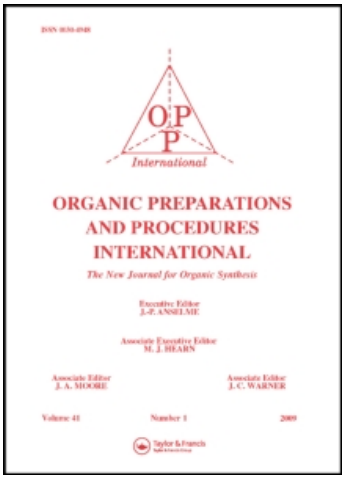

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SELECTIVE NITROSATION OF DIALKYLUREAS CONTAINING A BASIC β-NITROGEN†

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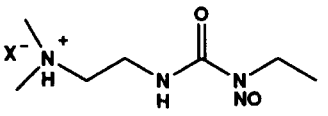
Alkylnitrosoureas have been extensively studied in cancer and mutagenesis research since they are considered to be direct acting alkylating agents.[1] Several of these nitroso compounds are used in cancer chemotherapy, presumably because of their alkylating properties.[2] In the course of our investigations, we became interested in the synthesis of two isomeric nitrosoureas, 1-nitroso-1-ethyl-3-[2-(N,N-dimethylamino)ethyl]urea (**2**) and 1-nitroso-1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea (**3**). The pursuit of these compounds stemmed not only from the necessity to assess the carcinogenic and mutagenic effect of alkylating agents containing a protonated amino residue, but also because nitrosation of ureas containing basic centers on the β-position are virtually unknown, with the exception of some pyridyl derivatives.[3]



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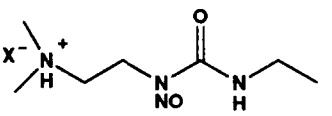
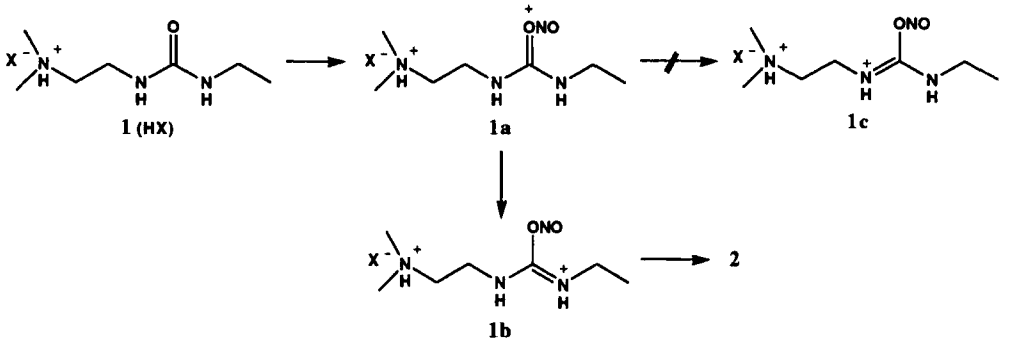


3

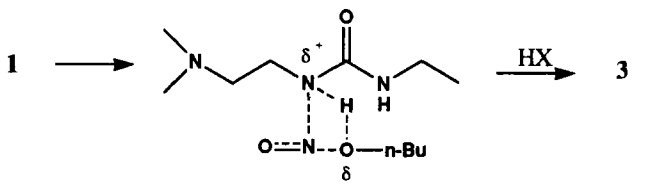
Nitrosation of the hydrochloride salt of 1-[2(N,N-dimethylamino)ethyl]-3-ethylurea **1** with *n*-butyl nitrite in dichloromethane gave a 75% yield of nitrosated urea. The NMR spectrum of the product indicated that 97% of the material was 1-nitroso-1-ethyl-3-[2-(N,N-dimethylamino)ethyl]urea **2**•HCl and only a trace corresponded to the isomer, 1-nitroso-1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea **3**•HCl. The product distribution was determined on the crude reaction mixture by NMR spectroscopy. Isomers **2** and **3** give two distinct sets of NMR signals which can be readily integrated to give reliable relative yields (see Experimental Section for specific peak assignments). The spectral identification of isomers is based on similarities to extensive NMR studies of unsymmetrical nitrosoureas.[4] Since conversion of the product into the free base resulted in its rapid decomposition, **2** was handled and stored as its stable hydrochloride salt. When the acetate salt of **1** was nitrosated with *n*-butyl nitrite in ether, a 98.5% relative yield of **3** was obtained together with 1.5% of **2**, this time as the minor product.



Scheme 1

The outcome of the nitrosation reactions to provide either **2** or **3** in a selective fashion can be attributed not only to the nature of the nitrosating species but also to the effect of the protonated amine moiety on the urea nitrogens. Extensive mechanistic studies by Castro *et al.*[5] suggested that in the nitrosation of ureas (*i. e.*, phenylurea) an O-nitroso intermediate is formed which, upon loss of a proton to the reaction mixture, gives two different conjugate bases. Considering the proposed O-nitrosation mechanism,[5] we envision the nitrosation of **1**•HCl to give the O-nitrosated intermediate **1a** which collapses into one or both of two possible intermediates, conjugate base **1b** or conjugate base **1c**, Scheme **1**. Intermediate **1c** is less likely to materialize due to the unfavorable charge repulsion between the immonium and the diethylammonium ions, which are only two carbons apart. Formation of an immonium ion **1b** on the ethyl side of the dialkylurea is expected to be a more favorable result. Nitroso transfer from the oxygen in **1b** to the ethylimino nitrogen gives the nitrosourea **2**•HCl, which is practically the sole product (Scheme 1).

The production of **3** may be reasoned as follows. Alkyl nitrites in the presence of strong acids and nucleophilic catalysts are protonated and may subsequently react with the nucleophile to produce nitrosating agents such as NOX (X = halide, nitrite, ROH, H_2O). On the other hand, in weakly acidic media the alkyl nitrite is not protonated and undergoes nucleophilic attack by the urea nitrogen at the sp^2 hybridized nitrogen of the alkyl nitrite to give 1-nitroso-1-[-2-(N,N-dimethylamino)ethyl]-3-ethylurea **3**•HCl. It is possible that the dimethylammonium ion center is assisting in the elimination of *n*-butyl alcohol leading to the nearly exclusive formation of isomer **3** as depicted in Scheme 2. Purification of the nitrosourea **3** was accomplished by allowing the product to precipitate out of solution as the crystalline nitrite salt **3** (HNO_2).[6]



Scheme 2

Attempted nitrosation of 2-(N,N-dimethylamino)ethylurea **4**, [$Me_2NCH_2CH_2NHCONH_2$] with sodium nitrite and one equivalent of hydrochloric acid resulted in the isolation of starting material. Considering the O-nitrosation mechanism discussed above, the intermediate **4**(NO) if formed would not collapse into the conjugate base on the dimethylaminoethyl side of the molecule. This is due to the unfavorable charge repulsion between the immonium and the dimethylammonium ions as described for the analog in Scheme 1. As a consequence, no trace of 1-nitroso-1-[2-(N,N-dimethylamino)ethyl]urea **5**, [$Me_2NCH_2CH_2N(NO)CONH_2$], was detected. Consistent with the proposed mechanism on the other hand, nitrosation of **4** with *n*-butyl nitrite in dichloromethane with two equivalents of acetic acid gave the nitrite salt of **5** in 65% yield.

The regioselective preparation of **2** has been accomplished by taking advantage of the O-nitrosation mechanism where the immonium-ammonium ion repulsions are avoided, and where the nitrosating species is a protonated alkyl nitrite of the type (NOX). Isomer **3** can be prepared with the virtual exclusion of **2** when less acidic conditions are used. Under these conditions, a non-protonated but electrophilic alkyl nitrite is apparently involved in the nitrosation step. A second application to the synthesis of nitrosoureas with a basic β-nitrogen substituent is found in the preparation of **5**.

EXPERIMENTAL SECTION

Proton NMR spectra were recorded using a Varian XL-200 with advance data system. Spectra were obtained in acetone-d_6, or in methanol-d_4. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Low and high resolution mass spectral measurements were carried out on a VG-Micromass Model 7070 spectrometer. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Ultraviolet spectra were run in buffer solutions (pH 6) on a Beckman MVI spectrophotometer. Elemental analyses were carried out at Galbraith Laboratories Inc.

WARNING: Most N-nitrosoureas are carcinogenic and/or mutagenic.

1-[2-(N,N-Dimethylamino)ethyl]-3-ethylurea (1).- To a solution of 1.606 g (18.2 mmol) of N,N-dimethylethylenediamine in 40 mL of dichloromethane was added dropwise 1.769 g (25.2 mmol) of ethyl isocyanate. The resulting solution was stirred at 25° overnight. The solvent was removed on a rotary evaporator and the resulting clear colorless oil was dried under high vacuum to give 3.26 g of 1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea **1**, which was not purified any further. IR (Film): 3330, 2980, 2940, 2780, 1645, 1570, 1460, 1257, 1050, 770 cm^{-1}. NMR(acetone-d_6): δ 1.037 (t, 3H), 2.155 (s, 6H), 2.296 (t, 2H), 3.119 (q, 2H), 3.155 (m, 2H), 5.318 (b, 1H), 5.571 (b, 1H). MS, m/z(%): 159 (M^+,1), 127 (3), 116 (2), 86 (15), 84 (23), 71 (28), 58 (100), 56 (7), 51 (10), 49 (33), 44 (9), 42 (9). Exact Mass: M^+ 159.1200, required for $C_7H_{17}N_3O$, M^+ 159.1371.

1-Nitroso-1-ethyl-3-[2-(N,N-Dimethylamino)ethyl]urea Hydrochloride (2).- To a slurry of 660 mg (4.15 mmol) of the hydrochloride salt of 1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea (**1**) in 20 mL of dichloromethane was added 0.0431 mL (3.69 mmol) of *n*-butyl nitrite. The resulting solution was stirred at 25°, and the progress of the reaction was monitored by NMR. After three days, the reaction mixture was chilled to give the crystalline hydrochloride salt of **2**. The product was collected, washed

with ether and dried to give 205 mg of 1-nitroso-1-ethyl-3[2-(N,N-dimethylamino)ethyl]urea hydrochloride **2**, mp. 124-125°, NMR (Methanol-d_4): δ 0.975 (t, 3H), 2.950 (s, 6H), 3.483 (t, 2H), 3.815 (q, 2H), 3.936 (t, 2H). MS (FAB$^+$), m/z (%), 189(MH$^+$,100), 160(42), 159(5), 144(2), 115(47), 75(14), 76(15), 71(22), 58(63), 57(15).

Anal. Calcd. for $C_7H_{17}ClN_4O_2$: C, 37.42, H, 7.63, N, 24.94. Found: C, 36.96, H, 7.30, N, 24.83

1-Nitroso-1-[2-(N,N-Dimethylamino)ethyl]-3-ethylurea Nitrite Salt (3).- To a solution of 2.08 g (0.013 mol) of 1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea (**1**) in 30 mL of ether was added 1.56 mL (0.026 mol) of glacial acetic acid. The solution was cooled to 0° and treated with 3.51 mL (0.03 mol) of *n*-butyl nitrite. A crystalline product began to form within 24 hrs at 0°; however, to obtain an optimum yield, the reaction mixture was allowed to stand in the cold for one week. The crystalline 1-nitroso-1-[2-(N,N-dimethylamino)ethyl]-3-ethylurea nitrite salt (**3**) was collected and washed with ether. A yield of 3.46 g (57%) of pure material, mp. 89-90° was obtained. IR (solid) 3530, 3340, 2985, 1718, 1525, 1480, 1180, 1100 cm^{-1}. UV. λ_{max} (ε): 394 (90); NMR (acetone-d_6): δ 1.282 (t, 3H), 2.504 (s, 6H), 2.865 (t, 2H), 3.523 (q, 2H), 4.026 (t, 2H), 6.94 (b, 1H). MS, m/z (%): 189 (MH$^+$, 100), 160 (38), 159 (8), 158 (6), 152 (3), 118 (15), 115 (21), 105 (2). Exact Mass (MH$^+$): 189.1340, required for $C_7H_{17}N_4O_2$. (MH$^+$): 189.1616.

Anal. Calcd. for $C_7H_{17}N_5O_4$: C, 35.74, H, 7.23. Found C, 35.43, H, 7.56

1-[2-(N,N-Dimethylamino)ethyl]urea (4).- To a solution of 8.03 g (0.091 mol) of N,N-dimethylethylenediamine in 17 mL of 12N hydrochloric acid and 25 mL of water was added 7.7 g (0.095 mol) of potassium cyanate in small portions. The resulting solution was heated to 100° for 15 min, then stirred at 25° overnight. The reaction mixture was evaporated to dryness to give a crystalline residue which contained potassium chloride and **1**•HCl. The residue was extracted with methanol, filtered and evaporated to dryness to give 14.5 g of the hydrochloride salt of 1-[2-(N,N-dimethylamino)ethyl]urea (**4**). NMR (CD_3OD): δ 2.937 (s, 6H), 2.988 (s, 1H), 3.242 (t, 2H), 3.487 (t, 2H). ^{13}C NMR, 36.423 ppm, 43.865, 59.347, 162.225. Free base **1**: NMR ($CDCl_3$): δ 2.292 (s, 6H), 2.500 (t, 2H), 3.286 (q, 2H), 4.816 (b, 2H), 5.489 (b, 1H).

Anal. Calcd. for $C_5H_{13}N_3O$: C, 45.80, H, 9.92, N, 32.06. Found C, 45.31, H, 9.97, N, 31.21

1-Nitroso-1-[2-(N,N-Dimethylamino)ethyl]urea Nitrite Salt (5).- A solution of 2.6 g (0.02 mol) of 1-[2(-N,N-dimethylamino)ethyl]urea (**4**) in 8 mL of glacial acetic acid and 100 mL of dichloromethane was cooled to 0°. To the cold solution was added 7 mL (0.06 mol) of *n*-butyl nitrite and the solution was stirred in the cold for 1 hr. The ice-bath was removed, and stirring was continued at room temperature for 120 hrs. The crystalline product was collected, washed with acetone and dried under vacuum to give 2.67 g (65%) of 1-nitroso-1-[2-(N,N-dimethylamino)ethyl]urea nitrite salt (**5**), mp. 87-8°. IR (solid), 3412, 3043, 2751, 1722, 1598, 1466, 1334, 1189, 1077, 1040, 1010 cm^{-1}. UV pH 4 λ_{max} (ε): 395 (85). NMR (DMSO-d_6): δ 2.799 (s, 6H), 3.106 (t, 2H), 4.045 (t, 2H), 8.007 (broad, 1H), 8.275 (broad, 1H), 9.28 (broad, 1H). MS, m/z (%): 161 (MH$^+$ 100), 132 (24), 131 (9), 118 (5), 115 (7), 72 (11), 71 (8), 69 (6), 58 (53), 55 (9); Exact Mass (MH$^+$): 161.1037, required for $C_5H_{13}N_4O_2$ (MH$^+$) 161.1038.

Anal. Calcd. for $C_5H_{13}N_5O_4$: C, 28.98, H, 6.28. Found C, 28.55, H, 6.14

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