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CHEMISTRY OF ENAMINES II[1]

THE STRUCTURE OF THE PYRROLIDINE ENAMINE OF 2-METHYLCYCLOHEXANONE

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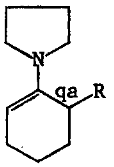
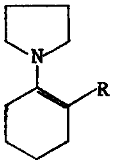
The position isomer (I), having a trisubstituted double bond was originally assigned by Stork and associates to the structure of the pyrrolidine enamine of a substituted cyclohexanone. The tetrasubstituted ethylenic isomer II which was excluded on the basis of N.M.R. spectrum, involves steric interference between the substituent R and the methylene adjacent to nitrogen, if an overlap between the electron pair on nitrogen and the double bond is to be maintained[2]. Johnson and Whitehead have recently demonstrated that even the isomer I suffers from similar steric interaction when the substituent R is quasi-equatorial. This interaction, however, vanishes when R is quasi-axially oriented. An inspection of the models confirms this conclusion. Consequently it is to be expected that the alkylation of isomer I would occur from an axial direction, in view of the necessity for continuous p-orbital overlap in the transition state, and this would be subject to 1,3-diaxial interaction[3].



I
Ia ($R = CH_3$)



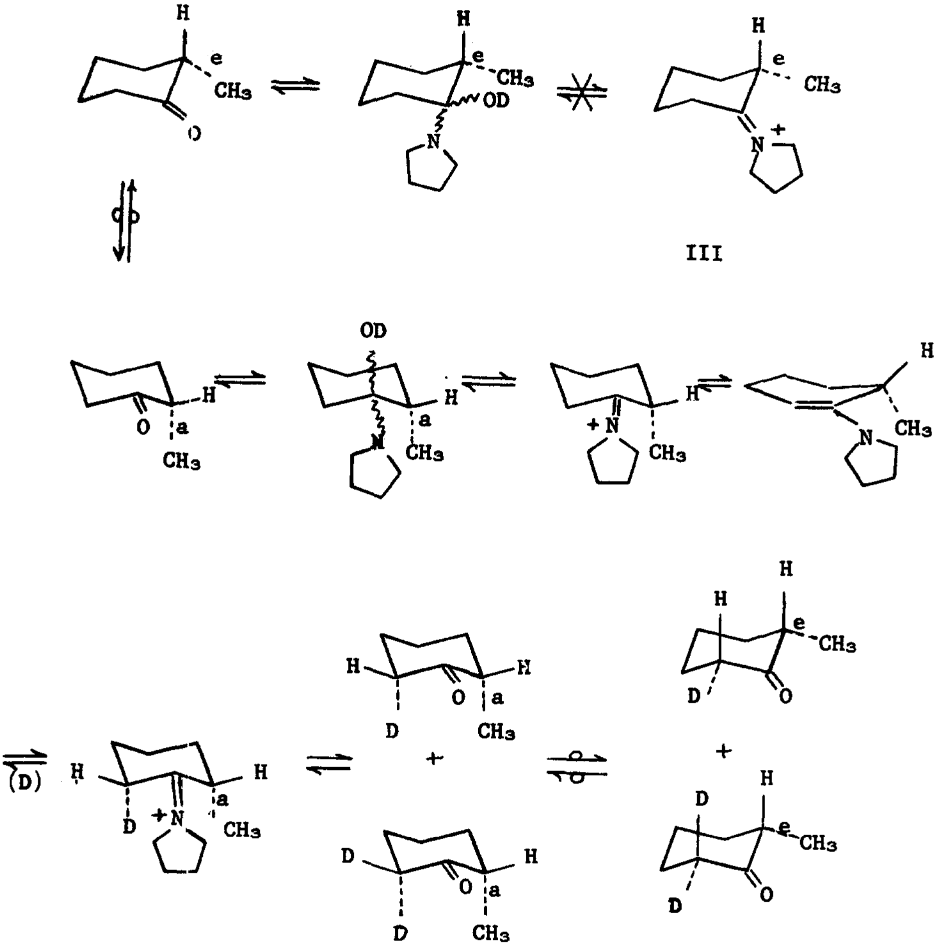
II
IIa ($R = CH_3$)

It has, however, been reported that the Michael addition of methyl acrylate to the pyrrolidine enamine of 2-methylcyclohexanone gives a 1:1 mixture of 2,2- and 2,6-disubstituted ketones, thus implying the enamine to be a mixture of isomers Ia and IIa[4]. On the other hand, this enamine has been reported to react with acrylonitrile in absolute ethanol giving the expected 2,6-disubstituted product in 55% yield.[2]

In order to make a careful study regarding the contribution of Ia and IIa to the structure of this enamine, we carried out its hydrolysis with 1.5 equivalents of 50% deuterioacetic acid-deuterium oxide in diglyme solution, under nitrogen, at room temperature. It was expected that the hydrolysis of Ia and IIa would result in the introduction of deuterium[6] at C-6 and at C-2 giving the 6- and 2-deuterated ketones respectively. Since the intermediate iminium salt could undergo deprotonation from C-2 or C-6 with the regeneration of the isomers IIa or Ia, the formation of 2,6- or 6,6-dideuterated ketones seemed quite likely. The hydrolysis was found to be complete within 5 minutes. The mass spectrum[7] of the product showed it to contain 6.8% d_0, 57% d_1, 34% d_2 and 2.2% d_3 species. The infrared spectrum displayed principal C-D stretching bands at 2190 (s) cm^{-1} (equatorial C-D) and 2220 (m) cm^{-1} ($-CD_2-$) indicating it to be a mixture of 6-e-deuterated (major) and 6,6-dideuterated (minor) products[8,9]. The presence of very weak bands at 2120 cm^{-1} and 2150 cm^{-1} (axial C-D) showed the formation of a very small amount of 2a or 6a deuterated ketone which could arise from trace amounts of either IIa or Ia with equatorial methyl group [10]. In the N.M.R. the methyl group appeared as a simple doublet centered at 0.97 p.p.m. (J=6.5 c.p.s.)[11] demonstrating the absence of virtually any deuterium at C-2. This evidence suggests unequivocally that the pyrrolidine enamine of 2-methylcyclohexanone consists almost exclusively of the trisubstituted ethylenic isomer[12], as previously concluded by Stork et.al., and unlike many enolate anions, the less highly substituted isomer is very highly favored at equilibrium. The formation of 6-e-deuterio-2-methylcyclohexanone would result from the ring flipping of 6-a-deuterio-2-a-methylcyclohexanone formed by the stereoelectronically controlled hydrolysis of Ia[13].

When the reaction time for the enamine hydrolysis was extended to 1 hr., the product was found to contain 5% d_0, 43% d_1, 48% d_2, and 3.5% d_3 species and showed C-D stretching bands at 2120 (v.w.) cm^{-1}, 2190 (S) cm^{-1} and 2220 (S) cm^{-1}. These results coupled with the appearance of the methyl group as a simple doublet in the N.M.R. point to the presence of only a very small amount of deuterium at C-2. That the additional D- incorporation occurred via the intermediacy of the enamine and not by the enolization of the ketone was demonstrated in the following manner.

Treatment of 2-methylcyclohexanone with 1 equivalent of pyrrolidine and 1.5 equivalent of deuterioacetic acid-deuterium oxide in diglyme under enamine hydrolysis conditions gave, after 5 minutes, the ketone containing 73.5% d_0, 13.5% d_1, and 13% d_2 species and the product obtained after 1 hr. exchange was found to contain 32.4% d_0 35.8% d_1 and 34.5% d_2 species. The presence of C-D stretching bands at 2190 cm^{-1} and 2220 cm^{-1} in the infrared spectra of these ketones showed them to be a mixture of undeuterated, 6-*e*-deuterated, and 6,6-dideuterated species. The formation of these species can be rationalized by the following mechanistic sequence.



Structure III appears to be as unstable as IIa, for similar steric reasons. Again the absence of any 2-deuterated species shown by the lack of any significant absorption in the infrared at 2120-2150 cm^{-1} (axial C-D) and the appearance of the methyl group as a simple doublet in the N.M.R. precludes the formation of the isomer IIa. *Cis*-2-methyl-4-*t*-butyl-cyclohexanone, which is incapable of ring flipping failed to undergo any D- incorporation under these conditions. This evidence eliminates the likelihood of any D-incorporation via acid— or base-catalyzed enolization and confirms the validity of the proposed mechanistic path outlined above.

Further studies on the structures of morpholine and piperidine enamines of 2-substituted cyclohexanone are in progress[14,15]

References

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2. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc*., *85*, 207 (1963).
3. W. R. N. Williamson, *Tetrahedron*, *3*, 314 (1958); M. E. Kuehne, *J. Am. Chem. Soc.*, *81*, 5400 (1959)
4. H. O. House and M. Schellenbaum, *J. Org. Chem*., *28*, 34 (1963)
5. Prepared by the treatment of 2-methylcyclohexanone with pyrrolidine and a catalytic amount of Dowex 50W (acid form) in benzene at reflux and separation of water azeotropically.
6. N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, *76*, 2781 (1965).
7. We express our appreciation to Roland S. Gohlke and John J. Flynn for the determination of mass spectra.
8. For the assignment of C-D stretching frequencies in the infra-red see H. O. House and V. Kramar, *J. Org. Chem*., *28*, 3362 (1963) and references cited therein.

9. The formation of the 6,6-dideuterated species would involve the loss of stereoelectronically unfavored equatorial proton which is obviously a consequence of primary deuterium isotope effect.

10. Since 2-methylcyclohexanone is a 19:1 mixture of equatorially and axially substituted conformers, the latter conformer would account for the weak bands at 2120-2150 cm^{-1}. (See E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Book Company, Inc., New York, 1962, pp. 210)

11. Determined at 60 Mc/sec. with a Varian A-60, N.M.R. Spectrophotometer-downfield from tetramethylsilane (internal reference).

12. The formation of the 2,2-disubstituted product, obtained by House and Schellenbaum[4] occurs most probably during the hydrolysis step; 2-methylcyclohexanone resulting from the hydrolysis of the unreacted starting material could undergo pyrrolidine catalyzed Michael addition with methyl acrylate to give the 2,2-disubstituted ketone.

13. Hydrolysis of the pyrrolidine enamine of 2-methyl-4-*t*-butylcyclohexanone with 50% deuterioacetic acid-deuterium oxide led to a mixture of 6-axially deuterated (2140 cm^{-1} C-D axial) and 6,6-dideuterated (2220 cm^{-1}) *trans*-2-methyl-4-*t*-butyl-cyclohexanone showing the hydrolysis to be subject to stereoelectronic control.

14. Very recently J. P. Schaefer and D. S. Weinberg (Tetrahedron *Letters*, 1801 (1963)) have reported that acid-catalyzed deuterolysis of the morpholine enamine of cyclohexanone at low temperature affords the 2-monodeuterated ketone.

15. We wish to thank Mr. D. F. Moakley for technical assistance.