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THE STEREOCHEMISTRY OF 2-SUBSTITUTED CYCLOHEXANONE ENAMINES AND THE CORRESPONDING SCHIFF'S BASES

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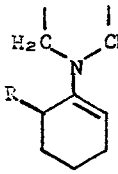
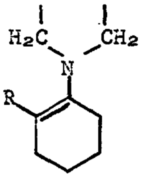
It has been suggested[1] that the formation of an enamine from a secondary amine and a 2-substituted cyclohexanone proceeds to give a compound having a structure such as I rather than II because in the latter, steric hindrance occurs between a methylene adjacent to nitrogen and the group R. Such interference could be expected to reduce the conjugation between the double bond and the lone pair of electrons on the nitrogen atom. In I it was presumed that this steric hindrance was small or non-existent. However, the orientation of the group R in I was not specified.



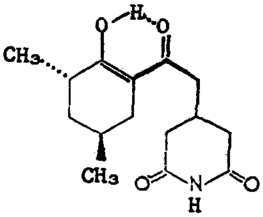
I



II

A close inspection of a model of I when R is quasi-equatorial reveals that there is little difference between I and II with respect to the steric effect under discussion. However, with R in the quasi-axial position no hindrance exists between the two groups concerned, when the unsaturated system is arranged for maximum overlap.

The original suggestion that 2-substituted cyclohexanone enamines have this substituent in the quasi-axial position is due to Williamson[2]. He used this idea to explain why these particular enamines are difficult to alkylate in stating that such an orientation would hinder axial approach of the reagent, the interaction being of a 1,3-nature. We, in fact, used these ideas in our total synthesis of cycloheximide[3] where the initial steps involved the conversion of cis-2,4-dimethylcyclohexanone (III) to the morpholine enamine followed by acylation of the latter with 3-glutarimidylacet chloride. The sole product (IV), had trans oriented methyl groups.



IV

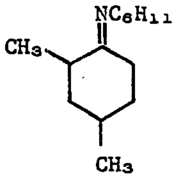
We have pursued this problem further and would like to present evidence that Williamson's suggestion is correct.

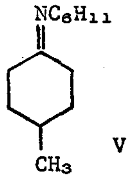
In view of the above arguments it seemed essential to avoid a hydrolytic decomposition of any enamine under study. Therefore, we treated the pyrrolidine enamine (V) of 2,4-dimethylcyclohexanone[4] with an equimolar mixture of lithium aluminum hydride and aluminum chloride in refluxing ether according to Lewis and Lynch[5]. After eighteen hours we were able to isolate approximately 50% of a 3,5-dimethylcyclohexene (VI) bp. 121° $n_D^{25^\circ}$ 1.3995 (Found: C, 86.9; H, 13.0) which by g.l.c. analysis appeared to be better than 96% pure. Reduction of this material by hydrogen in the presence of a platinum catalyst afforded *trans-1,3-dimethylcyclohexane* bp. 124° $n_D^{25^\circ}$ 1.4275 (lit[6] bp. 124°; $n_D^{25^\circ}$ 1.4284) (Found: C, 85.9; H, 14.1). The n.m.r. spectrum of this material was identical with that of a published spectrum[7] of trans-1,3-dimethylcyclohexane except for a very small peak at 56 cps. (downfield from TMS) which would be attributed to a trace of the cis isomer. This suggests that the same *trans* orientation of the methyl group exists in V.

If it can be assumed that the reduction of V to VI involves a simple addition of a chloroaluminum hydride to V followed by collapse of the >N-C-C-Al< system to a double bond, then one can only conclude that the act of converting *cis*-2,3-dimethylcyclohexanone to the enamine V is the process which causes the orientation of the 2-methyl group to be changed. Needless to say buffered acidic hydrolysis of V leads to *trans*-2,4-dimethylcyclohexanone bp. 178°, $n_D^{25^\circ}$ 1.4475 (lit[8] bp. 178.7°, $n_D^{25^\circ}$ 1.4788) whose infrared and n.m.r. spectra were essentially identical with those obtained from an authentic specimen[9] G.l.c. analysis indicated the material to be a mixture of 90:10::trans:cis isomers.

Similar experiments with <u>cis</u>-2-methyl-4-t-butylcyclohexanone have confirmed the above results.

In view of the recently announced[10] versatility of Schiff's bases for the preparation of α-substituted ketones, we have made some preliminary observations on the base VII bp. 132° (8mm), $n_D^{25°}$ 1.4838, (Found: C, 80.8; H, 12.15) prepared in the usual way


VII


VIII

from cyclohexylamine and <u>cis</u>-2,4-dimethylcyclohexanone.

Acidic hydrolysis of VII under the same conditions used for (V) led to a 3:1 mixture of <u>cis</u>- and <u>trans</u>-2,4-dimethylcyclohexanones which we consider reflects the stereochemical composition of VII. In addition initial results on the methylation of VIII bp. 131° (6 mm) $n_D^{25°}$ 1.4883 (Found: C, 80.7; H, 12.3; N, 7.3) in the form of its magnesiobromide anion[10] indicate that the ketonic product, obtained after careful acid decomposition of the intermediate, has the same composition as that derived by acid hydrolysis of VII.

In conclusion it can be stated that the versatility of enamines appears to be even greater than originally suspected. The processes described in this paper suggest strongly that in certain cases they may be used to accomplish the endergonic transformation of going from the more stable to the less stable isomer of a 2-substituted cyclic ketone. On the other hand the corresponding Schiff's bases would appear to lead predominantly to the more stable isomer.

Further studies in this area are being pursued and these together with the above results will be published at a later date.

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