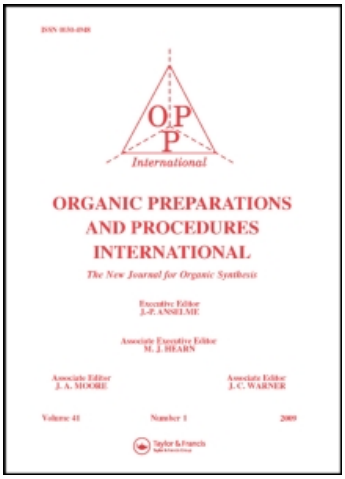


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF IMIDAZOLE AND IMIDAZOLIUM 2-CARBALDEHYDES

Fiore Ricciardi[a]; Madeleine M. Joullié[a]
[a] Chemistry Department, University of Pennsylvania, Philadelphia, Pennsylvania

To cite this Article Ricciardi, Fiore and Joullié, Madeleine M.(1983) 'PREPARATION OF IMIDAZOLE AND IMIDAZOLIUM 2-CARBALDEHYDES', Organic Preparations and Procedures International, 15: 1, 17 — 28
To link to this Article: DOI: 10.1080/00304948309355426
URL: http://dx.doi.org/10.1080/00304948309355426

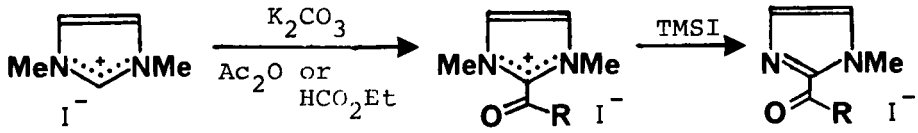
ORGANIC PREPARATIONS AND PROCEDURES INT. 15(1-2), 17-28 (1983)

PREPARATION OF IMIDAZOLE AND IMIDAZOLIUM 2-CARBALDEHYDES

Fiore Ricciardi and Madeleine M. Joullié*

Chemistry Department, University of Pennsylvania
Philadelphia, Pennsylvania 19104

During the course of investigations designed to elucidate the role of imidazoles as catalysts in the curing of epoxy resins,[1] we observed the ease of alkylation and acylation of imidazolium salts at the 2-position. 1,3-Dimethylimidazolium iodide (I) may be easily formylated or acetylated, in acetone and potassium carbonate, to afford good yields of 2-formyl-1, 3-dimethylimidazolium iodide (IIa) and 2-acetyl-1,3-dimethyl-imidazolium (IIb), respectively.



I II III

a) R = H b) R = Me

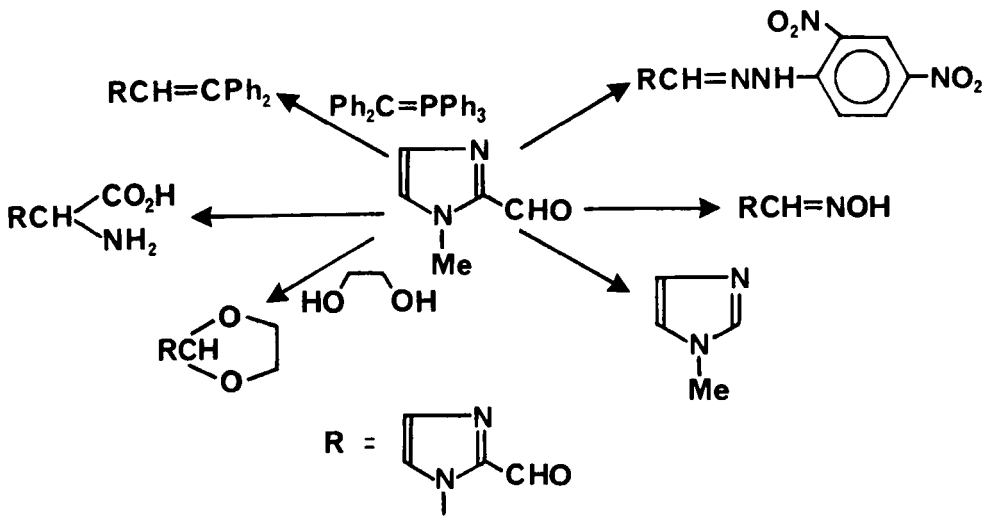
The easy formylation of imidazolium salts provides convenient access to the little studied imidazole and imidazolium 2-carbaldehydes. Imidazolium aldehyde IIa was elaborated to the corresponding dioxolane (IV), 2,4-dinitrophenylhydrazone (V), diphenylmethylidene (VI), amino acid (VII), and oxime (VIII), as shown in Scheme 1. None of these derivatives had been previously reported. Additionally, a small amount of decarbonylated starting material (I) was observed in all reactions. De-

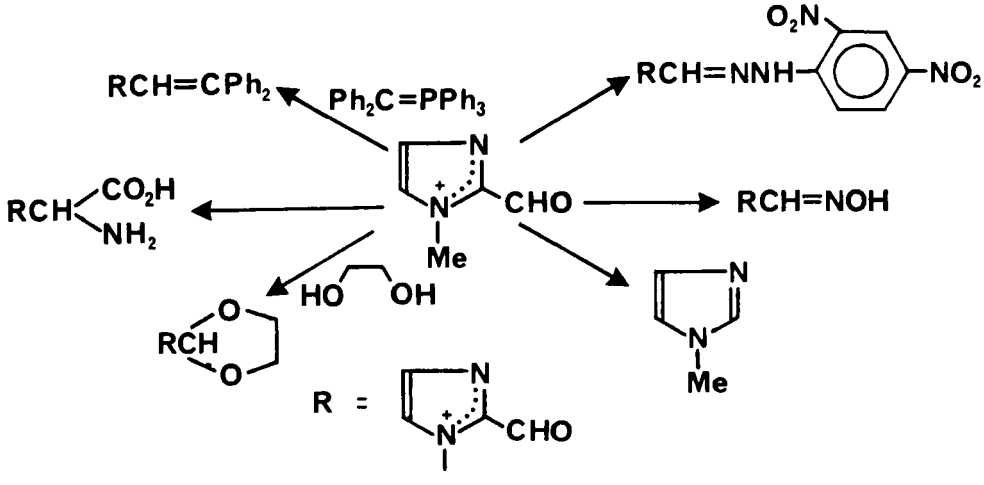
carbonylation may be accomplished in good yields upon heating IIa above 100°.

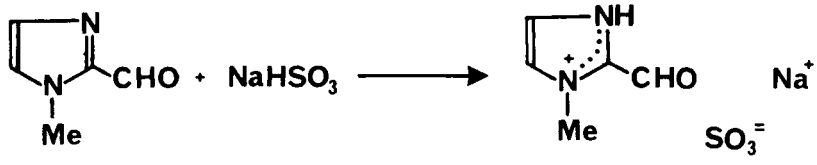
1-Methylimidazole-2-carbaldehyde (IIIa) had been previously prepared by oxidation of the corresponding 2-carbinol, reduction of the corresponding 2-carboxylic acid, and the low yield formylation of 1-methylimidazole deprotonated with alkyl lithium reagents.[2] As demethylation of the imidazolium derivatives is a facile process, formylation of I affords the best route to IIIa. Demethylation can be accomplished in quantitative yields with trimethylsilyl iodide, a reagent well known for its ability to cleave methyl ethers.

Aldehyde IIIa was reported to decarbonylate on attempted acetalization with ethanol.[3] We were able to prepare the dioxolane derivative (IX) in modest yield. The dinitrophenyl hydrazone derivative (X) had not been reported and was easily prepared. The Wittig reaction of IIIa with diphenyl phosphonium ylid afforded XI. The aldehyde (IIIa) was also elaborated to the corresponding amino acid (XII) using the Bucherer reaction. Aldehyde IIIa may be stored conveniently as its bisulfite addition product XIII (Scheme 1). Unexpectedly, XIII exhibited a strong carbonyl absorption (1690 cm^{-1}) in its infrared spectrum. This behavior is unusual as sodium bisulfite normally adds to carbonyl groups, and this addition is supported by the absence of a carbonyl absorption in the infrared region. A possible explanation for the behavior of XIII is that this compound is a salt between the basic imidazole and the acidic bisulfite. The presence of the aldehyde function in XIII is also supported by an absorption at δ9.8 in the ^1H NMR, typical of an aldehydic proton.

Some of the derivatives thus prepared could have inter-







XIII

esting pharmacological properties. For instance, 2-formyl-1,3-dimethylimidazolium iodide oxime (VIII) may be considered an analog of PAM and could show similar activity as a nerve gas antidote.

EXPERIMENTAL SECTION

All melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus (< 200°) or a Mel-temp capillary melting point apparatus (> 200°). All reported values are uncorrected. The elemental microanalyses were performed by Midwest Microlabs, Ltd., Indianapolis, Indiana. Analytical thin layer chromatography (tlc) was performed on precoated silica gel plates (250 μ) with fluorescent indicator, supplied by E. Merck. Visualization was effected with ultraviolet light (UV), 7% w/v ethanolic 12-molybdophosphoric acid (PMA), or ninhydrin (1% w/v in n-propanol). Preparative thin layer chromatography (plc) was performed on precoated silica plates (1000 μ) with fluorescent indicator, supplied by Analtech, Inc. Chromatography utilized columns packed with Merck SG-60 (70-230 mesh) silica gel, and dry column chromatography employed nylon columns, filled with Woelm silica gel for dry column chromatography, activity III/30 mm, containing 0.5% inorganic fluorescent indicator. Infrared spectra (IR) were obtained on a Perkin-Elmer 137 sodium chloride spectrophotometer. Proton nuclear magnetic resonance spectra (NMR) were recorded in the designated solvents on Varian EM-360 (60 MHz) or Bruker WP-250 (250 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) and are relative to tetramethylsilane (TMS) used as an internal standard. Where deuterium oxide (D_2O) was employed as the solvent, 3-(trimethylsilyl)tetradeuterio sodium propionate (TTP) was used as the internal standard. Coupling constants are reported in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were taken in the designated solvents on a Bruker WP-250 spectrometer (operating at 62.9 MHz). High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center either on a Hitachi Perkin-Elmer RMH-2 high resolution double focusing electron impact spectrophotometer or a V.G. Micromass 7070-H high resolution mass spectrometer interfaced with a Kratos FS-50-S data system.

2-Acylation of 1,3-Dimethylimidazolium Iodide.- 1,3-Dimethylimidazolium iodide (I) (1.12 g, 5.0 mmol) was dissolved in acetone (50 ml) and potassium carbonate (2.76 g, 20.0 mmol) was added. The mixture was refluxed for 1 hr, and cooled to room temperature. Acetic anhydride (0.50 ml, 545 mg, 5.3 mmol) or ethyl formate (0.43 ml, 392 mg, 5.3 mmol) was then added

over a period of 20 mins and the solution allowed to stir at room temperature overnight. Methanol (15 ml) was added to dissolve any precipitated product. Evaporation of the solvent and recrystallization from acetone/ethanol afforded 2-formyl-1,3-dimethylimidazolium iodide (IIa) (78%), 0.98 g, mp 233° and 2-acetyl-1,3-dimethylimidazolium iodide (IIb) (68%), 0.90 g, mp 245°. IIb, ^{1}H NMR (DMSO-d_6): δ 2.27 (3H, s, $COCH_3$), 3.96 (6H, s, NCH_3), 7.33 (2H, s, 4-and 5-H); IR (KBr): 3100 (m), 2830 (s), 1705 (s), 1490 (s), 1420 (s), 1335 (s), 1295 (s), 1160 (s), 1055 (m), 925 (s), 780 (s), 686 (m) cm^{-1}.

IIa, ^{1}H NMR (DMSO-d_6): δ 4.05 (6H, s, NCH_3), 7.37 (2H, s, 4- and 5-H), 10.10 (1H, s, CHO); IR (KBr): 3100 (m), 2810 (s), 1690 (s), 1485 (s), 1415 (s), 1395 (s), 1335 (s), 1295 (s), 1160 (s), 1095 (s), 920 (s), 780 (s), 690 (s) cm^{-1}.

2-Formyl-1,3-dimethylimidazolium Iodide Ethylene Ketal (IV).- Compound IIa (504 mg, 2.0 mmol) was added to a solution of ethylene glycol (272 mg, 4.4 mmol) and p-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) in acetonitrile (25 ml). Benzene (5 ml) was added and the solution was fractionally distilled. When 5 ml of distillate was collected, an additional 5 ml of benzene was added to the reaction flask and another 5 ml of distillate collected. The remaining solvent was evaporated *in vacuo*. Product separation was accomplished by dry-column chromatography on silica gel (45 g) using methanol:chloroform:hydriodic acid; 6:6:1 as the eluent to afford 397 mg (67.1%) of IV, mp 217° ^{1}H NMR (DMSO-d_6): δ 3.88 (3H, s, NCH_3), 4.0-4.4 (4H, m, OCH_2CH_2O-), 5.20 (1H, s, -O-CH-O-), 7.25 (2H, s, 4- and 5-H); IR (KBr): 3100 (m), 2950 (m), 2600 (s), 1520 (s), 1495 (s),

1415 (s), 1380 (s), 1340 (s), 1295 (s), 1240 (m), 1160 (s), 1080 (m), 890 (m), 815 (m), 775 (s), 686 (s) cm^{-1}.

Anal. Calcd for $C_8H_{13}N_2O_2I$: C, 32.45; H, 4.42; N, 9.46; Found: C, 32.66; H, 4.51; N, 9.28.

2-Formyl-1,3-dimethylimidazolium Iodide 2,4-Dinitrophenyl Hydrazone (V).- A solution of 2,4-dinitrophenyl hydrazine (0.5 g, 2.5 mmol) and p-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol) in methanol (10 ml) was warmed on a steam bath. Compound IIa (110 mg, 1.1 mmol) was added to the methanolic solution and the mixture was refluxed for 3 hrs. Cooling and addition of acetone (1 ml) caused the product to separate. The product was collected by filtration and recrystallized from acetone and ethanol to afford 238 mg (55%) of V, mp 268°; IR (KBr): 3200 (m), 3050 (m), 1620 (m), 1600 (m), 1510 (m), 1410 (m), 1330 (s), 1310 (m), 1260 (m), 1135 (m), 850 (m), 758 (m), 735 (m), 693 (m) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_6O_4I$: C, 33.35; H, 3.03; N, 19.45; Found: C, 33.55, H, 3.12; N, 19.23.

2-Formyl-1,3-dimethylimidazolium Iodide Diphenylmethylidene (VI).- Sodium hydride (88 mg, 60% dispersion in oil, 2.2 mmol) was washed free of oil with carbon tetrachloride (15 ml). To the dry solid was added dry dimethyl sulfoxide (10 ml). The mixture was heated at 65-70° until hydrogen evolution stopped (15 mins). The solution was cooled to 0° and (diphenylmethyl) triphenylphosphonium bromide (1.17 g, 2.0 mmol) was added and the solution allowed to stir for 30 mins at 0°. Compound IIa (504 mg, 2.0 mmol) was added and the solution was stirred at 0° for an additional hr. Methanol (25 ml) was added to decom-

pose excess base and complete precipitation of sodium bromide. The methanolic solution was evaporated in vacuo and ether (50 ml) was added to the solution to effect separation of the product. The product was collected by filtration and recrystallized from acetone and ethanol to afford 550 mg of VI (68%), mp 254° ^{1}H NMR (DMSO-d_6): δ 3.75 (6H, s), 6.41 (1H, s), 7.0-7.2 (10H, m), 7.25 (2H, s); IR (KBr): 3550 (w), 3100 (m), 3000 (s), 2910 (s), 2710 (m), 1645 (m), 1600 (s), 1500 (s), 1480 (m), 1310 (s), 1250 (m), 1220 (m), 1085 (m), 1055 (s), 990 (m), 940 (m), 890 (m), 690 (m) cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}N_2I$: C, 56.73; H, 4.76; N, 6.96; Found: C, 56.94; H, 4.84; N, 6.78.

α-Amino-2-acetic Acid-1,3-Dimethylimidazolium Iodide (VII).- 2-Formyl-1,3-dimethylimidazolium iodide (504 mg, 2.0 mmol) was added to a suspension of potassium cyanide (260 mg, 4.0 mmol) and ammonium carbonate (768 mg, 8.0 mmol) in 50% ethanol (10 ml). The reaction mixture was heated between 55-60° for 1 1/2 hrs. and 70-80° for 20 mins. The mixture was then acidified with 1 ml of 6N hydrochloric acid and held at 70-80° for another 15 mins. The solvent was removed in vacuo and the residue passed through a weakly basic ion exchange column (Amberlite IR-45), with ethanol as eluent, to effect product separation and hydrolysis of the intermediate hydantoin. The ethanol solution was concentrated at 35 ml by evaporation, and 15 ml of dry benzene containing 255 mg (2.0 mmol) of hydriodic acid was added to this residue. Water was removed by azeotropic distillation and the remaining solvent evaporated in vacuo to afford the product. Recrystallization from 2-propanol afforded 18.4 mg of the amino acid (3.1%) mp 288°; ^{1}H NMR (D_2O): δ 3.84 (1H,

s), 3.99 (6H, s), 7.30 (2H, s).

Anal. Calcd. for $C_7H_{12}N_3O_2I$: C, 28.30; H, 4.07; N, 14.14; Found: C, 28.62; H, 4.21; N, 13.76.

2-Formyl-1,3-dimethylimidazolium iodide, oxime (VIII).- Compound IIa (50 mg, 0.2 mmol) was added to a solution of hydroxylamine hydrochloride (100 mg) and crystallized sodium acetate (200 mg) in water (2 ml). The mixture was warmed on a water bath for 10 mins. The aqueous solution was saturated with potassium iodide and extracted with chloroform (3 x 10 ml). The chloroform solution was dried ($MgSO_4$) and evaporated in vacuo to afford 31.5 mg (61%) of the oxime, mp 225° d; ^1H NMR (DMSO-d_6): δ 3.34 (1H, s), 3.92 (6H, s), 7.79 (2H, s), 8.53 (1H, s).

Anal. Calcd. for $C_6H_{10}N_3OI$: C, 26.98; H, 3.77; N, 15.73. Found: C, 27.11; H, 3.86; N, 15.66.

2-Acetyl-1-methylimidazole (IIIb).- Trimethylsilyl iodide (0.25 ml, 375 mg, 1.88 mmol) was added to a solution of IIb, (100 mg, 0.37 mmol) in sulfolane (25 ml). The solution was heated with stirring at 60° for 2 hrs. The solution was filtered and methanol (1 ml) was added to the filtrate. The solvent was removed in vacuo to afford 45.5 mg (quantitative yield) of IIIb bp 104°-105°/15 mm, (lit.[4] bp 105°-106°/15 mm); ^1H NMR: δ 2.31 (3H, s), 3.98 (3H, s), 7.12 (1H, s), 7.25 (1H, s); IR (film, NaCl plates): 3100 (m), 2910 (m), 2820 (m), 1710 (s), 1530 (m), 1485 (s), 1415 (s), 1385 (s), 1340 (s), 1295 (s), 1260 (w), 1225 (m), 1160 (s), 1080 (m), 1050 (w), 923 (m), 869 (w), 778 (s), 696 (m), 686 (m) cm^{-1}.

2-Formyl-1-methylimidazole (IIIa).- Compound IIa (93 mg, 0.37 mmol) was used in the procedure described to prepare IIIb to

afford 40.1 mg (quantitative yield) of IIIa bp 88°-91°/12 mm, (lit.[4] bp 89°-95°/12 mm); ^{1}H NMR ($CDCl_3$): δ 4.01 (3H, s), 7.14 (1H, s), 7.24 (1H, s), 9.81 (1H, s); ^{13}C NMR ($CDCl_3$) δ 34.79 (q), 127.51 (d), 131.42 (d), 181.94 (d), 162.48 (s); IR (film, NaCl plates): 3100 (m), 2910 (m), 2820 (m), 1690 (s), 1520 (m), 1485 (s), 1415 (s), 1385 (s), 1335 (s), 1295 (s), 1225 (m), 1160 (s), 1095 (s), 1055 (m), 925 (s), 910 (w), 778 (s), 696 (m), 686 (m) cm^{-1}.

2-Formyl-1-methylimidazole Ethylene Ketal (IX).- Compound IIIa (220 mg, 2.0 mmol) was added to a solution of ethylene glycol (272 mg, 4.4 mmol) and p-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) in ether (25 ml). The solvent was removed in vacuo and the crude product recrystallized from ether and petroleum ether to afford 142 mg of IX (46%), mp 106°. The remainder of the product was found to be 1-methylimidazole. IX, ^{1}H NMR ($CDCl_3$): δ 3.52 (3H, s), 3.9-4.2 (4H, s), 5.15 (1H, s), 6.79 (1H, s), 6.84 (1H, s); IR (KBr), 2860 (m), 1515 (s), 1470 (m), 1400 (m), 1160 (s), 1080 (m), 1055 (m), 923 (s), 757 (m), 695 (m) cm^{-1}; exact mass calcd. for $C_7H_{10}N_2O_2$: 154.0742, found: 154.0740.

2-Formyl-1-methylimidazole, 2,4-Dinitrophenyl Hydrazone (X).- A mixture of 2,4-dinitrophenylhydrazine (0.5 g, 2.5 mmol), ethanol (10 ml), and concentrated hydrochloric acid (1 ml) was heated on a steam bath until a clear solution was obtained. Compound IIa (252 mg, 1.0 mmol) was added to the warm solution and the mixture heated at reflux for 5 mins. The mixture was made basic with sodium hydroxide and allowed to stand at room temperature to complete crystallization of the product. Filtration under reduced pressure and recrystallization from

ethanol afforded 234 mg (81%) of X, mp 117°-118°, (lit.[5] mp 116°-119°).

2-Formyl-1-methylimidazole, Diphenylmethylidene (XI). Sodium hydride (88 mg, 60% dispersion in oil, 2.2 mmol) was washed free of oil with carbon tetrachloride (15 ml). To the dry solid was added dry tetrahydrofuran (40 ml) and (diphenylmethyl) triphenylphosphonium bromide (1.17 g, 2.0 mmol). The solution was allowed to stir at room temperature for 1 hr. Compound IIIa (220 mg, 2.0 mmol) was added and the solution allowed to stir at room temperature for 2 hrs. The solution was acidified with dilute hydrochloric acid (1:1) to pH 3 and the tetrahydrofuran was evaporated in vacuo. The resulting aqueous solution was washed with ether (3 x 20 ml) and made basic with potassium carbonate. The aqueous solution was then saturated with sodium chloride and extracted with methylene chloride (5 x 20 ml). The methylene chloride was dried ($MgSO_4$) and evaporated in vacuo to afford 386 mg (74.1%), of XI, mp 135°-136°; ^1H NMR ($CDCl_3$): δ 3.58 (3H, s), 6.86 (1H, s), 7.02-7.2 (10H, m), 7.22 (2H, s); IR (KBr): 1650 (m), 1600 (s), 1500 (s), 1430 (m), 1290 (s), 1180 (m), 1145 (m), 1050 (s), 990 (m), 960 (m), 890 (m), 790 (m), 690 (m) cm^{-1}; exact mass calcd. for $C_{18}H_{16}N_2$: 260.1313; found: 260.1310.

α-Amino-1-methylimidazole-2-acetic Acid (XII).- The bisulfite addition product of 2-formyl-1,3-dimethylimidazole (XIII) (1.07 g, 5.0 mmol) was added to a suspension of potassium cyanide (650 mg, 10.0 mmol) and ammonium carbonate (1.92 g, 20.0 mmol) in 50% ethanol (30 ml). The reaction mixture was heated between 55°-60° for 3 hrs. and 70°-80° for 45 mins. The mixture was then acidified with 4 ml of 6N hydrochloric acid and held at 70°-80° for another 45 mins. Hydrochloric

acid (6N) was added to bring the solution to pH 3 and the mixture was washed with ether (3 x 30 ml). The solution was neutralized with potassium carbonate, saturated with sodium chloride, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated in vacuo to afford 5-(1-methyl-2-imidazoyl) hydantoin. The hydantoin (180 mg, 1.0 mmol) and recrystallized barium hydroxide (1.0 g, 5.8 mmol) were dissolved in water (5 ml). The mixture was heated to reflux for 2 hrs, and then diluted to 10 ml with hot (75°) water. Saturation with carbon dioxide effected the separation of excess barium carbonate. The precipitate was removed by filtration and the solution neutralized with acetic acid. The solvent was evaporated in vacuo and product separation was effected by column chromatography using silica gel (40 g) with 15% aqueous propanol as the eluent (R_f 0.31) to afford 23 mg (15%) of XII, mp 210°-211°C; ^1H NMR (D_2O): δ 3.56 (3H, s), 3.75 (1H, s), 6.79 (1H, s), 6.83 (1H, s); IR (KBr): 3000 (m), 1625 (s), 1600 (s), 1110 (m), 1015 (m), 850 (m), 823 (m), 690 (m) cm^{-1}; exact mass calcd. for $C_6H_9N_3O_2$: 155.0695, found: 155.0699.

Sodium 2-Formyl-1-methylimidazolium Sulfonate (XIII).- A solution of IIIa (5.5 g, 0.05 mmol) in saturated (65% w/v) sodium bisulfite was shaken vigorously for 15 mins. The mixture was allowed to stand in the refrigerator overnight during which time the product separated as a white solid. The solid was collected by filtration and dried in a desiccator under reduced pressure. Sublimation of the product (120°/0.1 mm) afforded pure bisulfite salt, 8.78 g (82%), mp 285°; ^1H NMR (D_2O): δ 3.89 (3H, s), 7.31 (1H, s), 7.33 (1H, s), 9.80 (1H, s); IR

(KBr): 3100 (m), 2920 (m), 2800 (m), 1690 (s), 1410 (s), 1380 (s), 1330 (m), 1320 (m), 1280 (s), 1240 (m), 1160 (s), 1090 (s), 925 (m), 777 (s), 690 (m) cm^{-1}.

Anal. Calcd. for $C_5H_7N_2O_4SNa$: C, 28.04; H, 3.29; N, 13.08; Found: C, 28.22; H, 3.21; N, 12.84.

REFERENCES

1. F. Ricciardi, M. M. Joullié, W. A. Romanchick, and A. A. Griscavage, J. Polym. Sci., Polym. Lett. Ed., 20, 127 (1982).

2. P. E. Iversen and H. Lund, Acta Chem. Scand., 20, 2649 (1966).

3. I. Antonini, G. Cristalli, P. Franchetti, M. Grifantini, U. Gulini, and S. Martelli, J. Heterocyclic Chem., 15, 1201 (1978).

4. L. M. Sitkina, A. F. Pozharskii, and A. M. Simmonov, Zh. Obshch. Khim., 37, 2215 (1967).

5. P. Fournari, P. deCointet, and E. Laviron, Bull. Soc. Chim. France, 2438 (1968).

(Received September 10, 1982; in revised form November 11, 1982)