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THE DIRECTION OF ENAMINE FORMATION FROM 2-ALKYL CYCLOALKANONES - INTERNAL ENAMINE FORMATION

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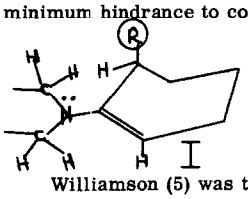
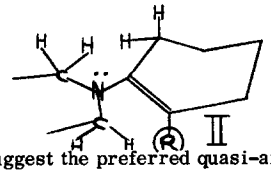
Stork's discovery that enamines can serve as controllable enolate equivalents has stimulated much research designed to elaborate on this concept (1, 2). During their studies, the Columbia workers noted that the formation of enamines from α-substituted cycloalkanones proceeds at a rate slower than that for their unsubstituted analogs. Similar retardation is exhibited in the subsequent reactions (alkylation, acylation) of such enamines, once formed; a phenomenon presumably of some relevance to the high yields of mono-alkylation obtained via the enamine method. Perhaps more surprising was their observation that the overwhelmingly predominant product from the formation reaction is that enamine whose double bond is least substituted. Subsequent studies by Kuehne (3) extended this apparent anomaly to the case of 2-phenylcyclohexanone. Further studies by Kuehne (4) in the 2, 4-dinitrophenyl series suggested the possibility that the tetrasubstituted double

bond isomer might be competitive in terms of stability, although some reservation was expressed (4) due to the uncertainty as to whether an equilibrium mixture was actually under study.

Aside from this uncertain case then, the rule i.e. the trisubstituted double bond isomer predominates, seems fairly general. Various workers (1,,3, 5) have interpreted this useful* phenomenon as being the result of steric inhibition of the planarity requisite for overlap between the "lone pair" on nitrogen with "p-electrons" of the double bond. An illustration is shown below for the case of a 2-substituted cyclohexenamine, which shows that by an axial conformation for the R group there is minimum hindrance to coplanarity in the trisubstituted isomer.



I



II

Williamson (5) was the first to suggest the preferred quasi-axial disposition of the "R" grouping as being responsible for the sluggish rate of alkylation of an enamine such as I. In Williamsons view, an incoming axially disposed electrophile encounters a serious 1, 3-diaxial interaction. Johnson and Whitehead (6) have recently brought forth evidence in support of the Williamson conformational hypothesis.

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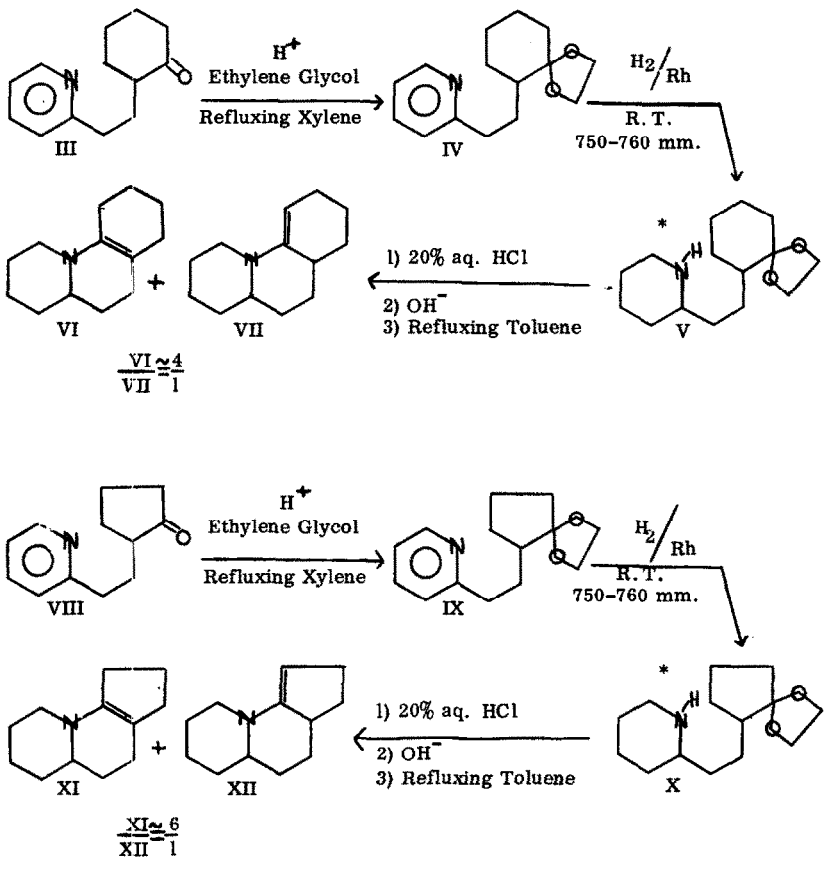
* Useful because it enables the synthesis of a series different from that obtainable via enolate reactions which predominantly involve the most substituted anion (1).

The purpose of this communication is to cite some recent results which strongly support the afore-discussed steric inhibition argument by showing that when this effect is equalized, the tetra-substituted isomer predominates. Collaterally we wish to demonstrate an instance of internal enamine formation whose application might well be envisaged as a route to bridgehead azasteroids. As starting materials we employ the α-pyridylethylated 2-cycloalkanones, III and IV themselves conveniently obtained by an application of the enamine method (7). Chart I sets forth a parallel series of reactions, with the pertinent data in Table I.

We have thusfar not been able to effect separation of the components of VI, VII or XI, XII. Efforts at vapor phase chromatographic separation have not, as yet, proven successful. The ratios set forth in Chart I were arrived at by examination of the n.m.r. spectrum of the mixtures. Thus integration of the signal at $\tau \cong 5.46$ p.p.m. (assigned to the vinylic hydrogen in VII) relative to the total led to a calculated figure of 20-25% of 1 hydrogen. Fortunately a recent publication and analysis of the n.m.r. spectrum of quinolizidine (8) provided us with an internal check. Thus in quinolizidine the Japanese workers were able to assign the lowest field signals (τ_{CDCl_3} 7.18, 7.34 p.p.m.) as due to the identical equatorial hydrogens at C_2 and C_{10} geminally coupled to the axial, more shielded protons. The spectrum of VI, VII exhibits its lowest field signal after the vinyl band as a doublet centering at $\tau \cong 6.55$ p.p.m., $J \cong 12$ c.p.s., which as expected integrates for one hydrogen. In appearance it is identical with the low field doublet published for quinolizidine (8). Its downfield shift relative to those of quinolizidine may be attributed to the enamine resonance which renders the nitrogen inductively more

CHART I



* Although the material obtained is almost certainly an erythro-threo mixture, neither v.p.c. nor n.m.r. data has verified this.

TABLE I

Compound	B. P. °c	λ max. μ, solvent		Yield*	Analysis					
					Calc'd			Found		
					C	H	N	C	H	N
IV	146-147 at 1.2 mm.	6.28, 6.30 sh.	CCl_4	81%	72.84	8.56	5.66	73.01	8.47	5.65
V	141-142 at 1.9 mm.	Blank from 5-6.9	CCl_4	83%	71.10	10.74	5.53	70.96	10.88	5.48
VI & VII	77-78 at 0.25 mm.	6.01, 6.2 sh.	Benzene	86%	81.61	11.06	7.32	81.40	11.13	7.15
IX	138-140 at 0.30 mm.	6.27, 6.29 sh.	CCl_4	83%	72.07	8.21	6.00	71.80	8.42	6.18
X	96-99 at 0.04 mm.	Blank from 5-6.9	CCl_4	88%	70.25	10.53	5.85	70.41	10.67	6.01
XI & XII	60-61 at 0.20 mm.	5.99, 6.16	Benzene	86%	81.30	10.80	7.90	81.26	10.61	7.64

* All yields refer to material on which analytical data were obtained.

electron withdrawing. (Similarly the vinyl hydrogens of enamines are shifted upfield relative to ordinary vinyl hydrogens). Relative integration of these two hydrogens leads to the same ratio. That we are dealing with an equilibrium mixture, is suggested by the fact that upon refluxing it in benzene containing para-toluene sulfonic acid, an identical spectrum is obtained after recovery by fractional distillation. Similar analysis established the ratio for the mixture XI-XII as ca 6:1.

Dreiding models indicate there is essentially no difference with respect to co-planarity inhibition in the tri or tetrasubstituted isomers. Hence it would be expected that the stability orders would revert to normal, an expectation which is in fact observed.

Several features of the process should be noted:

(a) infrared analysis indicates that the internal enamine reaction is essentially if not completely over in the aqueous solution. The refluxing toluene treatment results in only slight changes in the spectrum.

(b) in the acyclic analog i.e. the reaction of piperidine with 2-ethylclohexanone no enamine formation is observed even in refluxing toluene or refluxing xylene for 48 hours.

(c) the internal enamine method is the most expeditious to our knowledge for the synthesis of this type of system.

(d) even short exposure to air darkens these mixtures. Exposure to CCl_4 in the presence of moisture leads to red water soluble gums.

Further extensions of the process as well as studies of these internal enamines themselves are in progress.

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