LACTAM ACETALS

VII.* A STUDY OF THE ALKYLATION OF N-METHYLLACTAMS AND LACTIM ETHERS WITH DIMETHYL SULFATE

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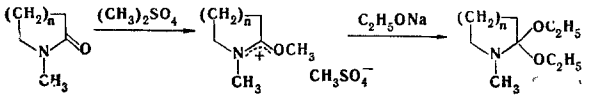
The alkylation of O- and N-methyl derivatives of butyrolactam, valerolactam, and caprolactam with dimethyl sulfate has been performed and the synthesis of the corresponding lactam acetals has been effected. It has been shown that the rate of alkylation depends fundamentally on the size of the ring of the initial compound.

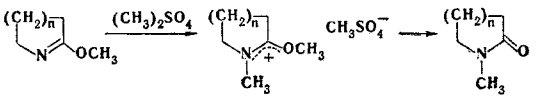
It has been established previously that lactam acetals (I) can be obtained by the alkylation of lactams (III) with dimethyl sulfate followed by treatment of the methosulfate complexes (III) with a sodium alkoxide [1-3].



II III I

a n=1; b n=2; c n=3

Of the methods for obtaining N-methyllactams (II) described in the literature, the best, from a preparative point of view, is that of Benson and Cairns [4], which is based on the reaction of lactim ethers (IV) with dimethyl sulfate, as follows:



IV III II

a n=1; b n=2; c n=3

As has been shown previously [5], the rearrangement of the ethers (IV) into the lactams (II) takes place intermolecularly with the intermediate formation of the complexes (III). Since the complexes (III) are intermediates both in the synthesis of the acetals (I) from the N-methyllactams (II) and in the preparation of the latter from the ethers (IV), it was natural to assume that the lactam acetals (I) could be synthesized directly from lactim ethers without passing through the stage of the formation of N-methyllactams. The diethyl acetal of 3-ethoxycarbonylpiperidin-2-one (V) has been synthesized previously [6] by the alkylation of a lactim ether of (V) with triethyloxonium tetrafluoroborate and the treatment of the resulting complex with sodium methoxide.

The synthesis of acetals of the lactams (I) from the O-methyl derivatives of butyrolactum (IVa), valerolactim (IVb), and caprolactim (IVc) has been performed similarly but with the use of dimethyl sulfate.

* For Communication VI, see [1].

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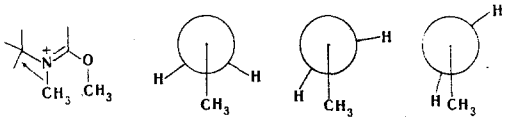
Thus, it may be assumed that the method of obtaining acetals from lactim ethers is a general one and can be used successfully for the synthesis of other acetals of lactams and amides.

It is known [7] that the rates of reactions (such as reactions involving the replacement of a halogen atom) in the cycloalkane and cycloalkene series, and also in their heterocyclic analogs, are determined to a considerable extent by the size of the ring of these compounds, similarity being usually found in the behavior of the five and seven-membered compounds, which differ in their reactivity from the six-membered rings. The qualitative laws deduced from a study of the reactions of lactim ethers with dimethyl sulfate also show a difference in the behavior of the initial compounds as a function of the size of the ring. However, in this case the reactivity apparently decreases monotonically with an increase in the size of the ring. Thus, in the alkylation of O-methylbutyrolactim the observed heat effect of the reaction is considerably higher than in the case of O-methylvalerolactim, while to bring the reaction of O-methylcaprolactim with $(CH_3)_2SO_4$ to completion, the reaction mixture must be held at an elevated temperature (40°C).

To compare the rates of reaction of the lactim ethers (IVa-c) with dimethyl sulfate we selected the method of the competing reactions of these compounds with a large excess of alkylating agent. The complexes (IIIa-c) formed by the selected method were separated and the residual mixture of lactim ethers was analyzed by the GLC method. The greater the amount of lactim ether remaining in the mixture, the lower was the rate of its reaction with dimethyl sulfate. According to the GLC analysis, the (IVa) : (IVb) : (IVc) ratio in the mixture was 1 : 1.13 : 1.36. However, it appears difficult to interpret the results obtained, since they do not give an unambiguous answer to the question of what is the structure of the transition state in the alkylation of the lactim ethers and what are the differences in the energies of the transition states with various sizes of the rings of the initial compounds (IVa-c). To answer these questions, the comparative reactivities of the N-methyllactams (IIa-c) in their reaction with dimethyl sulfate were evaluated by a similar method.

It is known [8] that the most favorable conditions for the conjugation of the lone pair of electrons of the nitrogen with a carbonyl group are realized in the case of a six-membered lactam (steric factors). Consequently, in (IIb) the partial negative charge on the amide carbonyl is the highest. In view of this, it may be expected that if the formation of the transition complex is achieved at an early stage of the process, the reaction will take place at the position of the highest electron density and, correspondingly, N-methylpiperidin-2-one should have the highest reactivity in the alkylation reaction. The results obtained from an experiment on competing alkylation [ratio of unchanged (IIa) : (IIb) : (IIc) 1 : 1.12 : 1.17] show, however, that in this case, as well, the five-membered ring is the most reactive. On this basis it may be assumed that the transition state in the reaction of (II) with $(CH_3)_2SO_4$ is reached in a later stage of the reaction, i.e., its structure is close to the final state – structure (III). Since the comparative rate of reaction has the same sequence (5 > 6 > 7) in both the series considered (IIa-c and IVa-c), it may be assumed that the conclusion on the structure of the transition state relates not only to the alkylation of the lactams (II) but also to the reaction with $(CH_3)_2SO_4$ of the lactim ethers (IV). By taking the quaternary salts (VIa-c) as an approximate model of the transition state it is possible to attempt to consider their characteristics as functions of the size of the ring. A consideration of Dreiding molecular models shows that with the introduction of a methyl group at the nitrogen atom (IVa-c), different conformational strains arise because of the nonbound interaction of the CH_3 group with the protons of the rings in positions 5, 6, and 7 for (VIa), (VIb), and (VIc), respectively.



VI a-c VI a VI b VI c

As can be seen from the projections given, in the case of (VIa) the reaction of the CH_3 group with the 5-H is the smallest in this series, and on passing to (VIb and c) the gauche conformation gradually changes into the completely eclipsed conformation.

A consideration of Dreiding molecular models of the N-methyllactams shows that in the process of O-alkylation, which is accompanied by an increase in the double-bondedness of the $N-C_2$ bond, the conformational strain increases in the six- and seven-membered rings while it scarcely changes in the case of the N-methylbutyrolactam (IIa). Thus, on the basis of the analysis performed it may be concluded that the change in the conformational stress in the formation of the complexes (IIIa-c) is an important factor in determining the comparative rates of alkylation of lactim ethers and lactams with different ring sizes. An

TABLE 1. Values of the Correction Coefficients (K) for the Mixtures Analyzed as Functions of the Relative Amounts of the Components (N)

Compound	Relative retention time	I		II		III	
		N	K	N	K	N	K
IIa	1,00	0,48	1,10	0,98	1,17	2,17	1,22
IIb	1,99	1,00	1,00	1,00	1,00	1,00	1,00
IIc	3,31	2,41	1,04	0,99	1,07	0,56	1,20
IVa	1,00	0,32	1,12	0,80	1,15	1,36	1,18
IVb	2,42	1,00	1,00	1,00	1,00	1,00	1,00
IVc	4,79	1,33	0,96	0,82	0,97	0,34	1,11

increase in the nonbound interactions in the transition state for the six-and seven-membered compounds (IIb, c, IVb, c) as compared with the five-membered compounds (IIa, IVa) leads to an increase in the free energy of activation and, correspondingly, to a decrease in the rate of the alkylation reaction. It must be noted that the facts presented relate only to the transformation of the N-methyllactams and lactim ethers into the complexes (IIIa-c) and do not make it possible to judge the comparative rates in the (III)→ (I) stage. In the process of obtaining the acetals (I) from the complexes (III) a change in the hybridization of the N and C_2 atoms ($sp^2 \rightarrow sp^3$) takes place, which, as is well known, is least favorable for five-membered rings [7].

EXPERIMENTAL

The gas-chromatographic analysis was performed on a JGC-810 instrument with a flame-ionization detector and a column 100 × 0.3 cm containing 2% of SE-30 on Chromosorb W as the stationary liquid phase. The rate of flow of the carrier gas (helium) was 60 ml/min. The separation of compounds (IVa-c) was performed at 60°C and the separation of (IIa-c) at 100°C.

For an accurate quantitative analysis, correction coefficients were determined. It was found that the coefficients of the components in the mixture changed with a change in their ratio (Table 1).

O-Methylbutyrolactim (IVa).* To 42.5 g (0.5 mole) of pyrrolidinone in 130 ml of dry benzene at 60°C, 47 ml (0.5 mole) of dimethyl sulfate was added over 40 min, the mixture was boiled for 4 h, the benzene layer was decanted off, the methosulfate derivative of (IVa) was washed with ether and then it was cooled and at ~7°C was added to a mixture of 500 ml of 40% K_2CO_3 and 120 ml of chloroform. The precipitate was filtered off and the layers were separated. The aqueous layer was extracted with chloroform (3 × 50 ml), and the combined chloroform solution was dried with Na_2SO_4 and evaporated, to give 26.9 g (~60%) of (IVa) with bp 115-121°C [10].

Diethyl Acetal of N-Methylpyrrolidinone (Ia). With the temperature not being allowed to exceed 40°C, 28 ml (0.296 mole) of dimethyl sulfate was added to 29.3 g (0.296 mole) of O-methylbutyrolactim. The mixture was stirred for 2 h and was washed with ether, and the ethereal solution was evaporated. The residue was added to a solution of sodium ethoxide (from 9 g of Na and 120 ml of absolute ethanol), the suspension was stirred for 1 h 30 min, the solid matter was filtered off, the filtrate was evaporated in vacuum, the residue was washed with ether, the ethereal extract was filtered, the ether was evaporated off, and the residue was distilled, giving 20 g of (Ia) with bp 88-90°C (78 mm) [11].

The diethyl acetal of N-methylpiperidinone (Ib) was obtained similarly with a yield of 52%; bp 69-70°C (12 mm) [1].

Diethyl Acetal of N-Methylcaprolactam (Ic). At 40-45°C, 19 ml (0.2 mole) of dimethyl sulfate was added to 25.6 g (0.2 mole) of O-methylcaprolactim, and the reaction mixture was stirred at 50°C for 3 h.

* The lactim ethers (IVa, b) were synthesized by known methods [4, 9]. However, in an attempt to repeat the method for the synthesis of O-methylbutyrolactim (IVa) [10] we came up against low and unstable yields of the desired product. It was shown by special experiments using polarography and GLC that in an acid medium (IVa) is less stable than in an alkaline medium. On this basis, the method for decomposing the complex (IIIa) was changed: instead of the gradual addition of an alkaline agent to the complex, the opposite order of mixing the reactants was used, as a result of which a pH of 8-9 was maintained throughout the addition process. This change in procedure enabled the O-methylbutyrolactim (IVa) to be obtained with stable yields of the order of 60%, calculated on the butyrolactam.

The product was worked up as in the preparation of (Ia), the yield of (Ic) with bp 84-89°C (17 mm) [3] being 60%.

Reaction of the Lactim Ethers (IVa-c) with Dimethyl Sulfate. To a mixture of the lactim ethers (0.05 mole of each) was added 0.01 mole of dimethyl sulfate, the reaction mixture was stirred for 3 h 30 min, ether was added, the ethereal solution containing the unchanged lactim ethers (IVa-c) was decanted off, and the solution was analyzed by the GLC method. The (IVa) : (IVb) : (IVc) ratio amounted to 1 : 1.13 : 1.36.

Reaction of the N-Methyllactams (IIa-c) with Dimethyl Sulfate. To a mixture of the N-methyllactams (0.03 mole each) was added 0.006 mole of dimethyl sulfate, the reaction mixture was kept at 60°C for 4 h, ether was added, and the ethereal solution containing the unchanged lactams (IIa-c) was decanted off and analyzed by GLC. The (IIa) : (IIb) : (IIc) ratio was 1 : 1.12 : 1.17.

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