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THE CHEMISTRY OF CYCLIC ENAMINOKETONES. I.

C vs O-METHYLATION; STERIC AND SOLVENT EFFECTS

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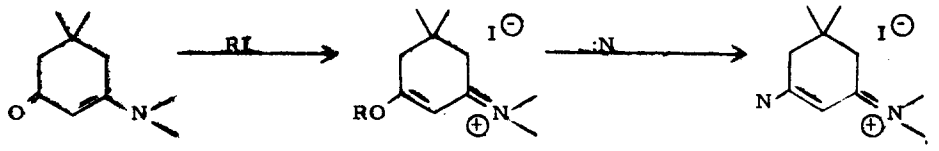
The alkylation of enaminoketones, I, was reported by Leonard and Adamcik[1,2] to give rise to O-alkylated salts, II. The latter was found to be readily displaced by nucleophiles (amines, thiols, etc.) at the ring carbon to give a variety of substituted iminium salts, III. In a program aimed at studying the chemistry of enaminoketones, we have examined the reaction of the cisoid system, IV [mp 69°; λ^{EtOH} 334 mμ (ε 16,600)][3] with methyl iodide in a variety of solvents (Table I). We have observed that, depending upon the nature of the solvent, it is possible to obtain the O-methyl derivative, V [mp 125°; λ^{EtOH} 334 mμ (ε 12,600); λ^{nujol} 5.95, 6.40 μ; nmr ($CDCl_3$), δ 4.13 (OCH_3)], and the C-methyl derivative, VI [mp 201-203°; λ^{EtOH} <220 mμ; λ^{nujol} 5.78, 5.95 μ; nmr ($CDCl_3$), δ 1.63 ($C-CH_3$)].



I II, R = Me, Et III, N: = NR_2, SEt

In protic solvents there was obtained varying amounts of the O-protonated iodo salt, VII [mp 170-173°; λ^{EtOH} 334 mμ (ε 16,700)] which was found to arise from nucleophilic displacement on the O-methyl group by the solvent. As the bulk of the solvent molecule increased

from methanol to t-butanol, substitution varied from attack on the hindered ring carbon (VIII, R=Me, Et) to exclusive attack at the more accessible methyl group (XI, R=i-Pr t-Bu). The identification of the methyl ethers, XII and XIII by gas chromatography[4] and the conversion of authentic O-methyl salt, V, in isopropanol and t-butanol to the same ethers confirmed this view. Furthermore, the small nucleophile, ammonia, readily displaced the O-methyl or O-ethyl derivative, IX [mp 143°; λ^{EtOH} 334 mμ (ε 12,000); λ^{nujol} 5.95, 6.41 μ; nmr ($CDCl_3$), δ 1.38(t), 4.41(q)] to the aminoquinolizidinium salt, X [mp 205°; λ^{EtOH} 348 mμ (ε 20,200) λ^{CHCl_3} 2.98, 3.16, 6.04, 6.51 μ].

Reaction of IV with methyl iodide in aprotic solvents (Table I) produced, in all cases except acetonitrile, predominantely the C-methyl salt, VI. However, when methylation in acetonitrile was studied over various time periods (Table II) it was found that the ratio of O-methyl to C-methyl product underwent a considerable change. When the C-methyl salt was treated for prolonged periods in acetonitrile, it was recovered completely unchanged whereas similar treatment of the O-methyl salt produced mixtures of the O- and C-methyl derivatives. Thus, from Table II, it is clear that O-methylation is kinetically controlled whereas C-methylation is thermodynamically favored. The reversal of the O-methyl product must proceed via nucleophilic attack by iodide ion and this was shown to be the case when the reversal was greatly enhanced by the addition of sodium iodide to a solution of V in acetonitrile. These results indicate that the ambident enaminoketone moiety in IV can behave both as an enamine (C-alkylation) and as an oxygen nucleophile (O-alkylation) depending upon the type of solvent interaction involved. In addition, the enaminoketone appears to possess favorable leaving group characteristics and its O-alkyl derivatives (i.e., V) could serve as potentially useful alkylating agents. These aspects are currently under investigation.

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TABLE I

REACTION OF IV WITH METHYL IODIDE IN VARIOUS SOLVENTS
(50 ± 5°, 48 hours)

	O-CH_3(V)	C-CH_3(VI)	OH (VII)
Methanol	75		25
Ethanol	80[a]		20
i-Propanol			100
t-Butanol			100
Acetonitrile	46[b]	54	
Benzonitrile	20	80	
Tetrahydrofuran	1	99	
Benzene	3	97	
Ethyl Acetate	7	93	

a) Product obtained was the O-ethyl salt (IX).

b) The product composition was determined by ultraviolet and nmr spectroscopy, utilizing the λ_{max} of V (334, ε12,600) and the O-CH_3 singlet of V (4.13 ppm) and C-CH_3 singlet of VI (1.63 ppm) in deuteriochloroform. The method was accurate to ± 2%.

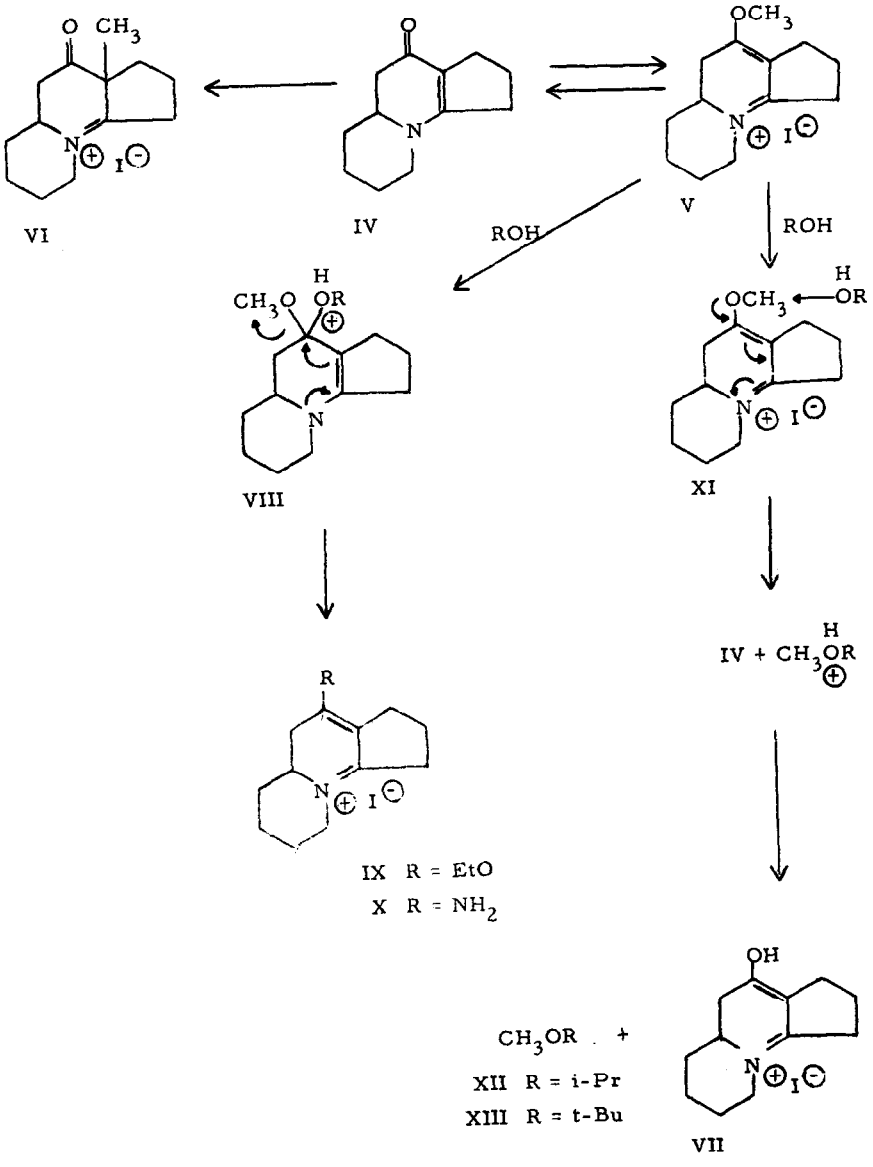
TABLE II

REACTION OF IV WITH METHYL IODIDE IN ACETONITRILE
(50° ± 2°)

Hr	%V[a]	%VI	% Overall Yield[b]
3	92	8	27
6	85	15	40
12	72	28	52
48	48	52	52
96	35	65	74

a) Product composition determined as in Table I.

b) Total V + VI, remainder of material isolated as unreacted IV.


VI
IV
V
ROH
ROH
VIII
XI
IV + CH3OR
IX R = EtO
X R = NH2
CH3OR +
XII R = i-Pr
XIII R = t-Bu
VII

REFERENCES

1. N.J. Leonard and J.A. Adamcik, J. Am. Chem. Soc., 81, 595 (1959).

2. O-Alkylation of enaminoketones has also been reported by H. Dugas, R.A. Ellison, Z. Valenta K. Wiesner, and C.M. Wong, Tetrahedron Letters, No. 18, 1279 (1965) and previous references cited therein.

3. Prepared in 70% yield utilizing the methods of a) Z. Horii, C. Iwata, I. Nimomiya, N. Inamura, M. Ito, and Y. Tamura, Chem. Pharm. Bull., (Tokyo), 12, 1405 (1964). b) W. Sobotka, J.C. Sircar, W.N. Beverung, and A.I. Meyers, J. Org. Chem., 30, 3667 (1965). A full account of the synthetic methods for preparation of cisoid and transoid enaminoketones will be forthcoming in a future publication.

4. The ethers, XII and XIII, were identified by vapor phase chromatography using authentic samples for comparison.

5. Satisfactory elemental analyses were obtained for all compounds.