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N-NITROSAMINES FROM THE DECARBOXYLATION OF α-NITROSAMINO ACIDS[†]

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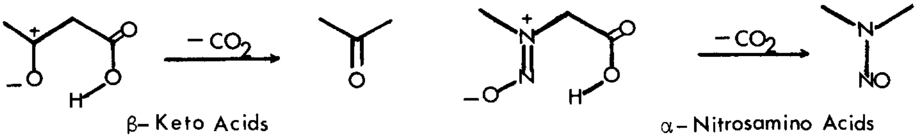
Summary. The thermal decarboxylation of sodium salts of N-nitroso α-amino acids in triglyme at reflux affords the corresponding N-nitrosamines in fair to excellent yields. N-Nitroso-N-benzyl α-phenylglycine undergoes decarboxylation to N-nitrosodibenzylamine (70%) in o-dichlorobenzene at reflux.

Over the past twenty odd years, N-nitrosamines have been the subject of intensive investigations as a result of the report that they possess carcinogenic and mutagenic properties.[1] The renewed interest in this hitherto rather prosaic class of compounds has made it apparent that much of the organic chemistry of N-nitrosamines remains to be established.[2]

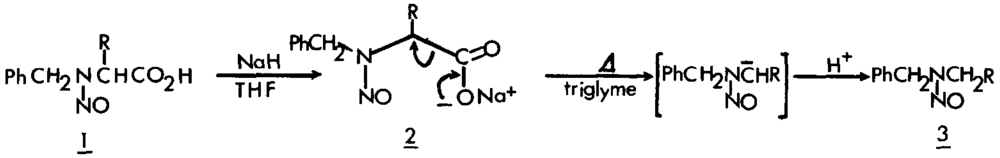
The identification and recognition of potential sources of N-nitrosamines in the environment and in the body have been major areas of concern. The important discovery that the N-nitrosamino group renders the α-hydrogen labile to bases,[3] suggests that α-nitrosamino acids (α-carboxy N-nitrosamines) could be regarded as analogues of β-keto acids. One important and useful reaction of β-keto acids is their decarboxylation to afford the corresponding ketones. Since α-amino acids are widely distributed in nature, a similar decarboxylation of α-nitrosamino acids would be of critical importance as this would lead to the parent nitrosamines (Scheme



Scheme 1

1). Indeed there have been several disclosures[4] suggesting that N-nitrosopyrrolidine arises from the decarboxylation of N-nitrosoproline during the cooking of bacon. However, to our knowledge there are only two brief descriptions of the actual conversion of α-nitrosamino acids to the corresponding N-nitrosamines. In 1899, Fischer reported[5a] very briefly and with no experimental details, the alkaline decarboxylation of N-nitroso-N-phenylglycine to N-nitroso-N-methylaniline. About seventy years later, traces of N-nitrosopyrrolidine and related N-nitrosamines were detected from heating alkaline solutions of the corresponding nitrosamino acids.[5b] This communication reports that the decarboxylation of anions of α-nitrosamino acids affords the corresponding N-nitrosamines in synthetically useful yields, thus establishing the fact that α-amino acids *via* their N-nitroso derivatives are possible sources of N-nitrosamines.

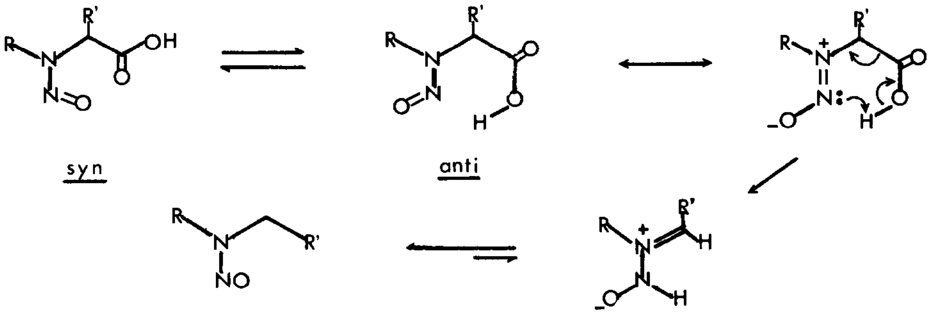
When the dry sodium salts of N-benzyl α-phenylglycine (2a), N-benzylalanine (2b) and N-benzylglycine (2c), obtained by treatment of corresponding acids with sodium hydride, were heated in triglyme, smooth evolution of carbon dioxide was observed. The corresponding N-nitrosamines (3a-c) were obtained in 41-83% yields. In the case of 2a, after the reaction mixture was quenched with dilute acid and extracted with ether, simple evaporation of the solvent gave 3a as a solid in 83% yield.[6] Chromatography of the residues left after careful evaporation of the ethereal extracts from similar work up of the reactions of 2b and 2c, afforded N-nitrosoethylbenzylamine (3b) and N-nitrosomethylbenzylamine (3c) in 41%



a) R = Ph b) R = CH_3 c) R = H

and 61% yields respectively. The N-nitrosamines were characterized by their spectral data and comparison with authentic samples or conversion to the amines by denitrosation. Although the mixtures were acidified at the end of the reaction, it is possible that trace amounts of water in the solvent (even after drying) effectively quenched the reaction *in situ*.

The analogy between α-nitrosamino acids and β-keto acids is further strengthened by the finding that α-nitrosamino acids themselves are unstable to heat. When N-nitroso-N-benzyl α-phenylglycine (**1a**) was heated to reflux in *o*-dichlorobenzene, smooth evolution of carbon dioxide was observed; N-nitrosodibenzylamine (**3a**) was isolated in 70% yield. This decarboxylation could be viewed as occurring *via* a cyclic concerted mechanism similar to that suggested for the decarboxylation of β-keto acids; in the case of α-nitrosaminoacids, the nitrogen atom of the nitroso group could be removing the acidic proton of the carboxylic acid with concurrent loss of carbon dioxide (Scheme 2). The suggested mechanism is only possible with the *anti*-conformation. Lijinsky, Keefer and Loo[5b] determined on



Scheme 2

the basis of nmr data that the N-nitroso derivatives of sarcosine, proline and pipecolic acid (but *not* that of azetidine-2-carboxylic acid) exist as the *syn*-conformers in the crystalline state; however, they also found that after a few minutes in solution at room temperature, some of the *anti*-conformers begin to form. Thus it is not unlikely that under the conditions of our reaction, the anti-conformers would exist.[7]

These findings are particularly important in light of the fact that α-nitrosamino acids, e.g. N-nitrosoproline, are generally not known to cause tumors while N-nitrosopyrrolidine for example is regarded as a potent carcinogen. We are actively pursuing the investigation of various parameters of these reactions.

REFERENCES

† This is the fifth of a series of publications dealing with N-nitrosamines; for preceding paper, see M. Nakajima and J.-P. Anselme, Tetrahedron Lett., 0000 (1979).

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2. A. L. Fridman, F. M. Mukametshin and S. S. Novikov. Russ. Chem. Rev., 40, 34 (1971); J.-P. Anselme in "N-Nitrosamines," J.-P. Anselme, Ed., ACS Symposium Series No. 101, American Chemical Society, Washington, D.C., 1979, p. 1.
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   b) W. Lijinsky, L. K. Keefer and J. Loo, Tetrahedron, 26, 5137 (1970).
6. Benzaldehyde and benzonitrile were detected in all the decompositions. *trans*-Stilbene was also identified (by tlc) as a minor product of the decarboxylation of 2a [See D. Seebach *et al.*, Helv. Chim. Acta, 61, 1622 (1978)].
7. Alternatively, the *syn*-conformation would be required if the nitroso-oxygen was abstracting the acidic hydrogen *via* a seven-membered ring transition state.

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