[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT OF THE CHEMSTRAND CORPORATION]

2-Vinylimidazole and 1-Methyl-2-vinylimidazole

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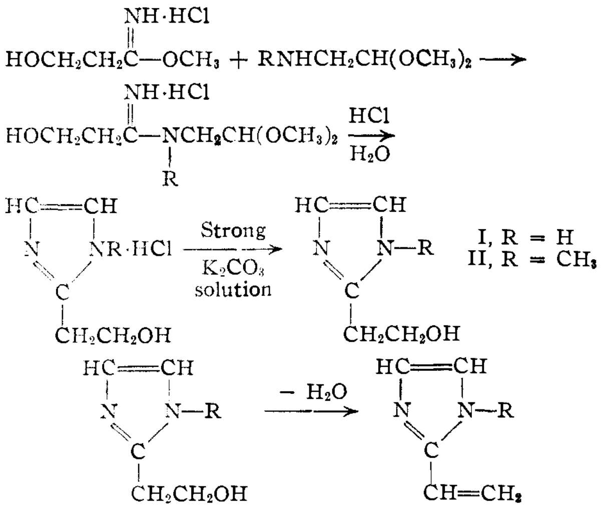
2-Vinylimidazole and 1-methyl-2-vinylimidazole have been prepared by the dehydration of the corresponding β-hydroxyethyl compounds. Both of the vinyl compounds were found to polymerize readily, and 1-methyl-2-vinylimidazole has been copolymerized with acrylonitrile, styrene and methyl methacrylate. The copolymer from acrylonitrile and 1-methyl-2-vinylimidazole exhibited good dyeability with an acid type dye.

As part of a program of investigation of basic vinyl monomers, the synthesis of some vinylimidazoles was undertaken. Among the more or less "aromatic" heterocycles of low molecular weight, imidazole is exceptional in its relatively high basicity, since its basic properties are even more pronounced than those of pyridine.[1] It seemed probable that these basic characteristics would be conferred in part at least on polymers and copolymers derived from vinylimidazoles. The 2-vinylimidazoles were considered to be of particular interest, since they bear a formal structural analogy to acrylic acid and its derivatives.

In synthesizing the β-hydroxyethyl compounds desired as intermediates, a procedure was developed which was somewhat similar to the recently published imidazole synthesis of Ellinger and Goldberg.[2] Since imidazoles unsubstituted in the 4- or 5-positions were desired, acetals of aminoacetaldehydes were employed instead of aminoketones. These were treated with methyl β-hydroxypropionimidate hydrochloride[3] in methanol to give substituted amidines, which were not purified but were used directly in a crude state for conversion to the imidazoles.



$$HOCH_2CH_2\overset{NH\cdot HCl}{\overset{\|}{C}}—OCH_3 + RNHCH_2CH(OCH_3)_2 \longrightarrow$$

$$HOCH_2CH_2\overset{NH\cdot HCl}{\overset{\|}{C}}—\underset{R}{\underset{|}{N}}CH_2CH(OCH_3)_2 \xrightarrow[H_2O]{HCl}$$

I, R = H
II, R = CH_3

III, R = H
IV, R = CH_3

Hydrolysis of the acetal groupings in these amidines by moderately concentrated hydrochloric acid was accompanied by ring closure which resulted in the formation of the desired imidazoles as their hydrochlorides. The imidazoles were liberated from their hydrochlorides by treatment with strong potassium carbonate solution.

The isolation of the β-hydroxyethylimidazoles in the pure state was difficult. Evaporation to dryness of the dark brown alkaline solutions from the carbonate treatment gave residues from which the imidazoles could be extracted with absolute ethanol or isopropyl alcohol. Repetition of this process with the alcoholic solutions finally gave residues essentially free from inorganic salts. 2-β-Hydroxyethylimidazole (I) was isolated from such a residue by repeated high-vacuum sublimation followed by crystallization from an isopropyl alcohol–acetone mixture. 1-Methyl-2-β-hydroxyethylimidazole (II) was purified by two distillations at 1 mm. or less, followed by crystallization from benzene. Although a considerable amount of time was spent on alternative purification procedures, none was found more satisfactory than these.

An appreciable difference in the ease of dehydration of these alcohols was observed. The 1-methyl compound (II) was dehydrated very smoothly to the corresponding vinyl derivative (IV) by the excellent procedure of Frank, Adams, Allen, Gander and Smith.[4]

Compound I could not be successfully dehydrated to III by this procedure, although some of the difficulties encountered in various attempts were purely mechanical in nature. A number of other methods of dehydration were investigated, but the only one which gave appreciable yields of III was the slow distillation of I from potassium bisulfate at 20 mm. under carefully controlled conditions.

2-Vinylimidazole (III) so obtained is a white crystalline solid possessing a melting point of 128–129°. It appears to be relatively stable at room temperature, but is slowly polymerized by heating, even below the melting point. Its 1-methyl derivative IV is a clear colorless liquid which boils at 75–77° under a pressure of 2 mm. At room temperature it polymerizes moderately rapidly and becomes brown, but it can be stored for fairly long periods of time at −78°.

Polymers and copolymers were prepared from III or IV by standard procedures; it was found that the copolymer of IV with acrylonitrile was very rapidly dyed by an acid-type dye.

Experimental

Aminoacetaldehyde Dimethylacetal.—This compound was prepared by an adaptation of the procedure used by Allen and Clark[5] to prepare the corresponding diethylacetal. The reaction between ammonia and chloroacetaldehyde

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[1] A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 405.

[2] L. P. Ellinger and A. A. Goldberg, *J. Chem. Soc.*, 263 (1949).

[3] C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 210 (1949).

[4] R. L. Frank, C. E. Adams, R. E. Allen, R. Gander and P. V. Smith, THIS JOURNAL, **68**, 1366 (1946).

[5] C. F. H. Allen and J. H. Clark, *Org. Syntheses*, **24**, 3 (1944).

dimethylacetal was carried out on a 3-*M* scale exactly as described by Allen and Clark.[5] The reaction mixtures from two such runs were combined, diluted with 2 liters of water, and treated with a solution of 300 g. of sodium hydroxide in 300 ml. of water. The alkaline solution was distilled to dryness under reduced pressure, and two 500-ml. portions of water were distilled from the residue to ensure thorough removal of the acetal. Alcohol and traces of ammonia were then removed from the distillate by fractionation through a column.

The solution remaining in the distilling flask was cooled, and the dissolved acetal was salted out by addition of commercial flake potassium hydroxide. After the layers were separated, the aqueous phase was extracted with two 500-ml. portions of ether, which were added to the organic layer. After thorough drying over pellets of potassium hydroxide, the ether solution was distilled through a 30-cm. vacuum-jacketed Vigreux column. The yield of product boiling at 137–139° (reported[6] 135°) was 443 g. (70%).

Methylaminoacetaldehyde Dimethylacetal.[6]—This acetal was prepared in 78% yield from chloroacetaldehyde dimethylacetal and methylamine, by a procedure identical with that given above.

Methyl β-Hydroxypropionimidate Hydrochloride.—This compound was prepared from ethylene cyanohydrin, methanol and hydrogen chloride in dry ether exactly as described by Price and Zomlefer.[8]

2-β-Hydroxyethylimidazole (I).—The cake of methyl β-hydroxypropionimidate hydrochloride from a 1-*M* run was washed repeatedly with dry ether and dissolved with external cooling in a mixture of 200 ml. of methanol and 115 g. (1.1 moles) of aminoacetaldehyde dimethylacetal. After one week of standing at room temperature, the solution was freed of methanol and excess acetal by distillation under reduced pressure at the temperature of a boiling water-bath.

The residue was taken up in 200 ml. of water and the solution was added to 500 ml. of concentrated hydrochloric acid. Evaporation of this solution on a steam-bath gave a dark residue which was treated with strong potassium carbonate solution until the mixture was definitely alkaline (*p*H 9 to 10). The reddish-black alkaline solution was evaporated on a steam-bath to give a residue which was taken up in 1 l. of absolute ethanol. Inorganic salts were removed by filtration and the ethanolic solution was evaporated. The steps of solution, filtration and evaporation were then repeated, with the use of 500 ml. of isopropyl alcohol instead of ethanol.

A crude product was isolated from the final residue by high-vacuum sublimation in a molecular still at a bath temperature of 100–125° and a pressure of 0.02–0.10 mm. This product was somewhat discolored from spattering, and was resublimed at 0.02–0.03 mm. to give 55 g. of almost pure white material, which was crystallized from a mixture of isopropyl alcohol and acetone (1:4). The product so obtained was analytically pure and weighed 45.0 g. (40% yield).

2-β-Hydroxyethylimidazole forms snow-white crystals, melting at 128–129°.[7] It is readily soluble in water and the lower alcohols, difficultly soluble in hot acetone, and insoluble in benzene, ether, chloroform, xylene, petroleum ether and kerosene.

Anal. Calcd. for $C_5H_8ON_2$: C, 53.92; H, 7.19; N, 24.99. Found: C, 53.92, 53.96; H, 7.23, 7.17; N, 24.82, 24.87.

The infrared spectrum of the compound was determined and found to agree with the structure assigned.

1-Methyl-2-β-hydroxyethylimidazole (II).—The preparation of this compound was conducted on a 2-*M* scale under conditions similar to those used in the synthesis of I. The final residue from the alcoholic extract was distilled under a pressure of 1 to 2 mm. to give 195 g. of crude distillate boiling at 110–145°. This discolored material was redistilled at 0.2–0.3 mm. and gave a light yellow liquid boiling at 85–105°. The distillate solidified readily on cooling, and was recrystallized twice from 225-ml. portions of benzene to give 165 g. (65.5%) of analytically pure product, melting at 68.5–69.5°. The pure solid retained a very faint yellow color.

Anal. Calcd. for $C_6H_{10}ON_2$: C, 57.13; H, 7.99; N, 22.21. Found: C, 56.96, 56.92; H, 8.02, 8.02; N, 22.22, 22.41.

The infrared spectrum of the compound was determined and found to be consistent with the assigned structure.

1-Methyl-2-β-hydroxyethylimidazole has a wider range of solubility in common solvents than I. It is soluble in acetone, chloroform and warm benzene, as well as water and the lower alcohols.

2-Vinylimidazole (III).—A mixture of 2-β-hydroxyethylimidazole (15 g.) and potassium bisulfate (0.75 g.) was placed in a small pot-type molecular still constructed from heavy-wall glass tubing of about 50 mm. outside diameter. The still was provided with a re-entrant condenser through which water at about 50° was circulated, and was evacuated to a pressure of 20 mm. (Lower pressures caused distillation of starting material without appreciable olefin formation.) A bath of Dow-Corning 710 silicone oil was preheated to 180° and then placed around the still. Over a period of one hour the bath temperature was gradually raised to 280°. At a bath temperature of 220–240° a white solid began to form on the re-entrant condenser. The reaction was stopped when the material in the still was entirely converted to a viscous yellow mass, probably polymeric in nature.

The solid on the condenser (4.0 g.) was collected and treated with 100 ml. of boiling benzene. The benzene solution was filtered and the filtrate was treated with 200 ml. of filtered hexane, which caused the separation of a quickly-crystallizing oil. The filtered crystals were subjected to high-vacuum sublimation at about 0.02 mm. (bath temperature 75–80°). Even under these conditions, a part of the compound was converted to involatile polymer. The sublimate was recrystallized from benzene–hexane mixture to give a final yield of 1.5 g. (11.9%).

2-Vinylimidazole is a white crystalline solid melting at 128–129° (capillary tube). Mixed melting points with the parent alcohol, which has about the same melting point, show large depressions; a value of 85–90° was found for a mixture of approximately equal parts. It is soluble in water and nearly all the common organic solvents except the paraffin hydrocarbons.

Anal. Calcd. for $C_5H_6N_2$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.15, 62.89; H, 6.49, 6.44; N, 29.29, 29.48.

The infrared spectrum of the compound indicated that the assigned structure was correct.

1-Methyl-2-vinylimidazole (IV).—The technique of dehydration of carbinols described by Frank, Adams, Allen, Gander and Smith[4] was employed essentially without alteration in the preparation of this compound from II. As a slight refinement an atmosphere of nitrogen was provided by drawing in a stream of this gas through a fine capillary. The dehydration of 63 g. of II by passage through 400 g. of molten potassium hydroxide at 180° and a pressure of 14 mm. followed by two redistillations of the crude product at 2 mm., gave 40.5 g. (75%) of 1-methyl-2-vinylimidazole. Compound II was conveniently added as a supercooled liquid in the dehydration operation.

It was found advantageous to cool the distillation receivers in a mixture of solid carbon dioxide and carbon tetrachloride–chloroform mixture. If the distillate was not cooled in this manner but was collected at room temperature, a small amount of polymer appeared to be formed almost immediately, since sticky streamers were observed when the distillate was transferred from one container to another.

1-Methyl-2-vinylimidazole is a clear, colorless liquid which boils at 75–77° at a pressure of 2 mm. and has a refractive index, $n^{25}\mathrm{D}$ 1.5520. The odor of the compound is peculiar, but not unpleasant in small quantities.

The infrared spectrum of the liquid was determined and was found to be entirely consistent with the assigned structure.

Anal. Calcd. for $C_6H_8N_2$: N, 25.91. Found: N, 25.47, 25.40.

An attempt was made to analyze for carbon and hydrogen. For undetermined reasons the combustion tube exploded. No further analyses were attempted.

Polymerization. (a) **2-Vinylimidazole.**—A solution of 0.5 g. of III in 5.0 ml. of distilled water was prepared, and 0.01 g. of potassium persulfate was added. The mixture was warmed very slowly and shaken until the persulfate dissolved. When the resulting solution was heated for one or two minutes on a steam-bath, a white, tacky polymer

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(6) W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1885 (1922).

(7) All melting points are uncorrected, and were determined on a Fisher–Johns block unless otherwise stated.

formed in granules on the container walls. The aqueous solution was decanted from the polymer, which was found to be soluble in warm dimethylacetamide or in warm 6 *N* hydrochloric acid. Polymer was also formed by prolonged warming of solutions in acetone or isopropyl alcohol.

(b) **1-Methyl-2-vinylimidazole.**—The residue (about 1.0 ml.) from the final distillation of IV was touched with a glass rod which had been dipped in cumene hydroperoxide, and was warmed and stirred. No immediate effect was noted, but on the next day the sample had been converted to a light-brown button of polymer, somewhat tacky at the surface.

A sample of IV which had become light brown and contained an appreciable quantity of low-molecular weight polymer was dissolved in somewhat more than an equal volume of distilled water and placed in a stoppered vessel. The original solution was almost clear; a brown color was present but no insoluble polymer was noted. After standing for about one week, the solution was converted to a thick gel. The gel was not entirely soluble in either hot water or hot dimethylacetamide, but it appeared to dissolve completely, although slowly, in a mixture of equal volumes of the two.

(c) **Copolymers Containing 1-Methyl-2-vinylimidazole.**—Copolymers of (IV) with methyl methacrylate and styrene were prepared by persulfate-catalyzed polymerization in aqueous suspension by conventional procedures. The original charge contained 10% of IV in each case. Analysis of reprecipitated samples showed the presence of 5.2% of IV in the styrene copolymer and 8% of IV in the methyl methacrylate copolymer.

A copolymer of IV with acrylonitrile was prepared similarly in such a way as to give approximately 5% of IV in the product. A film was prepared from the dried copolymer by casting an approximately 15% solution in dimethylacetamide on a glass plate and evaporating the solvent in an oven at 70°. The film so prepared was dyed in a bath containing 2% of Wool-Fast Scarlet G. Supra (a typical acid dye), and 10% each of sulfuric acid and sodium sulfate (based on film weight in each case). After about 20 minutes of heating at 95–100°, the dye-bath was exhausted and the film had been dyed to a deep red shade. Films of pure polyacrylonitrile are only slightly affected under similar conditions.

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[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Some Amide Derivatives of Certain Aminomethylpyridines

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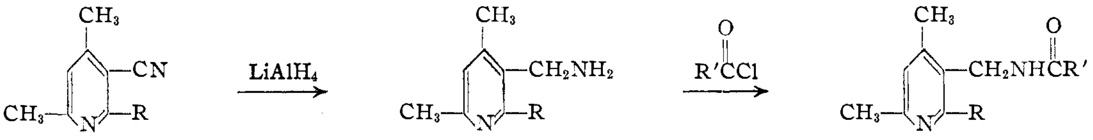
Several 3-acylaminomethylpyridines have been synthesized by the reduction of the corresponding 3-cyanopyridine with lithium aluminum hydride and subsequent acylation of the intermediate aminomethyl compound. Some α-aminoacetamidomethylpyridines were prepared when α-chloroacetamidomethylpyridines were warmed with amines. Two ethylenediamine derivatives were synthesized by the reduction of the α-aminoacetamidomethylpyridines with lithium aluminum hydride.

During the course of investigations in this Laboratory leading to possible precursors of 2,7-naphthyridines[2] a number of amide derivatives of some 3-aminomethylpyridines were prepared in which the acyl residue was derived from common acylating agents such as benzoyl chloride and acetic anhydride. The method selected for the synthesis of some of the amides involved the reduction of a 2-substituted 3-cyano-4,6-dimethylpyridine with lithium aluminum hydride followed by the addition of the acid chloride or anhydride directly to the reaction mixture without isolating the intermediate aminomethyl compound. Advantages of this method of preparation have been discussed by Brown.[4]

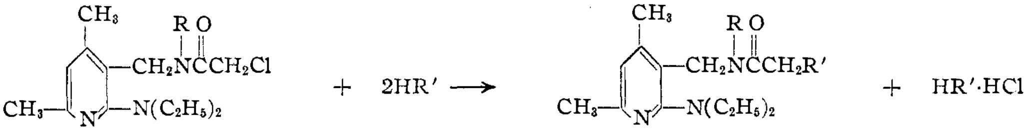
PROCEDURE A



I, R = OCH_3; R′ = C_6H_5
II, R = OCH_3; R′ = CH_2Cl
III, R = $N(C_2H_5)_2$; R′ = CH_3[3]
IV, R = $N(C_2H_5)_2$; R′ = C_6H_5
V, R = $N(C_2H_5)_2$; R′ = CH_2Cl
VI, R = Cl; R′ = CH_3[3]

In view of the known pharmacological applications of certain β-dialkylaminoethyl amides of quinoline and pyridine carboxylic acids, it also seemed of interest to prepare some isomers of amides of this type in which the acyl residue is an α-alkyl or dialkylamino aliphatic carboxylic acid derivative and where the amino residue is an aminomethylpyridine. Aminoacetamides were synthesized by acylating the aminomethylpyridine with chloroacetyl chloride and then warming the substituted chloroacetamide with an excess of the appropriate amine in ethanol solution.

PROCEDURE B



VIII, R = H; R′ = diethylamino
IX, R = H; R′ = cyclohexylamino
X, R = H; R′ = morpholino
XI, R = benzyl; R′ = dimethylamino

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(1) Parke, Davis and Company Fellow 1951–1952.

(2) C. F. H. Allen, *Chem. Revs.*, **47**, 275 (1950).

(3) Acetic anhydride used as the acylating agent.

(4) W. G. Brown in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 488.