warmed on a hot-water bath the mixture was poured into 100 mL of water and extracted with 100 mL of methylene chloride, and the organic phase was washed with 100 mL of water, dried (Na_2SO), and evaporated to dryness to give a pink residue which was taken up in 10 mL of dry tetrahydrofuran and reduced with 100 mg of lithium aluminum hydride as described above. After a similar workup, the product crystallized from methylene chloride/hexane and was demetalated by addition of trifluoroacetic acid, as described above. Chromatography of the product on alumina (Brockmann Grade III, elution with methylene chloride) followed by evaporation of the red eluates and crystallization from methylene chloride/hexane gave the **mono(hydroxypropyl)monopropyl isomeric mixture 18 and 19** (45 mg, 70%), mp >300 °C. Anal. Calcd for $C_{34}H_{38}N_4O$: C, 78.73; H, 7.38; N, 10.80. Found: C, 78.53; H, 7.10; N, 10.65. This material was retreated with methanesulfonyl chloride, as described above, to give the corresponding **monomesylate–monopropyl isomeric mixture 20 and 21**: mp >300 °C; NMR δ –3.64 (2 H, br s, NH), 1.05 (3 H, t, CH_2CH_2**Me**), 2.64, 2.72 (each 2 H, each m, CH_2CH_2Me and $CH_2CH_2CH_2O$), 2.90 (3 H, s, OSO_2Me), 3.55 3.70 (6 H, 6 H, each s, 1,3,5,8-Me), 3.85, 4.21 (each 2 H, t, CH_2CH_2Me and $CH_2CH_2CH_2O$), 4.48 (2 H, t, $CH_2CH_2CH_2O$), 6.05, 6.30 (each 2 H, m, $CH{=}CH_2$), 8.30, 8.40 (each 1 H, m, $CH{=}CH_2$, 9.83, 9.98, 10.52, 10.75 (each 1 H, each s, meso-H); mass spectrum, *m/e* (%) 580 (100), 534 (20), 516 (35), 445 (58), 429 (30); UV–vis λ_{max} 406 nm (ε 125 100), 505 (11 800), 539 (10 000), 576 (6000), 628 (5000). Anal. Calcd for $C_{35}H_{40}N_4O_3S$: C, 70.43; H, 6.76; N, 9.39. Found: C, 70.58; H, 6.81; N, 9.40. This material was then further reduced with lithium aluminum hydride, as described above, and gave the dipropylporphyrin **14**, identical with the authentic sample described previously.

Acknowledgment. We thank the National Institutes of Health (HL 22252) and the National Science Foundation (CHE 78-25557) for generous grants in support of this research.

Registry No. **2**, 76915-34-9; **4**, 31837-62-4; **5**, 76915-35-0; **6**, 54605-90-2; **7**, 76915-36-1; **8**, 76916-46-6; **9**, 76915-37-2; **10**, 76915-38-3; **11**, 76915-39-4; **12**, 76915-40-7; **13**, 76915-41-8; **14**, 76915-42-9; **14** Zn(II) complex, 61593-94-0; **15**, 76915-43-0; **16**, 76915-44-1; **17**, 76915-45-2; **18**, 76915-46-3; **19**, 76915-47-4; **20**, 76915-48-5; **21**, 76915-49-6; [(5-*tert*-butyloxy)carbonyl]-3′,4-bis(2-chloroethyl)-3,4′-dimethyldipyrrylmethane-5′-carboxylic acid, 76915-50-9; protoporphyrin IX dimethyl ester, 5522-66-7; 4-[(methoxycarbonyl)-methyl]-3,5-dimethylpyrrole-2-carboxylic acid, 76915-51-0; **17** zinc(II) complex, 76916-47-7.

Synthesis of *N*-Nitrosocimetidine Hydrate and Nitrate and Tritium-Labeling Studies

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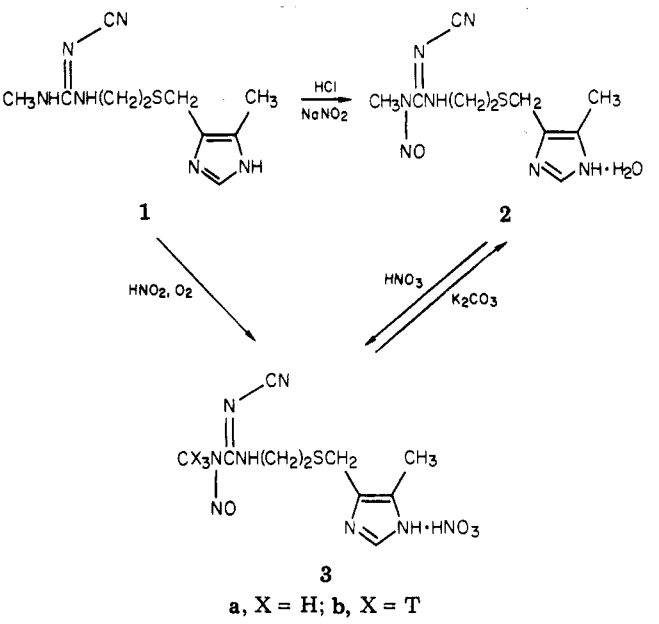
Received September 23, 1980

N-Nitrosamines have recently received much attention[1] since the discovery of their carcinogenic and mutagenic properties.[2] The ready availability of their precursors, nitrite and secondary amines, in the environment and in foodstuffs has prompted many investigators to study the kinetics of nitrosamine formation[3] and to develop various techniques for their quantitative determination.[4] Our interest in investigating the metabolic fate of nitrosamines[5] both in vivo and in vitro led us to prepare both cold (unlabeled) and hot (labeled) nitrosamines.

Scheme I



Cimetidine is a highly successful commercial anti-ulcer agent used widely both in Europe and the U.S. Cimetidine (**1**) is a secondary amine and therefore is potentially N-nitrosated readily under pH conditions existing in the stomach of humans (Scheme I).

N-Nitrosocimetidine monohydrate (**2**), mp 23–28 °C, was prepared in 85% yield by nitrosating cimetidine (**1**) with 3 equiv of sodium nitrite for 1 h at 0 °C in the presence of excess hydrochloric acid, followed by basification to pH 10 and extraction with ethyl acetate.

The ^1H NMR spectrum of **1** in Me_2SO-d_6 shows, among other signals, a resonance at δ 2.70 (d) for the methyl group, CH_3NH, of cimetidine which coalesces to a sharp singlet at δ 3.20 upon nitrosation as a consequence of nitrosation of the nitrogen adjacent to this methyl group. On the other hand, nitrosation for a period of 2 h at 0 °C with 5 equiv of sodium nitrite in an open system with atmospheric oxygen freely available results in the separation of nitrosocimetidine nitrate (**3a**) as a yellow solid, mp 143–144 °C (from ethanol),[6] in 75% yield. Its ^1H NMR spectrum matches that of **2**. Compounds **2** and **3a** could be interconverted. Addition of concentrated nitric acid to a solution of **2** in ether–ethanol (1:1) resulted in separation of **3a** and basification of an aqueous solution of **3a** with solid potassium carbonate caused separation of **2** as a yellow oil which solidified upon cooling.

The preparation of tritium-labeled nitrosocimetidine nitrate (**3b**) was undertaken for metabolic and animal carcinogenicity studies. The nitrate salt is convenient to work with as it is soluble in water. Labeled **3** had 83.1% retention of radioactivity and it was isolated in an overall yield of 75%.

Cimetidine and *N*-nitrosocimetidine were studied by differential pulse polarography (DPP).[7] Stock solutions were prepared in neutral water. The polarograms were

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(3) (a) E. Kalatzis and H. J. Ridd, *J. Chem. Soc. B*, **13**, 529 (1966); (b) K. L. Keefer and P. P. Roller, *Science*, **181**, 1245 (1973).

(4) S. Ray, *J. Chromatogr.*, **153**, 173 (1978), and references therin.

(5) W. K. Paik and G. Hard, private communication.

(6) G. J. Durant, Smith Kline and French Research Ltd., Hartfordshire, England, private communication.

(7) S. K. Chang, and G. W. Harrington, *Anal. Chem.*, **47**, 1857 (1975).

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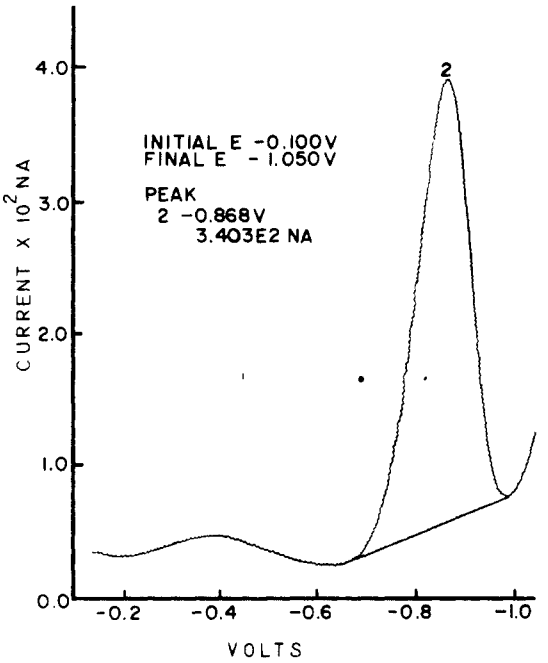

Figure 1. Cimetidine (10^{-5} M) in 0.1 M HCl.

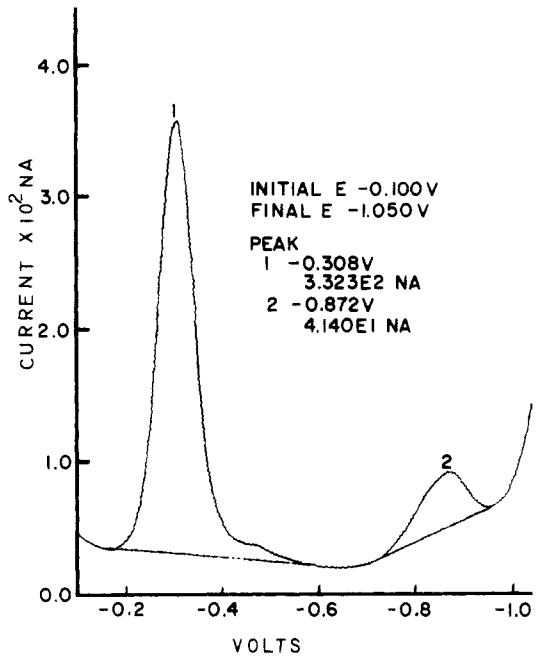

Figure 2. *N*-Nitrosocimetidine (10^{-5} M) in 0.1 M HCl.

determined in 0.1 M HCl, using usual degassing procedures. This supporting electrolyte and pH were chosen since it was found that both compounds yield maximum response and the sharpest peaks under these conditions. Nitrosocimetidine slowly decomposes at this acid concentration but at a rate of only about 5% per hour.

Over the time period of the polarographic run, about 5–10 min, no decompoisition was observed. The polarograms are shown in Figures 1 and 2. Cimetidine shows a characteristic peak potential at approximately –0.87 V; this peak is linear for concentrations ranging from 10^{-7} to 10^{-5} M. *N*-Nitrosocimetidine shows two characteristic peak potentials, the first at approximately –0.31 V and the second at approximately –0.87 V. The peak at –0.31 V is linear for nitrosocimetidine concentrations ranging from 10^{-4} to 10^{-7} M; the peak at –0.87 V is not linear over the same concentration range. The presence of the peak at –0.31 V allows one to distinguish *N*-nitrosocimetidine from cimetidine.

Experimental Section

All melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Unicam SP-1000 infrared spectrophotometer. The ^{1}H NMR spectra were determined by using a Varian XL-100 instrument and Me_4Si as internal standard. Differential pulse polarograms were determined as previously reported[7] except that an EG & G PARC Model 384 polarograph and Model 303 electrode were used. All potentials are reported vs. Ag/AgCl reference. The specific conditions were as follows: drop time, 1 s; scan rate, 4 mV/s; pulse height, 150 mV; drop size, large. [*N*-methyl-^{3}H]cimetidine (Code TRK 615) was purchased from Amersham. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***N*-Nitrosocimetidine Hydrate (2).** To a stirred solution of cimetidine (2.25 g, 9 mmol) in 2 M hydrochloric acid (45 mL) at 0 °C was added a solution of sodium nitrite (2.1 g, 30 mmol) in water (15 mL). Stirring was continued for 40 min at 0 °C, and the yellow solution was basified to pH 10 with potassium carbonate and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed successively with saturated aqueous sodium chloride and water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, yielding a pale yellow oily residue which solidified to a yellow solid when kept at 0 °C overnight: mp 23–28 °C; IR (neat) 1440 (NO), 1630 (C=N), 2150 (C≡N), 3300 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 2.15 (s, imidazole CH_3), 2.50–2.70 (m, NCH_2CH_2S), 3.15 (s, $ONNCH_3$), 3.65 (m, NCH_2CH_2S), 3.95 (s, SCH_2-imidazole), 9.0 (s, imidazole H), 9.7 (br, NH). Anal. Calcd for $C_{10}H_{15}N_7OS{\cdot}H_2O$: C, 40.13; H, 5.68; N, 32.77; S, 10.70. Found: C, 40.15; H, 5.16; N, 32.91; S, 10.69.

[*N*-methyl-^{3}H]Nitrosocimetidine Nitrate (3b). To a solution of cimetidine (100 mg, 0.45 mmol) in 3 mL of ethanol was added [*N*-methyl-^{3}H]cimetidine (1.5 mg, 0.0067 mmol, radioactivity 1 mCi) in 1 mL of ethanol. Ethanol was removed under vacuum and to the residual white solid in a wide mouth beaker were added sodium nitrite (150 mg, 2.3 mmol) and 1 mL of water. To the stirred mixture at 0 °C was added 0.3 mL of concentrated hydrochloric acid over a period of 10 min. Stirring was continued for an additional hour at 0 °C. The white solid which separated was filtered, dried, and recrystallized from ethanol–2-propanol (1:1) to afford 100 mg (75% yield) of **3b**: mp 144–146 °C; IR (KBr) 1340 (NO_3), 1480 (NO), 1615 (C=N), 2155 (C≡N), 3310 (NH); NMR (Me_2SO-d_6) 2.3 (s, imidazole CH_3), 2.7–2.9 (m, NCH_2CH_2S), 3.25 (s, $ONNCH_3$), 3.5–3.7 (m, NCH_2CH_2S), 3.95 (s, imidazole-CH_2), 9.0 (s, imidazole H), 9.6–9.75 (br, HN); specific radioactivity 8.31 μCi/mg (2.33 μCi/mmol).

Acknowledgment. We thank the National Cancer Institute, DHEW (Grants CA-18618 and CA-09214), the Samual S. Fels Fund, and Temple University for support of this work.

Registry No. 1, 51481-61-9; 2, 73785-40-7; **3a**, 75523-16-9; **3b**, 76999-44-5.

Coupling of Aryl Grignard Reagents by Electron Transfer to Unsaturated 1,4-Dihalo Compounds

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Received November 13, 1980

The coupling of aromatic compounds has been the subject of numerous past and current investigations.[1-5] Of

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