Mechanism and Stereochemistry of the Hydrolysis of 4-Arylamino-1,2,3,4-tetrahydroquinaldines

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Rates of acid-catalyzed hydrolysis of the benzylic amino group in stereoisomers of 4-arylamino-1,2,3,4-tetrahydroquinaldines have been determined by n.m.r. spectroscopy. Those isomers which have a pseudo-axial leaving group react more rapidly than those with a pseudo-equatorial leaving group, forming in each case the isomer with a pseudo-axial hydroxyl group as the kinetically controlled product. This product is converted in time to an equilibrium mixture of the two stereoisomeric alcohols. The reaction is inhibited by excess acid and appears to proceed through an intermediate carbonium ion which is stabilized by the heterocyclic nitrogen atom.

On a déterminé par spectroscopie r.m.n. les vitesses d'hydrolyse catalysé par les acides du groupe aminobenzylique des stéréoisomères de l'arylamino-4 de tétrahydro-1,2,3,4 de quinaldines. Les isomères dans lesquels le groupe nucléofuge est pseudo-axial réagissent plus rapidement que ceux dans lesquels le groupe nucléofuge est pseudo-équatorial et dans chaque cas le produit formé le plus rapidement est l'isomère ayant un groupe hydroxyle pseudo-axial. Ce produit se transforme avec le temps pour donner à l'équilibre un mélange des deux alcools stéréoisomères. La réaction est inhibée par un excès d'acide et il semble qu'il se produise par l'intermédiaire d'ion carbonium qui est stabilisé par l'atome d'azote de l'hétérocycle. [Traduit par le journal]

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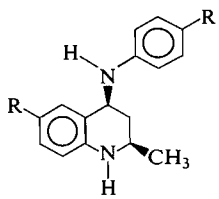
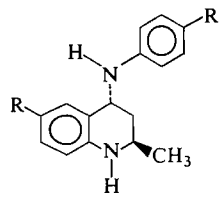
Although benzylamines do not normally undergo acid-catalyzed substitution reactions, the acid-catalyzed displacement of an arylamino group from the benzylic position of 1,2,3,4-tetrahydroquinolines by water (1) or hydroxylamine (2) occurs very readily. We wish to report on the determination of the mechanism and stereochemistry of this type of substitution reaction by an investigation of the reactivity of some 4-aminotetrahydroquinaldines in which the conformation of the heterocyclic ring is controlled by the methyl group.

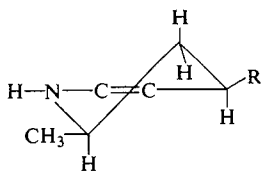
The conformations of the *cis*- and *trans*-4-anilino-1,2,3,4-tetrahydroquinaldines (**1** and **2**), formed by the reaction of aniline with acetaldehyde, have been established (3, 4) and are shown in projection formulae **1***a* and **2***a*. In both cases the methyl group assumes the pseudo-equatorial orientation thus yielding two isomers with different orientations of the amine group. An analogous pair of bases, *cis*- and *trans*-2,6-dimethyl-4-(*p*-toluidino)-1,2,3,4-tetrahydroquinoline (**3** and **4**), with the same stereochemistry is formed from the reaction of *p*-toluidine with acetaldehyde. The conformations are readily established from the coupling constants of the heterocyclic ring protons (see Experimental).



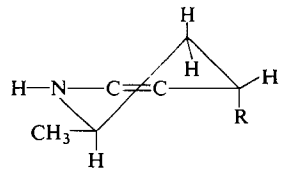
1 R = H
3 R = CH_3



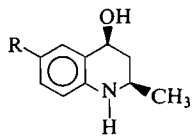
2 R = H
4 R = CH_3



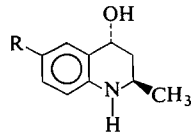
1*a* R = NHAryl or OH



2*a* R = NHAryl or OH



5 R = H
7 R = CH_3



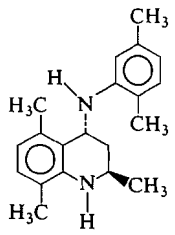
6 R = H
8 R = CH_3

The rates of the conversion of these four diamines to the amino alcohols were determined by monitoring the reaction in $DCl \cdot D_2O$ solutions by n.m.r. spectroscopy. In some cases the signals due to the C-4 protons were well separated from other signals permitting an accurate integration. In all of these cases, plots of the logarithm of concentrations of diamines against time gave linear plots indicating the reaction is first-order with respect to 4-aminotetrahydroquinaldine. In other cases where the peak due to HOD interfered with the C-4 proton signals, an estimate of the half-life of the reaction was obtained from the time required to obtain equivalent peak heights of the methyl groups of the substrate and product.

In all cases the kinetically controlled product was the *trans* hydroxy compound. The stereochemistry of the alcohols could be readily determined from the splitting pattern of the heterocyclic ring protons (see Experimental). The *cis* alcohols, **5** and **7**, have conformation **1***a* and the *trans* alcohols, **6** and **8**, have conformation **2***a*.

The fact that the same kinetically controlled product is obtained from the *cis* or *trans* diamine indicates that the same intermediate is formed in each case and that the reaction is S_N1 rather than S_N2. The lack of exchange of the protons on C-3 shows that the reaction does not proceed by an elimination–addition mechanism.

A comparison of the half-lives of the reactions shows that the *trans* isomer reacts more rapidly than the *cis* isomer in each case. It is unlikely that the greater reactivity of the *trans* isomer is due to the greater steric interaction of the pseudo-axial arylamino group. There appears to be little difference in the steric crowding of the arylamino group in the pseudo-axial and pseudo-equatorial positions since the conformation of both the *cis* and *trans* isomers is controlled by the single methyl group at C_2. In the equilibrium mixture of the alcohols the *trans* isomer with a pseudo-axial hydroxyl group is the predominant isomer.



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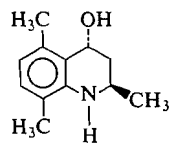

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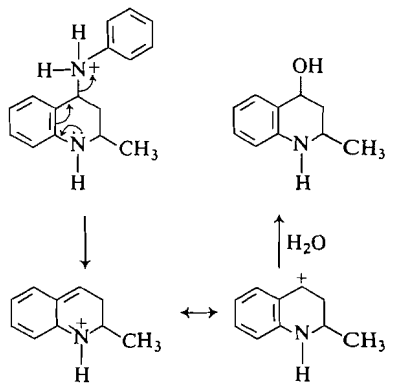
The rate difference is most likely due to the better orientation of the pseudo-axial arylamino group as a leaving group. In the *trans* isomer the bond being broken can maintain better overlap with the π orbitals of the aromatic ring which stabilizes the incipient carbonium ion. This conclusion is supported by the formation of the *trans* alcohol as the kinetic product indicating a lower-energy transition state for addition in the pseudo-axial manner. This principle of maintenance of maximum overlap of orbitals has been applied in a similar case by Eliel and Nader to explain the reactivity and product stereochemistry of 2-alkoxy-1,3-dioxanes (5).

The *cis* and *trans* alcohols (**7** and **8**) have been shown to be converted on standing in acid to an equilibrium mixture of the two (6). This equilibration was also observed in this investigation. The kinetically controlled *trans* products, **6** and **8**, are converted on standing in acid to an equilibrium mixture of the *cis* and *trans* isomers (*trans–cis* = 3:2). In the case of 2,5,8-trimethyl-4-hydroxy-1,2,3,4-tetrahydroquinoline (**9**), formed from the diamine **10**, only the kinetically controlled *trans* product was detected. This may be due to the steric interaction of the 5-methyl group and the pseudo-equatorial hydroxyl group which makes the *trans* isomer much more stable than the *cis* isomer.

Although the substitution is catalyzed by acid, the rate is decreased as the concentration of acid is increased from 0.5 to 3 *M* (Table 1). This behavior is in accord with a mechanism which requires resonance stabilization of the intermediate carbonium ion by the lone pair of the heterocyclic nitrogen (Scheme 1). The benzylic amino group would be converted to a better leaving



SCHEME 1

TABLE 1. Half-lives of diamines

Compound	Half-life (Acid concentration (*M*)) 3	2	1	0.5
1 (*trans*)	22 min*	5 min*	63 s*	
2 (*cis*)	2.5 h	50 min*	18 min	<1 min
3 (*trans*)	30 min	9 min	<2 min	
4 (*cis*)	6 h	3 h	40 min	4.5 min*

*Obtained from plot of log concentration *vs.* time.

group upon protonation but the reaction would be inhibited if both nitrogens were protonated.

The bases **3** and **4** which have methyl groups on the aromatic ring are seen to react slower than their analogs **1** and **2** (Table 1). This may be explained by the difference in basicity of the amines in the two series. The inductive effect of the methyl group would make **3** and **4** stronger bases so that the rate of reaction, in conditions of excess acid as employed here, would be decreased because of a higher concentration of the diprotonated species.

Experimental

Nuclear magnetic resonance spectra were recorded at 35 °C on a Varian T 60 spectrometer. Mass spectra were recorded on a DuPont model 21-110 mass spectrometer. Melting points are uncorrected.

*cis- and trans-2-Methyl-4-hydroxy-1,2,3,4-tetrahydroquinoline (**5** and **6**)*

cis-2-Methyl-4-anilino-1,2,3,4-tetrahydroquinoline (**1**) (4) (13.3 g, 0.05 mol) was dissolved in 2 *N* HCl (100 ml) and allowed to remain at room temperature for 8 h. The solution was then made basic with 2 *N* NaOH and steam distilled to remove the aniline. The residue from the distillation was cooled and extracted with benzene. The benzene was removed *in vacuo* and the *cis–trans* mixture of alcohols separated by chromatography on silica gel using benzene – petroleum ether (30–60°).

cis Isomer **5**: yield 2.9 g, 36%; m.p. 124 °C; n.m.r. ($CDCl_3$) δ 1.18, (d, J = 6 Hz, CH_3), 1.53 (H_{3a}), 2.10 (H_{3e}), 3.46 (H_2), 4.84 (H_4) ($J_{3e,3a}$ = 12.5 Hz, $J_{3e,2a}$ = 3 Hz, $J_{3e,4a}$ = 6 Hz, $J_{2a,3a}$ = 11 Hz, $J_{4a,3a}$ = 10 Hz), 6.34–7.45 (m, aromatic H's), 2.87 (bs, OH, NH). Mass spectrum, 163(44), 148(36), 146(18), 144(28), 130(100).

trans Isomer **6**: yield 4.1 g, 50%; m.p. 78 °C, n.m.r. ($CDCl_3$) 1.20 (d, J = 6 Hz, CH_3), 1.47 (H_{3a}), 1.92 (H_{3e}), 3.50 (H_2), 4.64 (H_4) ($J_{3e,3a}$ = 12.5 Hz, $J_{3e,2a}$ = 2.5 Hz, $J_{3e,4e}$ = 2.5 Hz, $J_{3a,4e}$ = 3 Hz, $J_{3a,2a}$ = 11 Hz), 6.40–7.20 (m, aromatic H's), 3.10 (bs, OH, NH). Mass spectrum 163(40), 148(30), 146(20), 144(30), 130(100).

*cis- and trans-2,6-Dimethyl-4-(p-toluidino)-1,2,3,4,-tetrahydroquinoline **3** and **4**.*

Acetaldehyde (4.9 g, 0.11 mol) was added to *p*-toluidine (10.7 g, 0.1 mol) in ethanol (100 ml) and allowed to sit at room temperature for 16 h. The ethanolic solution was decanted from the oily precipitate which had formed. Crystallization of the oily residue in benzene yielded the *cis* isomer (3 g, 23%). Chromatography of the mother liquors on silica gel using petroleum ether (30–60°) as eluant yielded the *trans* isomer as a yellow oil (4 g, 30%).

cis Isomer **3**: m.p. 114 °C; n.m.r. ($CDCl_3$) δ 1.20 (d, J = 6 Hz, CH_3), 2.22 (s, CH_3), 2.28 (s, CH_3), 1.43 (H_{3a}), 2.40 (H_{3e}), 3.56 (H_2), 4.76 (H_4) ($J_{3e,3a}$ = 12.5 Hz, $J_{3e,2a}$ = 2.5 Hz, $J_{3e,4a}$ = 6 Hz, $J_{3a,4a}$ = 11 Hz, $J_{3a,2a}$ = 11 Hz), 6.36–7.40 (m, aromatic H's), 3.40 (bs, NH's). Mass spectrum 266(14), 223(2), 160(100), 144(23).

trans Isomer **4**: n.m.r. ($CDCl_3$) δ 1.17 (d, J = 6 Hz, CH_3), 2.10 (s, CH_3), 2.16 (s, CH_3), 1.50 (H_{3a}), 2.14 (H_{3e}), 3.38 (H_2), 4.43 (H_4) ($J_{3e,3a}$ = 13 Hz, $J_{3e,2a}$ = 2.5 Hz, $J_{3e,4e}$ = 2.5 Hz, $J_{3a,4e}$ = 3.5 Hz, $J_{3a,2a}$ = 11 Hz), 6.40–7.10 (m, aromatic H's), 3.80 (bs, NH's). Mass spectrum 266(10), 233(2), 160(100), 144(30).

*cis- and trans-2,6-Dimethyl-4-(hydroxy)-1,2,3,4-tetrahydroquinoline **7** and **8***

These compounds were prepared following the procedure of Edwards *et al.* (6).

cis Isomer, m.p. 165°; n.m.r. ($CDCl_3$) δ 1.22 (d, J = 6, CH_3), 2.25 (s, CH_3), 1.57 (H_{3a}), 2.27 (H_{3e}), 3.48 (H_2), 4.90 (H_4) ($J_{3e,3a}$ = 12 Hz, $J_{3e,2a}$ = 3 Hz, $J_{3e,4a}$ = 6 Hz, $J_{3a,4a}$ = 11 Hz, $J_{3a,2a}$ = 11 Hz), 6.32–7.23 (m, aromatic H's), 2.2 (bs, OH, NH). Mass spectrum 177(64), 162(52), 160(12), 158(16), 144(100).

trans Isomer, m.p. 110°; n.m.r. ($CDCl_3$) δ 1.17 (d, J = 6, CH_3), 2.22 (s, CH_3), 1.43 (H_{3a}), 1.88 (H_{3e}), 3.37 (H_2), 4.55 (H_4) ($J_{3e,3a}$ = 13 Hz; $J_{3e,2a}$ = 2.5 Hz; $J_{3e,4e}$ = 2.5 Hz; $J_{3a,4e}$ = 3.5 Hz; $J_{3a,2a}$ = 11 Hz), 6.30–7.10 (m, aromatic H's), 3.05 (bs, NH, OH). Mass spectrum, 177(64), 162(52), 160(12), 158(16), 144(100).

*trans-2,5,8-Trimethyl-4-hydroxy-1,2,3,4-tetrahydroquinoline **9***

trans-2,5,8-Trimethyl-4-(2,5-dimethylanilino)-1,2,3,4-tetrahydroquinoline (**10**) (3 g, 0.01 mol), prepared as previously described for **3** and **4**, was dissolved in 6 *N* HCl (5 ml) and after dissolution the solution diluted with water to 2 *N*. After remaining at room temperature for 16 h, the solution was made basic and extracted with benzene. After removal of the benzene the residue was crystallized from benzene – petroleum ether (30–60°). Yield 1.7 g, 90%, m.p. 106°; n.m.r. ($CDCl_3$) δ 1.31 (d, J = 6 Hz, CH_3), 2.08 (s, CH_3), 2.35 (s, CH_3), 1.46 (H_{3a}), 2.03 (H_2), 4.85 (H_4) ($J_{3e,3a}$ = 13 Hz, $J_{3e,2a}$ = 3 Hz, $J_{3e,4e}$ = 2.5 Hz, $J_{3a,4e}$ = 3 Hz, $J_{3a,2a}$ = 12 Hz), 6.45 (d, J = 8 Hz, aromatic H),

6.88 (d, $J = 8$ Hz, aromatic H). Mass spectrum, 191(55), 176(22), 174(10), 172(33), 158(100).

Determination of Reaction Rates

The diamine under investigation was dissolved in $DCl{\cdot}D_2O$ solution in order to make a solution 0.25 *M* in diamine. The spectra were then determined at various time intervals. In those cases which yielded well separated H_4 peaks, integrals of these peaks were used to calculate the concentration of diamine substrate at any particular time. The plots of the logarithm of this concentration against time gave straight lines, the slopes of which were used to calculate half-lives. In other cases the half-life was estimated from the time required to obtain equal peak heights for the signals due to the methyl peaks of substrate and product.

The formation of the *trans* alcohols as the initial hydrolysis product was indicated by the splitting pattern of the C_4 proton. The signal developed initially as a triplet typical of the *trans* isomer and then changed to a mixture of the triplet and a double doublet typical of the mixture.

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