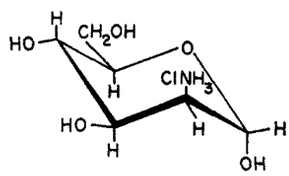
the anomeric effect.[25] In water, where considerable stabilization of an equatorial hydroxyl at C-1 can be achieved through solvation, the β-D anomer is the more stable.

It has been reported[12] that 2-amino-2-deoxy-D-mannose, prepared by treatment of an aqueous solution of the hydrochloride with sodium hydroxide, exhibits downward mutarotation. The present data clearly indicate that the free base present initially must have been an anomeric mixture. Since gross changes are possible under basic conditions, it is difficult to interpret the reported[12] mutarotation in terms of equilibria between tautomeric forms.



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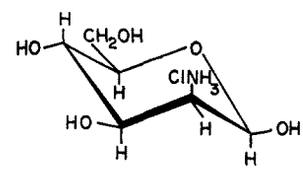

2

Experimental Section[26]

Nmr Measurements.—Spectra were measured with a Varian A-60 spectrometer; the temperature of the probe was approximately 40°. Sodium 4,4-dimethyl-4-silapentane-1-sulfonate (τ 10.00) was used as the internal standard for spectra measured in deuterium oxide, and tetramethylsilane (τ 10.00) was used as internal standard for spectra measured in methyl sulfoxide-d_6 or *N*,*N*-dimethylformamide. Chemical shifts were measured directly from spectra determined at a sweep width of 500 cps. The recorded J values are first-order coupling constants, as measured directly from spectra determined at a sweep width of 100 cps. Integrated peak intensities (±3%) are the mean of several integration curves, determined in both directions at a sweep width of 100 cps, and were also determined with the use of a planimeter. Deuteration was performed by adding 1 drop of deuterium oxide to the prepared sample. Each experiment was repeated a number of times, and concordant spectral data were recorded. Solutions were kept at room temperature except during spectral measurements.

2-Amino-2-deoxy-D-mannose Hydrochloride.—2-Acetamido-2-deoxy-D-mannose monohydrate[16,17] was hydrolyzed,[8] and the product was crystallized from water–ethanol–acetone as small, clear prisms: yield 88%; mp 178–180° dec; $[\alpha]^{22}D$ −3.7 ± 0.5° [3 min, unchanged after 24 hr (*c* 1.4, water)] [lit.[4,11] mp 178–180°, $[\alpha]^{25}D$ −3.2° (*c* 10, water)], $[\alpha]^{22}D$ −5.2 ± 0.6° (15 min) → −3.9 ± 0.6° (12 hr) → +0.6 ± 0.6° [7 days, final (*c* 3.6, methyl sulfoxide)]; λ_{max}^{Nujol} 12.06 μ (weak) (equatorial H-1 in pyranoid ring[18,19]); R_g[27] 1.13; X-ray powder diffraction data, 7.44 m, 6.71 s (4), 6.51 w, 5.61 m, 4.87 m, 4.62 vw, 4.33 vw, 4.21 s (3), 4.02 w, 3.95 vs (1,1), 3.69 vs (1,1), 3.41 s (2), 3.22 vw, 3.11 vw, 2.99 w, 2.87 vw, 2.79 w, 2.68 vw, 2.56 m, 2.51 vw, 2.44 m.

Anal. Calcd for $C_6H_{14}ClNO_5$: C, 33.26; H, 6.48; N, 6.50. Found: C, 33.04; H, 6.11; N, 6.66.

The X-ray powder diffraction pattern was identical with that recorded by Comb and Roseman.[7] The substance was recovered unchanged from the equilibrated solution in methyl sulfoxide, by evaporation and crystallization of the residue from water–ethanol–acetone.

2-Amino-2-deoxy-D-mannose hydrochloride, having all exchangeable hydrogens replaced by deuterium, was prepared by evaporating a solution of the sugar in deuterium oxide several times with small portions of deuterium oxide; the resultant syrup crystallized on standing. A portion of this product was dissolved in a small amount of deuterium oxide, ethyl deuterioxide was added, followed by acetone, and the substance was allowed to crystallize slowly. The clear prisms thus obtained had an X-ray powder diffraction pattern identical with that of the nondeuterated material.

Nmr Spectrum of 2-Amino-2-deoxy-D-mannose Hydrochloride.

A. In Deuterium Oxide.—A 28–35% solution of the sugar in deuterium oxide showed two doublets at lowest field, total integral of one proton, at τ 4.60 (broadened, $J_{1,2}$ = 1.1 cps, H-1 of α-D anomer, **1**) and 4.78 ($J_{1,2}$ = 1.5 cps, H-1 of β-D anomer, **2**), in relative proportion 43:57. The HOD signal was observed at τ 5.34, and the protons on C-2, -3, -4, -5, and -6 gave a six-proton multiplet, τ 5.85–6.60. There was little observable difference between a spectrum measured 30 sec after dissolution of the crystalline sample, and spectra measured 5 hr and 3 days later.

B. In Methyl Sulfoxide.—A 25% solution of the sugar in methyl sulfoxide-d_6 containing approximately 10% of deuterium oxide showed two signals, total integral 1 proton, below τ 5.5; a narrow, unresolved multiplet, 4.78, width at half-height of 3.2 cps (H-1 of α-D anomer, **1**) and a doublet at 5.00 [$J_{1,2}$ = 1.4 cps (H-1 of β-D anomer, **2**)]. Integration indicated that the α-D and β-D anomers were present in approximately 2 to 1 proportion. Signals of the protons on C-2, -3, -4, -5, and -6 gave a multiplet, τ 5.9–6.8. Addition of more deuterium oxide caused the signal at τ 5.00 to increase in intensity at the expense of the signal at 4.78.

The spectrum of the sugar, measured a few minutes after dissolution in dry methyl sulfoxide, showed a broad signal, τ 1.7–2.3 (NH_3^+) and a complex series of signals, 4.6–5.6. After 2 days the spectrum showed a broad signal, τ 1.90 (less than three protons, NH_3^+), a signal ~4.75 (H-1 of α-D anomer, **1**), and a broad multiplet, 4.95–5.3 (greater than four protons, OH, H-1 of β-D anomer, **2**). After deuteration, the solution gave a spectrum identical with that observed with a freshly prepared solution of the sugar in methyl sulfoxide–deuterium oxide.

Deuterium-exchanged 2-amino-2-deoxy-D-mannose hydrochloride (70 mg), which had been crystallized from a solvent mixture, was dissolved in methyl sulfoxide-d_6 (0.28 ml). Spectra measured 4, 8, 15, and 40 min after dissolution showed signals at τ 4.78 and 5.00 in approximate proportion 1:3; no difference in relative intensities of the two signals was observed during this period. After 2 days, the two signals were of approximately equal intensity, and after 4 days the intensity ratios were approximately 2:1, indicating a preponderance of the α-D anomer (**1**). Addition of a drop of deuterium oxide at this point caused little change in the intensity ratios of the two signals.

Deuterium-exchanged 2-amino-2-deoxy-D-mannose hydrochloride (crystallized syrup) gave signals at τ 4.78 and 5.00 in the approximate proportion 2:3 when first dissolved in methyl sulfoxide-d_6; after 4 days the relative proportions were 2:1.

C. In *N*,*N*-Dimethylformamide.—A freshly prepared solution of 2-amino-2-deoxy-D-mannose hydrochloride in *N*,*N*-dimethylformamide showed a complex series of signals in the range τ 3.0–5.5; deuteration of the sample gave, after 12 hr, two narrow doublets in this region, τ 4.54 ($J_{1,2}$ = 1.4 cps, H-1 of **1**) and 4.78 ($J_{1,2}$ = 1.6 cps, H-1 of **2**), in the approximate ratio of 11:9.

(25) Reference 13, pp 375–377.

(26) Melting points were determined with a Thomas–Hoover Unimelt apparatus (Arthur H. Thomas Co., Philadelphia, Pa.). Specific rotations were determined in a 2-dm polarimeter tube. Infrared spectra were measured with a Perkin-Elmer Infracord infrared spectrometer. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings (A) for Cu Kα radiation. Camera diameter was 114.59 mm. Relative intensities were estimated visually: s, strong; m, moderate; w, weak; v, very. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

(27) Mobility relative to 2-amino-2-deoxy-D-glucose, by tlc on microcrystalline cellulose [M. L. Wolfrom, R. M. de Lederkremer, and D. L. Patin, *J. Chromatog.*, **17**, 488 (1965)] with 5:5:1:3 pyridine–ethyl acetate–acetic acid–water as the developer; indication with alkaline silver nitrate and with ninhydrin.

Vilsmeier Reaction of Methylpyrazine

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In view of our recent finding[2] that condensation of 2-amino-3-methylpyrazines with the Vilsmeier reagent

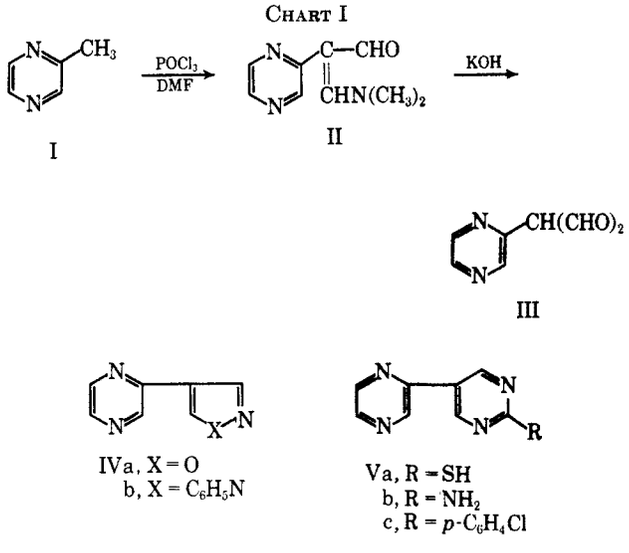
(1) Author to whom inquiries should be addressed.

(2) S. Klutchko, H. V. Hansen, and R. I. Meltzer, *J. Org. Chem.*, **30**, 3454 (1965).

results in the formation of 4,7-diazaindole-3-carboxaldehydes, it was of interest to extend this reaction to 2-methylpyrazine (I) itself. Addition of this heterocycle to a solution of 3 moles of phosphorus oxychloride in excess dimethylformamide, under conditions similar to those utilized by Arnold[3] with 4-picoline, furnished, in moderate yield, a new crystalline compound $C_9H_{11}N_3O$. Spectral data indicate the presence of an extended chromophoric system, in particular a vinylogous amide carbonyl function[4] giving rise to absorption at 1620 cm^{-1}. On this basis, the condensation product was assigned the structure 3-dimethylamino-2-(2-pyrazinyl)acrolein (II). Confirmation of this assignment was derived from its nmr spectrum, which showed the presence of two N-methyl groups (sharp singlet, 2.95 ppm) and three aromatic protons (multiplet, 8.3–8.8 ppm) in addition to signals at 9.1 and 7.18 ppm, due to the proton of the formyl group and the vinyl proton adjacent to nitrogen in the side chain, respectively. Alkaline hydrolysis of II gave the enolic malonaldehyde (III).

Thus, Vilsmeier acylation of methylpyrazine is strictly analogous to the previously reported reactions of 4-methylpyrimidine[5] and 4-picoline (but not the 2 isomer)[3] with this reagent. (See Chart I.)

CHART I



The Vilsmeier adduct (II) proved to be a versatile intermediate for the preparation of heterocycles substituted with a pyrazine ring. Thus, condensation with the carbonyl reagents hydroxylamine and phenylhydrazine furnished the isoxazole (IVa) and pyrazole (IVb), respectively. Similarly, reaction with urea derivatives or amidines gave the 5-(2-pyrazinyl)-pyrimidines (Va–c).

Experimental Section

3-Dimethylamino-2-(2-pyrazinyl)acrolein (II).—To a cooled solution of 250 g (1.63 moles) of phosphorus oxychloride in 500 ml of dimethylformamide was added, with stirring, 51 g (0.541 mole) of 2-methylpyrazine. The mixture was heated to 60° for 8 hr, then stirred overnight at room temperature. The dark mixture was then added slowly to a mixture of 500 ml of ethanol and 1200 ml of saturated aqueous potassium carbonate, containing excess solid carbonate. The resulting slurry was filtered from inorganics, the cake was washed well with ethanol, and the combined organic solutions were evaporated to dryness. The damp residue was taken up in fresh ethanol, filtered through solid potassium carbonate, and evaporated again. The residual material was next taken up in hot benzene, treated with charcoal, and filtered. Evaporation of the benzene solution to *ca.* 200 ml gave 58.5 g (61%) of the desired acrolein derivative, mp 95–100°.

Repeated recrystallization from benzene furnished a white analytical sample of 3-dimethylamino-2-(2-pyrazinyl)acrolein, mp 107.5–108°. Because of the large losses sustained on repeated recrystallization, it was found more convenient for further synthetic work to make up a solution of the crude acrolein derivative in a suitable solvent, treat with charcoal, filter, and use the resulting clarified solution directly in various reactions: λ_{max}^{EtOH} 287 mμ (ε 26,400), 322–338 mμ sh (ε 5280); $\nu_{C=O}^{Nujol}$ 1620 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 61.20; H, 6.38; N, 23.43, 23.46.

2-(2-Pyrazinyl)malonaldehyde (III).—A solution of 2.3 g (0.041 mole) of potassium hydroxide in 100 ml of water was added to 7 g (0.040 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein (I) in 5 ml of water. The mixture was heated on a steam bath until the evolution of dimethylamine was complete. After cooling, addition of dilute hydrochloric acid to a pH of *ca.* 4 caused precipitation of the crude dialdehyde. Purification by recrystallization from a large volume of ethanol gave 5.7 g (96%) of analytically pure 2-(2-pyrazinyl)malonaldehyde (III): mp 207–208.5°; λ_{max}^{EtOH} 259 mμ (ε 15,300), 286 sh (8350), 389–395 (5700); ν^{Nujol} 1640, 1615, 1585, 1565, 1550 cm^{-1}.

Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.90; H, 4.17; N, 18.72.

4-(2-Pyrazinyl)isoxazole (IVa).—To a solution of 8 g (0.045 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein in a minimum amount of water, 4 g (0.057 mole) of hydroxylamine hydrochloride was added. The resulting solution was refluxed until precipitation of the isoxazole derivative commenced. Cooling and filtration gave 5.75 g (86%) of 4-(2-pyrazinyl)isoxazole, mp 133.5–136.5°. Recrystallization from aqueous ethanol gave an analytical sample of mp 135–137°; λ_{max}^{EtOH} 234 mμ (ε 10,380), 286 (8040); ν^{Nujol} 1610 cm^{-1}.

Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.16; H, 3.59; N, 28.56.

1-Phenyl-4-(2-pyrazinyl)pyrazole (IVb).—An aqueous solution of 7 g (0.04 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein (II) and 5.8 g (0.04 mole) of phenylhydrazine hydrochloride was warmed briefly while the pyrazole derivative precipitated. After cooling overnight, filtration gave 6.85 g (74%) of 1-phenyl-4-(2-pyrazinyl)pyrazole, mp 135–139°. Recrystallization from ethanol (charcoal) gave pure material, mp 140–142°. This material gave consistently low values for nitrogen in microanalysis, although values found for carbon and hydrogen were well within limits; this may be a function of the compound: λ_{max}^{EtOH} 273 mμ (ε 15,800), 295 (16,500), 314 sh (13,450).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.35; H, 4.49; N, 24.19.

2-Mercapto-5-(2-pyrazinyl)pyrimidine (Va).—A solution of 9 g (0.051 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein and 3.9 g (0.053 mole) of thiourea in 135 ml of absolute ethanol was treated with 12.6 ml of concentrated hydrochloric acid and allowed to stand overnight. Filtration furnished 7.9 g (82%) of 2-mercapto-5-(2-pyrazinyl)pyrimidine, mp 184–188° dec. Purification was effected by solution in aqueous potassium hydroxide, treatment with charcoal, filtration, and acidification with dilute hydrochloric acid to pH 5. An analytically pure sample prepared by this technique had mp 246–247° dec.

Under certain circumstances, this compound may exist as the tautomeric 5-(2-pyrazinyl)-1,2-dihydro-(1H)-pyrimidine-2-thione: λ_{max}^{EtOH} 255 mμ (ε 4600), 340 mμ (ε 23,560); ν^{Nujol} 2620 (NH or SH), 1195 (C=S) cm^{-1}.

Anal. Calcd for $C_8H_6N_4S$: C, 50.51; H, 3.18; N, 29.45; S, 16.86. Found: C, 50.59; H, 3.34; N, 29.38; S, 16.99.

2-Amino-5-(2-pyrazinyl)pyrimidine (Vb).—A mixture of 7 g (0.04 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein and 3.5 g (0.02 mole) of guanidine carbonate in 200 ml of xylene was refluxed for 3 hr with continuous removal of the water formed in the reaction. Filtration, after cooling overnight gave 6.3 g (92%) of the crude pyrimidine derivative, mp 207–210°. Recrystallization from ethanol gave moderate recovery of pure

(3) Z. Arnold, *Collection Czech. Chem. Commun.*, **28**, 863 (1963).
(4) G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).
(5) H. Bredereck and G. Simchen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 738 (1963).

2-amino-5-(2-pyrazinyl)pyrimidine: mp 213–216°; λ_{max}^{EtOH} 236 mμ (ε 5670), 266 (16,300), 295 (20,500); ν^{Nujol} 3100, 3300 (NH), 1660 (C=N) cm^{-1}.

Anal. Calcd for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.28; H, 4.35; N, 40.22.

2-(*p*-Chlorophenyl)-5-(2-pyrazinyl)pyrimidine (Vc).—A mixture of 12 g (0.068 mole) of 3-dimethylamino-2-(2-pyrazinyl)acrolein and 11 g (0.0575 mole) of *p*-chlorobenzamidine hydrochloride[6] in 200 ml of dimethylformamide was refluxed for 2 hr and then allowed to cool overnight. Filtration furnished 9 g (50%) of substantially pure 2-(*p*-chlorophenyl)-5-(2-pyrazinyl)pyrimidine, mp 215–218°. Recrystallization from dimethylformamide gave analytical material: mp 215.5–217.5°, λ_{max}^{EtOH} 300 mμ (ε 36,200).

Anal. Calcd for $C_{14}H_9ClN_4$: C, 62.58; H, 3.38; Cl, 13.19; N, 20.85. Found: C, 62.77; H, 3.40; Cl, 13.27, 13.39; N, 20.71.

Acknowledgment.—The authors wish to thank Mr. S. Klutchko for many helpful discussions of this work. We are also indebted to Mrs. U. Zeek for the microanalysis and to Mr. R. Puchalski for the spectral data reported herein.

(6) P. A. Fanta and E. A. Hedman, *J. Am. Chem. Soc.*, **78**, 1434 (1956).

Electrolytic Reductive Coupling. XI.[1] Reaction with Acceptors of the Intermediates Produced by Electrolytic Cleavages

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While there is a considerable literature on the electrolytic reductive cleavage of a variety of organic structures (*e.g.*, quaternary ammonium[2] and phosphonium[3] salts, alkyl[4] and aryl halides, disulfides,[5] activated carbon–nitrogen and carbon–sulfur[6] bonds), there seems to have been no attempt to involve the intermediates produced by cleavage in *in situ* reactions with suitable organic acceptors. Previously the fragments have simply been allowed to react with proton donors available in the catholyte and the products obtained or postulated have formally been those that might have been expected from selective hydrogenolysis of the starting materials.[7]

In our continuing study of electrolytic reductive coupling as a synthetic tool we have examined the possibility of effecting condensations by producing by electrolytic fission donors—radicals, anion radicals, carbanions—in the presence of activated olefins (usually acrylonitrile) as acceptors. This principle of condensation was confirmed for two classes of electrolytically generated donors. Yields were poor because of competing reactions which will be discussed below. The following paper[8] reports a more intensive investigation of one type of cleavage–condensation reaction, that in which the donors are derived from certain cyanoalkylonium compounds.

Electrolyses at a mercury cathode of compounds LCH_2E[9] (L = "leaving group" liberated by electroreduction, E = electron-withdrawing group) in aqueous quaternary ammonium electrolytes containing excess acrylonitrile were used as one model system.

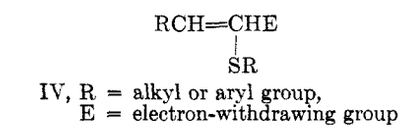
Dimethylcyanomethylsulfonium *p*-toluenesulfonate (I) took up 88% of the theory required for two electrons at a cathode voltage (sce) which gradually changed from −0.75 to −1.08 v. The only condensation product isolated was glutaronitrile (20% crude,[10] 10% distilled material).

Benzyldimethylsulfonium *p*-toluenesulfonate (II) underwent a (coulometric) two-electron reduction at a cathode voltage (sce) of −1.41 to −1.59 v. The crude condensation product (29%) on distillation was found to have 4-phenylbutyronitrile as the major component.

Carbethoxymethyltriphenylphosphonium bromide (III) took up 83% of two electrons at −1.5 to −1.6 v (sce). Triphenylphosphine, ethyl acetate and 4% of ethyl 4-cyanobutyrate were virtually the only products.

The achievement of satisfactory yields in the above electrolyses in which acrylonitrile is used as an acceptor is hampered by (a) the need for including a proton donor in the catholyte in order to eliminate the possiblity of initiating anionic polymerization by $(CH_2E)^-$, (b) the concomitant promotion of the neutralization of $(CH_2E)^-$ to CH_3E, (c) the tendency for the catholyte to become *acidic* (further improving the opportunity for forming CH_3E), because in a two-electron cleavage of LCH_2E one neutral moiety L is released and the resultant carbanion, either directly or after addition to the acceptor, reacts with water to liberate only *one* $(OH)^-$ while simultaneously *two* hydroxide ions are being discharged at the anode. It may be possible to compensate for this effect by adding base slowly to the catholyte (provided the base itself does not by nucleophilic attack cause disruption of LCH_2E) or by using an anhydrous anolyte in which the discharge of an anion, *e.g.*, bromide, would not lead to an accumulation of protons.

An even more complex situation obtains in the electrolysis of IV in the presence of acrylonitrile. The intact molecule IV, being an activated olefin, forms



IV, R = alkyl or aryl group,
E = electron-withdrawing group

hydro dimer, dihydro product, and the product of mixed reductive coupling.[11] In addition IV undergoes electrolytic fission[12] to yield RCH=CHE and RS^-.

(1) Paper X: M. R. Ort and M. M. Baizer, *J. Org. Chem.*, **31**, 1646 (1966).

(2) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, **82**, 1582 (1960).

(3) L. Horner, F. Röttger, and H. Fuchs, *Chem. Ber.*, **96**, 3141 (1963).

(4) P. J. Elving, I. Rosenthal, J. R. Hayes, and A. J. Martin, *Anal. Chem.*, **33**, 330 (1961).

(5) H. Lund, *Talanta*, **12**, 1065 (1965), and references cited therein.

(6) P. Zuman, O. Manoušek, and V. Horák, *Collection Czech. Chem. Commun.*, **29**, 2906 (1964).

(7) Coupling of radical intermediates has been reported in certain cases.[2,4]

(8) Paper XI: M. M. Baizer and J. H. Wagenknecht, *J. Org. Chem.*, in press.

(9) It is necessary to choose models which are reduced at a cathode voltage at least 0.2–0.3 v more positive than the voltage required for reduction of acrylonitrile (−1.9 v *vs.* sce) in order to avoid forming the reduction products of the latter.

(10) All yields given are based on current input assuming a two-electron process.

(11) M. M. Baizer, *Tetrahedron Letters*, 973 (1963).

(12) This fission was apparently unrecognized previously and may explain certain polarographic anomalies reported in the literature, *e.g.*, H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.*, **84**, 4752 (1962).