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The Reactions of Activated Amides. IV.[1] The Reactions of Amide Acetals with Esters[2]

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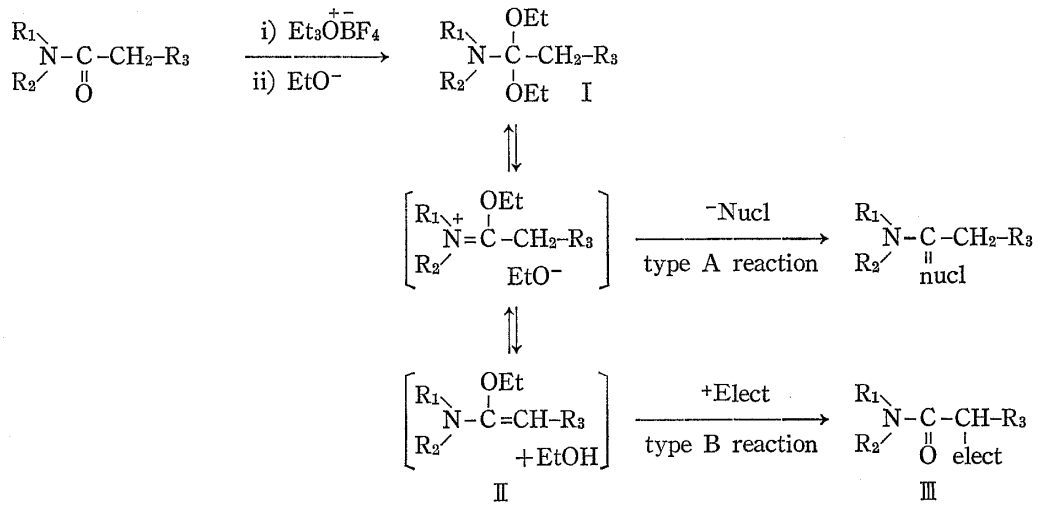
Attempted condensation of dimethylacetamide diethylacetal (Ia) with ethyl phenylacetate (IV) was unsuccessful whereas the reaction of N,N-dimethylvinylamine (IIa) with IV afforded crotonic acid derivative (V) (type A reaction). On the other hand, intramolecular condensation between amide acetals with ester carbonyl (type B reaction) was found to proceed smoothly. Thus, the enamino ketone derivatives (Xa,b) were obtained from the amide acetals (IXa,b) by simply refluxing them in *t*-butanol.

The reactions of amide acetals (I) with nucleophiles (type A reaction) have been described by several investigators.[4] Moreover, in a previous work from our laboratory[1] it was shown that amide acetals (I) react also with various electrophiles to give the amides (III) (type B reaction), establishing a new method for the introduction of a variety of substituents into the α-position of amide carbonyl. The condensation appeared to proceed through the α-ethoxyenamine (II), which could be in a rapid equilibrium with I at least during the reaction. The present paper deals with the inter- and intra-molecular condensation reactions between amide acetals and esters.



⁻Nucl : nucleophiles
+Elect : electrophiles

a : $R_1=R_2=CH_3$, $R_3=H$
b : $R_1=R_2=R_3=CH_3$

Chart 1

An attempt to condense dimethylacetamide diethylacetal (Ia) with ethyl phenylacetate (IV) was unsuccessful. Only the starting ester and dimethyl acetamide were recovered even

1) Part III: T. Oishi, M. Ochiai, M. Nagai, and Y. Ban, *Tetrahedron Letters*, **1968**, 497.
2) Presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Kita-12, Nishi-6, Sapporo.*
4) *a*) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Ann.*, **641**, 1 (1961); *b*) H. Bredereck, F. Effenberger, and H.P. Beyerline, *Chem. Ber.*, **97**, 3081 (1964).

if the mixture was refluxed for 17 hr under nitrogen. Then, the reaction of IV with 1-ethoxy-N,N-dimethylvinylamine (IIa)[4a] was carried out, as the latter compound (IIa) could be assumed to be the more reactive nucleophile than Ia.[1] The mixture was heated for 2 hr at 150° (bath temp.) under nitrogen and fractionally distilled to give viscous yellow oil (60%), the structure of which was assumed to be crotonic acid derivative (V) from spectral data. Silica gel chromatography of V gave the deaminated product, which without purification was refluxed in 10% HCl solution to afford phenyl acetone (VI) in the yield of 90% from V. Apparently, the type A reaction proceeded in this case[5] and none of the desired products expected from the type B reaction could be detected. It is noteworthy to find that the electrophilic reactivity of the ethoxyenamine derivative (IIa) is also superior to that of the amide acetal (Ia).

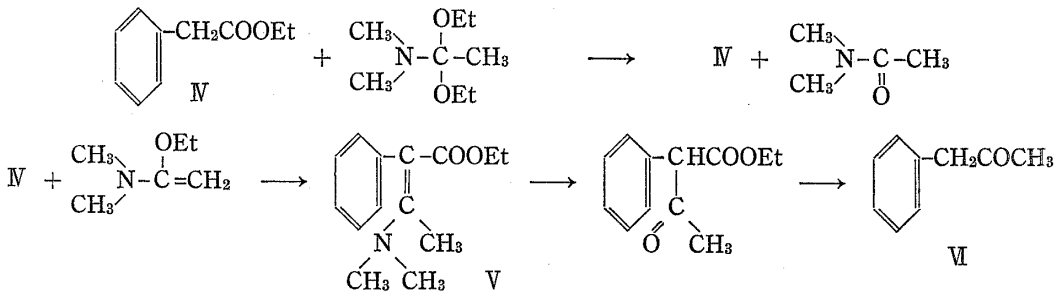


Chart 2

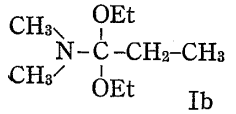
Subsequently, the intramolecular condensation of amide acetals with esters was attempted. For preparation of the requisite amide acetals, activation of amides should be made without affecting ester groups involved in the same molecule. Triethyloxonium tetrafluoroborate (Meerwein reagent) may be idealy suited for this purpose from its inertness toward an ester carbonyl. The simple acyclic amide ester (VIIa) was prepared by acetylation of the corresponding amino ester which was obtained from condensation of ethyl acrylate with methylamine.[6] Admixture of VIIa with a molar equivalent of Meerwein reagent yielded the salt (VIIIa), which was treated with sodium ethoxide in ether–CH_2Cl_2 mixture. The precipitated inorganic material was filtered off and the solvent was evaporated to give the amide acetal (IXa). On refluxing IXa in *t*-butanol for 10 hr under nitrogen afforded the expected cyclic enamino ketone (Xa) as an oil. The structure of Xa was deduced from its spectral characteristics and finally confirmed by its conversion into the amino ketone (XIa). The same cyclic compound (Xa) was also obtained by direct treatment of VIIIa with potassium *t*-butoxide. The total yield of Xa from VIIa by this modified procedure was comparable with that of the aforementioned method. Irreversible attack of ethoxyenamine moiety to the near-by located ester carbonyl would accounts for the ready cyclization leading to cyclic enamino ketone (Xa).[7]

Since the essential feature of this condensation should not be affected by replacing the acetyl group of VIIa with the other acyl group,[8] the present reaction could be extended to the general method for the synthesis of β-substituted γ-oxopiperidine derivatives (exemprified

5) The condensation of IIa with methylene groups activated only by one ester carbonyl did not take place.

6) R.W. Holly and A.D. Holly, *J. Am. Chem. Soc.*, **71**, 2124 (1940).

7) Intramolecular condensation of esters with enamines has been reported by several workers. Z. Horii, K. Morikawa, Y. Tamura, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966); A.I. Meyers, G. G. Nunoz, *Tetrahedron Letters*, **1965**, 255; C.A. Grob and H.J. Lutz, *Helv. Chim. Acta*, **48**, 791 (1968).



Ib

8) The condensation of amide acetal (Ib) with benzyl chloride and acrylonitril was carried out yielding the expected product. T. Oishi, M. Ochiai, H. Udo, and Y. Ban, to be published in the subsequent paper. Presented at the 1st Symposium of the Heterocyclic Chemistry, Osaka, November 1968.

by XII), which constitute the fundamental skeleton of a wide variety of isoquinoline and indole alkaloids.

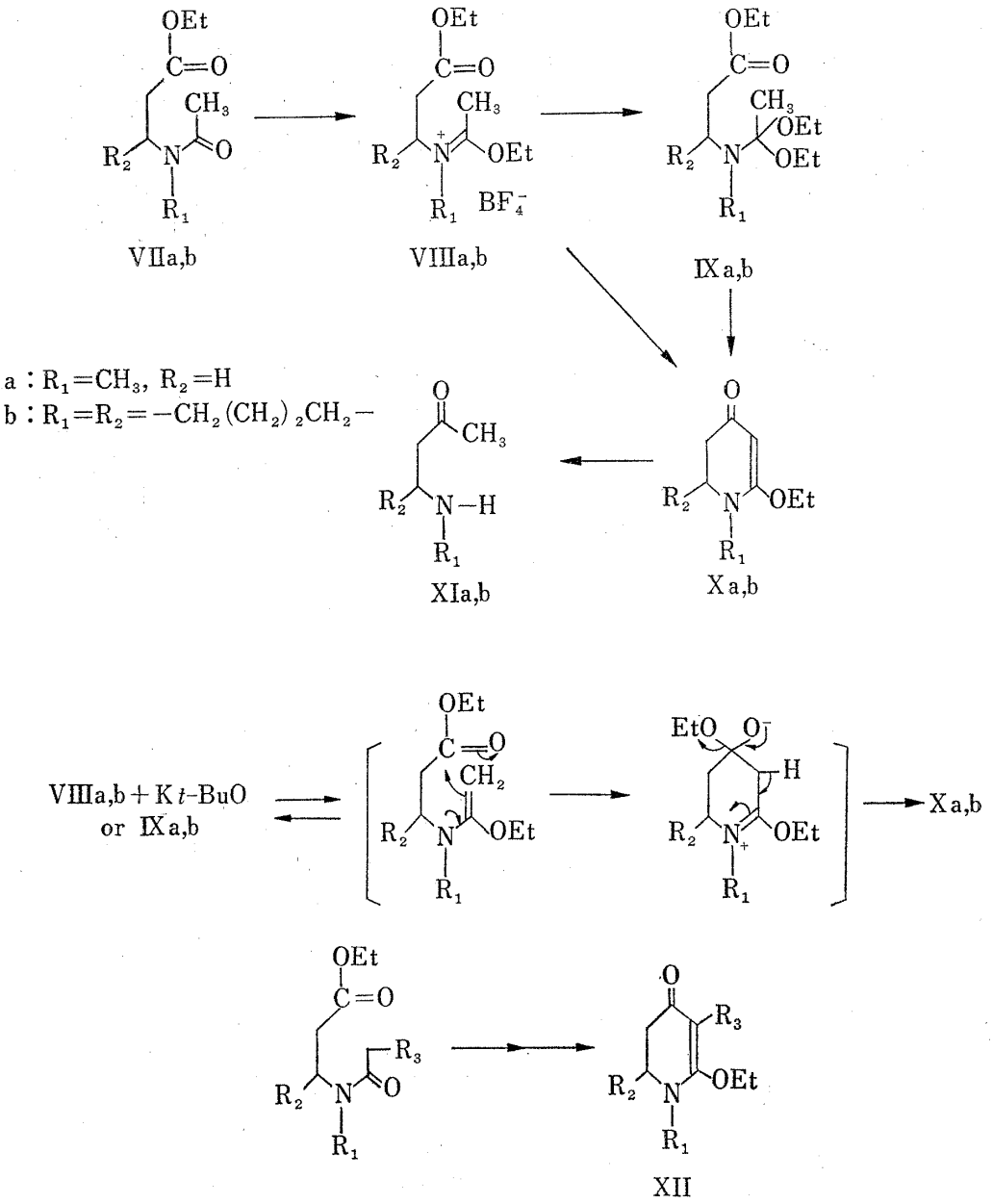
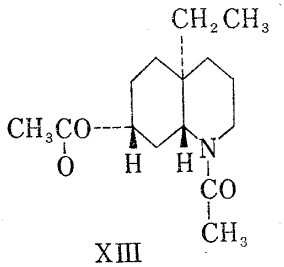


Chart 3

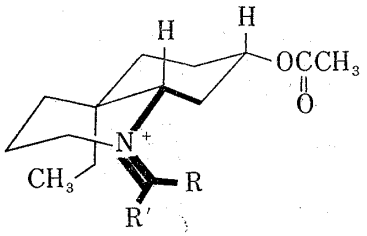
The cyclization of ethyl 2-(N-acetylpiperidyl)acetate (VIIb)[9] was then attempted. The conversion of VIIb into the corresponding salt (VIIIb) proceeded smoothly. Considering the difficulties encountered on the O-ethylation of octahydroquinoline derivatives (XIII),[10] this ready salt formation seems to be noteworthy. The main factor for the sluggish ethylation of XIII could be attributed to an allylic strain[11] involved in salt (XIV). A similar strain would be expected for the conformer (VIIIb-A). Therefore, it might be assumed that the contribu-

9) Part I of this series. T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, submitted to the *Chem. Pharm. Bull.* (Tokyo).
10) T. Oishi, Y. Sendo, K. Kamata, and Y. Ban, presented this work at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
11) S.K. Malhotra, D.F. Moakley, and F. Johnson, *Tetrahedron Letters*, **1967**, 1089; F. Johnson, *Chemical Reviews*, **68**, 375 (1968).

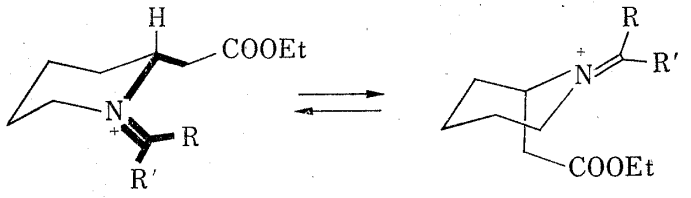
tion of the conformer (VIIIb-B) formed by ring inversion of VIIIb-A cannot be neglected, although the bulky substituent in the latter is axially oriented with respect to piperidine ring. Remarkably narrow nuclear magnetic resonance (NMR) signals due to ring protons (except protons attached to carbons adjacent to nitrogen) of VIIb and VIIIb (half-band width: 5 and 10 cps, respectively) suggest that the piperidine rings are interconverting rapidly,[12] which support the above assumption. Cyclization of VIIIb under the similar condition employed in the cyclization of VIIa afforded the quinolizidine derivative (Xb). The ethoxy-enamino-ketone structure of Xb was evident from its spectral characteristics. The unequivocal structnral proof was established by its hydrolysis into the β-keto acid and concomitant decarboxylation to give isopelletierine (XIb).



XIII



XIV : R=CH_3, R′=OEt or
R=OEt, R′=CH_3



VIIIb-A VIIIb-B

Chart 4

Experimental[13]

Phenyl Acetone (VI)——A mixture of 1.6 g of ethyl phenylacetate and 1.2 g of 1-ethoxy-N,N-dimethylvinylamine (IIa) was heated for 2 hr at 150° (bath temp.) under nitrogen. Excess IIa was evaporated off under reduced pressure and the residual oil was fractionally distilled to give 1.4 g of yellow oil, bp 115—123° (3 mmHg), to which structure V was assigned. IR ν_{max}^{neat} cm^{-1}: 1745 (weak), 1675, 1600, 1550. UV λ_{max}^{EtOH} mμ: 320. For the purpose of purification, 977 mg of aforementioned oil was subjected to silica gel chromatography. Elution with benzene afforded 790 mg of nitrogen free oil. IR ν_{max}^{neat} cm^{-1}: 1730—1760 (broad), 1640, 1620 (shoulder). Without further characterisation, 260 mg of this oil was refluxed in 4 ml of 10% HCl solution. Evolution of CO_2 gas was observed. After usual work up, 178 mg of phenyl acetone (VI) was obtained. IR ν_{max}^{neat} cm^{-1}: 1715, 1600. Semicarbazone, mp 192—193° (needles, recrystallized from EtOH).

1,2,3,4-Tetrahydro-1-methyl-6-ethoxy-4-oxopyridine (Xa)——Method (a): To a mixture of 7 g of ethyl (2-methylamino)propionate[6] and 6 g of K_2CO_3 (anhydrous) in 60 ml of acetone was added 5.4 g of acetyl chloride under ice cooling. After stirred for 2 hr at room temperature, acetone layer was separated from the precipitated solid. Solvent was evaporated and the residue was distilled under reduced pressure to give

12) J.A. Pople, W.G. Schneider, and H.J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, Inc., New York, N.Y., 1959, p. 399.

13) Melting points are uncorrected. All NMR spectra were measured with a Hitachi H-60 spectrometer. Chemical shifts are reported as values measured from tetramethylsilane as an internal standard.

8.5 g of VIIa as an oil, bp 129° (2.5 mmHg). Yield, 92%. IR ν_{max}^{neat} cm^{-1}: 1725, 1640. A mixture of 778 mg of VIIa and 860 mg of triethyloxonium tetrafluoroborate was kept for about 10 minutes and the separated oil was washed well with anhydrous ether to remove the unreacted amide ester. To a suspension of NaOEt (prepared from 125 mg of metallic Na) in ether was added the above salt (VIIIa) in a minimum amount of CH_2Cl_2. A mixture was stirred for 2.5 hr at room temperature and the precipitated inorganic material was filtered off. Evaporation of solvent gave the crude amide acetal (IXa). IR ν_{max}^{neat} cm^{-1}: 1740, 1640 (shoulder), 1585. Without purification, the above amide acetal (IXa) was dissolved in 10 ml of *t*-butanol and refluxed for 10 hr under nitrogen. The solvent was evaporated off under reduced pressure and the residue was digested with water and extracted with CH_2Cl_2. The solvent was dried over Na_2SO_4 and evaporated to give an oil, which was subjected to alumina chromatography. Elution by 1-1 mixture of CH_2Cl_2-acetone yielded 285 mg of Xa. Yield, 41% (calculated from VIIa), bp 127° (4 mmHg). UV λ_{max}^{EtOH} mμ (log ε): 298 (4.26). IR ν_{max}^{neat} cm^{-1}: 1615, 1545, 1555, 3260. NMR (in $CDCl_3$) δ: 1.42 (3H, triplet, $-OCH_2C\underline{H}_3$), 4.05 (2H, quartet, $-OC\underline{H}_2CH_3$), 2.97 (3H, singlet, $N-C\underline{H}_3$), 4.75 (1H, singlet, $C=C\underline{H}-$). *Anal.* Calcd. for $C_8H_{13}O_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.81; H, 8.34; N, 9.07.

Method (b): To a solution of 7.5 g of metallic K in 150 ml of *t*-butanol was added the salt (VIIIa) which was prepared from 8.5 g of VIIa and 28 g of triethyloxonium tetrafluoroborate. A mixture was refluxed for 21 hr under nitrogen. After the work up employed in method (a), 2.5 g of an oil was obtained. Yield, 32.6%. IR and other physical data were identical with those of Xa obtained by method (a).

1-Methylaminobutan-3-one (XIa)——A solution of 716 mg of Xa in 10% HCl solution was refluxed for 2 hr. Evolution of CO_2 was observed while refluxing. When all of the water was evaporated off under reduced pressure 634 mg of XIa hydrochloride was obtained. The free base was found to be extremely unstable. Therefore, the characterisation was done after converting it into the corresponding picrate. IR (free base) ν_{max}^{neat} cm^{-1}: 3400, 1715. Picrate, mp 127—129° (recrystallized from ethanol). *Anal.* Calcd. for $C_{11}H_{14}O_8N_4$ (picrate): C, 40.00; H, 4.27; N, 16.97. Found: C, 40.13; H, 4.46; N, 17.10.

4-Ethoxy-1,2,6,7,8,9-hexahydro-9aH-quinolizin-2-one (Xb)——a): By using 2.2 g of VIIb, 1.9 g of triethyloxonium tetrafluoroborate, and 300 mg of metallic Na, 868 mg of Xb was obtained according to the method (a) which involved a separation of amide acetal (IXb). Yield, 43%.

b): The salt (VIIIb) prepared from 2.2 g of VIIb and 2.0 g of triethyloxonium tetrafluoroborate was directly treated with potassium *t*-butoxide prepared from 410 mg of metallic K according to the method (b) to give 744 mg of Xb in addition to 422 mg of the starting amide (VIIb). IR ν_{max}^{neat} cm^{-1}: 1740, 1620, 1545. UV λ_{max}^{EtOH} mμ (log ε): 298 (4.16). NMR ($CDCl_3$) δ: 1.40 (3H, triplet, $-OCH_2C\underline{H}_3$), 3.95 (2H, quartet, $-OC\underline{H}_2-CH_3$), 4.65 (1H, singlet, $C=C\underline{H}-$). The structure was confirmed by converting it into isopelletierine (XIb).

Isopelletierine (XIb)——A solution of 744 mg of Xb in 5 ml of 10% HCl solution was heated for 2 hr at 150° (bath temp.). Water was evaporated off under reduced pressure and the resultant hydrochloride was made basic by the addition of 5N K_2CO_3 solution to give isopelletierine (XIb), which was converted into the corresponding picrate, mp 147—148° (lit.[14] mp 148°). The yield was almost quantitative. The IR and NMR spectra of free base were identical with those reported in part I of this series.

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14) J. Büchi, F. Kracher, and G. Schmidt, *Helv. Chem. Acta*, **45**, 729 (1962).