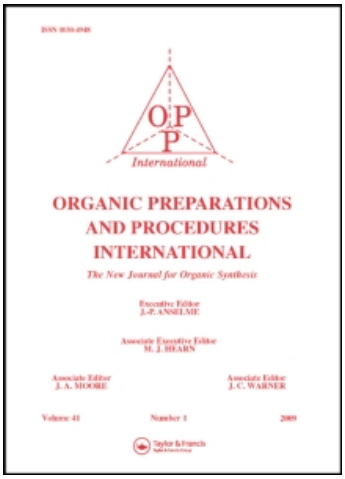

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SYNTHESIS OF THE SELECTIVE BLADDER CARCINOGEN, N-(*n*-BUTYL)-N-(3-CARBOXYPROPYL)NITROSAMINE (BCPN)

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SYNTHESIS OF THE SELECTIVE BLADDER CARCINOGEN, N-(n-BUTYL)-N-(3-CARBOXYPROPYL)NITROSAMINE (BCPN)

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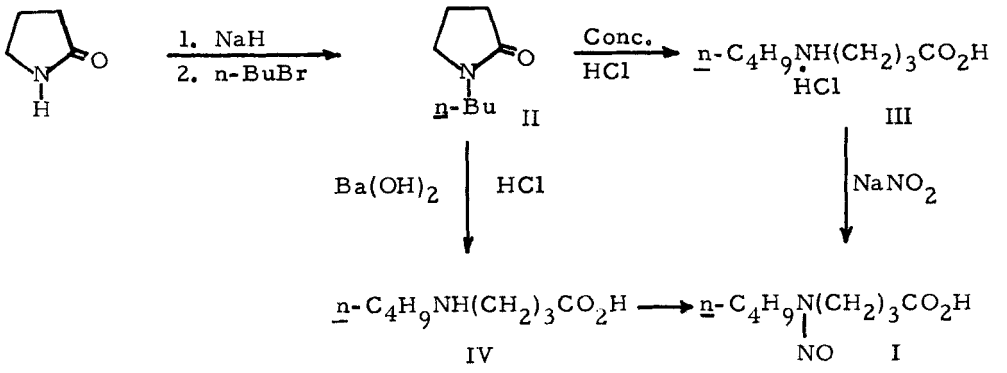
N-(n-Butyl)-N-(3-carboxypropyl)nitrosamine (BCPN) (I) appears to be a key compound in the production of bladder cancer in experimental animals.[1]



The widespread interest in bladder carcinogens,[2] together with our interest in synthesizing agents potentially useful for the isolation of nitrosamine metabolizing enzymes prompts us to report a short and efficient synthesis of BCPN.

The reaction of 2-pyrrolidone with sodium hydride in toluene afforded a salt which was alkylated with n-butyl bromide to give N-butyl-2-pyrrolidone(II). Hydrolysis of II with conc. hydrochloric acid gave 4-n-butylaminobutyric acid hydrochloride (III) which upon reaction with sodium nitrite afforded I. Alternatively, lactam II could be hydrolyzed with barium hydroxide to 4-n-butylaminobutyric acid (IV)[3] which upon reaction with sodium nitrite and hydrochloric acid yielded I. Due to some difficulty in obtaining IV in pure form, the former procedure was preferred.

Our synthetic method would appear to have two advantages over an alternative procedure[4] based on $KMnO_4$ oxidation of N-(n-butyl)-N-(4-hydroxybutyl)nitrosamine (BBN). The first is starting material accessibility; BBN is not commercially available in the U.S. and must itself be produced via a multistep synthesis,[5] while 2-pyrrolidone and n-butyl bromide are quite inexpensive. Perhaps more importantly, the carcinogenic nitrosamino group is introduced only in the last step of our preparation, whereas it is present in much of the alternative sequence[4] (including a step[5] involving cleavage of a nitrite ester function by refluxing in 30% NaOH), making the problem of hazard containment much simpler in the present procedure. An additional advantage of our approach is its potential for the synthesis of the homologous bladder-specific nitrosamino acid carcinogens (e.g. N-ethyl-N-(3-carboxypropyl)nitrosamine),[6] presumably accessible simply by changing the identity of the alkylating agent in the first step.

Finally, two improvements in the preparation of intermediates II and IV have been made. In the former case, Na metal[3] was replaced by NaH as condensing agent, since it does not react with the alkyl halide. Amino acid IV was purified by recrystallization of its HCl salt III from acetone, thus avoiding the undesired esterification which in our hands invaribly accompanied the recrystallization of IV from methanol-ether;[3] salt III could of course be used as such in the nitrosation step.

EXPERIMENTAL

WARNING! MOST N-NITROSAMINES ARE POTENT CARCINOGENS!

NMR spectra were obtained in pyridine-d_5 using a Varian HA-100 spectrometer with TMS as the internal standard. Gas chromatographic analyses were performed on a Hewlett-Packard 5700 instrument employing a SP-2401 column (10% on 100/120 Supelco) programmed from 110° to 200° at 8°/min with He flow rate of 30 ml/min. Mass spectra were obtained using a JEOL JMS-01SG-2 mass spectrometer at 70 eV ionizing voltage. Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus.

1-(n-Butyl)-2-pyrrolidone(II).—2-Pyrrolidone (11.5 g, 135 mmoles) was added dropwise with stirring to a 57% oil dispersion of sodium hydride (5.7 g, 135 mmoles) in toluene (45 ml). n-Butyl bromide (25.3 g, 185 mmoles) was then added with stirring. The reaction mixture was vigorously stirred and heated to reflux for 24 hrs and stirred an additional 12 hrs at room temperature. After filtration of the insoluble solid and removal of the solvent by distillation in vacuo, the crude product (19.1 g, 99%) was obtained. Distillation afforded 15.7 g (82%) of II, bp 135-137°/28mm, lit.[3] bp 127-131°/17-21mm, lit.[7] bp 121°/16mm; mass spectrum: m/e (rel. intensity) 141 (M^+,16), 99 (25), 98 (M^+-C_3H_7,100), 70 (45), 69 (17), 44 (30), 43 (13), 41 (24); glc retention times: 6.6 min for II, 4.8 min for 2-pyrrolidone.

4-(n-Butyl)aminobutyric acid hydrochloride(III).—1-(n-Butyl)-2-pyrrolidone (II) (8.5 g, 60 mmoles) was heated to reflux for 18 hrs in conc. HCl (7.5 ml). Removal of the water in vacuo followed by refrigeration of the resultant oil gave a crystalline product. Several recrystallizations from acetone and drying at 56° over P_2O_5 gave analytically pure III (6.0 g, 51%), mp. 93.0-95.5°.

Anal. Calcd for $C_8H_{18}O_2NCl$: C, 49.10; H, 9.27: N, 7.15. Found: C 48.92; H, 9.22; N, 7.23.

N-Nitroso-4-(n-butyl)aminobutyric acid (BCPN) (I).—4-(n-Butyl)aminobutyric acid hydrochloride (III) (5.3 g, 27 mmoles) was dissolved in water (27 ml)

and the solution was cooled in an ice-salt bath to 0-5°. A solution of sodium nitrite (4.5 g, 65 mmoles) in a few ml of water was added and the resulting solution was stirred overnight at room temperature. The yellow oil which separated from solution was extracted with methylene chloride and dried (Na_2SO_4). Removal of the solvent gave an oil which became a semi-solid mass upon standing overnight. Recrystallization from ether-pentane gave 2.9 g (57%) of I as glistening plates, mp. 39-40°, lit.[4] mp. 36°; NMR: δ 4.16 (m, 2, E-CH_2-N(NO)-),[8] 3.71 (m, 2, Z-CH_2-N(NO)-)[8], 2.57 (m, 2,-CH_2-CO_2H), 2.10 (m, 2, CH_2-CH_2-CO_2H), 1.82-0.96 (m, 4, CH_3-CH_2-CH_2-), 0.81 (m, 3, CH_3-); mass spectrum: m/e (rel intensity) 188 (M^+, 21), 171 (M^+-17, 8), 158 (M^+-30, 24), 116 (40), 98 (46), 87 (58), 84 (80), 70 (58), 57 (42), 56 (43), 45 (60), 43 (100), 42 (56), 41 (69), 30 (28); uv (CH_3OH) 350 nm (ε 82).

Anal. Calcd for $C_8H_{16}O_3N_2$: C, 51.05; H, 8.57; N, 14.88. Found: C 51.24; H, 8.94; N, 15.02.

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REFERENCES

1. M. Okada, E. Suzuki, J. Aoki, M. Iiyoshi and Y. Hashimoto, Gann Monogr. Cancer Res., 17, 161 (1975); C.A., 84, 84955k (1976).
2. L. Blattmann and R. Preussmann, Z. Krebsforsch. Klin. Onkol., 79, 3 (1973); W. Lijinsky and H. W. Taylor, Cancer Res., 35, 958 (1975); S. Fukushima, M. Hirose, H. Tsuda, T. Shirai, K. Hirao, M. Arai and N. Ito, Gann, 67, 81 (1976); M. Okada and M. Ishidate, Xenobiotica, 7, 11 (1977).
3. E. J. Corey and W. R. Hertler, J. Am. Chem. Soc., 82, 1657 (1960).
4. Y. Hashimoto, E. Suzuki and M. Okada, Gann, 63, 637 (1972).
5. D. Schmähl and F. W. Krüger, Arzneim.-Forsch., 22, 999 (1972).
6. Y. Hashimoto, M. Iiyoshi and M. Okada, Gann, 65, 565 (1974).
7. R. Adams and J. E. Mahan, J. Am. Chem. Soc., 64, 2588 (1942). Lactam II was formed by reaction of butyrolactone with n-butylamine.
8. The multiplets at δ 4.16 and 3.71 are each the sum of two protons, i.e. I exists as 1:1 mixture of E and Z isomers.

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