Synthesis of 3-Nitroso-5-oxazolidones and 3-Nitroso-6-oxotetrahydro-oxazines (Cyclic α-Acyloxy-*N*-nitrosamines)

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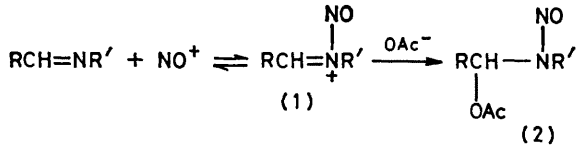
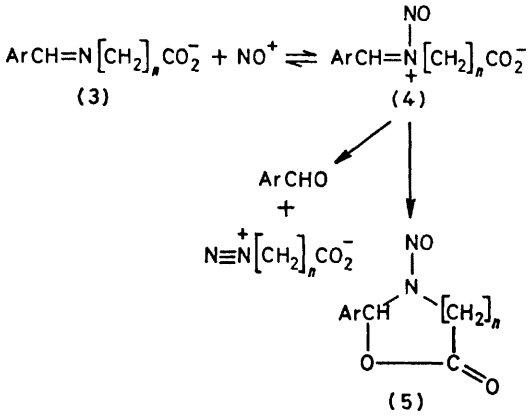
Summary Sodium salts of aryl imines of glycine and phenylalanine react with nitrosonium tetrafluoroborate in acetonitrile to yield 3-nitroso-2-aryl-5-oxazolidones and those of β-alanine give 3-nitroso-2-aryl-6-oxotetrahydro-oxazines.

THE importance of α-acyloxy-*N*-nitrosamines (**2**) in the study of the mechanism of the carcinogenic action of *N*-nitrosoalkylamines[1,2] led us to consider the synthesis of such nitroso-esters simply and directly by the addition of the nitrosonium ion (NO^+) and a carboxylate anion across the double bond of an imine. Preliminary experiments



were not satisfactory because it was difficult, owing to the insolubility of inorganic acetates in suitable solvents, to achieve high enough acetate ion concentrations to maintain a reaction rate which would compete with the spontaneous decomposition of the nitrosiminium ion (**1**). In order to circumvent this difficulty in testing the feasibility of the reaction and to find optimum conditions, we incorporated the carboxylate anion into the imine molecule and used sodium salts of aryl imines (**3**) of glycine[3] and β-alanine. This reaction would yield cyclic α-acyloxy-*N*-nitrosamines (**5**), hydrolysis of which would give open-chain α-hydroxy-*N*-nitrosamines. Decomposition could then give bifunctional alkylating agents whose fate would be expected to be of relevance to the mechanism of decomposition and hence the carcinogenicity of the structually similar α-hydroxy-*N*-nitrosamines from the hydrolysis of open-chain α-acyloxy-*N*-nitrosamines.

Treatment of the imines (**3**) with nitrosonium tetrafluoroborate ($NOBF_4$) (1 equiv.) at room temperature in acetonitrile yielded 3-nitroso-2-aryl-5-oxazolidones (**5**, $n = 1$) or 3-nitroso-2-aryl-6-oxotetrahydro-oxazines (**5**, $n = 2$) (see Table). The choice of a solvent such as acetonitrile, in



which nitrosonium tetrafluoroborate is soluble, is essential in order to obtain the yields stated; the use of chloroform in which neither reactant is appreciably soluble caused the yields to drop below 5%, as did the use of sodium salts which contained water. The products were isolated by adding ether to the reaction mixtures, and washing with water and then with aqueous hydrogensulphite to remove the small amounts of the accompanying aldehydes. Evaporation of the ether gave oily products which were recrystallised from suitable solvents (see Table). The cyclic α-acyloxy-*N*-nitrosamines have i.r. carbonyl absorptions at very high frequencies (see Table) resulting from the combined effect of an α-*N*-nitroso group[2] and incorporation of the carbonyl group in a five- or six-membered ring.

The reaction of the imines from (±) β-phenylalanine (**6**, R = H and OMe) has yielded cyclic α-acyloxy-*N*-nitrosamines (**7**, R = H, 49%, m.p. 78—90 °C; and R = OMe,

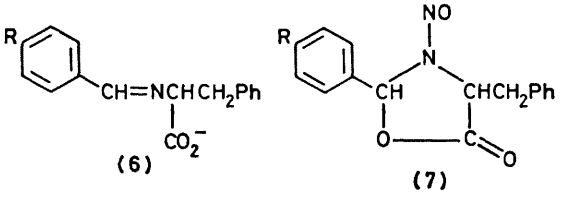


TABLE. Conversion of aryl imines (**3**) of glycine and β-alanine into 3-nitroso-2-aryl-5-oxazolidones (**5**, $n = 1$) and 3-nitroso-2-aryl-6-oxotetrahydro-oxazines (**5**, $n = 2$)[a]

Ar	*n*	Time/min	Solvent for crystallisation of (**5**)	M.p./°C	Yield/%	$\nu_{C=O}$ in $CHCl_3$/cm^{-1}
Ph	1	120	Et_2O–petrol	97—98	21	1820
Ph	2	30	EtOH	92—93	18	1770
p-$MeOC_6H_4$	1	120	MeOH	115—116	16	1814
p-$MeOC_6H_4$	2	120	MeOH	124—125	12	1768
p-$NO_2C_6H_4$	1	60	EtOH	116—117	14	1826
p-$NO_2C_6H_4$	2	60	EtOH	105—106	9	1769

[a] Elemental analysis and physical data confirmed the purity and structures of the compounds.

25%, m.p. 85—88 °C) as mixtures of diastereoisomers which contain two chiral carbon atoms. These compounds in optically active form could be valuable for the study of the mechanism of alkylations by the parent α-hydroxy-*N*-nitrosamines.

We believe that the mechanism of the reaction involves the addition of the nitrosonium ion to the imine anion (**3**) to give a zwitterion (**4**) (for which intermediates there is good evidence)[4] which reacts intramolecularly with the carboxylate anion to yield an α-acyloxy-*N*-nitrosamine (**5**). The small amounts of aldehydes produced probably arise from accompanying spontaneous decomposition of the zwitterion (**4**)[4] and the oily by-products which are stationary on t.l.c. may arise by intermolecular polymerisation of the zwitterion (**4**).

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[1] P. P. Roller, D. R. Shimp, and L. K. Keefer, *Tetrahedron Letters*, 1975, 2065; O. G. Fahmy, M. J. Fahmy, and M. Wiessler, *Biochem. Pharmacol.*, 1975, 1145, 2009; M. Okada, E. Suzuki, T. Anjo, and M. Mochizuki, *Gann*, 1975, **66**, 457.
[2] J. E. Baldwin, A. Scott, S. E. Branz, S. R. Tannenbaum, and L. Green, *J. Org. Chem.*, 1978, **43**, 2427.
[3] R. G. Hiskey and J. M. Jung, *J. Amer. Chem. Soc.*, 1963, **85**, 578.
[4] M. P. Doyle, W. Wierenga, and M. A. Zaleta, *J. Org. Chem.*, 1972, **37**, 1597; M. P. Doyle, M. A. Zaleta, J. E. DeBoer, and W. Wierenga, *ibid.*, 1973, **38**, 1663.