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THE STRUCTURE OF ENAMINES OF 2-SUBSTITUTED KETONES

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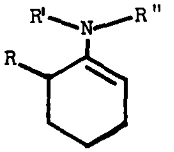
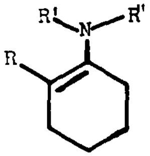
Enamines have found extensive synthetic use over the past dozen years, due mainly to the excellent explorations of Stork and his co-workers (1). However very little investigation has been done on the structure and properties of the enamines themselves. We would now like to report some preliminary findings on the structure of enamines derived from 2-methylcyclohexanone.

We have found that the commonly held belief that these exist as the isomer with the less substituted double bond (A) rather than the more substituted one (B) is highly dependent on the substituents on nitrogen and the 2-substituent; and in general does not hold for cyclohexanone derivatives.



A



B

The assumption that enamines exist as the less substituted double bond isomer has a dual basis. One is the fact that the product of reaction of these enamines is usually, after hydrolysis, the 2,6-disubstituted ketone, not the 2,2 (however see ref. 2);

the other appears to be an extrapolation from the fact that the pyrrolidine enamines of 2-substituted cyclohexanones have been briefly investigated and found to exist as the less substituted isomer. Stork (3) first stated this in 1959 for the 2-methyl derivative. The same conclusion was reached by Opitz (4). Subsequently, House, quoting unpublished results of Berchtold (5), gave the ratio of 85% A, 15% B ($R=CH_3$). Kuehne (6) using ultraviolet spectrometry concluded that the pyrrolidine enamine of 2-phenylcyclohexanone exists as the less substituted double bond isomer. However, treatment of the pyrrolidine enamine of 2-methylcyclohexanone with cyanogen chloride gave after hydrolysis a 66% yield of 2-methyl-6-cyanocyclohexanone and a 2% yield of 2-methyl-2-cyanocyclohexanone (6) indicating that some of the B isomer must have been present.

An excellent explanation for these facts was given by Stork (1,3). Essentially he stated that in the more-substituted double bond isomer B, the methylene attached to nitrogen sterically interferes with the R group of the cyclohexene ring. These groups and the atoms attached to them must be co-planar for effective overlap of the lone pair on nitrogen with the double bond. The steric interference prevents co-planarity and thereby decreases the overlap. This interference is eliminated and maximum overlap maintained by moving the R group out of the plane of the double bond, i.e. - the less substituted double bond should be favored. A further consequence of this steric interference was first brought forth by Williamson (7) who reasoned that the R group should be axial. Johnson and Whitehead (8) clearly demonstrated that the 2-methyl group in the enamine is indeed axial.

Recently Danishefsky and Feldman (9) using an internal enamine - a tricyclic system containing nitrogen - showed that when this steric interference is eliminated the more substituted double bond isomer is the stable one.

We have investigated the "common" enamines of 2-methylcyclohexanone by an NMR technique. The results are listed in Table I.

TABLE I [(a)]

Amine	%A(R=CH_3)	%B(R=CH_3)
Pyrrolidine (R'+R"=$-(CH_2)-_4$)	90[(b)]	10[(c)]
Morpholine (R'+R"=$-(CH_2)_2O(CH_2)_2-$)	52	48
Piperidine (R'+R"= $-(CH_2)_5-$)	46	54
Diethylamine (R'=R"=CH_3CH_2-)	25	75

(a) Values are for neat liquid. All compounds gave satisfactory analyses.

(b) Percentages are obtained by integration of the vinyl proton against an internal standard. Values are estimated to be accurate to ± 5%.

(c) Obtained by difference (100-% A).

Our data corraborate the earlier findings with the pyrrolidine enamine, i.e. - it exists predominantly as the less substituted double bond isomer. The morpholine and piperidine enamines, however, exist about equally in both forms, while with the diethylamine enamine, the more substituted isomer predominates!

Inspection of Table II quickly shows that is is not the basicity of the parent amines which is causing the variation in isomer ratio.

TABLE II

Amine	pKa(10)	% A($R=CH_3$)
Morpholine	8.36	52
Piperidine	11.20	46
Pyrrolidine	11.32	90
Diethylamine	11.00	25

Normally one would expect a more substituted double bond to be more stable than a less substituted one (11). This should be the case with enamines in the absence of other effects. The steric argument used previously (1,3,7,8) to explain the stability of the less substituted isomer of the pyrrolidine enamine of 2-methylcyclohexanone can still be used with a slightly different emphasis.

We propose that overlap of the lone pair on nitrogen with the π-electrons of the double bond is exceedingly important with the pyrrolidine enamines and is much less important with other enamines. Evidence for this is seen in the position of the vinyl proton in the NMR spectra of the various enamines as shown by Table III.

It is seen that all but the pyrrolidine enamines fall in the range 273 to 277; the pyrrolidine enamines absorb at 250 to 251. This difference cannot be attributed to the 2-methyl group as the vinyl proton absorption of the unsubstituted and the 2-methyl compounds are essentially identical.

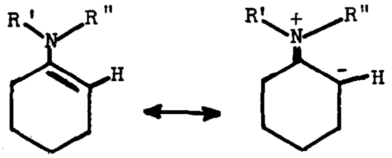
TABLE III

Vinyl H Absorption of Enamines

Amine	Parent Cyclohexanone	Vinyl H(a)
Pyrrolidine	2-Methyl	251
Morpholine	2-Methyl	276
Piperidine	2-Methyl	277
Diethylamine	2-Methyl	273
Pyrrolidine	unsubstituted	250
Morpholine	unsubstituted	273

(a) c.p.s. downfield from TMS. Spectra were run on a Varian A56/60 at 60 mc. and were calibrated with an audio-frequency side-band oscillator.

Strong overlap of the line pair on nitrogen with the double bond leads to delocalization of the type:



This causes an upfield shift of the proton on the carbon bearing the charge (12). The pyrrolidine enamines experience this delocalization as seen by the large upfield shift. The constancy and the lower field of the vinyl proton absorption of the other enamines argues against strong overlap of this type. This is in keeping with the postulate that a double bond exo to a 5 membered ring is more stable than a double bond exo to a 6 membered ring (13).

The methylene groups attached to nitrogen in the pyrrolidine ring must therefore be co-planar, or nearly so, with the double bond and the groups attached to it. In the more substituted isomer B, this would cause large steric interaction between the 2-methyl and the methylene groups; this would reduce or eliminate any overlap. Consequently the more stable isomer is the one with the less substituted double bond (and the 2-methyl group axial (7,8)) where no such steric interference exists.

With the enamines where delocalization is of diminished importance, the requirement for co-planarity is not as stringent. The steric interference is thereby reduced and the more substituted double bond isomer becomes of equal or greater stability than the less substituted one.

We have observed the more substituted double bond isomer both in the IR and NMR. Two olefinic bands in the IR are found in the enamines of 2-methylcyclohexanone at 5.97µ and 6.08µ. The 6.08µ band has been assigned to the less substituted double bond isomer and the 5.97µ to the more substituted one. The vinyl methyl group of the more substituted double bond isomer appears at 100-105 c.p.s. (downfield from TMS) in the NMR. The intensity of the bands both in the IR and NMR varies as the proportion of its respective isomer varies. Spectral details will be published in the near future.

Studies of the steric and electronic factors determining the structure of various enamines are continuing.

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