Tetrahedron Letters No. 8, pp 593 - 596, 1976. Pergamon Press. Printed in Great Britain.

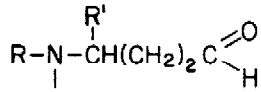
# SYNTHESIS OF N-NITROSAMINO ALDEHYDES[1,2]

Stephen S. Hecht,* Chi-hong B. Chen, and Dietrich Hoffmann

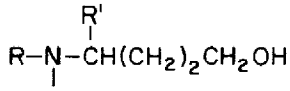
Naylor Dana Institute for Disease Prevention
American Health Foundation
Valhalla, New York 10595 U.S.A.

**(Received in USA 29 September 1975; received in UK for publication 7 January 1976)**

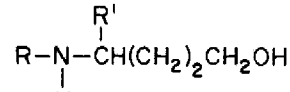
N-Nitrosamino aldehydes are a class of compounds which, according to recent studies, may be metabolic intermediates in the activation of certain carcinogenic nitrosamines or may occur as environmental carcinogens. However, to our knowledge, no representative of this structural class has yet been reported. In particular, it has been proposed that 4-(N-butyl-N-nitrosamino)-butanal (1a) may be a critical intermediate in the induction of bladder tumors in rats by N-nitrosodi-n-butylamine and 4-(N-butyl-N-nitrosamino)-butan-1-ol (2a,3). The latter compound and the corresponding carboxylic acid, 4-(N-butyl-N-nitrosamino)-n-butanoic acid, which are both bladder carcinogens in the rat, have been isolated from the urine of rats dosed with N-nitrosodi-n-butylamine (4-6). Similarly, 1b is a probable metabolite of N-nitrosobutylmethylamine, which causes esophageal tumors in rats when



1



2

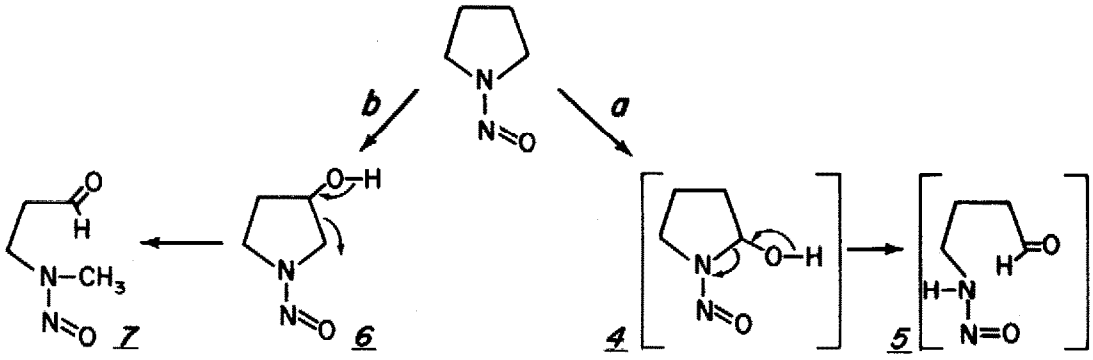


3

**a**; $R = CH_3(CH_2)_3-$, $R' = H$ **c**; $R = PhCH_2-$, $R' = H$

**b**; $R = CH_3-$, $R' = H$ **d**; $R = CH_3-$, $R' = 3\text{-Pyr}$

administered by inhalation (7). Both 2b and the corresponding acid are metabolic products of N-nitrosobutylmethylamine and the former is a bladder carcinogen in the rat (8,9). Primary (and presumably unstable) N-nitrosamino aldehydes may play a role in the metabolic activation of cyclic nitrosamines, such as N-nitrosopyrrolidine (scheme 1), if this proceeds by an initial enzymatic α-hydroxylation(path a) to give 4 followed by C-N bond cleavage to 5 (10, 11). Alternatively, β-hydroxylation (path b) followed by reverse aldol condensation (6→7) would also give rise to an N-nitrosamino aldehyde (12,13). Recent experiments on the decomposition of N-nitrosamines in strongly acidic media indicate

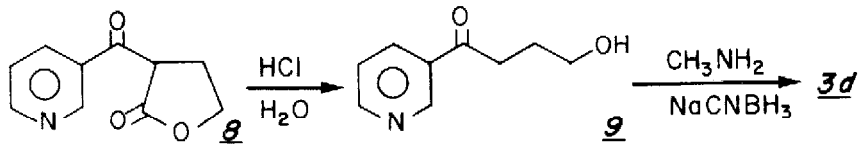



Scheme 1. Possible metabolic pathways for N-nitrosopyrrolidine activation.

that 4-(N-benzyl-N-nitrosamino)-butanal (1c) would react to give a benzyl carbonium ion and 5 *via* cleavage of the benzyl-N bond under these conditions and thus allow a study of the modes of decomposition of 5 (14). N-Nitrosamino aldehydes (and ketones) have also been suggested as constituents of tobacco and tobacco smoke (15,16). The carcinogenic tobacco component, N'-nitrosonornicotine, is believed to be derived from nicotine by $CH_3$-N' cleavage and nitrosation (17,18). If this is so, one also expects to find 4-(N-methyl-N-nitrosamino)-4-(3-pyridyl)-butanal (1d) and 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone in tobacco, by ring C-N' cleavage and nitrosation.

Since the parent amino aldehydes are unstable (19,20), the syntheses of 1a-d were begun with the corresponding amino alcohols 3a-d, which for 3a-c were obtained in 40-50% yield by reaction of 4-chlorobutan-1-ol (Chem. Samples Co., Columbus, Ohio) with the appropriate amine in refluxing methanol for 48 hrs. The preparation of 4-N-methylamino-4-(3-pyridyl)-butan-1-ol (3d) is summarized in Scheme 2. Sodium methoxide catalyzed condensation of ethyl nicotinate with butyrolactone gave dihydro-3-(3-pyridoyl)-2-(3H)-furanone (8) which was hydrolyzed and decarboxylated with aqueous HCl (3 hrs, 20°) to give 4-hydroxy-1-(3-pyridyl)-1-butanone (9). The latter was allowed to react with sodium cyanoborohydride and methylamine (21) to yield 3d.

Nitrosation of 3a-d at pH 5-6 with $NaNO_2$ in aqueous HCl gave the nitrosamino alcohols 2a-d. At this pH, nitrite ester formation was not observed (22). The nitrosamino alcohols 2a-d were oxidized to 1a-d with dimethylsulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) (23). In a typical procedure for the oxidation, 2a (10 mmol) was dissolved in 50 ml dry benzene and 50 ml dry DMSO. To this were added 1.2 ml dry pyridine, 0.6 ml freshly distilled $CF_3COOH$, and 9.0 g DCC. The mixture was stirred at room temperature for 24 hrs. and quenched with $H_2O$. The aqueous phase was extracted three times with benzene, and the combined benzene extracts were washed with $H_2O$, dried ($Na_2SO_4$), and concentrated. Column chromatography of the residue on silica gel with elution by $CH_2Cl_2$ and $CH_2Cl_2/Et_2O$: 90/10,




Scheme 2: Synthesis of 4-N-methylamino-4-(3-pyridyl)-butan-1-ol.

gave the nitrosamino aldehyde 1a (6 mmol, 60%). Distillation gave analytically pure 1a (3 mmol), bp 97-100°/0.15 mm. For the highly water soluble 1b and 1d, the original benzene solution was extracted 3 times with $H_2O$, and the $H_2O$ extracts were saturated with NaCl and re-extracted 6 times with equal volumes of $CH_2Cl_2$. The resulting concentrate was then purified by column chromatography, as above. The spectral properties of 1a-d are summarized in Table 1. In each case 1a-d were mixtures of Z-and E- isomers. The ratio E/Z was approximately 1.0 for 1a,c, but was 2.8 for 1b and 4.2 for 1d, as determined by nmr (24). All new compounds gave correct elemental analyses.

Table 1. Spectral properties of nitrosamino aldehydes 1a-d.

NMR ($CDCl_3$): δ values for R $CH_2N(NO)\overset{R'}{C}HCH_2CH_2$–CHO
a b c

| | Ha | | Hb | | Hc | others |
|---|---|---|---|---|---|---|
| | Z | E | Z | E | | |
| 1a | 4.28, t | 3.61, t | 3.61, t | 4.28, t | 9.55, m | 2.80-0.99, 11H, m |
| 1b | 3.70, s | 3.05, s | 3.54, t | 4.10, t | 9.70, s | 2.71-1.40, 4H, m |
| 1c | 5.22, s | 4.72, s | 3.42, t | 4.02, t | 9.56, m | 7.27, 5H, m<br>2.60-1.35, 4H, m |
| 1d | 3.48, s | 2.78, s | 6.20, t | 5.59, t | 9.70, s | 9.20-6.80, 4H, m<br>2.65-2.40, 4H, m |

IR (film): 1a-d: 2730, 1720 (-CHO), 1430 (N-N=O) $cm^{-1}$

UV (EtOH) $\lambda_{max}$ (ε): 1a: 234(7549), 350(92) 1b: 235(7800), 347(76)
1c: 237(7584), 355(75) 1d: 230(6486), 258(sh)(3726), 351(69)

MS, $m^+$ (rel. int.): 1a: 172(1), 155(23), 142(53), 127(16), 99(51), 98(56), 84(83), 71(100), 70(78), 57(50)
1b: 130(3), 100(88), 99(49), 85(48), 73(100)
1c: 206(.1), 176(11), 91(100), 65(15)
1d: 207(3), 177(3), 148(100), 120(30), 119(30), 92(49)

Alternate methods of oxidation of nitrosamino alcohol 2b including use of activated $MnO_2$, $CrO_3$/pyridine, and Jones reagent, and reaction of the chlorocarbonates or tosylates from 2b with DMSO and base gave low and irreproducible yields of the desired aldehyde. Nitrosamino aldehyde 1b could also be prepared by reaction of $NaNO_2$ with N-methyl-Δ-1-pyrrolinium chloride, but only in 5-10% yield. The major product was N-methyl-2-pyrrolidone. However, the formation of 1b in this reaction may be of biological importance

(13). This transformation is analogous to the formaldehyde catalyzed nitrosation of pyrrolidine (25).

The nitrosamino aldehydes (1a-d) are relatively stable compounds which did not develop detectable (by glc or tlc) impurities when stored in $CH_2Cl_2$, under $N_2$, and at 0° for 2 months or more. Storage of these compounds in the open air without solvent did lead to slow (<10% after 30 days) appearance of secondary products, presumably due to oxidation. The chemistry and carcinogenicity of 1a-d is currently under investigation.

## REFERENCES AND FOOTNOTES


1. Paper number 2 in a series entitled "A Study of Chemical Carcinogenesis".
2. This work was supported by N.C.I. Grant CA-12376-05.
3. R. Schoental, *Brit. J. Cancer* 28, 436-439 (1973).
4. M. Okada and E. Suzuki, *Gann* 63, 391-392 (1972).
5. Y. Hashimoto, E. Suzuki, and M. Okada, *Gann* 63, 637-638 (1972).
6. L. Blattmann and R. Preussmann, *Z. Krebsforsch.* 79, 3-5 (1973).
7. H. Druckrey, Ch. Landschütz, and R. Preussmann, *Z. Krebsforsch.* 71, 135-139 (1968).
8. L. Blattmann, N. Joswig, and R. Preussmann, *Z. Krebsforsch.* 81, 71-73 (1974).
9. N. Ito, personal communication.
10. H. Druckrey in W. Nakahara, S. Takayama, T. Sugimura, and S. Odashima, eds., "Topics in Chemical Carcinogenesis", University of Tokyo Press, Tokyo, 1972, pp. 73-103.
11. P.N. Magee and J.M. Barnes, *Adv. Cancer Res.* 10, 163-246 (1967).
12. F.W. Krüger in W. Nakahara, S. Takayama, T. Sugimura, and S. Odashima, eds., "Topics in Chemical Carcinogenesis", University of Tokyo Press, Tokyo, 1972, pp. 213-235.
13. F.W. Krüger and B. Bertram, *Z. Krebsforsch.* 83, 255-260 (1975).
14. G.A. Olah, D.J. Donovan, and L.K. Keefer, *J. Natl. Cancer Inst.* 465-472 (1974).
15. S.S. Hecht, I. Schmeltz, D. Hoffmann, and E.L. Wynder, *Proc. 3rd World Conference on Smoking and Health,* New York (1975) in press.
16. H. Klus and H. Kuhn, *Abstr. 7th Coresta Conf.,* Montreux, Switzerland (1974).
17. S.S. Hecht, R.M. Ornaf, and D. Hoffmann, *J. Natl. Cancer Inst.* 1237-1244 (1974).
18. D. Hoffmann, R. Raineri, S.S. Hecht, R. Maronpot, and E.L. Wynder, *J. Natl. Cancer Inst.* 55, 977-981 (1975).
19. E.B. Sanders, J.F. DeBardeleben, and T.S. Osdene, *J. Org. Chem.* 40, 2848-2849 (1975).
20. F. Galinovsky, A. Wagner, and R. Weiser, *Monatsch.* 82, 551-559 (1951).
21. R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Amer. Chem. Soc.* 93, 2897-2904 (1971).
22. H. Druckrey, R. Preussmann, S. Ivankovic, C.H. Schmidt, H.D. Mennel, and K.W. Stahl, *Z. Krebsforsch.* 66, 280-290 (1964).
23. J.G. Moffatt, *Org. Syn., Coll. Vol. V,* 242-244 (1973).
24. G.J. Karabatsos and R.A. Taller, *J. Amer. Chem. Soc.* 86, 4373-4378 (1964).
25. L.K. Keefer and P.P. Roller, *Science* 181, 1245-1247 (1973).