides, which, after removal of the ketal grouping, were converted to a mixture of two N-oxides of the ketone. N-Oxide XXVIII was isolated by crystallization of the picrates of the latter. The second epimer of the mixture was identified as the N-oxide XXXIII by chromatography.

Only one N-oxide of the ketal, the hydrolysis of which gave N-oxide XXIX, is formed in the oxidation of ketal XXXV (2*a*). It should be noted that individual N-oxide XXIX, in contrast to its picrate (XXXI), is extremely unstable and readily isomerizes (in a column filled with Al_2O_3 under the conditions of its formation and also simply on storage) to give a mixture of three N-oxides that correspond to both ketones, and the N-oxide oxygen is partially cleaved to give the starting ketone (XXXII).

The results provide evidence that the oxidation of ketals in which the carbonyl group is protected proceeds like the oxidation of amino alcohols without epimerization at the C_2 center and confirm the assumption that the epimerization of this center during the formation of N-oxides from epimeric 1,2-dimethyl-trans-decahydro-4-quinolones occurs with the participation of the carbonyl group. The mechanism of the epimerization is under study.





EXPERIMENTAL

The course of the reaction was monitored by means of TLC on Al_2O_3. The reaction mixture was chromatographed in the systems of solvents used both for the separation of the starting decahydroquinolones [acetone–hexane–ether (1 : 9 : 10)] and for the separation of their N-oxides [ethanol–acetone (1 : 2)].

Oxidation of 1,2-Dimethyl-4-ethynyldecahydro-4-quinolone. A 1 g (5 mmole) sample of alcohol I (2e4e, mp 114-115°) in 15 ml of methanol was oxidized with 4.92 g (15 mmole) of 10% hydrogen peroxide. After the usual workup, the product was converted to the picrate. A total of 0.80 g of picrate IV with mp 211-212° (from alcohol) and R_f 0.68 (the value corresponding to N-oxide II) precipitated on standing. Found: C 50.7; H 5.2%. $C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.4; H 5.3%. The mother liquor yielded 0.8 g of picrate V with mp 148-149° and R_f 0.46 (the value corresponding to N-oxide III). Found: C 50.6; H 5.4%. $C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.4; H 5.3%.

Oxidation of 1,2-Dimethyl-4-vinyldecahydro-4-quinolol. A) Oxidation of 0.75 g (4 mmole) of alcohol VI (2e4e, mp 96°) in 10 ml of methanol by means of 4 g (12 mmole) of 10% H_2O_2 gave 0.73 g of reaction product, which was converted to the picrate. Fractional crystallization of the mixture of picrates gave 0.6 g of picrate IX with mp 198-199° (from alcohol) and R_f 0.63 (the value corresponding to N-oxide VII). Found: C 50.3; H 5.8%. $C_{13}H_{23}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.2; H 5.7%. The mother liquor yielded 0.55 g of picrate X with mp 129-130° and R_f 0.5 (the value corresponding to N-oxide VIII). Found: C 50.2; H 5.7%. $C_{13}H_{23}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.2; H 5.7%.

B) A 1 g (5 mmole) sample of alcohol VI in 20 ml of chloroform was oxidized with 1.1 g (10 mmole) of 73% peracetic acid. The usual workup gave 1.1 g of a viscous substance. Fractional crystallization of the mixture of picrates from ethanol gave 0.85 g of picrate XII with mp 185-186° and R_f 0.60 [the value corresponding to 1,2-dimethyl-4-(1,2-epoxy-ethyl)decahydro-4-quinolol N-oxide (XI)]. Found: C 48.4; H 5.6%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6%. Two spots with R_f 0.60 and 0.50 (the latter was identical to that of N-oxide VIII) were detected on chromatography of the mother liquor. N-Oxide XI was also obtained by oxidation of N-oxide VII with 73% peracetic acid (1 mole) in chloroform and by oxidation of glycidic alcohol XIII with 10% hydrogen peroxide in methanol. Compound XIII (mp 112-113°, R_f 0.84) was obtained by oxidation of vinyl alcohol VI with performic acid. Found: C 69.4; H 10.2%. $C_{13}H_{23}NO_2$. Calculated: C 69.3; H 10.3%.

Oxidation of Isomeric 1,2-Dimethyl-4-acetyldecahydro-4-quinolols. A) Oxidation of 2 g (9 mmole) of ketol XIV (2e4*a*, mp 139-140°) by means of 2.8 g (9 mmole) of 10% hydrogen peroxide in methanol gave 1.9 g of a mixture of isomeric 1,2-dimethyl-4-acetyldecahydro-4-quinolol N-oxides. Fractional crystallization of 1 g of a mixture of the N-oxide from alcohol–ether gave 0.4 g of N-oxide XV (mp 226-227°, R_f 0.56. Found: C 64.8; H 10.0%. $C_{13}H_{23}NO_3$. Calculated: C 64.8; H 9.6%) and 0.2 g of N-oxide XVI (mp 195-196°, R_f 0.65. Found: C 65.1; H 9.8%. $C_{13}H_{23}NO_3$. Calculated: C 64.8; H 9.6%). Crystallization of the mixture of picrates obtained from 0.9 g of the crude mixture of N-oxides from ethanol gave 0.7 g of picrate XVII with mp 178-179° and R_f 0.56. Found: C 48.4; H 5.9%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6%. The mother liquor yielded 0.4 g of picrate XVIII with mp 154-156° and R_f 0.65. Found: C 48.4; H 5.7%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6%.

B) Reaction of 0.8 g (3.5 mmole) of ketol XIX (2e4e, mp 61-62°) with 1.2 g (3.5 mmole) of 10% hydrogen peroxide in methanol gave 0.9 g of a mixture of isomeric N-oxides. Crystallization of the mixture of picrates obtained from 0.7 g of the mixture of N-oxides from ethanol gave 0.8 g of picrate XXII with mp 162-163° and R_f 0.75 (the value corresponding to N-oxide XX). Found: C 48.6; H 5.5; N 12.0%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6; N 11.9%. The mother liquor yielded 0.1 g of picrate XXIII with mp 161-162° and R_f 0.57 (the value corresponding to N-oxide XXI). Found: C 48.4; H 5.8; N 11.8%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6; N 11.9%. A mixture of picrates XXII and XXIII melted at 140-145°.

C) A 0.8 g (3.5 mmole) sample of ketol XXIV (2*a*4e, mp 112-113°) gave 0.8 g of N-oxide XXV with R_f 0.50; a 0.4 g sample of crude N-oxide XXV was converted to the picrate, and crystallization of the latter from ethanol gave 0.7 g of picrate XXVI with mp 187-188° and R$_f$ 0.50. Found: C 48.6; H 5.4%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.6%. Thin-layer chromatography of the mother liquor gave one spot (R$_f$ 0.51).

Oxidation of Isomeric 1,2-Dimethyl-trans-decahydro-3-quinolones (XXVII and XXXII). A) A solution of 12.4 g (48 mmole) of 10% H_2O_2 in CH_3OH was added to 3 g (16 mmole) of decahydroquinolone XXVII [2e, bp 85-87° (1.5 mm), n_D^{20} 1.4956, R$_f$ 0.54]. Three spots (R$_f$ 0.54, 0.46, and 0) were detected 2 h after the start of the experiment by TLC of the reaction mixture in the system of solvents for ketones; two spots (R$_f$ 0.54 and 0) were detected 72 h after the start of the experiment. The starting ketone (XXVII) had been oxidized after 2 weeks to give 3.2 g of a mixture of N-oxides, TLC of which in the system for ketones gave one spot (R$_f$ 0), while three spots (R$_f$ 0.67, 0.57, and 0.35) were detected in the system of solvents for N-oxides. The mixture of N-oxides was converted to a mixture of picrates. Crystallization of the latter from ethanol–acetone (3 : 1) gave 3.8 g (59%) of picrate XXX with mp 175-176° and R$_f$ 0.67 (the value corresponding to N-oxide XXVIII). Found: C 47.8; H 5.2%. $C_{11}H_{18}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 47.9; H 5.2%. The mother liquor yielded 0.4 g (6%) of picrate XXXI with mp 137-138° and R$_f$ 0.57 (the value corresponding to N-oxide XXIX). Found: C 48.0; H 5.4%. $C_{11}H_{18}NO_2 \cdot C_6H_3N_3O_7$. Calculated: C 47.9; H 5.2%.

B) A 7.8 g (21 mmole) sample of 10% H_2O_2 was added to a solution of 1.3 g (7 mmole) of decahydroquinolone XXXII (2*a*, mp 51-52°, R$_f$ 0.46) in 10 ml of methanol. Thin-layer chromatography of the reaction mixture 10, 20, 30, and 40 days after the start of the experiment in the system of solvents for the separation of piperidones gave three spots (R$_f$ 0.54, 0.46, 0). The oxidation was complete after 50 days to give 1.3 g of a mixture of N-oxides as a viscous liquid, TLC of which in the system of solvents for the separation of piperidones gave one spot (R$_f$ 0), while TLC in the system for the separation of N-oxides gave three spots (R$_f$ 0.67, 0.58, and 0.36). The mixture of N-oxides was converted to the picrate. Fractional crystallization of the latter from ethanol gave 1.29 g (46%) of a picrate with mp 175-176° and R$_f$ 0.67, which did not depress the melting point of picrate XXX. The mother liquor yielded 0.02 g of a picrate with mp 136-137° and R$_f$ 0.58, which did not depress the melting point of picrate XXXI.

Catalytic Hydrogenation of N-Oxides XXVIII and XXIX. A) Hydrogenation of 0.1 g (0.4 mmole) of N-oxide XXVIII over a Lindlar catalyst (at 738 mm and 20°) resulted in the consumption of 23 ml (1 mmole) of hydrogen. Workup of the mixture gave 0.1 g of hydrogenation product, which gave one spot (R$_f$ 0.55) on TLC in the system for piperidones. The reaction product was treated to give its hydrochloride, mp 164-165°, which did not depress the melting point of a genuine sample of the hydrochloride of decahydroquinolone XXVII.

B) A total of 75 ml (10 mmole) of hydrogen was absorbed in the hydrogenation of 0.1 g of N-oxide XXIX in the form of picrate XXXI in the presence of Pd/$CaCO_3$ (at 729 mm and 27°). Workup of the mixture gave 0.1 g of a substance, which gave one spot (R$_f$ 0.46) on TLC in the system for piperidones. The substance was purified in a column filled with Al_2O_3 (1 : 15; $CHCl_3$) and converted to the hydrochloride with mp 145-146°. No melting-point depression was observed for a mixture of this hydrochloride with the hydrochloride of decahydroquinolone XXXII.

1,2-Dimethyl-trans-decahydro-4-quinolone Ketals. A) A solution of 0.4 g (2 mmole) of ketone XXVII, 0.5 g (6 mmole) of ethylene glycol, and 0.42 g (2 mmole) of p-toluenesulfonic acid in 30 ml of benzene was heated with a Dean–Stark trap until water liberation ceased. The benzene was then removed, and aqueous KOH solution was added until the mixture was alkaline. The reaction product was extracted with ether, the ether was removed from the extract by distillation, and the residue was fractionated to give 0.4 g of 1,2-dimethyldecahydro-4-quinolone ethylene ketal (XXXIV) as a viscous liquid. Found: C 69.5; H 10.5; N 6.1%. $C_{13}H_{23}NO_2$. Calculated: C 69.3; H 10.2; N 6.2%.

B) A total of 0.38 g of 1,2-dimethyldecahydro-4-quinolone ethylene ketal (XXXV), which was obtained as a viscous liquid, was similarly synthesized from 0.4 g (2 mmole) of ketone XXXII. Found: C 69.2; H 10.3; N 6.1%. $C_{13}H_{23}NO_2$. Calculated: C 69.3; H 10.2; N 6.2%.

Oxidation of Ketals XXXIV and XXXV with Hydrogen Peroxide. A) Oxidation of 0.4 g (1.7 mmole) of ketal XXXIV with 10% H_2O_2 [1.8 g (5.1 mmole)] in chloroform–methanol (1 : 1) gave 0.4 g of a mixture of ketal N-oxides; R$_f$ 0.73 and 0.34. The oxidation product (0.2 g) was converted to a mixture of picrates, crystallization of which from alcohol gave 0.1 g of a picrate (corresponding to N-oxide XXXVI) with mp 167-168° and R$_f$ 0.66. Found: C 48.3 H 5.5; N 12.0%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.5; N 11.9%. A mixture of this picrate with picrate XXX melted at 154-158°.

B) Similar oxidation of 0.3 g (1.3 mmole) of ketal XXXV with 10% H_2O_2 gave 0.3 g of N-oxide XXXVII (R_f 0.56), which was converted to picrate XXXIX with mp 204-205° (from alcohol). Found: C 48.4; H 5.6; N 12.2%. $C_{13}H_{23}NO_3 \cdot C_6H_3N_3O_7$. Calculated: C 48.5; H 5.5; N 11.9%.

Hydrolysis of Ketal N-Oxides XXXVI and XXXVIII. A mixture of N-oxides (R_f 0.67 and 0.36) was obtained by heating 0.1 g of the crude mixture of N-oxides obtained from ketal XXXIV with 4% hydrochloric acid at 80-90° for 40 min and subsequent workup of the reaction product (neutralization with potassium carbonate, extraction with chloroform, drying with $MgSO_4$, and removal of the solvent). Crystallization of the mixture of picrates gave 0.08 g of a picrate with mp 173-174° and R_f 0.67; it did not depress the melting point of picrate XXX. Similarly, a substance with R_f 0.56 (corresponding to N-oxide XXIX) was obtained from 0.1 g of crude N-oxide XXXIII by heating with 4% HCl.

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