ALKYLATION OF 3-ISOXAZOLIDONE

A. D. Voitenko, Ya. A. Kastron,
É. É. Liepin', and S. A. Giller

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The alkylation of 3-isoxazolidone and its metal salts with diazomethane and alkyl halides was investigated for the first time. The alkylation products are a mixture of two isomers – derivatives of the lactam and lactim forms of 3-isoxazolidone. The major component in all cases is the N-alkylation product. The percentage of isomeric imino ethers depends on the nature and structure of the reagents.

Up until now, little investigation has been devoted to the chemistry of 3-isoxazolidone (I), which is the structural basis of the antiobiotic D-cycloserine: only its metal salts and some N-acyl derivatives have been reported [1, 2].

In order to make a further study of the reactivity of 3-isoxazolidone, we investigated its alkylation. Ketone I and its potassium salt (II) were used as the starting compounds. Lactam and lactim structures were previously established [2, 3] for I and II, respectively, in the solid state. Since some of the details in the IR spectra of I in [2, 3] did not tally, we were faced with the necessity of making a more precise determination, particularly of the absorption band of the carbonyl group. It was found that, in conformity with [3], I has the absorption band of a free carbonyl group at 1700 cm^{-1}. It is interesting to note that the peak of this band is split and that the splitting depends only slightly on the medium and is also observed in the spectra of the products of alkylation of I (Fig. 1). An absorption maximum at 218 nm is detected in the electronic spectrum of I. A dilute aqueous solution of I has pH 5.60. Potentiometric titration was used to determine the protolysis constant of I (pK_a 6.80), the value of which attests to the extremely acid character of the amino group hydrogen; this is to a considerable extent a consequence of the −I effect of the oxygen heteroatom.

As one should have expected, I is methylated satisfactorily by diazomethane, but we were unable to alkylate it with alkyl halides and 5-bromo-2-nitrofuran, evidently because of the insufficient basicity of the amino group. The reaction of salt II with alkyl halides in absolute alcohol proceeds readily, and the corresponding alkyl derivatives (III-VII) are formed in good yields (Table 1).

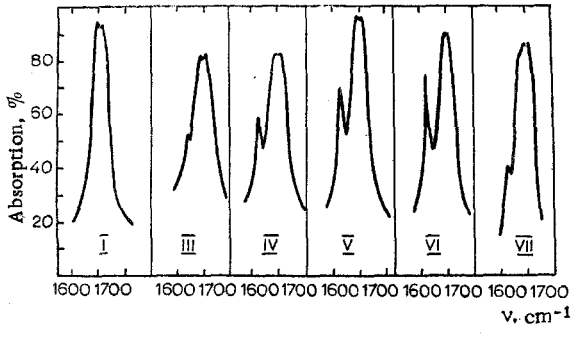
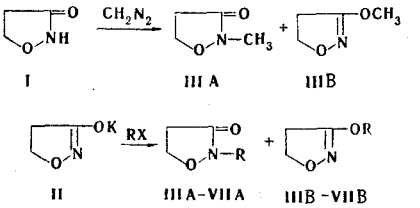


Fig. 1. IR spectra of 3-isoxazolidone (I) in chloroform and of its alkyl derivatives (III-VII).

Since the starting compounds are capable of giving two series of derivatives because of lactim–lactam tautomerism, we assumed the possibility of the formation of products of both N- and O-alkyalation (A and B):



III R=CH_3; IV R=C_2H_5; V R=n-C_3H_7; VI R=i-C_3H_7; VII R=CH_2–CH–CH_2 (O)

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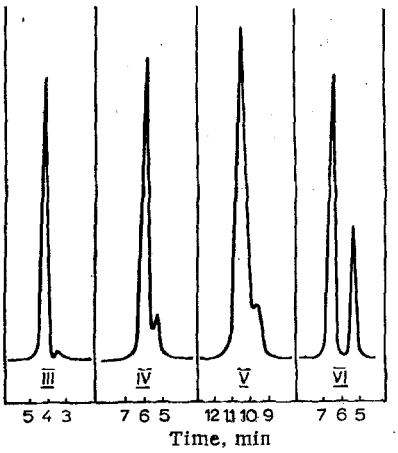


Fig. 2. Chromatograms of alkyl derivatives of 3-isoxazolidone (III-VI).

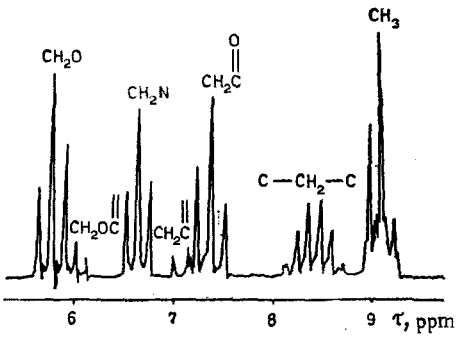


Fig. 3. PMR spectrum of the product (V) of the reaction of the potassium salt of 3-isoxazolidone with propyl bromide.

TABLE 1. Products of the Alkylation of the Potassium Salt of 3-Isoxazolidone with Alkyl Halides (mixtures of isomers A and B)

Alkylation product	R	Reaction conditions: time, h	Reaction conditions: Temp., °C	Bp, °C (mm)	d_4^{20}	n_D^{20}	Empirical formula
III	CH_3	72	20	67—68 (8)	1,1570	1,4600	$C_4H_7NO_2$
IV	C_2H_5	24	20	62—63 (3)	1,0835	1,4544	$C_5H_9NO_2$
V*	n-C_3H_7	2	Reflux	58—59 (2)	1,0536	1,4565	$C_6H_{11}NO_2$
VI	i-C_3H_7	10	Reflux	62—63 (2)	1,0435	1,4480	$C_6H_{11}NO_2$
VII	$CH_2—CH—CH_2$ (O)	48	40	108—109 (2)	1,2617	1,4840	$C_6H_{10}NO_3$ †

TABLE 1 (continued)

Alkylation product	Found, %: C	H	N	Calc., %: C	H	N	IR spectrum: $\nu_{C=O}$, cm^{-1}	$\nu_{C=N}$, cm^{-1}	Mixture composition from PMR data, %: A	B
III	47,8	7,0	14,0	47,5	7,0	13,8	1700	1630	96	4
IV	51,7	8,1	12,1	52,2	7,9	12,2	1700	1627	94	6
V*	55,7	8,4	10,6	55,8	8,6	10,9	1700	1625	87	13
VI	55,8	9,0	11,1	55,8	8,6	10,9	1700	1623	63	37
VII	49,7	6,8	9,8	50,0	7,0	9,7	1700	1630		

*Compound V, which was obtained by refluxing XI in C_3H_7Br for 20 h, contains isomers A and B in a ratio of 1 : 3.

†According to the method in [4], found: O (epoxide) 10.8%. Calculated: O (epoxide) 11.1%.

In addition to the carbonyl band near 1700 cm^{-1}, which confirms the formation of N-alkylation products, the IR spectra of III-VII also contain a band in the region of azomethine bond absorption (1620-1630 cm^{-1}); this indicates the presence of isomeric imino ethers B (Fig. 1). The results of gas-liquid chromatography (GLC) confirm the presence of two components in the analyzed substances; the ratio between them depends on the structure of the alkylating agent (Fig. 2).

It was established by means of the PMR spectra that the major components in III-VII are alkyl derivatives A; the percentage of isomeric products B ranges from 4% in III to 37% in VI.

The PMR spectrum of the product (V) of the alkylation of II with propyl bromide is shown in Fig. 3; the spectrum distinctly indicates the presence of both isomers. The ring protons of VA resonate in the form of two triplets: τ 5.78 (OCH_2) and 7.37 ($CH_2C=O$) (J = 7.6 Hz). The N-propyl group appears as three separate groups with a characteristic hfs: a triplet (J = 6.3 Hz) at τ 6.63, a sextet at τ 8.41, and a triplet (J = 6.4 Hz) at τ 9.10. The presence of VB is detected from two signals: at τ 7.14 ($CH_2C—O$, triplet,

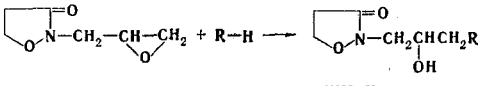
TABLE 2. Parameters of the PMR Spectra of 2-Alkyl Derivatives of 3-Isoxazolidone

Compound	R	Chemical shifts τ, ppm			$J_{5,4}$, Hz	J (in the substituent), Hz
		OCH_2	$CH_2C=O$	R		
I	H*	5,86	7,31	0,30	7,7	
IIIA	CH_3	5,80	7,39	7,02	7,6	
IVA	C_2H_5	5,77	7,37	6,55 (CH_2) 8,85 (CH_3)	7,6	6,7
VA	n-C_3H_7	5,78	7,37	6,63 (CH_2N) 8,41 (CH_2) 9,10 (CH_3)	7,6	6,3 (NCH_2CH_2) 6,4 (CH_2CH_3)
VIA	i-C_3H_7	5,81	7,42	5,94 (CH) 8,84 (CH_3)	7,7	6,7
VIIA		5,74	7,32	6,49 (CH_2N) 7,0 (CH) 7,4 (CH_2O)	7,6	4,0 (NCH_2CH)
VIII		5,77	7,37	6,60 (CH_2NCO) 6,10 (CH) 7,75 (CH_2N) 7,76 (CH_3N) 6,96 (OH)	7,6	—CO | 5,4 (NCH_2CH) 5,4 ($CHCH_2N$)
IX		5,70	7,31	6,55 (CH_2NCO) 6,18 (CH) 7,60 ($CH\mathbf{CH_2}N$) 7,43 ($N\mathbf{CH_2}CH_3$) 8,99 (CH_3) 5,96 (OH)	7,6	—CO | 5,4 (NCH_2CH) 5,4 ($CHCH_2N$) 6,5 (NCH_2CH_3)
X		5,72	7,30	6,52 (CH_2NCO) 6,11 (CH) 7,66 ($CH\mathbf{CH_2}N$) 7,50 (NCH_2) 6,39 (CH_2O) 6,0 (OH)	7,6	—CO | 5,4 (NCH_2CH)

* In CH_2Cl_2.

J = 8.8 Hz) and 6.00 (side chain CH_2O, triplet, J = 6.3 Hz). The chemical shifts of the remaining protons in isomers VB and VA are identical. The parameters of the spectra of III-VII are presented in Tables 2 and 3.

The product (VII) of the reaction of II with epichlorohydrin was investigated in somewhat greater detail than the other products. Its IR spectrum, like those of the other alkylated derivatives of I, displays an intense absorption band at 1700 cm^{-1} ($\nu_{C=O}$), the peak of which is split. The low-intensity band with a maximum at 1630 cm^{-1} attests to the presence of imino ether VIIB. The presence of a terminal epoxy group is confirmed by absorption bands at 860, 920, 1165, 1265, and 3015 cm^{-1}. The percentage of epoxide oxygen was determined by quantitative titration via the method in [4] and is close to the theoretical value. The reaction of VII with secondary amines gave amino alcohols VIII-X, the structures of which were elucidated by means of the PMR and IR spectra. It follows from the data in Table 2 that opening of the epoxide ring proceeds in conformity with the Kraus rule:



VIII-X

VIII R = $N(CH_3)_2$; IX R = $N(C_2H_5)_2$; X R = $N(CH_2CH_2)_2O$

The IR spectra of these compounds also display the characteristic absorption bands that correspond to the C–O stretching vibrations and the deformation vibrations of the O–H groups of secondary alcohols (absorption maxima at ~1100 and 1260-1350 cm^{-1}, respectively). Potentiometric titration confirmed the presence of an amino group in the side chain and was used to determine the pK_a of VIII-X (see the Experimental section).

We also alkylated the dry silver salt of 3-isoxazolidone (XI) [1] with propyl bromide. It is known that the alkylation of the Ag salts of enols under such conditions frequently leads to O-derivatives. However, it was found that XI undergoes the reaction with great difficulty. After the mixture was refluxed for 20 h, we were able to isolate, by vacuum distillation, a product that, according to PMR data, is a mixture of VA and VB in a ratio of 1:3.

TABLE 3. Parameters of the PMR Spectra of 3-Alkoxy-Δ^2-isoxazolines

Compound	R	Chemical shifts, τ, ppm			$J_{4,5}$, Hz	J (in the substituent), Hz
		OCH_2	$CH_2C=$	R		
IIIB	CH_3	5,80	7,15	6,26	8,7	—
IVB	C_2H_5	5,77	7,14	5,98 (CH_2) 8,69 (CH_3)	8,7	5,8
VB	n-C_3H_7	5,78	7,14	6,00 (CH_2O) 8,41 (CH_2) 9,10 (CH_3)	8,8	6,3 (NCH_2CH_2) 6,4 (CH_2CH_3)
VIB	i-C_3H_7	5,81	7,19	5,34 (CH) 8,72 (CH_3)	8,8	6,4

Thus, in the alkylation of II, as in the case of XI, one obtains a mixture of isomers; however, in the first case the major product is N-alkyl derivative A, while the reaction of XI with alkyl halide leads to primarily the isomeric O-derivative B. In this connection, it is impossible to fail to note the difference in the alkylation of metal derivatives of I from acylation, which forms only N-acyl derivatives for II and XI [1].

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrophotometer. The PMR spectra were obtained with a Perkin-Elmer R12A spectrometer (60 MHz) from 30% (by volume) solutions in CCl_4 with tetramethylsilane as the internal standard. The chemical shifts were measured with an accuracy of ±1% from the degree of scanning. The UV spectrum was recorded with a Specord spectrometer. The GLC analyses were performed with an AUK-3 chromatograph with a thermal conductivity detector. A 3 m by 4 mm column filled with Apiezon M and polyethylene glycol 2000 (5:1) in a 25% quantity on Chromosorb W was used. The column and vaporizer temperatures were 160 and 210°, respectively, and the carrier gas (helium) flow rate was 100 ml/min.

3-Isoxazolidone (I). This compound was obtained by passing an aqueous solution of II [1] through a column filled with KU-2 cation exchange resin and subsequent vacuum evaporation. Vacuum sublimation gave a product with mp 69-69.5° and pK_a 6.80 (potentiometric titration). IR spectrum: in Nujol 1645 (associated C=O), 1700 and 1715 (split maximum, C=O), and 2600-3500 cm^{-1} (broad band); in a KBr pellet 1645, 1695, and 1712, 2600-3500 cm^{-1}; in dilute chloroform solution 1695 and 1712 (free C=O), 3420 cm^{-1} (free NH). UV spectrum (in water): 218 nm (ε 4000). According to [3], this compound has mp 69-69.5°; IR spectrum: in Nujol 1639, 1667-1724, 2500-3333 cm^{-1}; in chloroform 1695, 2500-3333 cm^{-1}. According to [1], I has mp 69-70°; IR spectrum [2] (in mineral oil) 1670, 2944 cm^{-1}.

2-Methyl-3-isoxazolidone (III). A. A solution of 23.75 g (0.25 mole) of methyl bromide in 50 ml of ethanol was added to a solution of 6.25 g (0.05 mole) of II in 120 ml of absolute alcohol, and the mixture was held at room temperature for 3 days. The resulting precipitate was removed by filtration, and the mother liquor was evaporated at reduced pressure. The residue was purified by two vacuum distillations. The fraction with bp 67-68° (8 mm) was, according to PMR spectroscopy, IIIA containing a small amount (3-4%) of isomeric IIIB.

A similar procedure was used to obtain IV-VII, which were also mixtures of isomers. The compositions of the mixtures and the physicochemical characteristics of IV-VII are presented in Table 1.

B. A solution of 4.36 g (0.05 mole) of I in 100 ml of absolute methanol was added dropwise in the course of an hour with stirring at 10° to a solution of 6.3 g (0.15 mole) of diazomethane in 250 ml of ether, and the yellow solution was allowed to stand at room temperature for 12 h. The methanol was vacuum evaporated, and the residue was distilled twice at reduced pressure to give a product with bp 94-96° (40 mm). IR spectrum: 1630, 1700 cm^{-1}. According to the PMR data, the methylation product contains a mixture of isomers IIIA and IIIB in a ratio of 3:1. Found: C 47.6; H 7.0, N 13.8%. $C_4H_7NO_2$. Calculated: C 47.5; H 7.0; N 13.8%.

2-(3-Morpholino-2-hydroxypropyl)-3-isoxazolidone (X). A solution of 39.20 g (0.45 mole) of morpholine in 70 ml of 95% ethanol was added to 12.73 g (0.09 mole) of VII, and the resulting solution was allowed to stand at 40° for 12 h, after which it was evaporated at reduced pressure. The residue was vacuum dried. According to the results of potentiometric titration, the product had pK_a 6.30. IR spectrum: 1100 (ν_{C-O} of secondary alcohols), 1210 (ν_{C-N} of tertiary amines), 1250 (δ_{OH}), 1700 (ν_{C-O})

cm^{-1}. The hydrochloride had mp 154-156°. Found: C 44.8; H 7.3; Cl 13.3; N 10.5%. $C_{10}H_8N_2O_4 \cdot HCl$. Calculated: C 45.0; H 7.2; Cl 13.3, N 10.5%.

2-(3-Dimethylamino-2-hydroxypropyl)-3-isoxazolidone (VIII). This compound was obtained in the same way as X. According to the results of potentiometric titration, it had pK_a 8.30. IR spectrum: 1100, 1210, 1250, 1700 cm^{-1}. The hydrochloride had mp 128-130°. Found: Cl 15.7; N 12.2%. $C_8H_{16}N_2O_3 \cdot HCl$. Calculated: Cl 15.8; N 12.4%.

2-(3-Diethylamino-2-hydroxypropyl)-3-isoxazolidone (IX). This compound was obtained by the procedure used to prepare X. According to the results of potentiometric titration, it had pK_a 8.50. Found: C 55.4; H 9.5; N 12.8%. $C_{10}H_{20}N_2O_3$. Calculated: C 55.5; H 9.3; N 12.7%. IR spectrum: 1100, 1210, 1245, 1700 cm^{-1}.

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