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REACTIONS OF ENAMINES WITH VINYL HETEROCYCLES. I.

A CONVENIENT ROUTE TO THE "HETEROCYCLYLETHYLATION" OF CYCLIC KETONES

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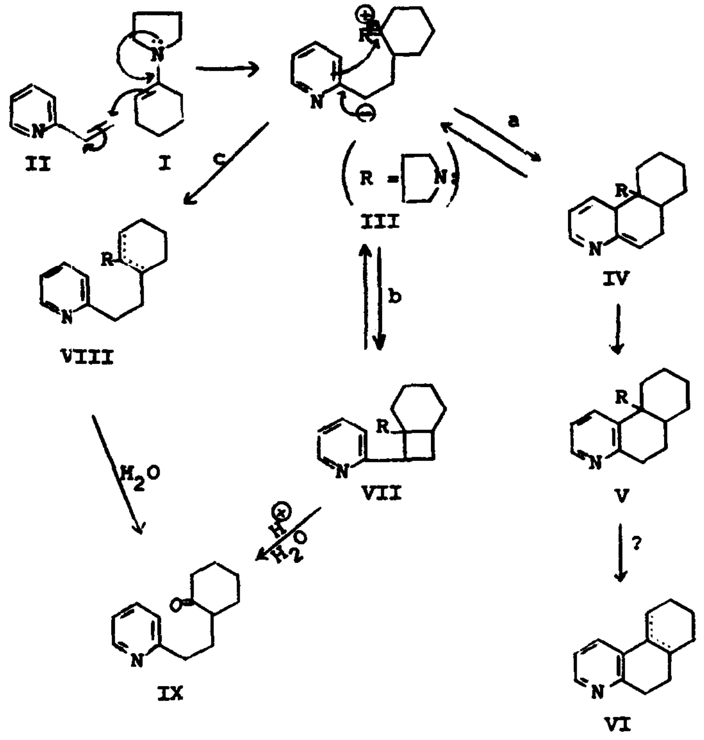
Doering (1) was the first to demonstrate the ability of suitably disposed vinylpyridines to serve as electrophilic olefins in Michael addition reactions. Subsequent studies (2,3) have elaborated the scope of this reaction.

In view of the known ability of enamines to function as nucleophiles towards Michael addition, (4) it appeared to be of interest to study the reaction of enamines with vinyl heterocycles. Of particular interest was the possibility that, in formal terms, such a process could potentially serve as a convenient entry to fused polycyclic systems related to steroids, azasteroids or alkaloids.

The purpose of this communication is to report the results of some model reactions, the long-range applications of which are currently under study in our laboratory.

The reaction first studied was that between the pyrrolidine enamine of cyclohexanone, I, and 2-vinylpyridine, II. *A priori* one could envisage three pathways for III, the first presumed intermediate for such an addition.

CHART I



Thus process III - IV (Chart I) would be a means of achieving charge neutralization via six-membered ring formation. Tautomerization would then afford V which could be isolated as such or, under appropriately forcing conditions, as its deamination product(s), VI.

The process III - VII would correspond to charge neutralization via four-membered ring formation.(5) Alternatively, charge neutralization could be achieved by proton transfer (III - VIII). Either VII or VIII could, upon appropriate hydrolytic conditions,(5) afford the known ketone IX.(3)

Treatment of I and II under a wide variety of conditions (benzene, xylene, dioxane, Diglyme as solvents) employing varying reaction times and thermal combinations produced, after hydrolysis in neutral water, IX in yields ranging from 14-71%. In no experiment was there any evidence for any of the "path a" (Chart I) products. All distillable material contained a carbonyl band as a major feature of its infrared spectrum. The distillation residue, which in no case exceeded 15% of the bulk material, also exhibited a carbonyl band as the major band in its infrared spectrum. On the basis of our experiments we can only conclude that "path a" is non-competitive, presumably because of the disruption of aromaticity involved in the step III - IV. In one experiment, I and II in a 1:1 ratio were heated in Diglyme at 185° for seventeen hours and the reaction mixture distilled *without aqueous treatment*. A 76% yield of a high-boiling oil (110-140° at 0.04 mm.) was obtained whose infrared spectrum exhibited a band at 6.10 μ, typical of enamines.(4)* Subjection of this material to neutral aqueous hydrolysis for two hours afforded a 78% yield of IX. Thus we conclude that VIII is probably the predominant species prior to aqueous work-up. One cannot exclude the possibility of the involvement of IV or VII in equilibrium steps (Mannich-retro Mannich) which are eventually irreversibly displaced towards the inert VIII, by proton transfer.

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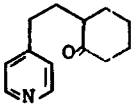
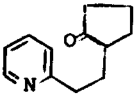
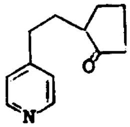
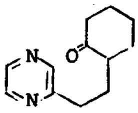
*This material also exhibited a carbonyl band at 5.86 μ reflecting partial hydrolysis of VIII during the course of our treatment. The band at 6.10 μ is clearly distinguishable from the pyridine band at 6.30 μ which is present also in the product IX.

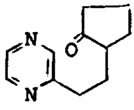
The reaction was extended to the pyrrolidine enamine of cyclopentanone as well as to 4-vinylpyridine and vinylpyrazine. Thus were obtained the heterocyclylethylated ketones X-XIV in 65-81% yield.


X


XI


XII


XIII


XIV

In no case was there any evidence for "path a" (Chart I) type products. Tables I and II list the pertinent preparative and analytical data. Structural assignments are based on infrared spectra and carbon and hydrogen analysis for all new compounds (XI-XIV). In the case of compounds IX and X, the infrared spectra were compared to previously prepared authentic samples.*

In all reactions there were employed freshly distilled enamine (4) and Diglyme distilled from calcium hydride. The workup in all cases consisted of pouring the Diglyme solution into *ca*. 300 ml. of water, stirring at room temperature for two hours, extraction three times with a total of *ca*. 1 l. of ether, drying over sodium sulfate, rapid distillation of the ether, fractionation of the residual Diglyme, and distillation of the product through a short path column. In all cases, a small forerun was obtained whose boiling point and infrared spectrum was indicative of the presence of unhydrolyzed enamine of unreacted starting material. The yields in Table I refer to

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*We wish to thank Professor R. Levine, University of Pittsburgh, for generously supplying authentic samples of compounds IX and X.

TABLE I

Pyrrolidine Enamine of	Olefin	Moles Enamine to Olefin	Diglyme (ml.)	Temperature	Time (hours)	Product	Yield
Cyclohexanone	Vinylpyrazine	.053/.050	100	175-180°	3	XIII	81%
Cyclopentanone	Vinylpyrazine	.053/.050	100	175-180°	3	XIV	66%
Cyclohexanone	2-Vinylpyridine	.11/.10	25	175-185°	17	IX	71%
Cyclohexanone	4-Vinylpyridine	.11/.10	25	175-185°	17	X	67%
Cyclopentanone	2-Vinylpyridine	.11/.10	25	175-185°	17	XI	66%
Cyclopentanone	4-Vinylpyridine	.11/.10	25	175-185°	17	XII	65%

TABLE II

Ketone	b. p.	$\lambda_{max}^{CHCl_3}$	Carbon-Hydrogen Analysis			
			Calc'd		Found	
			C	H	C	H
IX	108-111° at 0.08 mm.	5.86, 6.31 μ				
X	134-139° at 0.3 mm.	5.87, 6.28				
XI	102-106° at 0.1 mm.	5.75, 6.34	76.15	7.99	75.82	8.19
XII	116-117° at 0.2 mm.	5.73, 6.33	76.15	7.99	75.91	8.10
XIII	129-130° at 0.5 mm.	5.88	70.55	7.90	70.44	7.90
XIV	139-140° at 1.5 mm.	5.78	69.44	7.42	69.56	7.60

distilled material.*

Several features of this reaction should be noted.

(a) The use of Stork's cyanoethylation conditions(4) for pyridylethylation afforded a 14% yield of IX. This low yield under the now classical conditions is due to sluggishness of the reaction rather than polymerization of the olefin, as seen from the low amounts of distillation residue.

(b) Conditions for effecting high yield preparation of XIII are inadequate for IX. Since the distillation residues were comparable, we conclude that vinylpyridine is less reactive than vinylpyrazine towards enamines. The general subject of relative reactivities of various vinylheterocycles towards the Michael addition is currently under study.

(c) This process constitutes the most effective method to date of appending a heterocyclylethyl grouping α to a ketone. Attempts at base-catalyzed addition of the ketones to the vinylheterocycles resulted in serious losses <u>via</u> polyalkylation and self-condensation.

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*It will be noted that this procedure did not involve isolation of the ketone resulting from the unreacted and subsequently hydrolyzed enamine, as cyclohexanone and cyclopentanone co-distilled with the Diglyme. Thus the major losses were incurred from a lack of recovery of unreacted starting material rather than from resinification.

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