overnight; then it was directly chromatographed on silica gel (hexane/ether, 4:1) to yield 19 mg (88%) of acetonide **69**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, J = 2.8, 11.4 Hz, 1 H, OCH_2), 3.58 (dd, J = 1.7, 11.4 Hz, 1 H, OCH_2), 3.44 (dd, J = 2.3, 9.8 Hz, 1 H, OCH), 1.60–1.40 (m, 2 H, H-2 and H-4), 1.39 (s, 3 H, $(CH_3)_2C$), 1.38 (s, 3 H, $(CH_3)_2C$), 1.38–1.25 (m, 6 H, $(CH_2)_3$), 1.03 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 0.89 (d, J = 6.4 Hz, 3 H, $CHCH_3$), 0.87 (t, J = 6.9 Hz, 3 H, CH_2CH_3). Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.70; H, 12.17.

(2*S*,3*S*,4*R*)-2,4-Dimethyl-5-(benzyloxy)-1,3-(isopropylidenedioxy)pentane (70). The sequence described for **30** → **35** was employed with 52 mg (0.17 mmol) of alcohol **64h**. **70**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5 H, Ar H), 4.52, 4.44 (AB q, J = 12.0 Hz, 2 H, $ArCH_2O$), 4.05 (dd, J = 2.7, 11.4 Hz, 1 H, OCH_2), 3.71 (dd, J = 2.3, 9.6 Hz, 1 H, OCH), 3.53 (dd, J = 1.7, 11.4 Hz, 1 H, OCH_2), 3.35 (dd, J = 4.2, 9.3 Hz, 1 H, $BnOCH_2$), 3.30 (dd, J = 5.2, 9.3 Hz, $BnOCH_2$), 1.80 (m, 1 H, H-2), 1.50 (m, 1 H, H-4), 1.40 (s, 3 H, $(CH_3)_2C$), 1.38 (s, 3 H, $(CH_3)_2C$), 1.04 (d, J = 6.9 Hz, 3 H, $BnOCHCH_2CH_3$), 1.02 (d, J = 6.7 Hz, 3 H, $CHCH_3$); HRMS, calcd for $C_{17}H_{26}O_3$ 278.1882, found, 278.1884. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.42; H, 9.44.

Acknowledgment. This work was supported by research grants from the NSF (CHE 8912747) and the NIH (2R01-GM29475). We are indebted to James Audia of Eli Lilly for sample of *ent*-Darvon alcohol.

Registry No. **1a**, 62967-60-6; **1b**, 96429-42-4; **1c**, 81535-82-2; (*R*)-**2a**, 124126-37-0; (*R*)-**2b**, 137920-03-7; (*S*)-**2b**, 137920-04-8; (*R*)-**2c**, 133910-77-7; (*S*)-**2c**, 133910-89-1; (*S*)-**4a**, 138124-08-0; (±)-**4a**, 131043-65-7; (*S*)-**4b**, 137920-05-9; (*R*)-**4b**, 137920-30-0; (*S*)-**4c**, 133930-05-9; (*R*)-**4c**, 133930-07-1; (*S*)-**4d**, 133910-78-8; (*R*)-**4d**, 133910-90-4; (*S*)-**4e**, 133910-79-9; (*R*)-**4e**, 133910-91-5; (*S*)-**4f**, 137920-06-0; (*R*)-**4f**, 137920-07-1; (*S*)-**4g**, 137920-08-2; (*S*)-**4h**, 137920-09-3; (*R*)-**4h**, 137920-10-6; **5**, 133910-80-2; **6**, 73501-37-8; **7**, 137920-11-7; **9**, 133910-81-3; **10**, 133910-82-4; **11**, 133910-83-5; **12**, 133910-85-7; **14**, 133930-06-0; **15**, 133910-84-6; **19**, 42969-65-3; **20**, 137920-12-8; **21**, 137920-13-9; **24**, 131043-68-0; **25**, 138124-09-1; **26**, 138124-10-4; **27**, 131043-71-5; **30**, 137920-14-0; **31**, 137920-15-1; **33**, 137920-16-2; **34**, 137920-17-3; **35**, 137920-18-4; **37**, 137920-19-5; **39**, 131043-72-6; **40**, 131043-73-7; **42**, 131043-75-9; **43**, 137920-20-8; **44**, 137920-21-9; **45**, 137920-22-0; **47**, 79026-61-2; **48**, 81445-44-5; **49e**, 133910-87-9; **49h**, 137920-23-1; **50e**, 133964-09-7; **50h**, 138050-84-7; **51e**, 133964-10-0; **51h**, 138050-85-8; **52e**, 133964-11-1; **52h**, 138050-86-9; **56**, 137920-24-2; **57**, 137920-25-3; **58**, 137943-34-1; **59**, 138124-11-5; **60**, 137920-26-4; **61**, 79026-61-2; **62e**, 137920-27-5; **62h**, 137943-35-2; **63e**, 138124-12-6; **63h**, 138124-46-6; **64e**, 138124-13-7; **64h**, 138124-47-7; **65h**, 138124-48-8; **66**, 137943-36-3; **67**, 137920-28-6; **68**, 138124-14-8; **69**, 137943-37-4; **70**, 98102-72-8; (trimethylsilyl)acetylene, 1066-54-2; heptanol, 111-71-7; *rac*-1-(trimethylsilyl)-1-nonyn-3-ol, 135501-86-9; 1-(trimethylsilyl)-1-nonyn-3-one, 97367-36-7; 2-methyl-1,3-(methylenedioxy)nonane, 137920-29-7; trimethylacetaldehyde, 630-19-3.

Supplementary Material Available: Experimental procedures for *R* and *S* isomers of **2b–c**, **4b–c**, **49e**, **51e**, **52e**, **62h**, and **64h** and ^{1}H NMR spectra for **6**, **9**, **11**, **12**, **14**, **20**, **21**, **23**, **24**, **30**, **34**, **35**, **42**, **56**, **58**, **62e**, **63e**, **66**, **67**, **68**, **62h**, and **64h** (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

N-Nitrososulfamates: Sources of Carbonium Ions in Aqueous Media and Substrates in Solid-State Decompositions[1]

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Potassium *N*-nitrososulfamates of benzylamine, 2-phenylethylamine, and cyclohexylamine **2a–c** were synthesized and examined as sources of carbonium ions in aqueous media. The nitrososulfamates are crystalline compounds which decompose readily at low pHs (~2) under conditions where the parent amines are relatively stable to nitrous acid. In water solutions they produce the corresponding alcohols, principally, along with small percentages of the corresponding esters of potassium bisulfate. The decomposition of the benzyl analogue **2b** in the presence of sodium thiocyanate produced, principally, benzyl alcohol, but also benzyl thiocyanate and benzyl isothiocyanate in a ratio of 4.4/1, indicating a muted role for nucleophilicity in this carbonium ion reaction. In sulfate buffers they decompose by psuedo-first-order kinetics (rate constants are reported). In acetic acid they produce principally the corresponding acetate esters. A reaction mechanism is proposed in which the slow step involves the production of a diazohydroxide rather than a direct formation of a carbonium ion. The benzyl analogue **2b** is an inhibitor of the enzyme pepsin; it also undergoes a photoelimination reaction on irradiation. The nitrososulfamates are perfectly stable when dry, but they undergo a relatively rapid solid-state decomposition ($T_{1/2} \approx$ 2–5 days) when exposed to normal atmospheric humidity; surprisingly, the external appearance of the crystals does not change during the decompositions. The products are, principally, the esters of sulfuric acid and potassium bisulfate.

The deamination of aliphatic amines in organic solvents can be achieved through use of *N*-nitrosoamides,[2] *N*-nitroamides, and the acylation of nitroamine salts,[3] *N*-nitrosohydroxylamines,[4] triazenes,[5] sydnones,[6] and related compounds,[7] and through the reactions of amines with

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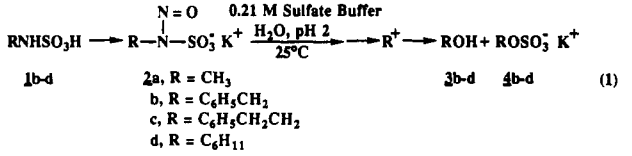
dinitrogen tetraoxide[8] and nitrosyl chloride.[9] For deamination in aqueous media,[10] the reaction of amines with nitrous acid has long been the standard method. This reaction produces complex mixtures of products, largely because of the exchange of the initial counterion (hydroxide ion) with the various acidic species present.[11] Further, the reaction does not proceed at low pHs (<~3) because of the formation of the unreactive ammonium ion.[12] A second general approach involves the protonation or acylation of diazotate salts[7d,14,15] (derivable from primary amines); because of the instability of the diazotates, this reaction has not been widely utilized, however. Several other approaches have been developed recently; they include the reaction of amines with nitrosylpentacyanoferrate III ion at neutral to high pHs,[15,16] the esterase-catalyzed hydrolysis of acetoxymethylnitrosoamines,[15] and the copper(II)-mediated hydrolysis of nitrosoureas.[17]

We report now that N-nitrososulfamates **2** are useful sources of carbonium ions in acidic aqueous media[18a] and, subsequently, of alcohols and other carbonium ion derived products (eq 1). Only two citations concerning alkyl ni-



1b-d **2a**, R = CH_3; **b**, R = $C_6H_5CH_2$; **c**, R = $C_6H_5CH_2CH_2$; **d**, R = C_6H_{11} **3b-d** **4b-d** (1)

trososulfamates have hitherto appeared in the scientific literature. Compound **2b** was synthesized in 1897 and reported to react with water, ethanol, and hydriodic acid to yield, respectively, benzyl alcohol, benzyl ethyl ether, and benzyl iodide (in unspecified yields).[18b] Compound **2a** was synthesized in 1919, but it was not examined as a substrate in deamination.[19]

Results and Discussion

The precursor sulfamates (1) are prepared by the reaction of the corresponding amines with chlorosulfonic acid.[20] The sulfamates are readily N-nitrosated in aqueous media through reaction with potassium nitrite.[18] The nitrososulfamates are obtained in the form of colorless crystals with a single UV absorption maximum in water at 365 nm, considerably shifted from the 409 nm value found for N-nitrosocarboxamides[21] in the same solvent and from the absorption maxima of N-nitrososulfonamides (413, 395, 380 sh) observed in aprotic solvents.[22] Potassium N-benzyl-N-nitrososulfamate was reported to be an explosive compound,[18] but we have been unable to detonate samples that we have prepared by percussion or heat.[23] Possibly the amine used in the 19th century work was contaminated with aniline, which on nitrosation would have produced explosive aryl diazonium salts.

Table I. Rate Constants for the Decomposition of N-Benzyl-N-nitrososulfamate (2b)[a] in Aqueous Media

pH	buffer constituents [$KHSO_4$] (M)	buffer constituents [K_2SO_4] (M)	other reagents HCl (M)	temp (°C)	k_{obs} (s^{-1}) × 10^{-4}	k (M^{-1} s^{-1}) × 10^{-2}
2.0	0.10	0.11		25	2.2	2.2
				26	2.4	2.4
2.0	0.050	0.055		25	1.7	1.7
2.0	0.67	0.73		25	8	
1.5	0.156	0.055		25	4.9	1.6
				26	6.7	2.2
2.0			0.01	26		1.7
5.0 (H_2O)[b]				26		1.9

[a] 0.012 M. [b] Distilled water has a pH of ~5 (dissolved carbon dioxide and carbonic acid).

The nitrososulfamates decompose readily at low pHs; half-lives for the decomposition of **2b**, **2c**, and **2d** in a pH 2 sulfate buffer (0.21 M) at 25 °C are approximately 1 h, 0.5 h, and 1 min, respectively. The high rate in the cyclohexyl case is presumably a case of steric acceleration.[3d]

The products (and yields) for decompositions of the nitrososulfamates in a pH 2 (pD 2) sulfate buffer (0.21 M) are as follows: from **2b**, benzyl alcohol (**3b**, 98%) and potassium benzyl sulfate (**4b**, 2%); from **2c**, 2-phenylethanol (75%), 1-phenylethanol (17%), and potassium 2-phenylethyl sulfate (8%); from **2d**, cyclohexanol (84%), cyclohexene (8%), and potassium cyclohexyl sulfate (8%). Similar product yields, with slightly lower sulfate ester yields, were obtained when samples were allowed to decompose in water. In a more concentrated sulfate buffer (1.4 M), the yields for **2b** were altered somewhat in favor of the sulfate: benzyl alcohol, 96%; potassium benzyl sulfate, 4%. In acetic acid, **2b** produced benzyl alcohol (12%) and benzyl acetate (88%). Somewhat similar results have been reported for nitrous acid mediated deaminations. For 2-phenylethylamine, Lee and Spinks[24] report 50–66% yields of 2-phenylethanol with no mention of 1-phenylethanol, Coke[25] reported a ratio of 82% of 2-phenylethanol and 18% of 1-phenylethanol, while Roberts and Regan[26] report 20–50% yields of 2-phenylethanol (as the N-phenylcarbamates) with "no appreciable amounts of 1-phenylethanol"; styrene yields were not reported in any case. Using ^{14}C-labeled amine (position 1), all three groups measured the extent of ^{14}C rearrangement; 27%, 27% and 28% rearrangement, respectively, was found and interpreted in terms of the intermediacy of phenonium ions. The low yields of 1-phenylethanol probably are a result of the phenonium ion participation, the low popu-

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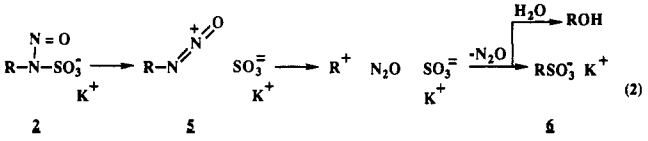
lation of conformers with a trans antiplanar arrangement of the diazonium group and a β-hydrogen, and the possible conversion of 1-phenylethyl carbonium ions preferentially to styrene.[26] In the case of the deamination of cyclohexylamine in 10% aqueous acetic acid, Hückel and Wilip[27] report 34% yields of cyclohexanol, 2% yields of cyclohexyl acetate, and 10% yields of cyclohexene. The nitrous acid deamination of benzylamine does not appear to have been reported in the literature; Tafel[13] has stated, in fact, that with strong cooling and in acidic solutions (presumably rather low pHs were used) benzylamine is stable to nitrous acid.[12]

No products were detected from possible free-radical decompositions; e.g., 1,2-diphenylethane was not formed in the decomposition of **2b** (maximum yield <1%). Nitrous oxide was not detected as a product (IR spectra), eliminating from consideration a direct ionization pathway for **2b** (eq 2) that has been observed in the decomposition

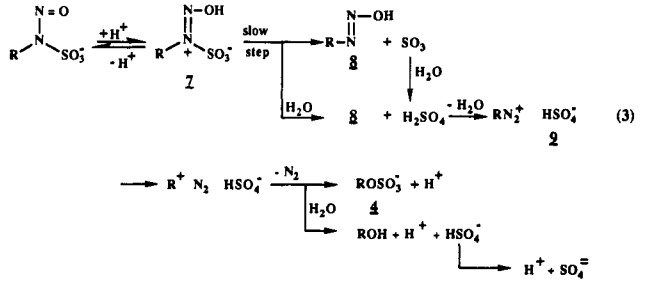


(2)

of related compounds with benzoate ions as the leaving group[4]; further, no potassium phenylmethanesulfonate[28] (**6**, R = $C_6H_5CH_2$) was observed in the solvolysis of **2b**.

The decomposition of compound **2b** in water has an induction period and it shows complex kinetics; this behavior results from a combination of the requirement for acid catalysis and the production of acid during the alcohol-forming reaction (eq 3). The decomposition of **2b** in a 0.21 M, pH 2 sulfate buffer at 25 °C is first order in **2b** and first order in H^+ ($k_{obs} = k[H^+] = 2.2 \times 10^{-4}$ s^{-1}; $k = 2.2 \times 10^{-2}$ M^{-1} s^{-1}) (Table I). At pH 1.5, $k = 1.6 \times 10^{-2}$ M^{-1} s^{-1}. In pH 2 sulfate buffers at buffer concentrations of 0.105, 0.21, and 1.4 M, k_{obs} values (×10^4) of 1.7, 2.2, and 8 were measured, suggesting that general acid catalysis by the bisulfate ion may be occurring.

The kinetic observations and product distributions support the reaction mechanism outlined in eq 3.[29]



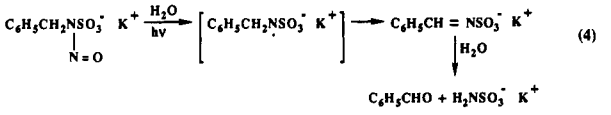
(3)

With respect to synthetic applications the nitrososulfamates will be useful where alkylation of protic solvents or of an added acid is desired. The reactions with water and acetic acid have been given in an earlier section. The role of nucleophilicity in carbonium ion reactions was examined through the decomposition of **2b** in the presence of 0.1 M NaSCN (conditions as entered on eq 1). Benzyl thiocyanate and benzyl isothiocyanate were formed in a ratio of 4.4/1. This result reveals a muted role for the nucleophilicity of sulfur in deamination[30] relative to, e.g., the role of nucleophilicity in SN^2 reactions where the alkali metal thiocyanates generally yield with alkyl halides only the alkyl thiocyanates.[32]

The nitrososulfamates appear not to be useful as crystalline substitutes for diazoalkanes in the alkylation of stoichiometric amounts of acids. They are insoluble in ether (and like solvents), and although they react rapidly with acids under those conditions, the concurrent decomposition within the solid yields side products characteristic of those from the spontaneous decomposition of the nitrososulfamates in the solid state (next section). For example, the reaction of **2b** with benzoic acid in ether produces large amounts of **4b** and dibenzyl sulfate in addition to benzyl benzoate.

For reactions in protic solvents (eq 3), there is a close relationship between the reactions of the nitrososulfamates and reactions of salts of alkyl diazotates; the ease of synthesis and the greater stability of the nitrososulfamates, however, favors their use in deamination.

Photochemical Decomposition. The photochemistry of a nitrososulfamate was briefly examined to determine whether the excitation energy might lead to a direct ionization of the molecule as illustrated in eq 2. The irradiation of degassed, aqueous solutions (D_2O) of *N*-benzyl-*N*-nitrososulfamate (**2b**) in either Pyrex or quartz vessels with a medium-pressure mercury discharge lamp produced within minutes a signal at 8.95 ppm, which was assigned to potassium benzylidenesulfamate. When the solution stood for a few hours, a 10.03 ppm signal for benzaldehyde appeared at the expense of the 8.95 ppm peak (eq 4). The ammonium salt of benzylidenesulfamate



(4)

was synthesized by the condensation of benzaldehyde with ammonium sulfamate (eq 5);[33] the NMR spectrum of this material showed the expected peak at δ 8.95 (D_2O). Ni-

$$C_6H_5CHO + H_2NSO_3^-\ NH_4^+ \xrightarrow{CH_3OH} C_6H_5CH{=}NSO_3^-\ NH_4^+ \quad (5)$$

trososulfamate **2b** thus undergoes a photoelimination reaction reaction of a type that has been observed in the case of the *N*-nitrosocarboxamides.[34]

Inhibition of Pepsin. The inhibition of pepsin[35] by diphenyldiazomethane,[36] diazoacetylnorleucine,[37] and

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(29) RN(NO)SO_2OH (7′) is unlikely to be the protonated reaction intermediate since (1) analogs, RN(NO)$SO_2C_6H_4CH_3$ (i), require elevated temperatures for decomposition in organic solvents (via ii, R-N=N-OS-$(O_2)C_6H_4CH_3$; compare to 7′ → R-N=N-OS(O_2)OH), (2) reaction rates for the thermal rearrangement (for i → ii) are fairly independent of the nature of the solvent, and (3) the oxygen of the nitrosoamino group is most probably more basic than that of the sulfamate ion, which in this case bears, in addition, an electron-withdrawing group on the α-position.
(30) The deamination of isobutylamine with nitrous acid in the presence of thiocyanate ion yields both the alkyl thiocyanate and isothiocyanate (ratio for isobutyl products = 5.3 and for *tert*-butyl products = 1.9).[31]
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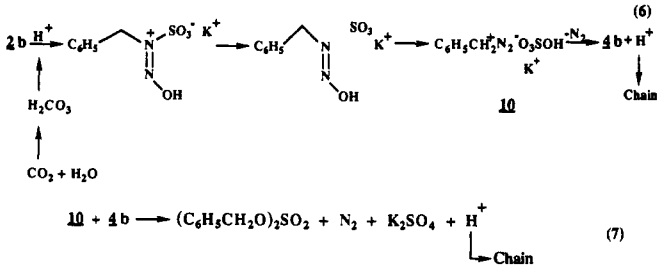
1,2-epoxy-3-(aryloxy)propanes[38] has been interpreted in terms of protonation of the substrates with formation of carbonium ion species as the proximate agents. The insolubility of many of these compounds in water leads to obvious experimental difficulties. The nitrososulfamates are quite water-soluble, and they clearly react with protons to ultimately yield carbonium ions (eq 3 and text). Hence, the action of one of these, the *N*-benzyl analogue **2b**, on pepsin was examined. Weak inhibition was observed, 25% in 2 h with an inhibitor/enzyme ratio of 138. The slow rate is similar to the rates observed for the inhibitors outlined above. More efficient nitrososulfamates will undoubtedly be prepared *via* modification of the structure of the alkyl group.

Solid-State Decomposition. *N*-Nitrososulfamates **2b** and **2c** are stable in the dry state; under vacuum (10^{-2} Torr), no decomposition was noted during 1 month at 25 °C. Exposed to air, however, they decompose in the solid state with lifetimes that are surprisingly short relative to values for the decompositions in solution. The values are dependent on the humidity and are thus somewhat variable in uncontrolled environments; we have observed values of ~2–5 days for full decomposition of **2b** and 5 days for **2c** at 25 °C. For **2b** at 25 °C, the products are benzyl potassium sulfate **4b** (90%), dibenzyl sulfate (10%), and potassium sulfate; for **2c** at 50 °C (17 h), the products are potassium 2-phenylethyl sulfate (40%), bis(2-phenylethyl) sulfate (53%), styrene (<1%), three 1-phenylethyl compounds (~2%), and potassium sulfate. It has been observed that crystals of nitrososulfamates **2b** and **2c** do not collapse during the decompositions (during which the loss of molecular nitrogen occurs). Surprisingly, except for an increase in opacity, the plate-like crystals of **2b** and **c** undergo no obvious changes during the decompositions; the sharp crystal edges and planes are unaltered. The products of the solid-state decompositions and the relatively fast decomposition rates can be accounted for in terms of chain reactions dependent on the close proximity of neighboring molecules and involving the diffusion of protons through the crystal in the propagation steps (eqs 6 and 7);[39] initiation presumably results from water (or possibly carbonic acid) acting on surface molecules.



$$\mathbf{10} + \mathbf{4b} \longrightarrow (C_6H_5CH_2O)_2SO_2 + N_2 + K_2SO_4 + H^+ \quad (7)$$

Chain

Experimental Section

Instrumentation. Spectra were measured with Varian XL-400 and Bruker AMX-300 NMR spectrometers, a Perkin-Elmer 1600 Series FTIR spectrometer, a Beckman Model 25 UV–vis spectrometer, and a VG Instruments 70-S mass spectrometer. The pH (pD) values of the buffers, made up in redistilled and deionized water, were measured with a Beckman Model 4500 pH meter. Melting points were determined on a Thomas/Hoover Unimelt apparatus.

***N*-Benzylsulfamic Acid (1b).** Using a procedure adapted from that of Audrieth et al.,[20] a solution of benzylamine (6.42 g, 60 mmol) in 40 mL of $CHCl_3$ was cooled in an ice–water bath. Chlorosulfonic acid (2.37 g, 20 mmol) was added dropwise over a period of 15 min, during which time a white precipitate formed. The mixture was stirred for another 10 min, then filtered to yield 6.73 g of a white solid (77%). The solid was suspended in 30 mL of water to produce an emulsion. Upon the addition of 7 mL of concd HCl (85 mmol), crystals were produced which were filtered and dried in vacuo (1.12 g, 30% based on benzyl amine), mp 165 °C dec:[40] NMR (DMSO-d_6) δ 8.3 (s, 1 H, broad), 7.6–7.2 (m, 5 H), 4.21 (s, 2 H); IR (KBr) 3131, 1341, 1288, 1253, 1070 cm^{-1}.

Potassium *N*-Nitroso-*N*-benzylsulfamate (2b).[18] To a suspension of *N*-benzylsulfamic acid (**1b**) (250 mg, 1.34 mmol) in 4 mL of water at 25 °C was added with stirring 262 mg of KNO_2 (3.08 mmol). An almost clear solution was formed within 1 min, which was immediately cooled to 4 °C and stored at that temperature for 20 min. Large plates were formed which were collected by filtration (164 mg, 48%), mp 115 °C dec:[23] NMR (DMSO-d_6) δ 7.30–7.15 (m, 5 H), 4.79 (s, 2 H); NMR (D_2O) δ 7.23 and 7.13 (m, 5 H), 4.93 (s, 2 H); IR (KBr) 1438, 1403, 1306, 1257, 1064 cm^{-1}; UV (pH 5, 0.1 M acetate buffer) 365 nm (ϵ ~50). The product was stable when kept dry (storage under vacuum). Because of the unstable nature of the nitrososulfamates (text and ref 23), elemental analyses were not obtained. The proof of structure rests on the method of synthesis and the physical data.[41]

Potassium Benzyl Sulfate (4b). Under vigorous magnetic stirring, chlorosulfonic acid (1.58 g, 13.5 mmol) was added in 10 min to a mixture of benzyl alcohol (1.33 g, 12.3 mmol) and pyridine (10 mL, 124 mmol) at 0 °C. The viscous solution was then allowed to warm to 25 °C, and the resulting clear solution was stirred for an additional 5 h. The solution was cooled to 0 °C, and a 50% KOH solution was added dropwise until the pH reached 8. Ether (30 mL) was added; a white precipitate formed, which was collected by filtration. It was extracted with 50 mL of hot H_2O/EtOH (1/4, v/v), and the extract was filtered. Cooling the filtrate to −10 °C gave 800 mg of needles (3.92 mmol, 29%), mp 220 °C dec:[42] NMR (DMSO-d_6) δ 7.36–7.25 (m, 5 H), 4.76 (s, 2 H); NMR (D_2O) δ 7.4–7.3 (m, 5 H), 4.98 (s, 2 H); IR (KBr) 1286, 1260, 1220, 1069, 1011 cm^{-1}.

***N*-(2-Phenylethyl)sulfamic Acid (1c).** This compound was synthesized from 2-phenylethylamine and chlorosulfonic acid using the procedure outlined for compound **1b** (43%):[43] mp 152 °C dec.; NMR (DMSO-d_6) δ 10.2 (s, broad, 1 H), 7.8 (s, broad, 1 H), 7.4–7.2 (m, 5 H), 3.22–3.18 (m, 2 H),[44] 2.91–2.87 (m, 2 H);[45] NMR (D_2O) δ 7.4–7.2 (m, 5 H), 3.27 (t, 2 H, J = 7.6 Hz), 2.87 (t, 2 H, J = 7.6 Hz); IR (KBr) 3026, 1316, 1293, 1261, 1053 cm^{-1}.

Potassium *N*-Nitroso-*N*-(2-phenylethyl)sulfamate (2c). This compound was synthesized from compound **1c** in 62% yield using the procedure described for compound **2b**: mp 130 °C dec; NMR (DMSO-d_6) δ 7.30–7.15 (m, 5 H), 3.81 (m, 2 H),[46] 2.66 (m, 2 H);[47] NMR (D_2O) δ 7.23–7.16 (m, 5 H), 3.95 (t, 2 H, J = 6.4 Hz), 2.73 (t, 2 H, J = 6.4 Hz); IR (KBr) 1472, 1286, 1240, 1062, 942 cm^{-1}.

Potassium 2-Phenylethyl Sulfate (4c). The synthesis followed the procedure used for compound **4b**, except that the workup was modified as follows. At the end of the reaction, the product mixture [resulting from 2-phenylethyl alcohol (0.74 mL, 6.2 mmol) and chlorosulfonic acid (0.75 mL, 6.8 mmol) in 5 mL of pyridine] was taken to pH 9 and the solution was extracted with ethyl acetate (3X). A light precipitate in the aqueous solution was partially dissolved by the addition of a few drops of water;

(38) Tang, J. *J. Biol. Chem.* **1971**, *246*, 4510.

(39) Similar equations can be written for the solid-state decomposition in which the proton binds initially to the sulfate moiety and for analogous chain reactions in which the transfer of $C_6H_5CH_2^+$ is involved in propagation.

(40) The sodium salt of compound 1 is described in ref 20; a satisfactory analysis for nitrogen was reported.

(41) Compound **2b** was described in ref 18, but a mp was not listed.

(42) The corresponding sodium salt has been reported (Clapp, J. J.; Young, L. *Biochem. J.* **1970**, *118*, 765) but the mp was not given.

(43) The sodium salt of this compound was reported in ref 20.

(44) This multiplet appeared as a set of six peaks (chemical shift (relative intensity)): 3.219 (0.8), 3.204 (0.7), 3.199 (0.9), 3.191 (0.65), 3.189 (0.6), 3.711 (1).

(45) This multiplet appeared as a set of four peaks (chemical shift (relative intensity)): 2.912 (1), 2.898 (0.7), 2.891 (1), 2.871 (0.8).

(46) This multiplet in DMSO-d_6 appeared as a set of five peaks (chemical shift (relative intensity)): 3.825 (1), 3.812 (0.6), 3.805 (0.8), 3.797 (0.6), and 3.784 (1).

(47) This multiplet in DMSO-d_6 appeared as a set of five peaks (chemical shift (relative intensity)): 2.680 (1), 2.667 (0.6), 2.659 (1), 2.652 (0.6), and 2.639 (1).

the solution was then filtered. The filtered solution was concentrated by $^1/_2$ and cooled to 4 °C to give 340 mg of fine crystals. The mother liquor was taken to dryness in vacuo, and the solid was extracted with 25 mL of hot EtOH/H_2O (4/1, v/v) solution. The hot extract solution was filtered and cooled to 4 °C to yield a second crop of 156 mg of fine crystals. A total yield of 496 mg (2.11 mmol, 34%) of product was obtained, mp 254 °C dec: NMR (DMSO-d_6) δ 7.3–7.1 (m, 5 H), 3.92 (t, 2 H, J = 6 Hz), 2.83 (t, 2 H, J = 6 Hz); NMR (D_2O) δ 7.31–7.18 (m, 5 H), 4.17 (t, 2 H, J = 6.3 Hz), 2.91 (t, 2 H, J = 6.3 Hz); IR (KBr) 1282, 1272, 1247, 1225, 1064, 1004 cm^{-1}. Anal. Calcd for $C_8H_9KO_4S·0.75H_2O$: C, 37.86; H, 4.17. Found: C, 37.76; H, 3.69.

***N*-Cyclohexylsulfamic Acid (1d).** A procedure adapted from that of Audrieth et al.[20] was employed. Cyclohexylamine (5.95 g, 60 mmol) in 18 mL of $CHCl_3$ was cooled in an ice–water bath, and chlorosulfonic acid (2.34 g, 20 mmol) was added dropwise with vigorous stirring over a period of 30 min. The reaction solution was then allowed to warm to room temperature, and the stirring was continued for another 8 h. The white precipitate was filtered (5.28 g, 63%). An aliquot (2.00 g, 4.84 mmol) was suspended in 7 mL of water, and 2 N NaOH solution was added dropwise until the pH reached 12. The basic solution was extracted with ethyl acetate to remove free amine (Note: cyclohexylamine hydrochloride is soluble in CH_2Cl_2–i-PrOH (2/1, v/v), and thus, unless removed it would contaminate the product in the next step). The extracted solution was acidified with concd HCl to pH 0 and then it was extracted with CH_2Cl_2/i-PrOH (2/1, v/v) (3x, 60 mL total). The extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 0.620 g of crystals (3.46 mmol, 72%), mp 161–163 °C (lit.[20] mp 169–170 °C, uncorrected): NMR (DMSO-d_6) δ 9.85 (s, 1 H, broad), 3.18 (m, 1 H), 2.14–1.08 (m, 10 H); IR (KBr) 3125, 2931, 1537, 1266, 1252, 707 cm^{-1}.

Potassium *N*-Nitroso-*N*-cyclohexylsulfamate (2d). *N*-Cyclohexylsulfamic acid (**1d**) (20 mg, 0.11 mmol) was dissolved in 0.3 mL of water at room temperature and KNO_2 (24 mg, 0.28 mmol) was added. The solution became weakly yellowish in color, and a few bubbles were formed. A small amount of crystalline material separated within a few min. The solution was cooled to 4 °C for 20 min; white plates formed, which were collected by filtration (12 mg, 44%), mp (66 °C, partial dec; 191 °C, crystals sintered; still solid at 230 °C): NMR (DMSO-d_6) δ 4.36 (m, 1 H), 2.1–1.0 (m, 10 H); IR (KBr) 2938, 1458, 1275, 1268, 1257, 1248 cm^{-1}.

Attempts To Synthesize (1-Phenylethyl)sulfamic Acid. Several attempts to synthesize the title compound failed; the following methods were used: (a) the original method of Audrieth et al.;[20] (b) the modified method of Audrieth et al. used to synthesize **1b** in this report; and (c) the general method of Boyland et al.[48] (1-phenylethylamine with chlorosulfonic acid in pyridine). The optically active analogue was reported in a patent.[49]

Decomposition of Potassium *N*-Benzyl-*N*-nitrososulfamate (2b). In D_2O. The decomposition of a 12 mM solution of compound **2b** in D_2O was followed via NMR spectroscopy. Little or no reaction occurred during the first 3 h. The subsequent reaction accelerated in rate; after 24 h, the decomposition of **2b** was complete. The products were benzyl alcohol (**3b**; 99.5%) and potassium benzyl sulfate (**4b**; 0.5%).

In a pD 2.0 Sulfate Buffer. In 2.0 mL of D_2O was dissolved 57.2 mg (0.42 mmol) of potassium bisulfate and 14.1 mg (87.5% assay, 0.22 mmol) of potassium hydroxide ($[SO_4^{2-}]$ + $[HSO_4^-]$ = 0.21 M) (pD = 2.0). The solution was freeze-dried then dissolved in 2.0 mL of D_2O. This procedure is repeated once more. About 3 mg of compound **2b** was dissolved in 1.0 mL of this buffered D_2O solution, and the decomposition was followed by NMR spectroscopy. After 15 h the compound was totally decomposed. The NMR spectrum showed that the products were benzyl alcohol (**3b**; 98%) and potassium benzyl sulfate (**4b**; 2%); the δ 4.19 peak[28] of phenylmethanesulfonic acid (eq 2) was not detected.

In a 1.4 M, pD 2.0 Sulfate Buffer. To 3.0 mL of distilled water was added 572.0 mg (4.2 mmol) of potassium bisulfate and 141.0 mg (2.2 mmol) of potassium hydroxide; the pH was 2.0. The "freeze-drying and dissolution in D_2O procedure" described in the entry above was carried out twice. Above 3 mg of compound **2b** was dissolved in 1.0 mL of this buffered D_2O solution. After 22 h, the NMR spectrum showed that the products formed were benzyl alcohol (**3b**; 96%) and potassium benzyl sulfate (**4b**; 4%).

In a pD 2 Sulfate Buffer Containing Sodium Thiocyanate. Compound **2b** (2.4 mg, 0.0094 mmol) and sodium thiocyanate (6.5 mg, 0.08 mmol) were dissolved in 0.8 mL of a pD 2.0 sulfate buffer ($[KHSO_4]$ = 0.1 M and $[K_2SO_4]$ = 0.11 M). To the tube was added 0.8 mL of $CDCl_3$. After a reaction time of 1.5 h, the NMR spectrum of the $CDCl_3$ phase showed signals for the methylene groups of benzyl alcohol (**3b**; δ 4.71 ppm) and benzyl thiocyanate (**5b**; 4.17). Since compound **3b** has the same chemical shift as benzyl isothiocyanate (**6b**) in $CDCl_3$, the chloroform phase was separated and dried over anhydrous sodium sulfate. After removal of the solvent (aspirator vacuum), the remaining product was dissolved in C_6D_6; the NMR spectrum showed signals for the methylene groups of **3b** (4.29 ppm), **5b** (3.07), and **6b** (3.63). The product distribution was 96% of **3b**, 3.2% of **5b** and 0.8% of **6b**.

In a 61 mM Acetate Buffer. In 2.0 mL of D_2O was dissolved 7.0 μL (0.122 mmol) of glacial acetic acid and 2.8 μL of 40% potassium deuteroxide in D_2O. Additional KOD solution was added to adjust the pH to 4.2. About 2.4 mg of compound **2b** was dissolved in 0.8 mL of this buffer, and the decomposition was followed by NMR ($t_{1/2}$ = 11 days at 25 °C). The major product was benzyl alcohol (**2b**) (>99%); trace amounts of compound **4b** and benzyl acetate (**7b**) were also observed (<1%).

In Acetic Acid. Compound **2b** (2.4 mg; 0.0094 mmol) was added to 0.8 mL of acetic acid-d_4; decomposition was immediate with copious evolution of bubbles. The products formed, as determined by NMR techniques, were benzyl alcohol (**3b**) (12%) and benzyl acetate (**7b**) (88%).

In Ether Containing Benzoic Acid. Diethyl ether (~0.1 mL) was added to a mixture of 5 mg (0.019 mmol) of **2b** (freshly made) and 3.3 mg (0.027 mmol) of benzoic acid. The mixture was left at room temperature for 4 h, then the ether was allowed to evaporate. The remaining solid was evacuated to a pressure of $\sim 10^{-2}$ Torr. The NMR spectrum in DMSO-d_6 showed 34% benzyl benzoate (δ 5.36 (s, 2 H)), 5% dibenzyl sulfate (δ 5.31 (s, 4 H)), 37% **4b** (δ 4.76 (s, 2 H)), 12% **2b** (δ 4.79 (s, 2 H)), and 12% **3b** (δ 4.53 (s, 2 H)). In a similar run, 2.4 mg (0.019 mmol) of benzoic acid was used together with 5 mg (0.019 mmol) of freshly made **2b**. After 46 h, the solution was treated in the same way as described for the first run and the residue was dissolved in 0.6 mL of DMSO-d_6. The NMR spectrum showed 46% benzyl benzoate, 1% dibenzyl sulfate,[50] 28% **4b**, and 25% **3b**.

In the Solid State at 25 °C. A sample of compound **2b** which was not vacuum dried after preparation was kept in a closed bottle for 30 h at 25 °C. The crystals (2 mg) were washed with 0.6 mL of $CDCl_3$, and the residue was dissolved in 0.6 mL of D_2O. The NMR spectrum of the $CDCl_3$ solution showed only two compounds, dibenzyl sulfate[50] [δ 5.15 (s, 2 H)] and **3b** [4.57 (s, 2 H)] in a ratio of 3.4:1. The NMR spectrum of the D_2O solution showed three compounds: **4b** [δ 4.96 (s, 2 H)], **2b** [4.92 (s, 2 H)], and **3b** [4.52 (s, 2 H)] in a ratio of 6:6:1.

In the Solid State at 50 °C. Compound **2b** was ground with KBr crystals, and the mixture was compressed into a disk. The first IR spectrum was taken at 25 °C before the sample had been heated to 50 °C. The decomposition thereafter was followed by IR. It was found that the decomposition was first order with a half-life of approximately 10 h (based on the absorption peak at 1438 cm^{-1}). By a comparison with authentic samples, it was found that approximately 90% potassium benzyl sulfate (**4b**) and 10% potassium sulfate (ν 1115 and 619 cm^{-1}) were formed (estimate based on a comparison of IR intensities and the assumption that K_2SO_4 had the same IR absorption coefficiency as potassium benzyl sulfate). Benzyl bromide and benzyl alcohol lack strong characteristic IR frequencies, and they were not detected.

Decomposition of Potassium *N*-Nitroso-*N*-(2-phenylethyl)sulfamate (2c). In D_2O. Compound **2c** (3 mg) was dissolved in 0.5 mL of D_2O at 25 °C, and NMR spectra were run

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(49) Spicer, L. D.; Hand, J. J. (Am. Cyanamide Co.) Ger Offen. 2,061,770, July 1, 1971, Appl. Dec 15, 1970; *Chem. Abstr.* **1971**, *75*, 110308n.
(50) Grinev, A. I.; Krichevskii, É. S.; Romanova, O. B.; Filipenko, T. Ya.; Polezhaeva, A. I. *Pharm. Chem. J.* **1984**, *17*, 635 (Engl. Translation of Khimikofarmatsercheskii Zhurnal **1983**, *17*, 1066. Dietz, K. Ger 1,079,319, Apr 7, 1960.

at invervals. No decomposition was noted after 19 h. After 44 h, the compound was completely decomposed; the products were 2-phenylethyl alcohol (85%) and 1-phenylethyl alcohol (15%). No sign of styrene was seen in an $CDCl_3$ extract of the D_2O solution.

In a pD 2.0 Sulfate Buffer. Compound **2c** (3 mg) was dissolved in a pH 2, 0.21 M sulfate buffer in D_2O at 25 °C, and NMR spectra were run at regular intervals. The decomposition of **2c** was found to be a first-order reaction with $t_{1/2}$ 26 min. Among the decomposition products were 2-phenylethyl alcohol (75%), 1-phenylethyl alcohol (17%), and potassium 2-phenylethyl sulfate (8%).

In the Solid State at 25 °C. A mixture of compound **2c** and KBr was ground together and compressed into a disk. IR spectra taken at regular intervals at 25 °C showed that the decomposition half-life was about 6 days. In a second run, crystals of **2c** were allowed to decompose at 25 °C for 3 weeks. The yellowish crystals formed were extracted with $CDCl_3$; the ^{1}H-NMR spectrum showed the presence of essentially pure bis(2-phenylethyl) sulfate[51] (no styrene or 2-phenylethyl alcohol was observed). An IR spectrum of the residue showed 85% of K_2SO_4 (1115 and 619 cm^{-1}) and 15% of potassium 2-phenylethyl sulfate (**4c**) (1247 and 1225 cm^{-1}).

In the Solid State at 50 °C. Crystals of compound **2c** were heated at 50 °C for 17 h, and the reaction residue was dissolved in DMSO-d_6. An NMR spectrum showed that compound **2c** had completely decomposed during this time to give 53% of bis(2-phenylethyl) sulfate, 40% of potassium 2-phenylethyl sulfate, 2% of rearranged products,[52] and a trace amount of styrene.

In the Solid State at −10 °C. Compound **2c** was kept at −10 °C without desiccation for 10 days. No decomposition was observed (note that **2b** without desiccation decomposed at −10 °C within a week).

Decomposition of Potassium *N*-Nitroso-*N*-cyclohexylsulfamate (2d). In a pD 2 Sulfate Buffer. Compound **2d** (3 mg) was dissolved in 0.7 mL of a pD 2, 0.21 M sulfate buffer. Bubbles were immediately formed, and the decomposition was essentially over in 3 min, as evidenced by the cessation of gas evolution and the invarience of subsequent NMR spectra. It was found that the products were cyclohexyl alcohol (84%), cyclohexene (8%), and potassium cyclohexyl sulfate (8%).

In the Solid State at 25 °C. Compound **2d** was ground with KBr, and the mixture was compressed into a disc and stored at 25 °C. It was estimated (IR) that 90% of **2d** had decomposed in 33 h based on the intensity of the peak at 1458 cm^{-1} (NO group); product absorption frequencies were noted at 1123 and 621 cm^{-1}.

A Search for Nitrous Oxide. In 2 mL of a pH 1.5 sulfate buffer ($[KHSO_4]$ = 0.156 M and $[K_2SO_4]$ = 0.055 M) was dissolved 16 mg (0.062 mmol) of **2b**. The solution was kept in a 15-mL sealed glass tube for 30 h at 25 °C. The tube was then connected to an evacuated 50-mL IR cell, and by means of a stopcock the pressures were allowed to equilibrate. The IR spectrum showed no sign of nitrous oxide (which exhibits three strong peaks at 2214, 1285, and 590 cm^{-1}).[53]

The Photochemical Decomposition of Potassium *N*-Benzyl-*N*-nitrososulfamate (2b). A 0.05 M solution of compound **2b** in D_2O in a quartz vessel was cooled in a stream of tap water at ~20 °C. Irradiation was carried out with a 450-W Hanovia medium-pressure mercury discharge lamp held ~1 in. from the sample. An NMR spectrum taken after 4 min of irradiation time showed a singlet at 8.95 ppm as the only new signal (the $t_{1/2}$ of photodecomposition was ~30 min.

Within a few hours of the start of irradiation, a signal for benzaldehyde appeared at 10.03 ppm. Extraction of the irradiated solution with $CDCl_3$ gave solutions that contained benzaldehyde, but not the salts (starting material and potassium benzylidenesulfamate). Similar results were obtained for irradiations carried out in a Pyrex vessel.

The ammonium salt of benzylidenesulfamic acid was prepared by condensing benzaldehyde with an equimolar amount of ammonium sulfamate in methanol (concentration ~0.05 M). Although the generalized directions for this reaction (eq 5) recommend a period of reflux,[33] the reaction is apparently complete within 5 min at 25 °C. Evaporation of the reaction solution gave a crystalline solid, which decomposed rapidly on attempted purification. The mp observed (in a sealed, evacuated capillary tube) was 178 (s), 250–272 °C dec: NMR (D_2O) δ 8.95 (s, 1 H), 7.5–8 (m, 5 H) (the solutions also gave a weak signal for benzaldehyde, δ 10.03 ppm, which grew in time at the expense of the 8.95 peak); NMR (DMSO-d_6) 8.72 (s, 1 H).

Inhibition of Pepsin with Compound 2b. Pepsin (5.0 mg, 1.4×10^{-4} mmol) was dissolved in 2 mL of pH 2.0, 50 mM sulfate buffer at 25 °C. Compound **2b** (2.0 mg, 7.9×10^{-3} mmol)[54] was added as solid (inhibitor/enzyme = 55); it quickly dissolved in the solution. The activity of the solution was followed using the assay method of Spencer et al.[55] After 1 h, the activity was 89%. A second batch of **2b** (5 mg, 2.0×10^{-2} mmol) was added 80 min after the first inhibitor addition (ratio = 138 now). After a total reaction time of 2 h, the measured enzyme activity was 75%.

Kinetics of Decomposition. The sulfate buffer solutions were prepared from weighed amounts of potassium bisulfate and potassium hydroxide dissolved in redistilled water; when necessary, additional amounts were added to reach the desired pH value. The pH 2 HCl solution was prepared by adding 5 N HCl to 10 mL of redistilled water until the pH reached 2.00. The working solution was prepared by dissolving 3 mg of **2b** in 1.0 mL of the buffer solution in a quartz cell (path length 1.0 cm) at room temperature. The decomposition rates were monitored by following the decreasing absorbance of the nitroso group at 365 nm. The temperature was controlled by circulating water through the cell holder.

In the sulfate buffer solutions, the proton concentration is constant so the decomposition is a pseudo-first-order reaction with $k_{obs} = k[H^+]$ (eq 1a). The plot of ln (absorbance) vs time gives

$$\text{rate} = -\text{d}[\mathbf{2b}]/\text{d}t = k[H^+][\mathbf{2b}] \quad (1a)$$

a straight line whose slope generates the k_{obs}, and from the proton concentrations in each buffer solution the second-order rate constant, k, for the decomposition of **2b** can be calculated.

When the nitroso compound **2b** is dissolved in pure distilled water or in a pH 2 HCl solution, the decomposition is no longer a pseudo-first-order reaction. As shown in eq 3a a proton is generated whenever a benzyl alcohol molecule (**3b**) is formed. This proton joins the other protons already present in the solution in catalyzing the decomposition of **2b**. Therefore, the decomposition reaction becomes a self-catalyzing second-order reaction. If we suppose that m percent of the total decomposed **2b** becomes **3b**, the relationship between the concentration of the nitrososulfamate, [**2b**], and the reaction time, t, will be established as following:

$$\text{d}[\mathbf{2b}]/\text{d}t = k([H^+]_0 + m([\mathbf{2b}]_0 - [\mathbf{2b}]))[\mathbf{2b}] \quad (2a)$$

$$\ln [\mathbf{2b}] - \ln ([H^+]_0 + m([\mathbf{2b}]_0 - [\mathbf{2b}])) = -k([H^+]_0 + m[\mathbf{2b}]_0)t + \ln [\mathbf{2b}]_0 - \ln [H^+]_0 \quad (3a)$$

$[H^+]_0$ and $[\mathbf{2b}]_0$ are, respectively, the concentrations of proton and the nitroso compound (**2b**) at the beginning of the reaction. A Macintosh computer was used to run the line-fitting program (Kaleida Graph). The program accepts the input values of $[H^+]_0$, $[\mathbf{2b}]_0$, [**2b**]'s and t's and it fits the plot of t vs [**2b**] by independently varying the values of k and m until it reaches the best fit.

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(51) This compound, previously unreported, was characterized as follows: NMR ($CDCl_3$) δ 7.3–7.1 (m, 5 H), 4.23 (t, 2 H, J = 6.8 Hz), 2.94 (t, 2 H, J = 6.8 Hz); NMR (DMSO-d_6) δ 7.4–7.1 (m, 5 H), 4.30 (t, 2 H, J = 7 Hz), 2.94 (t, 2 H, J = 7 Hz); HRCIMS m/e calculated ($C_{16}H_{18}O_4S + NH_4^+$) 324.1270; m/e found 324.1275; EIMS m/e 105 (100), 104 (58), 91 (72).

(52) Three small doublets near 1 ppm were noted; these presumably stem from different 1-phenylethyl compounds.

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(54) Compound **2b** was characterized by NMR (both in D_2O and DMSO-d_6) and IR (KBr) spectra immediately before the inhibition; both kinds of spectra showed that **2b** was very pure.

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hong Song for carrying out the photochemical reaction and James Chou for valuable assistance.

Registry No. **1b**, 46119-69-1; **1c**, 138337-13-0; **1d**, 100-88-9; **2b**, 138337-14-1; **2c**, 138337-15-2; **2d**, 138337-16-3; **3b**, 100-51-6; **3c**, 60-12-8; **3d**, 108-93-0; **4b**, 18687-57-5; **4c**, 138337-17-4; **4d**, 18687-60-0; **5b**, 3012-37-1; **6b**, 622-78-6; **7b**, 140-11-4; $PhCH_2NH_2$, 100-46-9; $ClSo_3H$, 7790-94-5; $Ph(CH_2)_2NH_2$, 64-04-0; NaSCN, 540-72-7; $PhCO_2H$, 65-85-0; AcOH, 64-19-7; $PhCO_2CH_2Ph$, 120-51-4; $PhCH_2OSO_3CH_2Ph$, 18495-74-4; $Ph(CH_2)_2OSO_3(CH_2)_2Ph$, 138337-18-5; PhCHO, 100-52-7; cyclohexylamine, 108-91-8; 1-phenylethylamine, 98-84-0; 1-phenylethyl alcohol, 98-85-1; cyclohexene, 110-83-8; ammonium benzylidenesulfamate, 22102-31-4; ammonium sulfamate, 7773-06-0; pepsin, 9001-75-6.

Synthesis of Multidentate Imidazole-Containing Macrocycles

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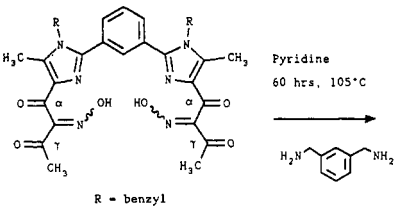
All three possible monomeric macrocyclic products and one dimeric product have now been isolated and spectrally characterized from the recently described[3] macrocyclization reaction which leads to imidazole-containing coronands. Alkali metal ion promoted reactions provide a small selectivity for the largest of the three monomeric macrocycles, coronand 1, and leads to improved yields (5–7%). Regioselective internal vs external N-alkylation of the imidazole derivatives of 1 is controlled by the counter cation employed. Small cations lead to external N-alkylation, while large cations lead to internal N-alkylation. This is evidence of selective cation binding within the cavity for the lithium and sodium imidazolates, but for potassium and larger ions, binding is at the external peripheral nitrogen atoms. Larger ions are likely excluded from the cavity because of the higher conformational energy costs involved. The X-ray structure of the symmetrically protected derivative of 1 has been obtained and confirms previous structural assignments.

Polydentate imidazole-containing ligands have found to be of general interest among bioinorganic research groups interested in metalloprotein model chemistry.[1] An active area of pursuit arising from such research is the synthesis of specially designed ligands with increasing degrees of conformational constraint.[2] Our own interests in this area prompted us to explore syntheses of imidazole-containing macrocycles, and in a recent communication[3] we reported the preparation and spectral characterization of the first member of a new imidazole coronand system, 1. In this paper we report improved experimental details and further coronand products that are obtained from this macrocyclization reaction. The X-ray crystal structure of the symmetrical 3,11,17,25-tetra-*N*-benzyl derivative of 1 has been determined and unambiguously confirms previous structural assignments.

Preparation of the Coronands. Coronand 1 is prepared from the reaction of *m*-xylylenediamine with 1,3-bis[1-benzyl-4-(2-(hydroxyimino)-1,3-dioxobutyl)-5-methylimidazol-2-yl]benzene, eq 1.[3] The macrocyclization reaction utilizes an imidazole condensation between benzylamines and oximes of β-dicarbonyl compounds.[4] Although yields in the final step are quite low, the synthetic route is both highly convergent and general, utilizing readily available starting materials. The precursor itself is prepared from *m*-xylylenediamine and 2-oximidopentanedione, and other (aminomethyl)heteroaromatics will also function in the imidazole-ring condensation.



1, 3, 4, 5 (1)

Table I lists conditions of macrocyclization experiments in various solvents, in the presence of various metal ions, and in both batch and high dilution conditions. Dry pyridine has so far proved to be the best solvent. Although from the outset we have carried out these reactions using high-dilution techniques, equal yields have been obtained from simple batch reactions in cases without addition of metal salts (entries 5 and 10). By stepwise increases of reaction temperatures in batch experiments in pyridine, no reaction progress was observed to occur at temperatures up to 90 °C over a 24-h period. Aliquots of the reaction solution only showed unreacted starting materials (entry 9). Slow reaction progress begins to be observed at temperatures above 100 °C, and complete consumption of reactants occurs within 24 h at reflux temperatures. The near equivalence of both the high dilution and batch methods may be due to the slow reaction rate at 105 °C, the temperature used for most of the high-dilution experiments. The reaction in pyridine solvent eliminates the triimidazole side products, **2a** and **2b**, that were routinely isolated from reactions in sulfolane. Product **2a** and **2b**

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