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CARCINOGENIC NITROSAMINES. SYNTHESIS AND HYDROLYSIS OF α-UREIDONITROSAMINES

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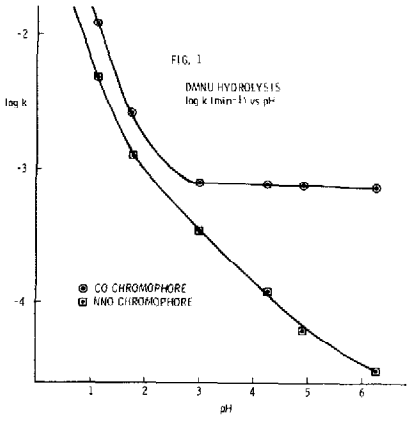
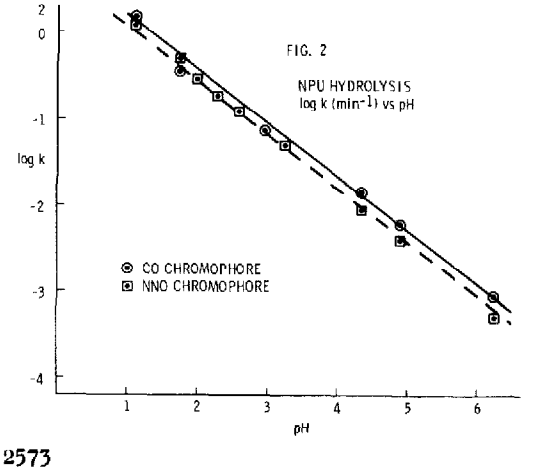
Since the pioneering work of Magee and Barnes,[1] dialkylnitrosamines have been recognized as potent carcinogens that may have considerable environmental significance. As is the case with many carcinogens, nitrosamines require metabolic activation to become truly carcinogenic. This activation is usually thought to be hydroxylation by a mixed function oxygenase. In the case of methyl alkylnitrosamines, the resulting α-hydroxymethyl alkylnitrosamine suffers a rapid decomposition to formaldehyde and an alkyl diazotate, the latter acting as a strong alkylating agent for a plethora of nucleophilic sites in the cell. The steps are summarized in Scheme I.

Thus, the key intermediate, the proximate carcinogen, in the metabolism of nitrosamines is thought to be the α-hydroxylated species. Up to now -hydroxynitrosamines have eluded isolation because of their rapid decomposition. Recently, the preparation of -acyloxy-nitrosamines has been resported.[2] These materials are extremely potent carcinogens and mutagens. Hydrolysis of the acyloxy group, however, leads to decomposition; the -hydroxy compound, if formed, does not have an appreciable lifetime. In this communication we wish to report the preparation of derivatives of the closely related -aminonitrosamines and some of their hydrolytic behavior.

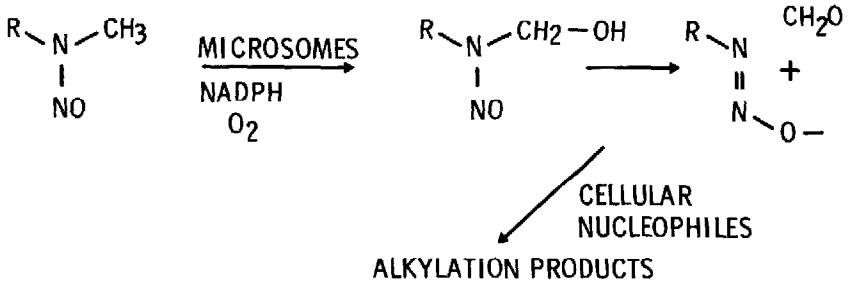
The preparation of α-ureidodimethylnitrosamine (1, DMNU) and α-ureidonitrosopyrrolidine (2, NPU) were carried out according to Scheme II.[3]

DMNU (mp 110°, dec.) and NPU (mp 143°, dec.) were prepared in 50% overall yields from N-nitrososarcosine and N-nitrosoproline, respectively. It was of interest to examine the hydrolysis of the ureas for two reasons: 1) It is possible, structurally, for the nucleophilic[4] nitroso oxygen to participate in the hydrolysis and 2) the product of the hydrolysis could be the amine analog to the elusive α-hydroxynitrosamine. Both of those suppositions are borne out by experiment. Figures 1 and 2 shows some of the kinetic data for DMNU and NPU as a function of pH. Kinetic data were also obtained as a function of total acid and show only a weak dependence on total acid.[5]

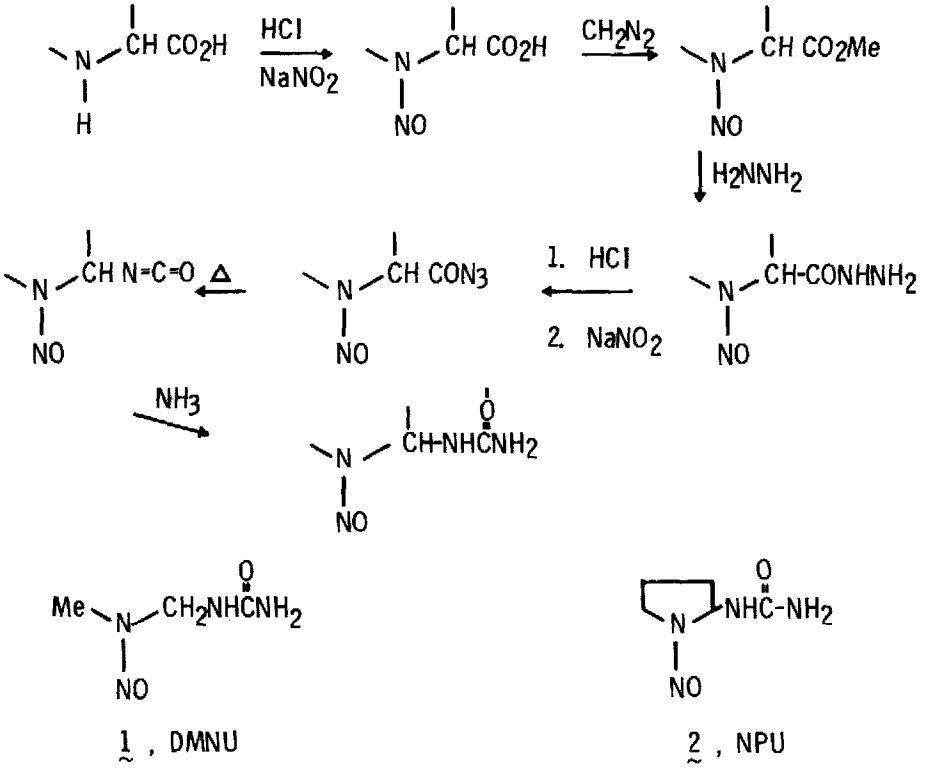




SCHEME I



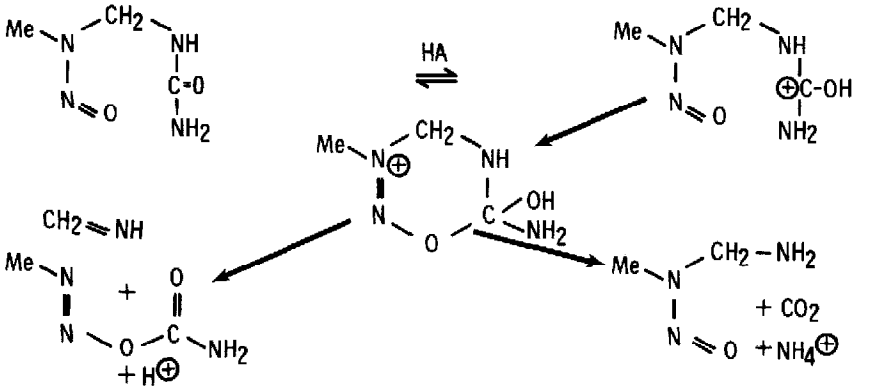
SCHEME II



1 , DMNU

2 , NPU

The rates were measured spectrophotometrically by following the disappearance of both the N-nitroso chromophore (235 nm, 1cm cell) and the carbonyl chromophore (345 nm, 10cm cell) in a buffered[6] aqueous solution at 25±.2°. The rates were first order and the rate constants were tabulated in min^{-1}. The hydrolysis of NPU (fig.2) is dependent on pH over the whole range studied (pH 1 - 6). Moreover, the rate of carbonyl loss closely parallels the loss of the nitroso function. This means that under the conditions of the hydrolysis, α-amino-N-nitrosopyrrolidine, if formed at all, has only a transitory existence. This is to be contrasted with the hydrolysis of DMNU (fig.1). Here, the carbonyl loss parallels the nitroso function loss only from pH 1 to pH 2.5 whereupon the loss of carbonyl becomes pH independent[7] while the loss of the nitroso function changes phase slightly but continues to decrease with increasing pH. This can only mean that above pH 2.5 the urea is hydrolyzed faster than the N-nitroso function loses integrity. This suggests that α-aminodimethylnitrosamine has a finite existence and can, perhaps, be isolated. Compared to urea itself (whose hydrolysis is pH independent[7]) the rates of both the N-nitrosamino ureas are many orders of magnitude more rapid. This suggests strongly that the N-nitroso oxygen participates in the hydrolysis with, perhaps, the formation of a tetrahedral intermediate, as indicated in the following scheme. This scheme also suggests the possibility that the intermediate may open to a diazotate derivative without the intervention of an α-aminonitrosamine.



WARNING!!! All nitrosamines should be handled with great caution, but particularly those which are oxidized in the α-position. Preliminary evidence shows that DMNU causes severe liver necrosis in mice at extraordinarily low dose levels. These materials should be considered contact carcinogens and only well trained personnel should be allowed to handle them.

Acknowledgement: The authors express their gratitude to the Research Corporation, a Foundation and the National Science Foundation for financial support.

REFERENCES

1. cf. P.N. Magee and J.M. Barnes, Advan. Cancer Res., 10, 164 (1967)

2. P.P. Roller, D.R. Shimp and L.K. Keefer, Tetrahedron Lett. 2065 (1975); M. Wiessler, Ang. Chem. Int. Ed., 742 (1974); M. Wiessler, Tetrahedron Lett. 2575, (1975); K. Eiter, K.F. Hebenbrock, and H.J. Kabbe Leibigs Ann. Chem., 765, 55 (1972); J.E. Baldwin, S.E. Branz, R.F. Gomez, P.L Kraft, A.J. Sinskey, and S.R. Tannenbaum, Tetrahedron Lett., 333, (1976).

3. The details of the preparation will be published in a full paper. The products were characterized spectroscopically and by analysis of mass spectra. Elemental analyses were consistent with the empirical formulas.

6. G.A. Olah, D.J. Donovan, and L.K. Keefer, J. Natl. Cancer Inst., 54, 465 (1975).

5. Total acid was varied from .3M to 1M. The largest observed change in rate constants was a little over two-fold in that range.

6. The phosphate buffer system was used for all runs above pH 3.0, and the bisulfate buffer was used at lower pH's. All the solutions had unit ionic strength.

7. In this pH range the behavior with respect to pH is similar to urea itself. cf. W.H.R. Shaw and J.J. Bordeaux, J. Amer. Chem. Soc., 77, 4729 (1955).