LACTAM ACETALS

VI.* REACTION OF THE DIETHYL ACETAL OF N-METHYLPIPERIDIN-2-ONE WITH BENZOYL CHLORIDE

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

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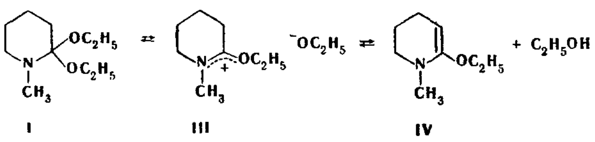
The acylation of the diethyl acetal of N-methylpiperidin-2-one with benzoyl chloride has been studied. It gives a mixture of 1-methylpiperidin-2-one, ethyl benzoate, 3-benzoyl-1-methylpiperidin-2-one, 3-(benzoyloxyphenylmethylene)-1-methylpiperidin-2-one, 3-benzoyl-2-ethoxy-1-methyl-1,4,5,6-tetrahydropyridine, and ethyl N-benzoyl-N-methyl-δ-aminovalerate.

In an investigation of the properties of the diethyl acetal of N-methylpiperidin-2-one (I) it was shown that it readily reacts with compounds having active methylene groups and may act as an alkylating agent in C- and O-alkylation reactions. This permits the conclusion that (I), like the diethyl acetal of N-methylcaprolactam (II) [2] exists in equilibrium with the ambident cation (III), the presence of which explains the ease with which the acetal (I) reacts with nucleophilic reagents. It is logical to assume that in the equilibrium system, in addition to the acetal (I) and the cation (III) the α-alkoxyenamine – 2-ethoxy-1-methyl-1,4,5,6-tetrahydropyridine (IV) – must also exist:



In this case, because of the conjugation of the unshared pair of electrons of the nitrogen atom with the double bond and a marked increase in the electron density in position 3 of the ring, the prerequisites are created for reaction with electrophilic reagents. As a model reaction in the present investigation we selected the acylation of (I) with benzoyl chloride in the presence of triethylamine. On performing this reaction in chloroform, a substance was isolated from the reaction mixture the elementary analysis of which corresponded to the product of the reaction of (I) with 2 moles of benzoyl chloride. The IR spectrum of this compound had absorption bands which can be ascribed to the vibrations of the carbonyl of an aromatic ester group at 1720 cm^{-1} (s), of a lactam carbonyl at 1624 cm^{-1} (s), and of a C=C bond at 1670 cm^{-1} (w). On the basis of these facts, the substance obtained was ascribed the structure of 3-(benzoyloxyphenylmethylene)-1-methylpiperidin-2-one† (V). The saponification of the ester group of the latter under mild

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*For communication V, see [1].

†In this case, in contrast to the seven-membered analog of compound (V) [3], of the two possible geometric isomers practically only one is formed. The building of molecular models has shown that the formation of the isomer with the trans arrangement of the amide group and of the benzoyloxy group is substantially more favorable sterically. Traces of the second isomer were detected by the GLC method in an investigation of the mother solutions after the separation of (V).

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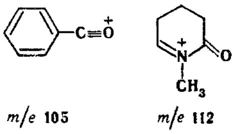
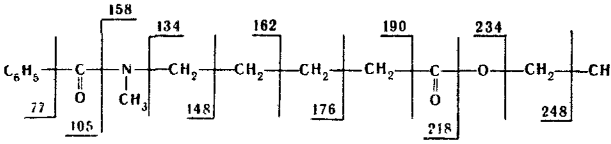
conditions yielded 3-benzoyl-1-methylpiperidin-2-one (VI), the structure of which was confirmed by its mass spectrum. In the spectrum of the lactam (VI) there are strong peaks of the molecular ion (m/e 217) and of two daughter ions (m/e 112 and 105). The presence of metastable peaks showing the direct production of these fragments from the molecular ion and also their subsequent decomposition permits the following structures to be ascribed to them:

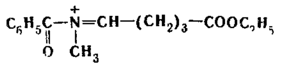


Apart from these ions and the ions obtained on their decompositon with m/e 84, 77, and 55, the spectrum shows the presence of the fragments M^+-1, M^+-Ph, M^+-CO, M^+-OH, M^+-H_2O, which also confirms the proposed structure.

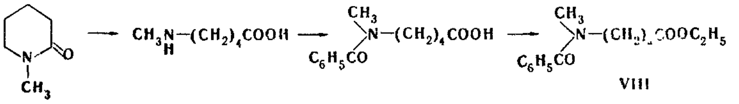
A detailed study of the reaction of (I) and C_6H_5COCl was performed with the aid of gas-liquid chromatography. According to GLC, the reaction mixture contained benzoyl chloride (τ_{rel} 0.42),* ethyl benzoate (τ_{rel} 0.68), 1-methylpiperidin-2-one (VII) (τ_{rel} 1), the lactam (VI) (τ_{rel} 6.22), and compound (V) (τ_{rel} 9.63), and also two other compounds (A, B) with relative retention times of 5.88 and 6.51 (the ratio of the substances found in the mixture was 1.94 : 1.3 : 2.04 : 1 : 4.2 : 1.28 : 4, respectively). By the repeated fractionation of the mixture of compounds A, B, and (VI) [obtained from the mother solutions after the separation of the bis derivative (V)] it was possible to isolate in the individual state substance B, with τ_{rel} 6.51. The IR spectrum of this compound had absorption bands characteristic for ester and amide carbonyls at 1730 and 1630 cm^{-1}. These facts, and also the results of elementary analysis, permitted this compound to be ascribed the structure of ethyl N-benzoyl-N-methyl-δ-aminovalerate (VIII). The proposed structure is also confirmed by the results of mass spectroscopy. The spectrum of (VIII) shows the peak of the molecular ion with a mass number m/e 263 and a number of peaks with m/e values of 248, 234, 218, 190, 176, 162, 148, 134, 158, 105, and 77, obviously belonging to fragments formed by the following successive decompositions of the molecule:



In addition, the spectrum shows the peak of the ion M^+-1, obviously arising on the elimination of a hydrogen atom with the formation of the following stable ion:


$$C_6H_5\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{\overset{+}{N}}=CH-(CH_2)_3-COOC_2H_5$$

The ions with m/e 113 and 127 can be assigned to fragments formed by the splitting off of a C_6H_5CO group from the ions with m/e 218 and 234, respectively. To prove the structure of the amide-ester (VIII), it was also synthesized independently in the following way:



The product obtained by this method proved to be identical with the compound (VIII) isolated from the reaction mixture (GLC, IR and mass spectra). It was impossible to isolate compound A from the reaction mixture, this compound being formed with a yield of ~6%. On the basis of the molecular weight known for this substance of 245,† it appeared possible to assume for it one of the three structures

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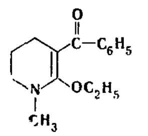
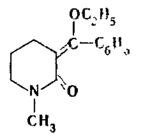
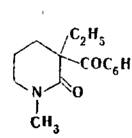
* In all cases, the retention time (τ_{rel}) is given in relation to the retention time of 1-methylpiperidin-2-one.

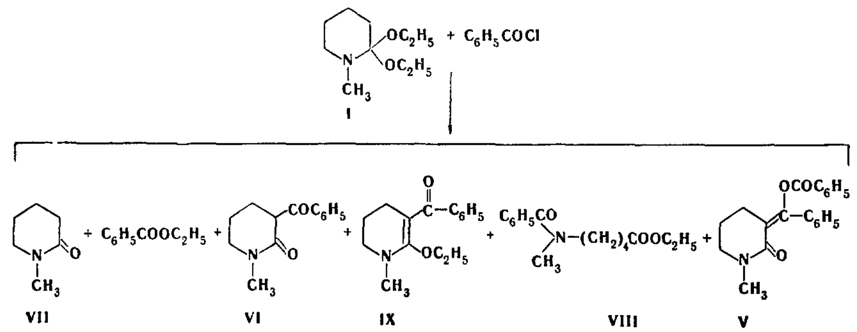
† Established by a mass-spectral analysis of a mixture of substance A, the lactam (VI), and compound (V).



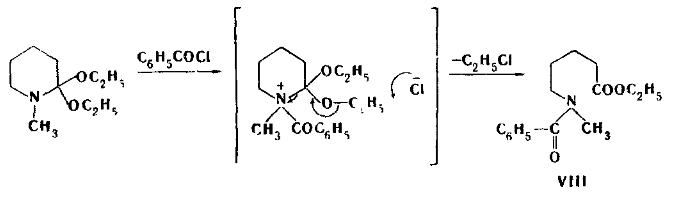




The last two structures were proposed on the basis of the assumption that the C_2H_5Cl liberated in the reaction can alkylate (VI) both at C_3 and at the oxygen of the benzoyl group. The titration of a mixture of compound A, (VI), and (VIII) in acetic acid showed that this mixture contains one strong base. Starting from the fact that under these conditions lactams and amides cannot titrate as strong bases, with some certainty compound A can be ascribed the structure of 3-benzoyl-2-ethoxy-1-methyl-1,4,5,6-tetrahydropyridine (IX). Thus, the benzoylation of (I) with benzoyl chloride can be represented by the following scheme:



Compounds (V), (VI), (VII), and (IX)* and ethyl benzoate are apparently formed by a mechanism analogous to the reaction of (II) with C_6H_5COCl. So far as concerns (VIII), it is most likely that its formation is due to an attack by the benzoyl chloride on the nitrogen atom in (I). The hypothesis that we have put forward is in harmony with the results of a recently published paper devoted to the reaction of the dimethyl acetal of dimethylformamide (X) with alkylating and acylating agents [4] in which it was shown that an acylating agent attacks the nitrogen atom of (X), as a result of which the corresponding dimethylamides are formed. In view of this, it may be assumed that the formation of (VIII) takes place in accordance with the following scheme:



EXPERIMENTAL

The IR spectra of the substances were taken in the form of mulls with paraffin oil on a UR-10 spectrophotometer. The UV spectra of ethanolic solutions of the substances ($\sim 10^{-4}$ M) were taken on an EPS-3 recording spectrophotometer (layer thickness 1 cm). The gas-chromatographic analysis was performed under the conditions described previously [1]. The mass spectra were obtained on an MKh-1303 mass spectrometer fitted with a direct inlet of the sample into the source (ionizing voltage 50 eV).

3-(Benzoyloxyphenylmethylene)-1-methylpiperidin-2-one (V). To 4.85 g of (I) in 13 ml of dry chloroform was added 2.63 g of triethylamine and then, with cooling, so that the temperature did not exceed 25-30°C, a solution of 3.64 g of benzoyl chloride in 9 ml of dry chloroform was added dropwise. The mixture was stirred at room temperature for 1 h, and then a 50% aqueous solution of K_2CO_3 was added to pH $\sim$ 8 and the chloroform layer was separated off, after which the aqueous layer was extracted with chloroform. The combined extracts were dried with anhydrous Na_2SO_4, the solution was filtered, the chloroform was evaporated off, and from the residue a fraction was distilled with bp not above 100°C (12 mm), and the residue was treated with ether. After the mixture had been kept at 0°C for some time, 1.22 g of (V) with

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* In a study of the reaction of the acetal (II) and C_6H_5COCl it was impossible to detect the seven-membered analog of the enamine (IX), nor the analog of the amide (VIII) in the reaction mixture.

mp 120-123°C was filtered off. For analysis, the product was crystallized from 15% of ethanol, mp 126-127°C, λ_{max} 236 nm (ε 2.4 · 10^{-4}). Found, %: C 74.5; H 5.9; N 4.3. $C_{20}H_{19}NO_3$. Calculated, %: C 74.8; H 5.9; N 4.4.

Ethyl N-Benzoyl-N-methyl-δ-aminovalerate (VIII). a) The combined mother solutions from several experiments on the reaction of (I) with C_6H_5COCl [total amount of (I) 28.6 g], after the separation of the (VI), were evaporated, and the residue was subjected to vacuum distillation with the collection of a fraction boiling at 167-186°C (1 mm) (10.1 g). The oil so obtained was fractionated twice more, with the collection of a product boiling between 184 and 186°C (1 mm), which consisted of (VIII). IR spectrum: $\nu_{\text{ester CO}}$ 1730 cm^{-1}; $\nu_{\text{amide CO}}$ 1630 cm^{-1}. Found, %: C 68.7; H 7.7; N 5.9. $C_{15}H_{21}NO_3$. Calculated, %: C 68.4; H 7.98; N 5.32.

b) A solution of 15 g of N-methylpiperidin-2-one in 50 ml of conc. HCl was boiled for 2 h and evaporated in vacuum to give the hydrochloride of N-methyl-δ-aminovaleric acid, mp 85-90°C. At 0°C, 9.1 g of benzoyl chloride was added over 2 h to a solution in alkali (8.12 g of NaOH in 29 ml of water) of 6.2 g of the hydrochloride obtained, and then the mixture was stirred at 20°C for 12 h, the cooled solution was made acid to Congo Red with 15% HCl, it was extracted with chloroform, the extract was dried with Na_2SO_4, and the chloroform was distilled off. Without purification, the product obtained was dissolved in 13 ml of ethanol, 0.6 ml of conc. H_2SO_4 was added, the mixture was kept at 20°C for 90 h and was brought to pH 9, the ethanol was distilled off, and the residue was extracted with chloroform. After the usual working up and vacuum distillation, a product with bp 190-195°C (2-3 mm) was obtained which, according to IR and mass spectra and also to GLC, was identical with compound (VIII) obtained by method (a).

3-Benzoyl-1-methylpiperidin-2-one (VI). To a solution of 3 g of KOH in 100 ml of methanol was added 5 g of the lactam (V), the solution was kept at 20°C for 20 h and was then acidified with alcoholic HCl, the KCl formed was filtered off, the ethanol was distilled off, water was added and the product was extracted with chloroform. The chloroform extract was dried with Na_2SO_4 and filtered, the chloroform was evaporated off, and the residue was distilled at 180-190°C (2-3 mm). The oil obtained was triturated with petroleum ether to give 2.8 g of (VI), mp 81-82°C (literature: [5]).

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