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Conformations of some decahydroquinolin-4-ols: Study by kinetics of chromic acid oxidation

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Some 2-aryl-*trans*-decahydroquinolin-4-ones and 3-methyl-2-aryl-*trans*-decahydroquinolin-4-ones have been subjected to sodium *n*-butanol, MPV and sodium borohydride reductions. The sodium borohydride reduction gives both the epimers, the sodium *n*-butanol reduction gives almost exclusively the equatorial alcohol (α-form) and the MPV reduction the axial alcohol (β-form). The second order rate constants for the oxidation of the epimeric 2-aryl-*trans*-decahydroquinolin-4-ols and their 3-methyl and 1,3-dimethyl derivatives by chromic acid have been determined in acetic acid-water in the presence of perchloric acid at 30°C. The rate constants reveal the steric environment of the hydroxy group in these alcohols. Introduction of methyl substituent in 1 and 3 positions of decahydroquinoline system results in the distortion of the heterocyclic ring from the regular chair conformation.

In the present investigation some 2-aryl- and 2-aryl-3-methyl-*trans*-decahydroquinolin-4-ones (I-IV) were reduced to the corresponding alcohols and the steric environment of the hydroxy group in these was studied kinetically by subjecting them to chromic acid oxidation.

Compounds I-IV were prepared according to the procedure given earlier[1]. The *trans* ring fusion in these was established by us earlier[2].

The reduction of homogeneous cyclic ketones generally gives epimeric pairs of alcohols[3-7]. In some cases only one of the epimers (α or β) is formed predominantly[3,4] or exclusively[4,5]. In the present study sodium *n*-butanol reduction according to the procedure of Balasubramanian and Padma[3] gave almost exclusively the OH-equatorially oriented alcohols (α-form) in 70-75% yields. The MPV reduction gave the OH-axially oriented alcohols (β-form) in 75-85% yields. The sodium borohydride reduction gave both the epimers, the α-forms were predominant in the case of I and II (65%) while the β-isomers were obtained in 10% yield. In the case of III the yields of both the isomers were identical (40%). $NaBH_4$ reduction of IV gave α- and β-forms in 40 and 55% yield, respectively.

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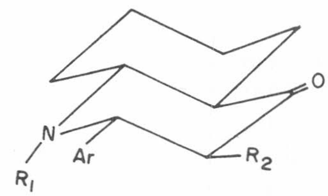
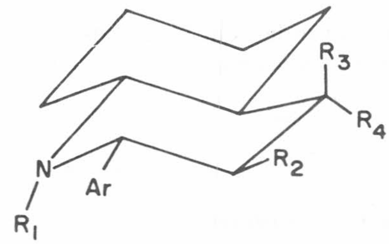


I Ar = Ph, $R_1 = R_2 = H$
II Ar = *p*-Tolyl, $R_1 = R_2 = H$
III Ar = Ph, $R_1 = CH_3$, $R_2 = H$
IV Ar = Ph, $R_1 = R_2 = CH_3$



V Ar = Ph, $R_1 = R_2 = R_3 = H$, $R_4 = OH$
VI Ar = Ph, $R_1 = R_2 = R_4 = H$, $R_3 = OH$
VII Ar = *p*-Tolyl, $R_1 = R_2 = R_3 = H$, $R_4 = OH$
VIII Ar = *p*-Tolyl, $R_1 = R_2 = R_4 = H$, $R_3 = OH$
IX Ar = Ph, R_1 = Me, $R_2 = R_3 = H$, $R_4 = OH$
X Ar = Ph, R_1 = Me, $R_2 = R_4 = H$, $R_3 = OH$
XI Ar = Ph, $R_1 = R_2$ = Me, $R_3 = H$, $R_4 = OH$
XII Ar = Ph, $R_1 = R_2$ = Me, $R_4 = H$, $R_3 = OH$

The reduction product in each case was chromotographed on alumina. The order of elution on chromatography provides usually sufficient evidence to predict the conformations of the epimeric alcohols[3]. The axial alcohol was eluted first. The relevant details about the decahydroquinolin-4-ols are given in Table 1.

We studied the kinetics of chromic acid oxidation of the epimers of 2-aryl-*trans*-decahydroquinolin-4-ols and their 1-methyl and 1,3-dimethyl derivatives in acetic acid-water (3 : 1, v/v) in the presence of $HClO_4$ (0.1 *M*) at 30°C. The second order rate constants for the oxidation of the α- and β-forms of 2-aryl-*trans*-decahydroquinolin-4-ols (V-XII) are given in Table 2.

The rate data indicate that the axial alcohols are oxidised faster than the equatorial alcohols. The 2-*p*-tolyl compounds (VII and VIII) react faster than the 2-phenyl compounds; and rate difference is much more in the case of the axial alcohol pair (VI and VIII). The slightly higher rate of VII over V may be due to *p*-tolyl being more electron-releasing than phenyl (electron-releasing groups favour Cr(VI) ox-

Table 1—Decahydroquinolin-4-ols

trans-Decahydroquinolin-4-ol	m.p. (°C)	Mol. formula	Found (%)		Calc. (%)	
			C	H	C	H
2-Phenyl-(α-form)	98-99	$C_{15}H_{21}NO$	78.3	9.4	77.9	9.2
(β-form)	177-78	$C_{15}H_{21}NO$	77.8	9.4	77.9	9.2
2-*p*-Tolyl-(α-form)	137-38	$C_{16}H_{23}NO$	78.4	9.8	78.3	9.5
(β-form)	208-209	$C_{16}H_{23}NO$	78.1	9.7	78.3	9.5
3-Methyl-2-phenyl-(α-form)	131-32	$C_{16}H_{23}NO$	78.0	9.7	78.3	9.5
(β-form)	154-55	$C_{16}H_{23}NO$	78.0	9.5	78.3	9.5
1,3-Dimethyl-2-phenyl- (α-form)	111-12	$C_{17}H_{25}NO$	78.8	10.0	78.7	9.7
(β-form)	92-93	$C_{17}H_{25}NO$	79.0	9.9	78.7	9.7

Table 2—Second-order Rate Constants for Chromic Acid Oxidation of Decahydroquinolin-4-ols

No.	Alcohol	$k \times 10^4$ (dm^3 mol^{-1} s^{-1})	
		α-form	β-form
1	2-Phenyl-*trans*-decahydroquinolin-4-ol	11.4	23.9
2	2-*p*-Tolyl-*trans*-decahydroquinolin-4-ol	12.0	29.2
3	3-Methyl-2-phenyl-*trans*-decahydroquinolin-4-ol	4.1	19.2
4	1,3-Dimethyl-2-Phenyl-*trans*-decahydroquinolin-4-ol	3.8	13.6

idation[8]). Due to steric factor the rate of VIII is much higher than that of VI (*p*-tolyl is bulkier than the phenyl group). Both the epimers of 3-methyl-2-phenyl-*trans*-decahydroquinolin-4-ol (IX and X) are expected to react faster than the epimers (V and VI) of 2-phenyl-*trans*-decahydroquinolin-4-ol due to electron-releasing nature of the methyl group and the nonbonded interactions of methyl with the hydroxy groups. But IX and X react slower than V and VI, respectively. The observed rate trend suggests a distortion of the heterocyclic ring from a regular chair conformation. In the α- and β-forms of 3-methyl-2-phenyl-*trans*-decahydroquinolin-4-ol, there are many gauche interactions involving substituents at C-2, C-3, C-4, C-9 and C-10 which can be relieved by a flattening of the heterocyclic ring. This will decrease the net steric hindrance faced by the hydroxy group at C-4 thereby making it less reactive. In the epimers (XI and XII) of 1,3-dimethyl-2-phenyl-*trans*-decahydroquinolin-4-ol, this distortion is even greater because they react even slower than IX and X. A similar situation was observed in the chromic acid oxidation of α- and β-forms of 3,5-dimethyl-2, 6-diphenylpiperidin-4-ol[9].

1,3-Dimethyl-2-phenyl-trans-decahydroquinolin-4-one (IV)

A mixture of 3-methyl-2-phenyl-*trans*-decahydroquinolin-4-one[1] (III, 5 g) formic acid (5 ml) and formaldehyde solution (40%; 6 ml) was heated on a water-bath for 8 hr. The mixture was poured into ice-water and made distinctly ammoniacal. The N-methyl derivative (IV), which separated out as a solid, was filtered off, washed, dried and recrystallised from pet ether; yield 90%, m.p. 99-100° (Found: C, 79.6; H, 9.2. $C_{17}H_{23}NO$ requires C, 79.3; H, 9.0%).

MPV reduction

The ketone (0.02 mol) in isopropyl alcohol (40 ml) was added to a solution of aluminium isopropoxide in isopropyl alcohol (prepared from 2.2 g of aluminium wire and 80 ml of isopropyl alcohol as described by Wilds[10]). The mixture was refluxed for 30-40 min and distilled slowly[10]. After a negative test for acetone, most of the isopropyl alcohol was removed by distillation under reduced pressure. The cooled residue was hydrolysed with ice-cold water containing sodium hydroxide (50 g). After allowing to stand for 1 hr, the mixture was extracted with benzene several times, the extract was washed with water and dried. The crude product was subjected to chromatography.

Reduction with sodium borohydride

To a solution of the ketone (2 g) in isopropyl alcohol (100 ml), powdered sodium borohydride (1-1.5 g) was added and the mixture refluxed on a steam-bath for 6-8 hr. After removing most of the solvent, the residue was treated with water. The mixture was acidified with acetic acid. After the evolution of hydrogen ceased, ammonia was added. The solid that separated was filtered off, dried, dissolved in benzene, filtered, the solvent removed and the residue chromatographed.

Chromatography of the reduction products

For 1 g of the product, 50 g of alumina were used. Elutions were carried out with pet ether (b.p. 60-80°), pet ether-benzene (1 : 1), benzene, benzene-ether (1 : 1), and ether in the order given. The reduction product was dissolved in the minimum quantity of benzene and fixed on the column. About five fractions were collected with each eluent. The solvent was removed and the m.p. of each fraction was determined. The fractions melting at the same temperature were collected and further purified by recrystallisation from benzene or benzene-pet ether.

Kinetic measurements

The titrimetric method of Wiberg and Mill[11] was used for following the kinetics. Purified acetic acid (AR) was mixed with water in the ratio 3 : 1 (v/v). All the other reagents were AR grade chemicals. Doubly distilled water was used for all purposes. The reaction mixture was adjusted to 0.1 *M* with respect to perchloric acid. All measurements were made at $30.0 \pm 0.1°$. The rate constants were calculated using the second order rate equation for unequal concentrations.

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