Rearrangement of Carboxylates derived from *N*-Acetyl-*N*-nitroso-α-amino-acids

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Summary While *N*-acetyl-*N*-nitrosophenylalanine thermally decomposes by the known mechanism, its carboxylate anion undergoes facile rearrangements initiated by carboxylate attack in methanol or water to give 2-methoxy- or 2-hydroxy-3-phenylpropanoic acid, respectively.

IN view of the fact that nitrosamines are carcinogens[1] that are widely distributed in environmental samples and are readily formed in biological systems,[2] it is surprising that nitrosamides derived from *N*-acyl-α-amino-acids or from simple polypeptides with general formula $R^2CON(NO)CH(R^1)CO_2H$ have not been prepared nor their chemistry studied. The nitrosamides (**1**)—(**3**) were obviously formed in the reaction of the respective *N*-acetyl-α-amino acids with nitrosyl tetrafluoroborate in the presence of pyridine, but readily decomposed during isolation because of their sensitivity to heat and, more importantly, to the presence of bases. The pure nitrosamides (**1**)—(**3**) could be obtained† if the extracts from the reactions were carefully washed with very dilute acid and evaporated at about 10 °C. As preliminary experiments demonstrated that the nitrosamides derived from *N*-acetyl-α-amino-acids and dipeptides are mutagenic† and are formed in the presence of nitrite ion in aqueous solutions of pH 2—3, we report the facile rearrangements that cause instability of these compounds.

$MeCON(NO)CHRCO_2H$	$PhCH_2CHR^1CO_2R^2$
(**1**) R = CH_2Ph	(**4**) R^1 = OMe, R^2 = H
(**2**) R = Bu^t	(**5**) R^1 = OH, R^2 = H
(**3**) R = CH_2OCOMe	(**6**) R^1 = OMe, R^2 = Me

N-Acetyl-*N*-nitroso-DL-phenylalanine (**1**) exhibits a series of u.v. absorptions in the 380—440 nm region typical of nitrosamides and is practically stable in methanol or water in the dark at room temperature. However, the corresponding carboxylate (**7**) of (**1**), prepared by the addition of 1 mol. equiv. of potassium hydroxide or methoxide, decomposes rapidly with strict first-order kinetics as examined by decreases of the adsorption peak at 405 nm. Heat-induced decomposition of (**1**) itself also cleanly follows first-order kinetics, but with slower rates. Their rate constants (Table) indicate that the reaction pathways for both cases are different and the decomposition of the carboxylate (**7**) is considerably accelerated.

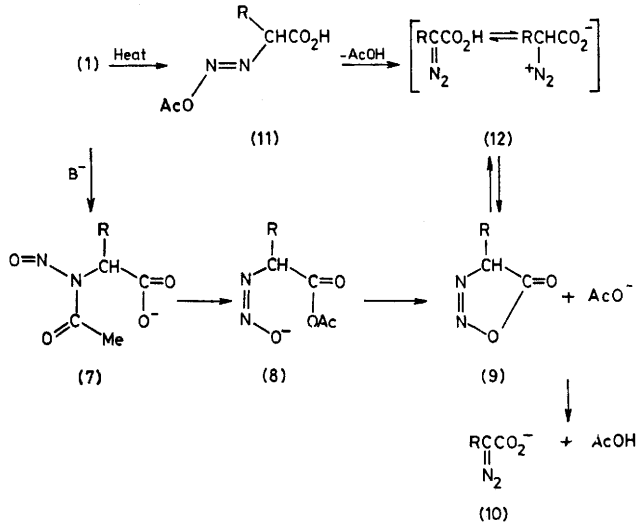

TABLE. First-order rate constants (k/s^{-1}) in methanol.

T/°C	(**1**)	(**7**)
22	$<0{\cdot}01 \times 10^{-4}$	$0{\cdot}97 \times 10^{-4}$
40	$0{\cdot}17 \times 10^{-4}$	$8{\cdot}22 \times 10^{-4}$
80	$2{\cdot}30 \times 10^{-4}$	
	$(1{\cdot}50 \times 10^{-4})$[a]	

[a] Rate constant in MeOD.

The carboxylate (**7**) in methanol was cleanly decomposed to give >90% of 2-methoxy-3-phenylpropanoic acid (**4**), and in water *ca.* 95% of the corresponding 2-hydroxycarboxylic acid (**5**). In analogy with the base-initiated decomposition of nitrosamides,[3,4] the carboxylate (**7**) in methanol was decomposed in several minutes with an excess of potassium hydroxide to the diazo-carboxylate (**10**) showing λ_{max} 330 and 410 nm.[5] The solution was neutralized to afford >96% yields of the methoxy-acid (**4**) and the hydroxy-acid (**5**) in a 4 : 1 ratio. Both nitrosamides (**2**) and (**3**) also showed a similar reaction pattern to give the corresponding methoxy- and hydroxy-carboxylic acids. Thermolysis of (**1**) in methanol gave, rather unexpectedly, methyl 2-methoxy-3-phenylpropanoate (**6**) (20%) in addition to (**4**) (58%) and the parent amide (*ca.* 10%).

From well established nitrosamide chemistry it is certain that both (**4**) and (**5**) are formed from the diazo-carboxylate (**10**) in the decomposition of the carboxylate (**7**)[3] and from the diazo-carboxylic acid (**12**) (and/or the corresponding zwitterion)[4] in the decomposition of (**1**). In both cases, acetic acid generated in the process provides acid catalysis for the reaction yielding (**4**) and (**5**). In view of the kinetic acceleration and the failure to detect methyl acetate in the reaction using sodium methoxide in methanol, it is likely that the carboxylate (**7**) decomposes by a series of rearrangements (**7**) → (**8**) → (**9**) → (**10**). Methyl acetate is shown to be stable under the reaction conditions. The reaction (**7**) → (**8**) is analogous to the intermolecular attack of an acetate ion at a nitrosamide linkage[6] which generally leads to a *syn*-diazoate[7] such as (**8**). The reaction (**8**) → (**9**) is reminiscent of the intramolecular participation of nitrosamino-groups in the sydnone synthesis[8] and in certain nucleophilic reactions.[9] The oxadiazolinone (**9**) may be readily converted into (**10**) by acetate anion. Thermolysis of (**1**) should give the diazo-acid (**12**) *via* the *anti*-diazoate derivative (**11**).[4,7] While there is no viable mechanism for the formation of the methyl ester (**6**) from diazo-compounds such as (**12**), the absence of acetate anion in the reaction mixture is the most likely reason for the formation of (**6**). Among other possibilities, the most straightforward suggestion is that (**6**) is formed from the oxadiazolinone (**9**) by repeated methanolysis and also in the absence of acetate anion, the diazo-acid (**12**) and the oxadiazolinone (**9**) may be interconvertible. The methyl ester (**6**) obtained from thermolysis of (**1**) in MeOD contains only 40% deuterium label at the α-position. This observation is in agreement with the suggested interconvertibility.

The facile rearrangement of the carboxylate (**7**) to generate the diazo-acid (**10**) has serious implications in terms of nitroso-compound hazards. Firstly, nitrosamides similar to (**1**)—(**3**) may be formed in foods and environ-

† The nitrosamides (**1**)—(**3**) were characterized by i.r., u.v., ^1H n.m.r., ^{13}C n.m.r., and mass spectroscopy and gave satisfactory analysis. The mutagenesis tests were carried out by the Environmental Carcinogenesis Unit, Cancer Research Centre, Vancouver, British Columbia, Canada.

mental samples, but easily escape detection because of instability. Secondly, such nitrosamides, which may form in animal digestive tracts, rearrange readily to form alkylating agents under ambient conditions. It should be pointed out that alkylation is currently believed to be a cause of carcinogenic activity.[10]

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