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The Reactions of Activated Amides. V.[1] The Reactions of Cyclic Amide Acetals with Electrophiles

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The condensations of 1-methyl-2-piperidone diethylacetal(VI) and 1-methyl-2-pyrrolidone dimethylacetal(XX) with several electrophiles were carried out and it was found that VI afforded the 3,3-disubstituted compounds. When benzyl chloride was used, even the compound VI afforded the 3-monosubstituted compound. The mechanism for this anomaly is discussed.

Simple amide acetals (I), a kind of activated amide, have been shown to react with various electrophiles yielding the products (II),[3] the functional groups being introduced into the β-position of the nitrogen. Even an ester carbonyl combines with amide acetals when they are involved in the same molecule.[1] In this way, the four membered ketones (III),[3] the new type of acetal (IV),[3] and the cyclic enamino ketones (V)[1] have been prepared.

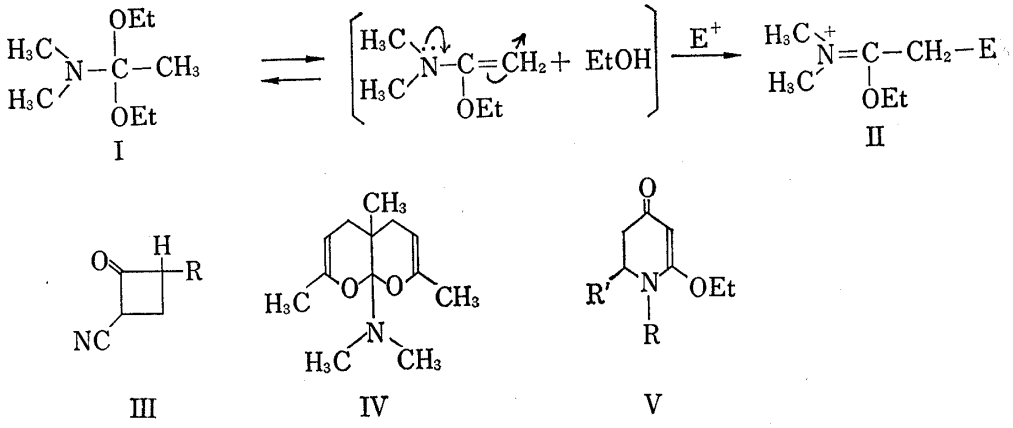

Chart 1

In continuation of the reaction of this type, the condensation of cyclic amide acetals with several electrophiles were carried out in the present study. The six-membered amide acetal (VI) was prepared from the corresponding lactam by the O-alkylation followed by the alkoxide treatment. As an electrophile, methyl acrylate (VII), acrylonitrile (VIII), methyl vinyl ketone (IX), and benzyl chloride (X) were employed. In every case, two molar equivalents of electrophiles were used and the mixture was heated for 14—17 hr at 70—80° (bath temp.) in a sealed tube. The resulting oily materials were subjected directly to Silica Gel chromatography to yield the products.

When VII, VIII, and IX were used, the 3,3-disubstituted compounds XI, XII, and XIII were mainly obtained along with a small amount of monosubstituted compounds, whereas only the 3-monosubstituted compound (XIV) was isolated when benzyl chloride (X) was employed.

1) Part IV: T. Oishi, M. Ochiai, T. Nakayama, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **17**, 2314 (1969).
2) Location: *Kita-12, Nishi-6, Sapporo.*
3) T. Oishi, M. Ochiai, M. Nagai, and Y. Ban, *Tetrahedron Letters*, **1968**, 497.

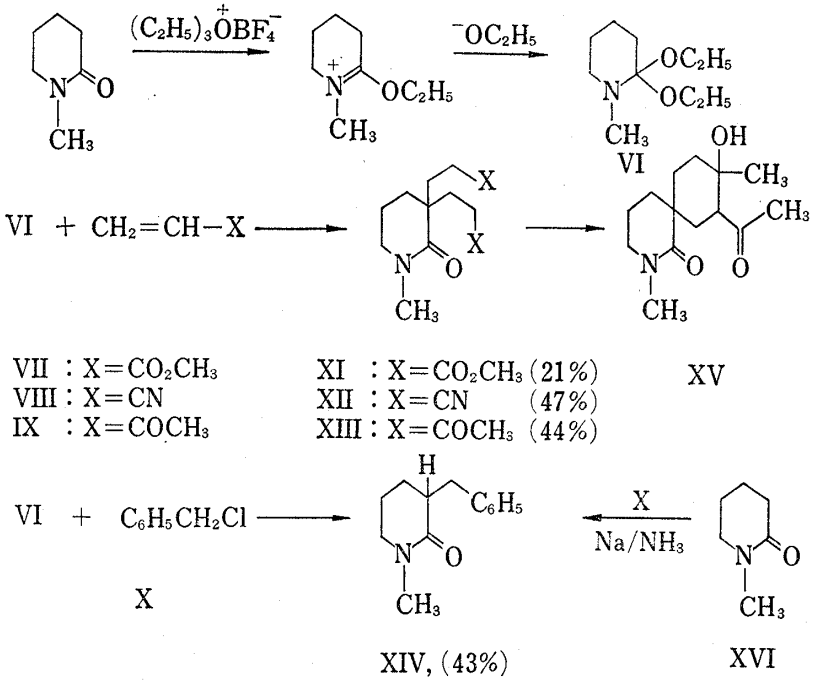

Chart 2

The dinitril (XII) is converted by CH_3OH–HCl treatment into the corresponding diester (XI), the structure of which can be determined readily by the analysis of its nuclear magnetic resonance (NMR) spectrum. When the diketone (XIII) was treated with CH_3OH–KOH, the spiro-compound (XV) was obtained as a crystalline compound. The structure of the monobenzyl compound (XIV) was comfirmed in comparison with the compound obtained by the benzylation of the lactam (XVI) in thepresence of Na in liquid ammonia.[4]

The different substitution pattern observed in the reaction of VI with benzyl chloride (X) would be ascribed to the fact that the counter anion (Cl^-) liberated from X is susceptible to attack on the O-ethyl group in the supposed intermediate (XVII) to give the stable lactam (XIV), which cannot be reacted with the second molecule of benzyl chloride any longer. On the other hand, it is presumed that the salts(XVIII) where the counter anion must be an alkoxide anion would be in equilibrium with the amide acetals (XIX), and hence could react with the reagent again to give the β,β-disubstituted compounds.

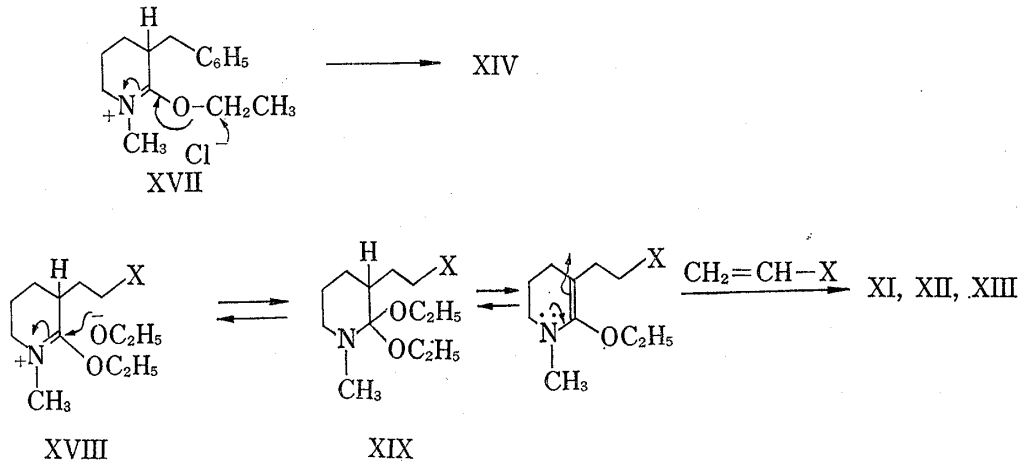

Chart 3

4) P. G. Gassman and L. L. Fox, *J. Org. Chem.*, **31**, 982 (1966).

Then, the reaction of five-membered amide acetal (XX)[5] was studied. The condensation took place readily but only the monosubstituted derivatives (XXI, XXII, and XXIII) were obtained as shown in Chart 4. These findings are in sharp contrust with those obtained in the reactions of the six-membered acetal (VI) giving the disubstituted derivatives.

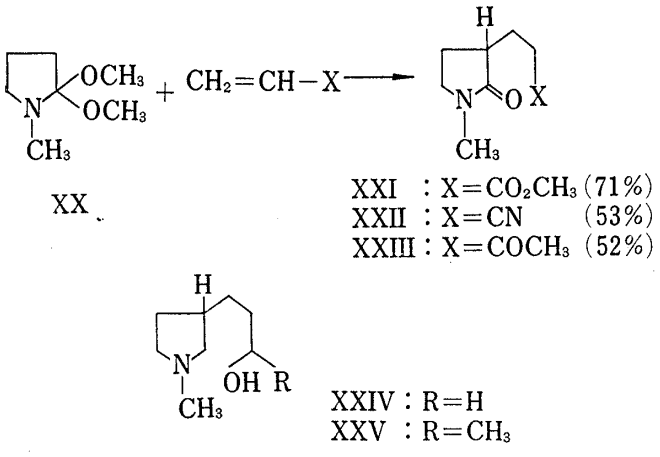

Chart 4

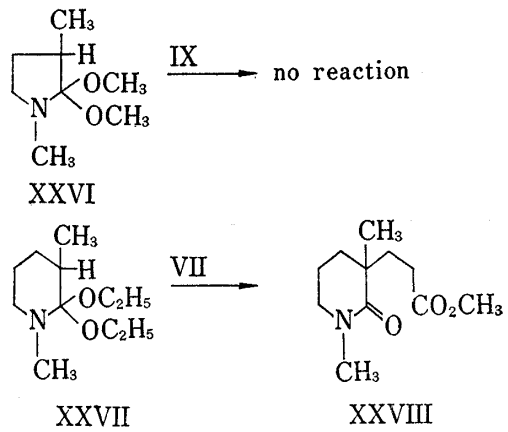

Chart 5

The structures of the compounds (XXI and XXIII) were characterized after $LiAlH_4$ reduction into the corresponding aminoalcohols (XXIV and XXV, respectively) and that of the nitril (XXII) was verified by the convertion into the ester (XXI).

From these experiments, it became apparent that the reactivities of six-membered and five-membered amide acetales toward electrophiles were different. This may be attributed either to the intrinsically unstable nature of the intermediary 3-monosubstituted five-membered amide acetals or to their decreased reactivity to the electrophiles. The latter was found to be more probable because there was no difficulty in the preparation of 1,3-dimethyl-2-pyrrolidone dimethylacetal (XXVI), whereas XXVI thus obtained failed to condense with the electrophiles. As the corresponding 3-monosubstituted six-membered amide acetal (XXVII) reacts smoothly with VII yielding XXVIII, it is apparent that the ring size dominate the reactivity toward electrophiles. However, the exact mechanism is not known at present.

It is noteworthy that the cyclic products such as III and IV obtained by the reaction of acyclic amide acetals with electrophiles were not detected in the present reactions.

As far as we are aware, base induced condensation reaction of lactams is limited to simple alkylation.[4,6] Therefore, it should be emphasized that the cyclic amide acetals, an activated amide, reacted with even the Michael acceptors such as XI, XII, and XIII. The reaction products, XXVIII or its congeners for example, are considered to be a key intermediate in the synthesis of Aspodosperma or other related indole alkaloids. Synthetic studies using these intermediates are being continued.

Experimental[7]

1-Methyl-2-piperidone Diethylacetal(VI)——A mixture of 1-methyl-2-piperidone (5 g) and triethyloxonium tetrafluoroborate (8.4 g) was allowed to stand for 30 min at room temperature. The deposited white solid was washed several times with ether and was added without further purification to the well stirred suspension of $NaOC_2H_5$ prepared from 1.1 g of Na in ether. After being stirred for 4 hr, the remaining

5) H. Bredereck, F. Effenberger, and H.P. Beyerlin, *Chem. Ber.*, **97**, 3081 (1964).
6) R.E. Stenseth and F.F. Blicke, *J. Org. Chem.*, **34**, 3007 (1969).
7) 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.

solid was centrifuged off. The solvent was evaporated and the oil was distilled in vacuo to give 3.5 g of pale yellow oil, bp 76—78 (16 mmHg), in the yield of 42%. NMR (neat) δ: 1.06 (3H, triplet, $OCH_2\underline{CH}_3$), 2.20 (3H, singlet, N-CH_3), 3.39 (2H, quartet, $O\underline{CH}_2CH_3$).

3,3-Bis(2-carbomethoxyethyl)-1-methyl-2-piperidone(XI)——A mixture of the amide acetal(VI) (4 g) and methyl acrylate(VII) (3.7 g) was heated for 12 hr at 70° in a sealed tube. A cooled reaction mixture was chromatographed with Silica Gel. Elution with ethyl acetate afforded a pale yellow oil (1.3 g) of XI in the yield of 21%. IR ν_{max}^{neat} cm^{-1}: 1746 (ester), 1635 (lactam); NMR ($CDCl_3$) δ: 2.90 (3H, singlet, N-CH_3), 3.65 (6H, singlet, OCH_3). This compound was subjected to elemental analysis after distillation, bp 207° (0.9 Hg) (bath temp.). *Anal.* Calcd. for $C_{14}H_{23}O_5N$: C, 58.93; H, 4.91. Found: C, 59.07; H, 8.14; N, 4.62.

3,3-Bis(2-cyanoethyl)-1-methyl-2-piperidone(XII)——The condensation of VI (0.9 g) and acrylonitrile (0.3 g) under the above reaction conditions and work-up afforded XII (0.49) in the yield of 47%. IR ν_{max}^{neat} cm^{-1}: 2300 (CN), 1630 (lactam). The compound(XII) was converted to the diester(XI) by refluxing it in CH_3OH-HCl for 3 hr, which confirmed the structure XII.

3,3-Bis(3-oxobutyl)-1-methyl-2-piperidone(XIII)——The condensation of VI (2.5 g) and methyl vinyl ketone (1.88 g) under the above reaction conditions and work-up afforded XIII in the yield of 44%. IR $_{max}^{neat}$ cm^{-1}: 1720 (C=O), 1630 (lactam). NMR ($CDCl_3$) δ: 2.90 (3H, singlet, N-CH_3), 2.15 (6H, singlet, $\underset{\underset{O}{\|}}{C}CH_3$).

The structure of this compound was confirmed by the conversion to the spirocompound (XV).

2′-Acetyl-3′-hydroxy-3,3′-dimethylspiro[piperidine-3,1′-cyclohexan]-2-one(XV)——A solution of the diester(XIII) (200 mg) in 10 ml of alcohol containing 5 ml of 10% alcoholic KOH was warmed for 30 min at 65° and another 30 min at 80°. The progress of the reaction was monitored by thin layer chromatography. After all of XIII had been consumed, the mixture was neutralized by the addition of 10% HCl. After alcohol had been evaporated off, the residual oil was dissolved in CH_2Cl_2, dried with Na_2SO_4 and evaporated to give a brown oil, which partially solidified by the addition of ether. The solid was recrystallized from ethyl acetate to give a white needles of XV, mp 177—179°, in the yield of 31%. IR ν_{max}^{nujol} cm^{-1}: 3450 (OH), 1705 (C=O), 1605 (lactam). NMR ($CDCl_3$) δ: 2.90 (sh, singlet, NCH_3), 2.16) singlet, $-\underset{\underset{O}{\|}}{C}CH_3$), 1.27 (3H, singlet, $-\underset{\underset{I}{}}{C}-CH_3$), 3.55 (1H, OH). *Anal.* Calcd. for $C_{14}H_{23}O_3N$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.25; H, 9.06; N, 5.39.

3-Benzyl-1-methyl-2-piperidone(XIV)——A mixture of VI (2 g) and benzyl chloride (1.8 g) was heated for 48 hr at 130° in a sealed tube. After the same work-up as noted in the reaction of VI with methyl acrylate, XIV (0.92 g) was obtained in the yield of 43%. IR ν_{max}^{neat} cm^{-1}: 1640; NMR ($CDCl_3$) δ: 7.29 (5H, singlet, C_6H_5), 2.99 (3H, singlet, NCH_3). This compound was found to be identical from every respect with the sample prepared by the method of Gassman and Fox.[5]

3-(2-Carbomethoxyethyl)-1-methyl-2-pyrrolidone(XXI)——A mixture of 1-methyl-2-pyrrolidone dimethylacetal(XX) (5 g) and methyl acrylate (7.5 g) was heated for 17 hr at 100° in a sealed tube. After the same work-up as noted in the reaction of VI with methyl acrylate, an oil(XXI) (4.4 g) was obtained in the yield of 71%. IR ν_{max}^{neat} cm^{-1}: 1745 (ester), 1690 (lactam); NMR ($CDCl_3$) δ: 2.82 (3H, singlet, NCH_3), 3.65 (3H, singlet, OCH_3). The reduction of XXI with a large excess of $LiAlH_4$ in tetrahydrofuran afforded the pyrrolidine alcohol(XXIV). Picrate, mp 115—117° (from ethanol). *Anal.* Calcd. for $C_{14}H_{20}O_8N_4$:C, 45.16; H, 5.41; N, 15.05. Found: C, 45.31; H, 5.24; N, 14.89.

3-(2-Cyanoethyl)-1-methyl-2-pyrrolidone(XXII)——The condensation of XX (2.5 g) and acrylonitrile (1.85g) under the same reaction conditions and work-up afforded XXII (1.65 g) as a pale yellow oil in the yield of 53%. IR ν_{max}^{neat} cm^{-1}: 2348 (CN), 1690 (lactam). The mononitrile(XXII) was converted to the monoester(XXI) by refluxing it in CH_3OH-HCl for 3 hr, which confirmed the structure XXII.

3-(3-Oxobutyl)-1-methyl-2-pyrrolidone(XXIII)——The condensation of XX (15 g) and methyl vinyl ketone (15 g) under the same reaction conditions and work-up afforded XXIII (7.8 g) as a colorless oil in the yield of 52.2%. IR ν_{max}^{neat} cm^{-1}: 1710 (C=O), 1690 (lactam); NMR ($CDCl_3$) δ: 2.92 (3H, singlet, NCH_3), 1.28 (3H, singlet, $\underset{\underset{O}{\|}}{C}-CH_3$). The reduction of XXIII with a large excess of $LiAlH_4$ in tetrahydrofuran afforded the pyrrolidine alcohol(XXV). Picrate, mp 100—104° (from ethanol). *Anal.* Calcd. for $C_{15}H_{22}O_8N_4$: C, 46.63; H, 5.95: C, 46.75; H, 5.81.

1,3-Dimethyl-2-pyrrolidone dimethylacetal(XXVI)——To liquid ammonia surrounded by the dry-ice-acetone bath was added metalic Na (2.3 g) and 1-methyl-2-pyrrolidone (9.9 g), successively. After the mixture had been stirred for 30 min, methyl iodide (14.2 g) was added slowly. Ammonia was allowed to evaporate off and the residue was taken up in ether, the solvent was dried and evaporated to give an oil, which was distilled to give 6.0 g of 1,3-dimethyl-2-pyrrolidone, bp 98° (50 mmHg), in the yield of 53%. NMR ($CDCl_3$) δ: 0.94 (3H, doublet, J=6 Hz, $-\underset{\underset{H}{}}{C}-CH_3$), 2.60 (3H, singlet, NCH_3). A mixture of lactam (5 g) thus obtained and dimethyl sulfate (5.5 g) was heated for 2 hr at 100°. The precipitated salt was treated with sodium methylate in the same way as noted in the preparation of VI to afford 2.03 g of XXVI, bp 62° (24 mmHg), in the yield of 29%.

1,3-Dimethyl-2-piperidone diethylacetal(XXVII)——Methylation of 1-methyl-2-piperidone was carried out in the same way as above [NMR($CDCl_3$) δ: 2.80 (3H, singlet, NCH_3), 1.10 (3H, doublet, J=6 Hz, -C(H)CH_3)] (57%) and the subsequent acetal formation was carried out in the same way as noted in the preparation of VI. The acetal(XXVII), bp 77° (21 mmHg), was obtained in the yield of 40% (from 1,3-dimethyl-2-piperidone). This compound is contaminated with a small amount of 1,3-dimethyl-2-piperidone but was subjected to the condensation reaction without further purification.

3-(2-Carbomethoxyethyl)-1,3-dimethyl-2-piperidone(XXVIII)——The afore-mentioned acetal(XXVII) (1.5 g) was heated for 14 hr with acrylonitrile(VIII) (650 mg) in a sealed tube. After cooling, the mixture was subjected to Silica-Gel chromatography. Elution with a mixture of acetone and ethyl acetate (1:5) afforded a yellow oil of XXVIII in the yield of 37%. IR ν_{max}^{neat} cm^{-1}: 1743 (ester), 1633 (lactam); NMR ($CDCl_3$) δ: 3.60 (3H, singlet, OCH_3), 2.85 (3H, singlet, NCH_3), 1.18 (3H, singlet, -$\dot{C}$-CH_3).