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THE ALKYLATION OF ENAMINES FROM α,β-UNSATURATED KETONES[1]

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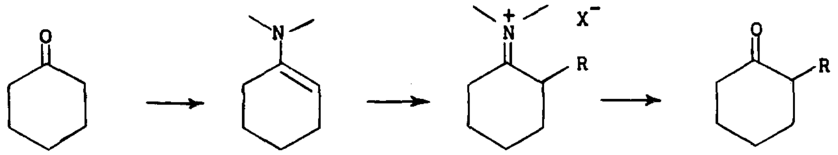
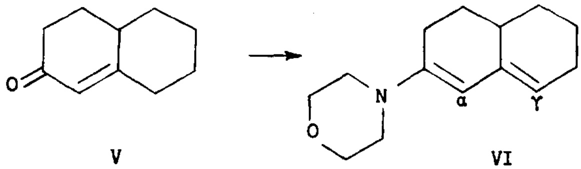
WE have extended our studies on the introduction of alkyl groups in the α-position of carbonyl compounds *via* initial transformation into enamines[2] (cf. I - II - III) to a study of the position of alkylation in the enamines of α,β-unsaturated ketones.



I II III IV

There are obviously three *a priori* possibilities which we can illustrate with the enamine derived from the unsaturated ketone $\Delta^{1(9)}$octalone-2 and morpholine:



V VI

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[1] *cf*. G. Birnbaum, Ph.D. Thesis, Columbia University, New York (1961).

[2] G. Stork, R. Terrell and J. Szmuszkovicz, *J.Amer.Chem.Soc.* **76**, 2029 (1954).

Reaction with an alkylating agent could take place on the nitrogen with formation of a quaternary salt; or C-alkylation could result with the formation of either α- or γ-alkylated products. That introduction of alkyl groups on carbon takes place at the α position was demonstrated as follows: The morpholine enamine of $\Delta^{1(9)}$octalone-2 was prepared by refluxing a solution of 30 g of $\Delta^{1(9)}$octalone-2 (V) and three equivalents of morpholine in 300 ml of toluene for 36 hr. Distillation gave the morpholine enamine (VI) in 75% yield, (b.p. 135-137°/0.3 mm); $\lambda_{max}^{CHCl_3}$ 6.24 $\lambda_{max}^{Et_2O}$ 270 mμ, ε 13,000. (Found: C, 76.36; H, 9.59. Calc. for $C_{14}H_{21}$ ON: C, 76.66; H, 9.65). In the same general way the pyrrolidine and hexamethylene imine enamines were also prepared but did not prove as satisfactory.

Alkylation of VI with methyl iodide was carried out by refluxing for 20 hr a solution of 5 g of the enamine in 50 ml of dry dioxane with an equimolar amount of methyl iodide. A solution of 1.5 g of sodium acetate in 3 ml of acetic acid and 3 ml of water was then added and the mixture was refluxed for 4 hr to hydrolyze the enamine. Extraction with ether followed by washing with 5% hydrochloric acid, saturated bicarbonate, and finally saturated salt solution gave, after removal of solvent, a mixture of α,β- and β,γ-unsaturated ketones (by infrared) which was isomerized to the conjugated form by stirring overnight under nitrogen with 4% methanolic potassium hydroxide. The resulting ketonic material was shown to contain in addition to some unreacted ketone V the product of <u>alkylation on the α-carbon atom</u>: 1-methyl $\Delta^{1(9)}$octalone-2 (VII). No other substance could be detected by careful gas chromatography on a column of Craig polyester succinate. The identity of the ketone was established by direct comparison with authentic VII made by addition of ethyl vinyl ketone to the pyrrolidine enamine of cyclohexanone.[3] The infrared and ultraviolet spectra of the

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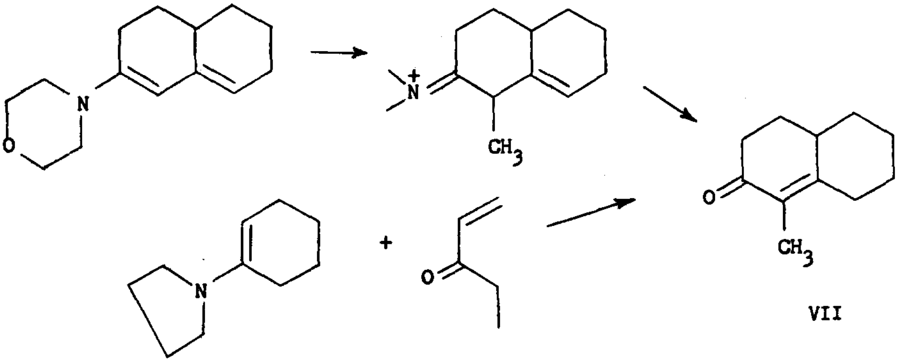
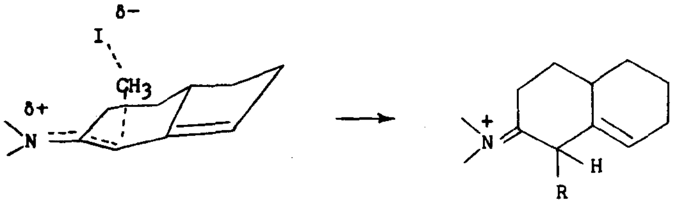
[3] G. Stork and H. K. Landesman, J.Amer.Chem.Soc. **78**, 5128 (1956).



VII

substances prepared by both methods were identical, as were their 2,4-dinitrophenylhydrazones, m.p. 177.5-178.5°.

It is thus clear that carbon alkylation of the enamine of an α,β-unsaturated ketone results in alkylation at the same position as alkylation of the metal enolate ion[4] (except, of course, that, as usual, <u>mono</u>alkylation results <u>via</u> the enamine route). This result suggests that an important factor may be the lowering of the energy of the transition state resulting from release of halide anion in close proximity to the positively charged ammonium ion:



It should also be noted that other electrophilic reagents appear to react in similar fashion with enamines:[5] Reaction with perchloryl fluoride

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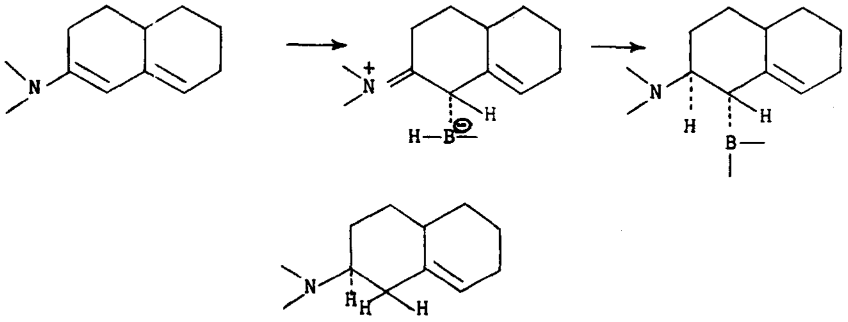
[4] <u>cf</u>. J. M. Conia, <u>Bull.Soc.Chim.</u> 690 (1954).

[5] A recent use of the enamine alkylation reaction for the α-alkylation of an unsaturated ketone has been reported by L. Velluz, G. Nomine, R. Bucourt, A. Pierdet and P. Dufay, <u>Tetrahedron Letters</u> No. 3, 127 (1961).

attacks the α-position[6] and the reduction of enamines of α,β-unsaturated ketones with sodium borohydride[7] can be interpreted similarly assuming that the reducing agent is diborane:



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[6] S. Nakanishi, K. Morita and E. V. Jensen, J.Amer.Chem.Soc. 81, 5259 (1959).

[7] W. S. Johnson, V. J. Bauer and R. W. Franck, Tetrahedron Letters No. 2, 72 (1961).