LACTAM ACETALS

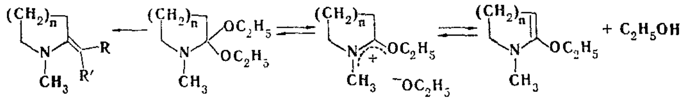
XI.* REACTIONS OF N-METHYL-2-PYRROLIDONE DIETHYLACETAL WITH SOME NUCLEOPHILIC AND ELECTROPHILIC REAGENTS

A. M. Zhidkova, V. G. Granik,
N. S. Kuryatov, V. P. Pakhomov,
O. S. Anisimova, and R. G. Glushkov

UDC 547.745

It is shown in the case of the reaction of N-methylbutyro-, N-methylvalero-, and N-methylcaprolactam diethylacetals with benzyl cyanide that the five-membered acetal is the most reactive in the reaction with compounds having an active methylene link. 1-Methyl-3-(ω-phenyl-ω-benzoxymethylene)-2-pyrrolidone is primarily formed in the reaction of N-methyl-2-pyrrolidone diethylacetal with C_6H_5COCl. The reaction of N-methylcaprolactam diethylacetal with acrylonitrile gives a mixture of N-methylcaprolactam, 1-methyl-2-ethoxy-3-(β-cyanoethyl)-4,5,6,7-tetrahydroazepine, and 2-methyl-1,9-dehydro-9-cyano-2-azabicyclo-[5.2.0]nonane.

The aim of the present research was to study the reactions of N-methyl-2-pyrrolidone diethylacetal (Ia) with some nucleophilic and electrophilic reagents and to compare the data obtained with the results of analogous reactions of N-methylvalero- (Ib) and N-methylcaprolactams (Ic). In 1961, Meerwein and coworkers [2] proposed, on the basis of measurements of the electrical conductivities of solutions of acetal Ia, that it dissociates with splitting out of an ethoxide anion and the formation of ambident cation IIa. The ability of lactam acetals Ia-c to act as alkylating agents may be a direct consequence of this sort of dissociation. In fact, ethyl benzoate is formed in practically quantitative yield [according to gas–liquid chromatography (GLC)] when a solution of acetal Ia and benzoic acid in chloroform is refluxed, while ethylmalonic ester and N-methyl-2-pyrrolidone (IV) in a ratio of 1:1 were detected in addition to the condensation product – 1-methyl-2-(2-dicarbethoxymethylene)pyrrolidine (III) – by GLC in the reaction of acetal Ia with malonic ester. It should be noted that this ratio of the amounts of lactam IV and ethylation product formed in the reaction indicates indirectly that the rate of simultaneous ethylation and condensation is apparently higher in this case than in the case of acetals Ib, c, for which predominance of the amount of the N-methyllactam over the ethylation product (due to decomposition of the acetals during the reaction) has always been observed [3, 4]. As seen from the fact of the formation of III, acetal Ia readily undergoes condensation with compounds that have an active methylene link, and qualitative observations have even shown that the rate of this reaction depends substantially on the size of the lactam ring. Competitive reaction of a mixture of acetals Ia-c with benzyl cyanide and subsequent analysis of the reaction mixture by GLC



III, V, VI I a-c, n=1-3 II a-c VII a-c

III n=1, R=R'=$COOC_2H_5$; V a-c n=1-3, R=C_6H_5, R'=CN; VI n=3, R=$COOC_2H_5$, R'=CN

---

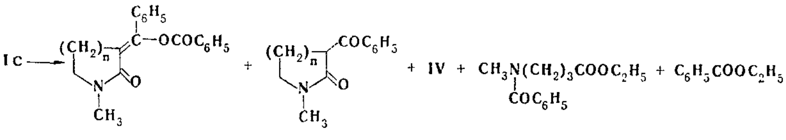
* For Communication X see [1].

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1089-1093, August, 1974. Original article submitted August 21, 1973.

showed that the target enamines (Va-c) are formed in a ratio of 15 : 2 : 1, i.e., five-membered acetal Ia is substantially more reactive than its six- (Ib) and seven-membered (Ic) analogs. It was found that, in addition to the ring size, the character of the substituent in the compound with the active methylene link also has a substantial effect on the condensation. Thus, enamine VI (GLC) is exclusively formed in the reaction of acetal Ic with a mixture of $C_6H_5CH_2CN$ and $CNCH_2COOC_2H_5$. The increased reactivity of five-membered acetal Ia indicates that conformational changes play an important role in the rate-determining step in this case, and the process includes a change in the sp^3 hybridization of the reaction center to sp^2.

It should be noted that just as in the lactam acetal series, the greatest reactivity of pyrrolidone derivatives in reactions with compounds that have an active CH_2 group is also characteristic for the corresponding lactim ethers. Thus, while O-methylbutyrolactim undergoes reaction with $C_6H_5CH_2CN$ relatively readily, O-methylcaprolactim and O-methylvalerolactim cannot be made to undergo this reaction [5, 6].

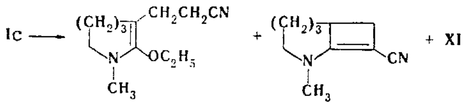
As shown in [7], in addition to ambident cations of the IIa-c type, α-alkoxyeneamines VIIa-c also participate in the equilibrium with acetals Ia-c, and this creates the prerequisites for carrying out the reactions with electrophiles in the 3-position of the lactam ring. Carrying out the reaction of acetal Ia with benzoyl chloride showed that the reaction, on the whole, proceeds via a previously described scheme [7]. At the end of the reaction, the mixture contained (GLC) lactam IV, ethyl benzoate, 1-methyl-3-(ω-phenyl-γ-benzoxymethylene)-2-pyrrolidone (VIII), 1-methyl-3-benzoylpyrrolidone (IX), and ethyl N-methyl-N-benzoyl-γ-aminobutyrate (X) in a ratio of 3 : 7 : 12 : 1 : 2. Compounds IX and X could not be isolated from the reaction mixture,* and they were identical (GLC) to the compounds obtained by alternative synthesis. Compound IX was obtained by hydrolysis of VIII, while ester X was synthesized from N-methyl-γ-aminobutyric acid via a known method [9].



VIII IX X

A comparison of the results of benzoylation of acetal Ia with the results obtained in the reaction of acetals Ib, c with benzoyl chloride shows that an open ester of the X type is formed in significant amounts only in the case of six-membered acetal Ib. Inasmuch as the formation of this compound is apparently associated with attack of benzoyl chloride at the N-atom of the lactam acetals [8], it can be assumed that conformational factors are the decisive factors in this case. In the case of the six-membered ring, approach of the C_6H_5CO group to the nitrogen atom is least hindered, while the barriers that arise during similar reaction of acetals Ia, c with C_6H_5COCl exert considerable hindrance to N-benzoylation.

A recent communication [10] indicated that the reaction of acetals Ia, b with $CH_2=CHCN$ gives, respectively, 1-methyl-3-(β-cyanoethyl)-2-pyrrolidone and 1-methyl-3,3-bis(β-cyanoethyl)-2-piperidone. Reaction of acetal Ic with acrylonitrile gives a mixture of N-methylcaprolactam (XI),† 1-methyl-2-ethoxy-3-β-cyanoethyl-2,3,4,5-tetrahydroazepine (XII), and 2-methyl-1,9-dehydro-9-cyano-2-azabicyclo[5.2.0]-nonane (XIII) in a ratio (GLC) of 1 : 5 : 4 (τ_{rel} values of 1, 5.6, and 6.9, respectively). The IR spectrum of



XII XIII

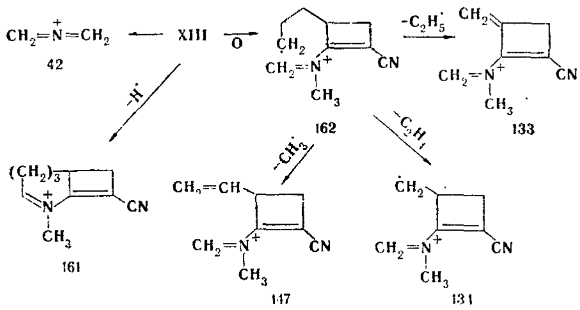
two-ring compound XIII contains absorption bands characteristic for enaminonitriles at 2180 (C≡N group) and 1640 cm^{-1}. A maximum at 277 nm (log ε 4.19), which is also characteristic for the $-N-C=C-CN$

---

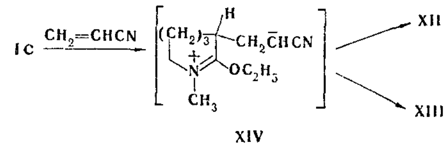
[*] The mixture of IX and X was subjected to mass spectrometric analysis, and it was shown that it contains two compounds with mass numbers of 203 and 249, respectively. In addition, it was observed that a small admixture of a substance with molecular weight 231, to which the 1-methyl-2-ethoxy-3-benzoyl-2-pyrroline structure can be assigned in analogy with [8], is present in this mixture.

[†] Special experiments by means of GLC showed that under the reaction conditions, acetal Ic is partially converted to lactam XI and diethyl ether, i.e., ambident cation IIc is an alkylating agent with respect to the ethoxide anion.

fragment, is observed in the UV spectrum. The structure of XIII was established by means of mass spectrometric analysis. The molecular weight (162) and the character of the spectrometric fragmentation correspond to the proposed two-ring structure – VII. The principal pathways of the fragmentation are presented in the scheme below:



The remaining ions observed in the spectrum (119, 110, 108, 107, 93, 82, 68, and 55) are explained by subsequent disintegration of the fragments depicted in the scheme and also by other possible pathways for the disintegration of the molecular ion. The formation of two-ring compound XIII could be the result of subsequent cyclization of enamine XII. However, an increase in the time that the reagents are heated in benzene does not lead to any appreciable change in the ratio of XII and XIII. It can therefore be assumed that these compounds are formed via independent schemes, for example, as follows:



In other words, stabilization of intermediate dipolar ion XIV may proceed via two paths: by prototropic transition ($H^3 \rightarrow \bar{C}H$) or by cyclization with subsequent splitting out of an alcohol molecule.

However, the possibility of the conversion of XII to XIII was shown by heating XII at a higher temperature (in diethylene glycol). In this case, cyclization of enamine XII to two-ring compound XIII is observed (according to GLC).

EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions (~10^4 M) of the compounds were recorded with an EPS-3 spectrophotometer. Gas–liquid chromatographic analysis (GLC) was carried out with an IGC-810 chromatograph with a flame-ionization detector and a 60 by 0.3 cm chromatographic column; the stationary phase was 1% SE-30 and 1% OV-17 on Chromosorb W. The carrier gas (helium) flow rate was 60 ml/min. The components of the mixtures were separated with temperature programming: T_{in} 75° (2 min) and T_{fin} 200°. The heating rate was 6 deg/min. Quantitative calculations were made from the data obtained with a Chromalog-2 electronic integrator. The mass spectra were recorded with an MKh-1303 spectrometer equipped with a device for direct introduction of the samples into the source at an ionizing volatage of 50 eV.

Reaction of Acetal Ic with Malonic Ester. A mixture of 3.46 g (0.02 mole) of acetal Ia and 3.2 g (0.02 mole) of malonic ester was held at 100° for 3 h. Analysis of the mixture by GLC showed that it contained 12.5% lactam IV (τ_{rel} 1), 12.4% ethylmalonic ester (τ_{rel} 1.8), and 68.6% III (τ_{rel} 14.3). Distillation of the reaction mixture gave III with bp 156-157° (3 mm) and n_D^{20} 1.5181. UV spectrum: λ_{max} 289 (log ε 4.23). IR spectrum: 1580 (C=C), 1695 (ester C=O) cm^{-1}. Found: C 59.9; H 8.1%. $C_{12}H_{20}NO_4$. Calculated: C 59.5; H 8.3%.

N-Methyl-2-(2-phenyl-2-cyanomethylene)pyrrolidone (Va). A mixture of 3.8 g (0.022 mole) of acetal Ia and 2.6 g (0.022 mole) of benzyl cyanide was heated for 6 h (the bath temperature was 115-120°), after which the alcohol was evaporated, and the residue was distilled to give Va with bp 206-207° (4 mm) and n_D^{20} 1.6206 in 69% yield. UV spectrum: λ_{max} 299 nm (log ε 4.19). IR spectrum: 1585 (C=C), 2170 (C≡N) cm^{-1}. Found: C 78.6; H 7.1; N 14.1%. $C_{13}H_{14}N_2$. Calculated: C 78.8; H 7.2; N 14.1%.

Competitive Reaction of Acetal Ic with Benzyl Cyanide and Cyanoacetic Ester. Acetal Ic (0.004 mole) was added to a mixture of benzyl cyanide and cyanoacetic ester (0.02 mole of each), and the mixture was stirred at 20° for 1 h. Analysis by GLC showed the quantitative formation of VI.

Competitive Reaction of a Mixture of Acetals Ia-c with Benzyl Cyanide. Benzyl cyanide (0.002 mole) was added to a mixture of acetals Ia-c (0.02 mole of each), and the mixture was stirred at 90-96° for 2 h, after which it was analyzed by GLC. The ratio of Va to Vb to Vc was 15 : 2 : 1.

1-Methyl-3-(ω-phenyl-ω-benzoxymethylene)-2-pyrrolidone (VIII). Triethylamine (6.5 g) was added to 7.5 g (0.43 mole) of acetal Ic in 20 ml of dry chloroform, after which the mixture was cooled and maintained at 25-30° while a solution of 4.7 ml (0.43 mole) of benzoyl chloride in 10 ml of dry chloroform was added dropwise. The mixture was stirred at room temperature for 1 h, after which water was added, and the chloroform, and the combined extracts were dried with anhydrous Na_2SO_4. The solution was filtered, the chloroform was removed by distillation, and the residue was distilled to give a fraction with a boiling point no higher than 100° (12 mm). The residue was dissolved in alcohol, and the solution was treated in the cold with activated charcoal. The solution was then filtered and evaporated. The residual oil was triturated with petroleum ether, and the mixture was filtered to give 3.8 g (29%) of VIII with mp 110-112°. A sample for analysis was crystallized from 50% ethanol to give a product with mp 127-127.5°. IR spectrum: 1635 (C=C), 1670 (lactam C=O), and 1725 (ester C=O) cm^{-1}. Found: C 74.4; H 5.6%. $C_{19}H_{17}NO_3$. Calculated: C 74.3; H 5.5%.

1-Methyl-3-benzoyl-2-pyrrolidone (IX). A 2.0-g sample of lactam VIII was added to a solution of 2.0 g of KOH in a mixture of 5 ml of water and 30 ml of methanol, and the solution was refluxed for 5 min, after which it was acidified to pH 6 with 15% HCl, and the alcohol was removed by distillation. Water was added to the residue, and the reaction product was extracted with chloroform. The extract was dried with Na_2SO_4 and filtered, and the chloroform was removed from the filtrate by distillation. The residue was fractionated at 164-165° (5 mm). The yield of IX was 1.2 g (90%). IR spectrum: 1675 (lactam C=O), 1695 (ketone C=O) cm^{-1}. UV spectrum: λ_{max} 282, 247 nm (log ε 3.26, 4.11). Found: C 71.0; H 6.6; N 6.6%. $C_{12}H_{13}NO_2$. Calculated: C 71.0; H 6.4; N 6.7%.

Reaction of N-Methylcaprolactam Diethylacetal (III) with Acrylonitrile (IV). A mixture of 10.8 g (53.9 mmole) of acetal IIc and 2.86 g (53.9 mmole) of acrylonitrile in 40 ml of dry benzene was refluxed for 20 h, after which the benzene was removed by distillation, and the residue was fractionated to give 1 g of lactam XI with bp 70-72° (1 mm) and n_D^{21} 1.4825, and 2.9 g of enamine XII with bp 129-130° (1 mm) and n_D^{21} 1.4912. UV spectrum: λ_{max} 236 nm (log ε 3.69). IR spectrum: 1660 (C=C), 2230 (C≡N) cm^{-1}. Found: C 69.3; H 9.5; N 13.6%. $C_{12}H_{20}N_2O$. Calculated: C 69.2; H 9.6; N 13.5%. Two-ring compound XIII (2.4 g) with bp 142-144° (1 mm) and n_D^{21} 1.5432, was also obtained. Found: C 73.9; H 8.8; N 16.8%. $C_{10}H_{14}N_2$. Calculated: C 74.1; H 8.6; N 17.3%.

LITERATURE CITED

1. A. M. Zhidkova, V. G. Granik, R. G. Glushkov, T. F. Vlasova, O. S. Anisimova, T. A. Gus'kova, and G. N. Pershin, Khim. Geterotsikl. Soedin., 670 (1974).
2. H. Meerwein, W. Florian, N. Schön, and G. Stopp, Ann., 641, 1 (1961).
3. V. G. Granik, A. N. Akalaev, and R. G. Glushkov, Zh. Organ. Khim., 7, 2429 (1971).
4. V. G. Granik, A. G. Sukhoruchkin, N. S. Kuryatov, V. P. Pakhomov, and R. G. Glushkov, Khim. Geterotsikl. Soedin., 954 (1973).
5. T. Onaka, Tetrahedron Lett., 5711 (1968).
6. V. G. Granik and R. G. Glushkov, Zh. Organ. Khim., 7, 1146 (1971).
7. V. G. Granik, N. S. Kuryatov, V. P. Pakhomov, E. M. Granik, I. V. Persianova, and R. G. Glushkov, Zh. Organ. Khim., 8, 1521 (1972).
8. V. G. Granik, A. G. Sukhoruchkin, N. S. Kuryatov, V. P. Pakhomov, O. S. Anisimova, and R. G. Glushkov, Khim. Geterotsikl. Soedin., 958 (1973).
9. F. Korte, K. Büchel, H. Mäder, O. Römer, and H. Schulze, Ber., 95, 2424 (1962).
10. T. Oishi, H. Nakakimura, H. Mori, and Y. Ban, Chem. Pharm. Bull., 20, 1735 (1972).