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THE REACTIONS OF ACTIVATED AMIDES. PART (III).
AN ACTIVATION OF THE α-POSITION OF SECONDARY AMIDE CARBONYL.

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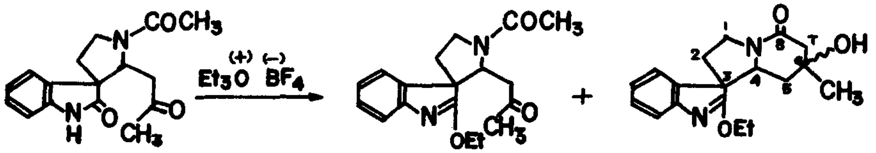
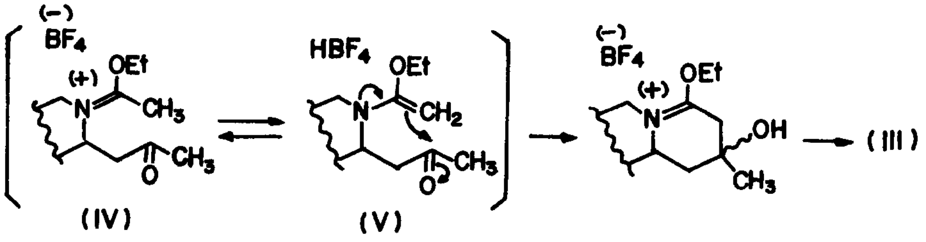
In the preceding paper of this series (Part II)(1), we reported that upon treatment of ββ-disubstituted oxindole derivatives(Ia,b) with the Meerwein's reagent, followed by neutralization with aqueous potassium carbonate, the tertiary alkohol(III), m.p.229-230° was isolated in 5-10% yield in addition to the expected iminoethers(IIa,b). The structure of this compound(III) was deduced mainly by its n.m.r. spectrum(DMSO-d6); δ 1.25(s, 3H, $\geq$C-C$\underline{H}_3$),1.52 (t, 3H, -OCH$_2$-C$\underline{H}_3$), and 3.95(d,[*1] 2H, C$_1$-$\underline{H}$). Elemental analysis, u.v. and i.r. spectra and mass spectrum(M$^+$=314) are all compatible with the assigned structure.



(I)a,b (II)a,b (III)

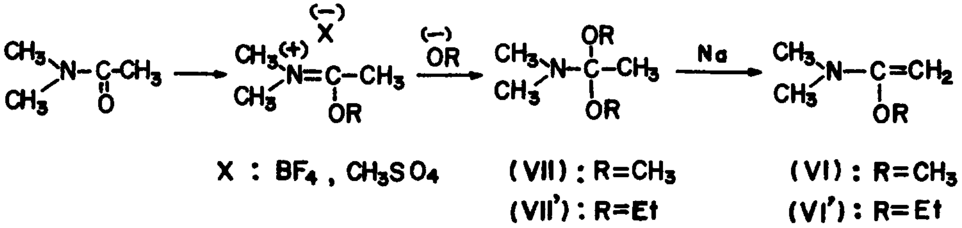
[*1] This band is characteristic of the C$_1$-protons of 8-oxoindolizidine derivatives. T.Oishi, T.Ohnuma and Y.Ban; unpublished data.

The mechanism of this anomalous reaction could be understood as follows.



The α-ethoxyenamine moiety of V, which may be formed during the reaction, should be a rather stronger nucleophile than the corresponding enamine and might be reactive enough to attack the carbonyl carbon,[*2] since the participation of oxygen π-electrons is also expected in the present system.

Based on the above consideration, we attempted to examine the reactivity of α-ethoxyenamine derivatives in general. 1-Ethoxy-N,N-dimethylvinylamine (VI') which had been synthesized by Meerwein and his coworkers(2) was chosen for this purpose. The reaction of VI' with several alkyl halides, acyl chlorides and acrylonitrile was undertaken, affording the anticipated compounds.[*3,*4] However, the preparation of α-alkoxyenamines(VI and VI') required the drastic condition such as direct treatment of the amide acetals(VII and VII') with metallic sodium at the last step, which limited the applicability of this method for the preparation of various α-ethoxyenamines. Therefore, to avoid this disadvantage, the other methods for producing these species are desired.

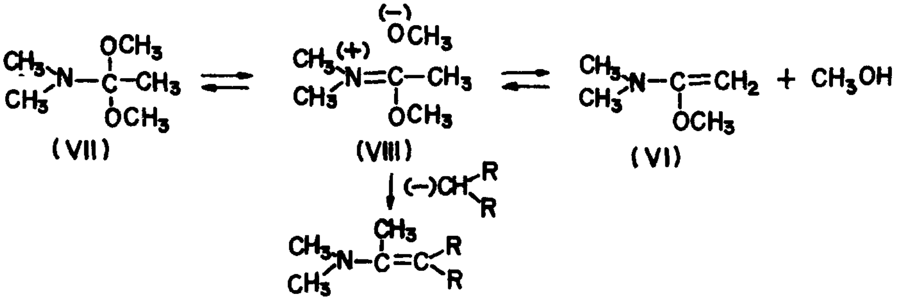


[*2] This type of condensation seems not to have been reported.

[*3] The details of these experiments will be described in the forthcoming paper.

[*4] Upon checking the literatures, the reactions of VI with acetylenic esters(3), ketenes(4), methanesulfonyl chloride(5), and methyl acrylate(6) have been published, giving the expected results.

Meanwhile, the n.m.r. spectrum of VII was examined. Three main signals[*5] appearing at δ 3.00(s, 6H), 2.10(s, 6H), and 1.00(s, 3H)(neat)[*6] are reasonably assigned to O-methyl, N-methyl, and C-methyl protons, respectively. On the other hand, the i.r. spectrum of VII exhibited two unexpected peaks[*7] at 1662(strong) and $1630cm^{-1}$(medium). The former could be ascribed to the absorption of the immonium salt($\overset{(+)}{>N=C<}$) and the latter, to the double bond of the enamine, since the compound(VI) has also an intense peak at the same position. These data could be reasonably explained by considering that the amide acetal(VII) is in rapid equilibrium with VIII and VI.[*8] Moreover, the compound(VII) is known to react with the nucleophiles to give enamine derivatives(2), which shows that the immonium salt(VIII) must be involved in the reaction mixture. The latter species could be in equilibrium with the α-ethoxyenamines in the absence of nucleophiles, since even the stable salt (IV) is considered to liberate V during the reaction. From these observations, the amide acetal(VII) was assumed to be used equally as the α-ethoxyenamine and was subjected directly to the reactions with several electrophiles.



[*5] Several small signals presumably due to impurities involved, were also observed, but signals due to VI and the initial amide were not detected.

[*6] The chemical shifts of pure liquids were measured in ppm from TMS external reference.

[*7] No absorptions were observed in the i.r. spectrum of triethyl orthoformate in these regions.

[*8] Although the mean lifetime(τ) of each component involved in this equilibrium satisfies the infrared spectrum time scale, it could be too short compared with the transition times for excitation of the nuclei in the n.m.r. spectroscopy (cf. J.D.Roberts, Nuclear Magnetic Resonance. Application to Organic Chemistry. p. 63. McGraw-Hill Book Company, Inc., New York(1959)). Therefore, only average value of chemical shifts for protons of each component must have been observed.

Treatment of VII with one molar equivalent of acrylonitrile in benzene afforded IXa,[*9] b.p.$_{22}$118-9°; ν_{max}^{neat} 2250 and 1665cm^{-1}; n.m.r.(neat) δ 3.45(s, 3H), and 2.43(s, 6H) (54%) and the cyclic compound(Xa), m.p.117-8°, λ_{max}^{EtOH} 274 mμ(log ε 4.21); ν_{max}^{neat} 2250, 2180, and 1650cm^{-1}; n.m.r.($CDCl_3$) δ 2.98(s, 6H) (14% from VII). The latter was also obtained by the further reaction of the former with acrylonitrile. Mild acid hydrolysis of IXa gave the ester(XIIa), which was saponified to glutaric acid, establishing the structure of XIIa and IXa. When stirred with aqueous ethanolic hydrogen chloride, Xa yielded the cyclic ketone(XIa). The similar condensation of VII with 1.5 molar equivalents of methyl acrylate produced IXb, b.p.$_{5}$81-2°(22.2%) and the cyclic compound(Xb), b.p.$_{3}$151-3°; ν_{max}^{neat} 1735, 1680, and 1630cm^{-1}; n.m.r.(CCl_4) δ 3.68 (s, 3H), 3.57(s, 3H), and 3.19(s, 6H) (45.8% from VII). The compound(Xb) was formed on heating IXb with methyl acrylate.

The reaction of VII with methyl vinylketone gave di-3,4-dihydro-2H-pyrane derivatives(XIII), b.p.$_{7}$95-6°, ν_{max}^{neat} 1698cm^{-1}; n.m.r.(neat) δ 4.34(broad, s, 2H) and 1.70(broad, s, 6H) (55% from VII), the structure of which was established by its conversion to XIV (10% HCl; stirred at room temp.) and XV (10% HCl; refluxed for 5 hr.).

The reactions of VII with alkyl halides and acyl halides were then investigated. In the preliminary experiments, benzyl chloride and benzoyl chloride were chosen as a typical example of each group. On heating VII with slight excess of benzyl chloride for 20 hours, followed by aqueous base treatment, there was obtained the amide(XVI) in 40.5% yield. A solution of 2.4 molar equivalents of VII and benzoyl chloride in absolute benzene was stirred for 5 hours. After base treatment, an approximately 3:2 mixture of XVII, m.p.84.5-85°, ν_{max}^{Nujol} 1620 and 1600cm^{-1}; and XVIII, m.p.97-9°, ν_{max}^{Nujol} 1730, 1655, 1615, and 1580cm^{-1} was obtained in 63% yield.

Thus, the various electrophiles were found to react with the amide acetal (VII). However, its reactivity was proved to be somewhat less than that of the

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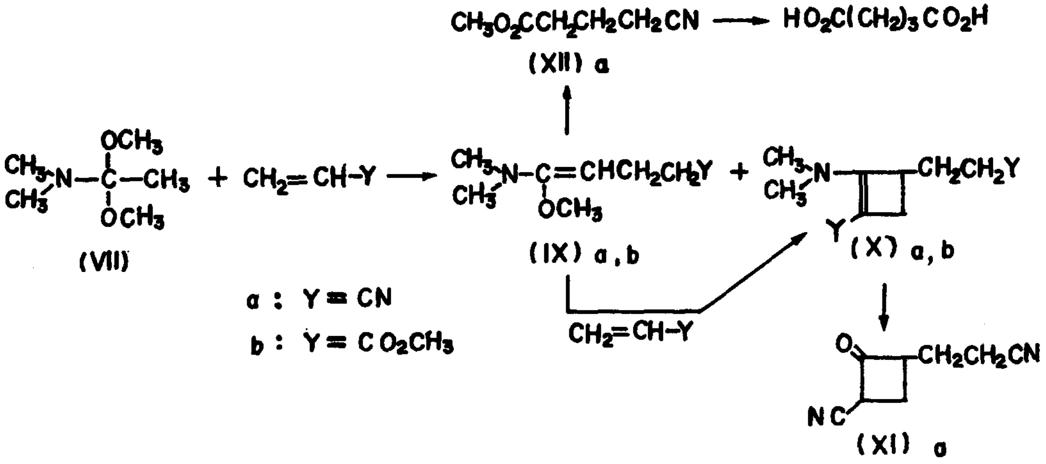
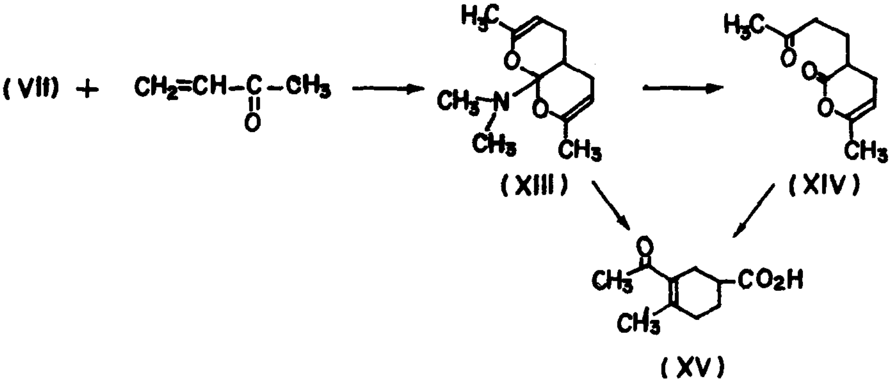
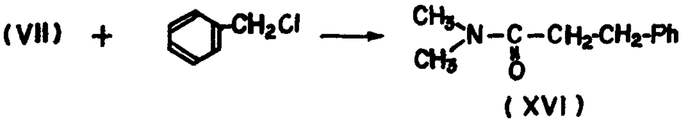
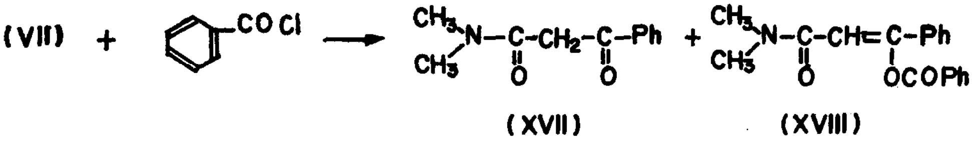
[*9] Satisfactory elemental analytical data have been obtained for all new compounds.


CH3O2CCH2CH2CH2CN ⟶ HO2C(CH2)3CO2H
(XII) a
(VII)
CH2=CH-Y
(IX) a, b
(X) a, b
a : Y = CN
b : Y = CO2CH3
CH2=CH-Y
(XI) a


(VII) +
CH2=CH-C-CH3
(XIII)
(XIV)
(XV)


(VII) +
CH2Cl
(XVI)


(VII) +
COCl
(XVII)
(XVIII)

2-ethoxyenamine(VI'). As the compound(VII) was prepared in fair yield from the corresponding N,N-dimethyl acetamide, the above results mean that the substituents were introduced successfully into the α-position of an amide carbonyl without using vigorous metallic alkali treatment. Extention of this method is now in progress.

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