[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN, BROOKLYN 1, N. Y.]

# Imidazole-containing Polymers. Synthesis and Polymerization of the Monomer 4(5)-Vinylimidazole[1]

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For the purpose of preparing polymeric model enzyme systems, 4(5)-vinylimidazole was synthesized by two routes, one starting with histidine, and the other with 2-butyne-1,4-diol. Attempts to dehydrochlorinate 4(2′-chloroethyl)-imidazole were unsuccessful. The polymerization and copolymerization of this monomer, to give polymers containing pendant imidazole, hydroxyl and carboxyl groups, is described.

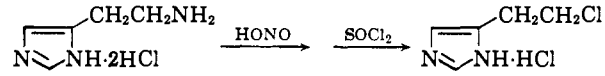
Studies of the mechanism of catalytic action of proteolytic and esterolytic enzymes, such as α-chymotrypsin, have indicated that the hydroxyl group of a serine residue, an imidazole group of a histidine residue, and a proton-donating source are involved in the active site of these enzymes. A single serine residue has been definitely established as part of the active site from studies of the reaction of organophosphorus inhibitors with the enzymes,[2] and from spectral and kinetic studies of the acyl-enzyme intermediate formed in the reaction of chymotrypsin with esters.[3] Aspartic acid is found adjacent to serine at the active site of many enzymes.[4] Histidine has been implicated from kinetic studies of the *p*H dependence of the hydrolysis reaction,[5] from photooxidation studies of the enzymes,[6] reaction of chymotrypsin with dyes,[7] and from the behavior of simple imidazole derivatives as hydrolysis catalysts.[8]

It was desired to prepare polymers containing pendant imidazole, hydroxyl and carboxyl groups and to evaluate them as possible enzyme models, since these polymers would contain the groups probably necessary for proteolytic enzyme action, and in an environment capable of developing tertiary structure in solution. This paper will describe the synthesis of polymers of this type, using as the key monomer 4(5)-vinylimidazole.[9]

**Synthesis of 4(5)-Vinylimidazole.**—The literature contains two brief references to this monomer. Pasini and Vercellone[10] obtained from the distillation of *trans*-urocanic acid (β-4-imidazolylacrylic acid) (I) a viscous, colorless liquid, which gave on standing a solid of melting point 86–88°. This compound was claimed to be a dimer of 4-vinylimidazole on the basis of an approximate elemental analysis and a molecular weight determination. This work was repeated in this Laboratory and the compound was obtained in a purer form and was shown to be actually the desired monomeric material. The assignment as a dimer based on the molecular weight determination is incorrect, since imidazoles are known to associate in non-polar solvents, and give erroneous molecular weight results.[11] Masuda[12] suggested the presence of 4-vinylimidazole (I) in the preparation of *cis*- and *trans*-urocanic acid from α-carboxy-β-4-imidazolylacrylic acid (III).

The monomer has been prepared in this Laboratory *via* two routes, one starting with histidine and the other from 2-butyne-1,4-diol. Dehydrochlorination of 4-(β-chloroethyl)-imidazole was unsuccessful.

4-(β-Chloroethyl)-imidazole (III) was prepared from histamine (II) by diazotization at 60° using a 100% excess of nitrous acid and conversion of the resulting mixture of alcohol and chloride to the chloro compound by reaction with thionyl chloride, and by a known[13] synthesis from γ-butyrolactone.

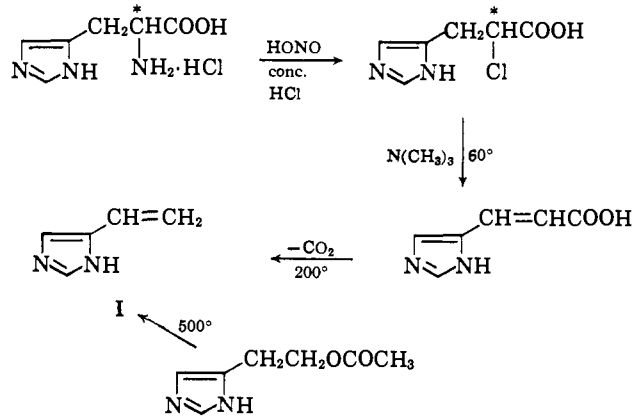



II III

Attempts to dehydrochlorinate III were unsuccessful. Use of aqueous or alcoholic base and attempted isolation of the monomer as the hydrochloride led to oils and sirups which could not be crystallized. Attempts to isolate the desired monomer as the free base either by crystallization or distillation from the basic reaction mixture also failed. Reaction with *s*-collidine also led to a brown, intractable tar, which was probably the impure polymerized monomer, which could easily have occurred at the high reaction temperatures used.

The monomer was successfully synthesized by two routes, shown in Chart I.

CHART I




In the first route,[14] histidine was diazotized in concentrated hydrochloric acid stereospecifically, the re-

(1) Taken from the dissertation submitted by N. Vorchheimer to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), 1962.

(2) A. K. Balls and E. F. Jansen, in "Advances in Enzymology," F. F. Nord, ed., Vol. 13, Interscience Publishers, Inc., New York, N. Y., 1952, p. 321; N. J. Schaffer, L. Simet, S. Harshman, R. R. Engle and R. W. Drisko, *J. Biol. Chem.*, **225**, 197 (1957).

(3) (a) A. K. Balls and H. N. Wood, *ibid.*, **219**, 245 (1956); (b) M. L. Bender, G. R. Schonbaum, G. A. Hamilton and B. Zerner, *J. Am. Chem. Soc.*, **83**, 4656 (1961); (c) T. Spencer and J. M. Sturtevant, *ibid.*, **81**, 1874 (1959).

(4) D. E. Koshland, Jr., and M. J. Erwin, *ibid.*, **79**, 2657 (1957).

(5) E. A. Bernard and W. D. Stein, in "Advances in Enzymology," F. F. Nord, ed., Vol. 20, Interscience Publishers, Inc., New York, N. Y., 1958, p. 51.

(6) L. Weil, S. James and A. R. Buchert, *Arch. Biochem. Biophys.*, **46**, 266 (1953); W. J. Ray, Jr., and H. G. Latham, Jr., M. Katsoulis and D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **82**, 4743 (1960).

(7) J. R. Whitaker and B. J. Jandorf, *J. Biol. Chem.*, **223**, 751 (1956); B. S. Hartley and V. Masset, *Biochem. Biophys. Acta*, **21**, 58 (1956).

(8) (a) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652, 1656 (1957); (b) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); (c) T. C. Bruice and J. M. Sturtevant, *ibid.*, **81**, 2860 (1959); (d) B. M. Anderson, E. H. Cordes and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

(9) Reaction of these polymers with substrates will be reported separately.

(10) C. Pasini and A. Vercellone, *Gazz. Chim. Ital.*, **85**, 349 (1955).

(11) K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1953, p. 3.

(12) K. Masuda, *J. Pharm. Soc. Japan*, **76**, 325 (1956); *C. A.*, **50**, 13880 (1956).

(13) R. A. Turner, *J. Am. Chem. Soc.*, **71**, 3476 (1949).

(14) S. Edlbacher and H. von Bidder, *Z. physiol. Chem.*, **276**, 126 (1942); *C. A.*, **37**, 5404 (1943).

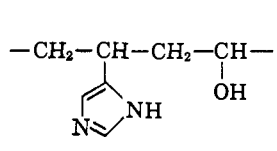
sulting chloro acid dehydrochlorinated with trimethylamine in a steel bomb, and the resultant urocanic acid decarboxylated *in vacuo* at the melting point. The second method utilized the general method of Reppe,[15] in which 2-butyne-1,4-diol was hydrated and isomerized with a mercuric sulfate–sulfuric acid catalyst, the resultant 1,4-dihydroxybutanone-2 (not isolated) oxidized with copper(II) sulfate, ammonolyzed, and cyclized with formaldehyde in one step to form 4-(β-hydroxyethyl)-imidazole as the copper(I) salt, which was decomposed with hydrogen sulfide. The alcohol was di-acetylated with acetic anhydride and the labile N-acetyl group removed with mild base. The acetate was then smoothly pyrolyzed.

The infrared spectrum of the monomer contained strong absorptions at 890, 980 and 1630 cm.$^{-1}$, typical of terminal vinyl compounds,[16] in addition to the broad absorption at 2300–3200 cm.$^{-1}$, typical of imidazole compounds with an N–H bond. The remainder of the spectrum was consistent with the proposed structure. The ultraviolet absorption maximum and its extinction coefficient (243 mμ and 12,600, respectively) of the monomer were similar to those of styrene, as expected (244 mμ, 12,000).[17]

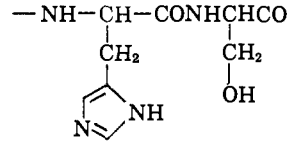
Further confirmation that the compound was monomeric was the identification of formaldehyde as an ozonolysis product. The correct structure was also proved by elemental analysis and hydrogenation data. This compound showed remarkable solubility in a broad range of solvents, being very soluble in water and other polar solvents, moderately soluble in benzene and ethers, and slightly soluble in the lower straight-chain hydrocarbons.

**Polymerization of 4-Vinylimidazole.**—Homopolymerization proceeded readily with free radical initiation in benzene solution, giving a white, powdery solid. Analysis indicated that one-half mole of water was bound to the polymer. This could not be removed by prolonged heating at 100° over phosphorus pentoxide. Similar behavior has been noted for poly-L-histidine[18] and for poly-5(6)-vinylbenzimidazole.[19]

Copolymerization with vinyl acetate followed by hydrolysis would give IV as a typical repeat unit in the polymer, which would resemble a –his–ser– sequence in a peptide (V).



IV



V

It was found that 4-vinylimidazole was so much more reactive as a monomer than vinyl acetate in free radical polymerization that the polymers always contained large amounts of imidazole and the composition of the copolymers could be varied only within a limited range. The conversions were also roughly proportional to the feed of 4-vinylimidazole, which was of necessity kept low (Table I). The copolymers were water soluble and exhibited association at high concentrations, as shown by gel formation.

The acetate groups were successfully hydrolyzed in dilute acid solution. Attempted basic hydrolysis generally led to degradation, shown by loss upon dialysis. Some hydrolysis occurred in the copolymers by mere dissolution in water, as shown by infrared spectra and elemental analysis. It is assumed that this ready water hydrolysis occurred by participation of neighboring imidazole groups on the polymer chain.

Table I shows typical feed and copolymer compositions in reactions with a series of comonomers. As can be seen, 4-vinylimidazole was the more reactive monomer with all of the comonomers used.

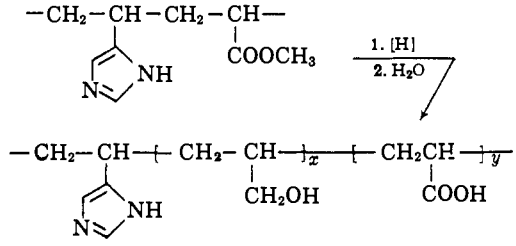
TABLE I

FEED AND COPOLYMER COMPOSITIONS IN COPOLYMERIZATIONS WITH 4-VINYLIMIDAZOLE; INITIATOR, AIBN

| Comonomer | Reaction time, hr. | Conversion, % | Imidazole in feed, mole/100 g. | Imidazole in polymer, mole/100 g. |
|---|---|---|---|---|
| Vinyl acetate | 18 | 3 | 0.06 | 0.80 |
| Methyl acrylate | 0.5 | 10 | .10 | .34 |
| Vinylene carbonate | 85 | 2 | .05 | .48 |
| Acrylic acid | 0.5 | 65 | .05 | .20 |
| Acrolein | 42 | 7 | .04 | .09 |
| Vinyl acetate, methyl acrylate | 18 | 36[a] | .05 | .06[a] |
| Vinyl acetate, acrylic acid | 1.0 | 9[b] | .02 | .24[b] |

[a] Benzene-soluble fraction. [b] Benzene-insoluble fraction.

As expected, methyl acrylate was more reactive in copolymerizations with 4-vinylimidazole than vinyl acetate, and the composition of these copolymers could be more readily varied. Here too, some hydrolysis of ester groups occurred on solution in cold dilute mineral acid. The desired hydroxyl groups would be obtained by reduction of the ester functions. The polymers formed were not soluble in solvents in which lithium aluminum hydride could be used. Attempted reduction in water or aqueous alcohol with sodium borohydride or calcium borohydride[20] was unsuccessful. Sodium in alcohol was effective in reducing some of the ester groups. The remaining esters on the polymer were hydrolyzed during the work-up of the reaction mixture.



Acrolein was an attractive comonomer because of the easily reducible aldehyde groups[21] or the possibility of an intramolecular Cannizzarro reaction[22] to give the desired hydroxyl and carbonyl groups.

Polyacroleins are usually insoluble due to intramolecular acetal formation, but can still undergo the usual aldehyde reactions, forming soluble polymers.[23]

Copolymerization of acrolein and 4-vinylimidazole gave a yellowish, insoluble polymer whose infrared spectrum was similar to that reported for polyacrolein.[24] Heterogeneous reaction with sodium borohydride in water resulted in at least partial reduction, as shown by the infrared spectrum. The resulting polymer was also insoluble. Heterogeneous reaction with aqueous base gave, at least partially, the expected Cannizzarro

(15) W. Reppe and co-workers, *Ann.*, **596**, 38 (1955).

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1958, p. 34.

(17) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 2000 (1950).

(18) A. Patchornik, A. Beyer and E. Katchalski, *J. Am. Chem. Soc.*, **79**, 5227 (1957).

(19) C. G. Overberger and B. Kösters, unpublished results.

(20) J. Kollonitsch, O. Fuchs and V. Gábor, *Nature*, **175**, 346 (1955).

(21) R. C. Schulz and P. Elzer, *Makromol. Chem.*, **42**, 205 (1961).

(22) R. C. Schulz, E. Müller, and W. Kern, *Naturwissenschaften*, **45**, 440 (1958).

(23) R. C. Schulz, *Kunststoffe*, **48**, 257 (1958).

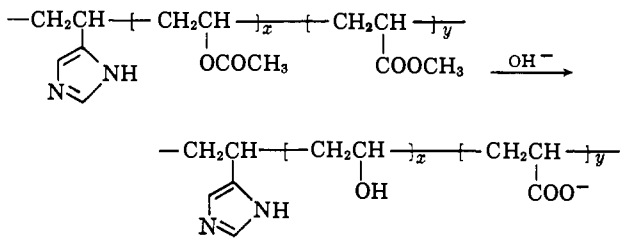
(24) R. C. Schulz, H. Cherdron and W. Kern, *Makromol. Chem.*, **29**, 190 (1959).

reaction, shown by infrared analysis, but here too, the product was insoluble. The insolubility of the product in these two cases may have been due to the formation of intermolecular acetal linkages which were unreactive because of shielding by the polymer chains, and thus kept the polymer from dissolving after reaction.

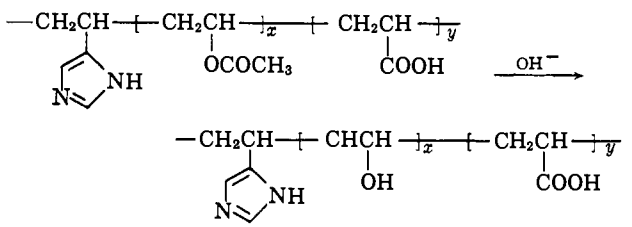
Copolymerization with vinylene carbonate would give a product, after hydrolysis, which would contain a hydroxyl group which could be hydrogen bonded to an imidazole nitrogen in a six-membered ring. A serine hydroxyl might be hydrogen-bonded to imidazole in the active enzyme site.[3c]

Copolymerization of 4-vinylimidazole and vinylene carbonate gave a colored, insoluble polymer, whose infrared spectrum showed imidazole and carbonate absorptions. Heterogeneous acidic treatment resulted in some hydrolysis, shown by infrared analysis, but the product was again insoluble.

Vinyl acetate, methyl acrylate and 4-vinylimidazole were terpolymerized, using large ratios of acetate and acrylate to imidazole. At high conversions, two polymers were formed and fractionated with benzene. The benzene-insoluble fraction was hydrolyzed in base, giving an insoluble product. The benzene-soluble fraction was predominantly a copolymer of vinyl acetate and methyl acrylate, but contained a small amount of imidazole (Table I). This polymer was hydrolyzed in aqueous base, giving a water-soluble product. Vinyl acetate, acrylic acid and 4-vinylimidazole were also terpolymerized to high conversion, giving two polymers. Here the benzene-soluble fraction was poly-



(vinyl acetate). This terpolymer was hydrolyzed in aqueous methanol with potassium hydroxide. The infrared spectra of the two hydrolyzed terpolymers were similar.



**Acknowledgment.**—We wish to thank the Smith, Kline, and French Foundation, the Hooker Chemical Company, and the United States Army Chemical Corps for their generous financial support.

## Experimental[25]

**Diazotization of Histamine.**—To 25.0 g. (0.14 mole) of histamine dihydrochloride and 60 ml. of 6 *N* hydrochloric acid (100% excess) in 100 ml. of water heated to 60° was slowly added over a period of 2 hours a solution of 20.0 g. (0.29 mole) of sodium nitrite in 100 ml. of water. Heating and stirring were continued an additional 15 min. The solution was allowed to cool and evaporated to dryness on a rotary evaporator. The yellowish oil was extracted with absolute ethanol, filtered, and the filtrate evaporated to dryness. The residual oil was treated with thionyl chloride until the vigorous reaction ceased. The resulting mixture was heated under reflux on a steam-bath for 30 min. The excess thionyl chloride was removed *in vacuo* and the solid residue recrystallized from a propanol–ethyl acetate solution, giving 15.0 g. (66%) from successive crops, m.p. 123–125°; mixed m.p. with the 4-(2′-chloroethyl)-imidazole hydrochloride prepared from 2-mercapto-4-(2′-hydroxyethyl)-imidazole, m.p. 123–126° (*vide infra*), 123–126°.

**4-(β-Chloroethyl)-imidazole hydrochloride** was prepared according to the procedure of Turner[13] by bromination of γ-butyrolactone, reaction of the resultant α-bromo-γ-butyrolactone with ammonia, reduction of the α-amino-γ-butyrolactone with sodium amalgam, cyclization with ammonium thiocyanate, desulfurization of the resulting 2-mercapto-4-(β-hydroxyethyl)-imidazole with W-2 Raney nickel, and reaction of the resulting alcohol with thionyl chloride; m.p. 123–126° (124°[13]). All attempts at dehydrohalogenation failed.

**4-(β-Hydroxyethyl)-imidazole** was prepared according to the procedure of Reppe,[15] by hydration and isomerization of 2-butyne-1,4-diol, reaction *in situ* of the resultant 1,4-dihydroxybutanone-2 with cupric sulfate, ammonia and formaldehyde, and decomposition with hydrogen sulfide; b.p. 180–185° (0.3 mm.), m.p. 88.0–89.2° (b.p. 170–175° (1 mm.)[15]) (m.p. 92°[26]).

**4-(β-Acetoxyethyl)-imidazole** was prepared by reaction of 4-(β-hydroxyethyl)-imidazole with acetic anhydride, and hydrolysis of the diacylated product with potassium carbonate, according to the procedure of Bruice and Sturtevant[8c]; b.p. 145–147° (0.2 mm.), m.p. 73–75° (75–76°[8c]).

Urocanic acid was prepared as the dihydrate according to the procedure of Edlbacher and von Bidder[14] by diazotization of histidine in concentrated hydrochloric acid and dehydrochlorination of the resultant α-chloro-β-imidazolylpropionic acid with trimethylamine in a steel bomb at 60°; m.p. 228–230° dec., with loss of water at 85° (229–230° dec.[27]).

**4(5)-Vinylimidazole.**—Anhydrous urocanic acid (5.0 g., 0.053 mole) was heated *in vacuo* in a distilling apparatus. At a temperature of 220°, the material melted and began to decompose, as noticed by a decreased vacuum. On careful heating at 220–240°, the product distilled as a colorless sirup which crystallized in the receiver; 1.8 g. (53%), b.p. 118° (0.3 mm.), m.p. 83.2–84.5°, $\lambda_{max}^{H_2O}$ 243 mμ, ε 12,600.

*Anal.* Calcd. for $C_5H_6N_2$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.88; H, 6.55; N, 29.50.

The compound absorbed the theoretical quantity of hydrogen upon hydrogenation in absolute ethanol over 10% palladium-on-carbon. The infrared absorption spectrum (KBr) had strong peaks at 1630, 980 and 890 cm.$^{-1}$ (vinyl), and at 2600–2700 (very broad), 1520 (quintet), 935 and 832 cm.$^{-1}$ (imidazole). The compound was ozonized in ethyl acetate with a stream of oxygen containing 3% ozone. The ozonide was reduced by a mixture of zinc dust and aqueous ethyl acetate and the formaldehyde formed removed by steam distillation and identified as the dimedone derivative, m.p. 193°, mixed m.p. 193° with an authentic sample of formaldehyde-dimedone. The infrared spectra of the two formaldehyde-dimedone derivatives were identical.

Molten 4-(2′-acetoxyethyl)-imidazole (7.0 g., 0.06 mole) was slowly added under nitrogen from a dropping funnel heated by heating tape to a pyrolysis tube packed with cut-glass tubing and heated to 500°. The dark brown eluent was distilled, giving 1.8 g. (50%) of 4(or 5)-vinylimidazole, b.p. 118–122° (0.7 mm.). The material crystallized when seeded with crystals of 4-vinylimidazole prepared from histidine. The infrared spectra of the compounds prepared by these two different methods were identical.

**Poly-(4-vinylimidazole).**—A solution of 1.0 g. (0.01 mole) of 4-vinylimidazole and 2 mg. (0.1 mole %) of azo-bisisobutyronitrile in 125 ml. of benzene was heated at reflux with stirring under nitrogen for 42 hours. The precipitated polymer was removed by filtration and washed several times with benzene, giving 0.3 g. (30% conversion) of a white powder; [η] 0.34 in a 0.05 *N* tris-(hydroxymethyl)-aminomethane (TRIS)–hydrochloric acid buffer of *p*H 7.0 in 28.5% (v./v.) ethanol–water.

*Anal.* Calcd. for $[C_5H_6N_2 \cdot 1/2H_2O]_x$: C, 58.23; H, 6.84, N, 27.17. Found: C, 60.98; H, 6.99; N, 26.57.

**Copolymerization of Vinyl Acetate and 4-Vinylimidazole.**—A solution of 10.0 g. (0.12 mole) of freshly distilled vinyl acetate, 0.55 g. (0.006 mole) of 4-vinylimidazole and 0.028 g. (0.1 mole %) of azo-bisisobutyronitrile in 30 ml. of benzene was heated at reflux under nitrogen for 18 hours. The polymer, which had begun to precipitate as soon as refluxing began, was filtered from the solvent and unreacted monomers, giving 0.36 g. (3% conversion) of a white powder. The infrared spectrum (Nujol mull) showed the presence of ester carbonyl (1725 cm.$^{-1}$) and of imidazole (3200 broad, 1640 weak, 1550, 1100 and 850 cm.$^{-1}$). This material was dissolved in water and added dropwise to a tenfold excess of dioxane. The precipitated polymer weighed

(25) Melting and boiling points are uncorrected. All melting points were determined on a Fisher–Johns melting point block. Intrinsic viscosities were determined in a Ubbelohde-type viscometer at 29.2°. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(26) B. Garforth and F. L. Pyman, *J. Chem. Soc.*, 489 (1935).

(27) Z. Horii, K. Sakurai and K. Tomio, *J. Pharm. Soc. Japan*, **74**, 408 (1954); *C. A.*, **49**, 5451 (1955).

0.25 g. The infrared spectrum showed a marked decrease in the carbonyl absorption (1725 cm.$^{-1}$) compared to the imidazole absorption.

*Anal.* Found: C, 58.63; H, 7.16; N, 22.51 (corresponds to 0.80 mole of imidazole per 100 g. of polymer).

This polymer was again dissolved in water, precipitated with dioxane, redissolved in water, and lyophilized, giving a fluffy, white solid; [$\eta$] 0.06 in a 0.05 *N* TRIS–hydrochloric acid buffer of *p*H 7.0 in 28.5% ethanol–water.

*Anal.* Found: C, 56.08; H, 6.57; N, 22.86 (0.81 mole of imidazole per 100 g. of polymer).

**Hydrolysis of Copolymer of Vinyl Acetate and 4-Vinylimidazole.**—A copolymer of vinyl acetate and vinylimidazole containing 0.64 mole of imidazole per 100 g. of polymer (0.5 g.) was suspended in 200 ml. of 0.2 *N* hydrochloric acid and allowed to stand. After 5 weeks the mixture had become a clear solution, which was neutralized with saturated aqueous sodium bicarbonate, dialyzed against deionized water for 1 week, and partially concentrated. The concentrated solution was precipitated into a tenfold excess of dioxane, giving 0.12 g. of a white powder. The infrared spectrum showed only a very weak absorption at 1725 cm.$^{-1}$; [$\eta$] 0.37 in a 0.05 *N* TRIS–hydrochloric acid buffer of *p*H 7.0 in 28.5% ethanol–water.

*Anal.* Found: C, 56.40; H, 7.19; N, 18:81 (0.67 mole of imidazole per 100 g. of polymer).

**Copolymerization of Methyl Acrylate and 4-Vinylimidazole.**—In a polymerization tube was placed 5.3 g. (0.065 mole) of freshly distilled methyl acrylate, 0.55 g. (0.006 mole) of vinylimidazole and 0.013 g. (0.1 mole%) of azo-bisisobutyronitrile. The solution was degassed under nitrogen, sealed *in vacuo*, and heated at 73° for 35 min. The tube was opened, and the unreacted monomer decanted from the polymer, which had adhered to the sides of the tube. The polymer was dissolved in cold dilute hydrochloric acid and precipitated into saturated aqueous sodium bicarbonate. The solid was removed by filtration, dissolved in water and precipitated into dioxane. The precipitated solid was dissolved in water and dialyzed against deionized water for 1 week. The solution was then lyophilized, giving a white solid; [$\eta$] 0.89 in 0.06 *N* potassium bromide. The infrared spectrum (film) showed the presence of both ester (1725 cm.$^{-1}$) and carboxylate (1580 cm.$^{-1}$) groups.

*Anal.* Found: C, 54.81; H, 6.65; N, 9.65 (0.34 mole of imidazole per 100 g. of polymer).

**Reduction of Copolymer of Methyl Acrylate and 4-Vinylimidazole.**—Attempted reduction of this copolymer with sodium borohydride in water or with calcium borohydride in aqueous ethanol at −30° gave little or no reduction as shown by infrared analysis. More success was achieved with sodium in alcohol, as follows: To a suspension of 0.2 g. of a copolymer of vinylimidazole and methyl acrylate containing 0.34 mole of imidazole per 100 g. of polymer in 125 ml. of dried absolute ethanol was added rapidly, with stirring, 8.0 g. (0.35 g. atom) of sodium in large pieces. The polymer became yellowish and agglomerated. After the sodium had completely dissolved, the mixture was heated on a steam-bath for 30 min., 150 ml. of water added and the ethanol removed by distillation. The residual solution was neutralized with 2 *N* hydrchloric acid, dialyzed against tap water overnight, filtered, and the filtrate lyophilized, giving a slightly yellowish powder. The infrared spectrum (Nujol) showed the presence of hydroxy (3400 cm.$^{-1}$, broad) and carboxylate (1570 cm.$^{-1}$) groups.

*Anal.* Found: N, 10.27 (0.37 mole of imidazole per 100 g. of polymer).

**Vinylene carbonate** was prepared according to the procedure of Newman and Addor[28] by chlorination of ethylene carbonate and dehydrochlorination with triethylamine; b.p. 69.5–70.5° (26 mm.), $n^{25}$D 1.4268 (b.p. 74° (33 mm.), $n^{25}$D 1.4218[29]).

**Copolymerization of Vinylene Carbonate and 4-Vinylimidazole.**—Vinylene carbonate (11.0 g., 0.12 mole), vinylimidazole (0.5 g., 0.005 mole) and azo-bisisobutyronitrile (0.02 g., 0.1 mole %), in a polymerization tube were degassed and allowed to react at 75° for 85 hours. The small amount of precipitated solid was filtered from the dark brown solution and washed with benzene, giving 0.3 g. (2%) of a yellow powder, whose infrared spectrum (Nujol) showed typical imidazole absorption, and a strong peak at 1800–1850 cm.$^{-1}$ (cyclic carbonate carbonyl). This material was insoluble in water, dilute acid, and hot concentrated potassium hydroxide.

*Anal.* Calcd. for $(C_5H_6N_2)_{43.3}(C_3H_2O_3)_{56.7}$: C, 51.90; H, 4.18; N, 13.56. Found: C, 52.27; H, 5.46; N, 13.55 (0.48 mole of imidazole per 100 g. of polymer).

(28) M. S. Newman and R. W. Addor, Jr., *J. Am. Chem. Soc.*, **75**, 1263 (1953).

(29) C. G. Overberger, H. Biletch and R. G. Nickerson, *J. Polymer Sci.*, **27**, 381 (1958).

**Copolymerization of Acrylic Acid and 4-Vinylimidazole.**—In a polymerization tube, 10.1 g. (0.14 mole) of distilled acrylic acid, 0.5 g. (0.005 mole) of vinylimidazole and 0.02 g. (0.1 mole %) of azo-bisisobutyronitrile were degassed and allowed to react at 75° for 15 min. The reaction was essentially complete after 10 seconds. The polymer plug was dissolved in 3% aqueous ammonia, the solution neutralized to *p*H 7.0 with 6 *N* hydrochloric acid, dialyzed against deionized water for one week, and lyophilized, giving 6.7 g. (63%) of white, brittle solid; [$\eta$] 1.2 in a 0.05 *N* TRIS–hydrochloric acid buffer of *p*H 7.0 in 28.5% ethanol–water.

*Anal.* Found: N, 9.59 (0.34 mole of imidazole per 100 g. of polymer).

**Copolymerization of Acrolein and 4-Vinylimidazole.**—A solution of 11.75 g. (0.21 mole) of freshly distilled acrolein, 0.5 g. (0.005 mole) of 4-vinylimidazole, 0.02 g. (0.05 mole %) of azo-bisisobutyronitrile and 16.0 g. (0.5 mole) of methanol[30] in 300 ml. of benzene was refluxed under nitrogen, with stirring, for 42 hours. The solid which had precipitated was removed by filtration and washed thoroughly with benzene, giving 0.85 g. (7%) of a yellow powder, which was insoluble in acidic, neutral and basic aqueous solutions and common organic solvents. The infrared spectrum (Nujol) had absorption peaks at 3500 cm.$^{-1}$ (broad, O–H stretch), 2750 and 1720 cm.$^{-1}$ (aldehyde) and 1100 cm.$^{-1}$ (very broad, C–O–C stretch) and was very similar to that reported for polyacrolein.

*Anal.* Found: N, 3.05 (0.11 mole of imidazole per 100 g. of polymer).

Attempts at reduction of this polymer with aqueous sodium borohydride or reaction of the polymer with base gave products whose infrared spectra showed that partial reaction had taken place, but which could not be further characterized.

**Terpolymerization of Vinyl Acetate, Methyl Acrylate and 4-Vinyl Imidazole.**—A degassed mixture of 8.0 g. (0.09 mole) of freshly distilled vinyl acetate, 2.5 g. (0.03 mole) of freshly distilled methyl acrylate, 0.5 g. (0.005 mole) of vinylimidazole and 0.02 g. (0.1 mole %) of azo-bisisobutyronitrile was heated in a polymerization tube at 75° for 18 hours. The mixture obtained was extracted with benzene, leaving 0.8 g. (7%) of a benzene-insoluble fraction. This fraction was heated at reflux in 100 ml. of 10% aqueous potassium hydroxide for 50 hours, then cooled. The mixture was neutralized with 2 *N* hydrochloric acid and dialyzed against deionized water for 72 hours. The milky suspension was added to a tenfold excess of dioxane and the precipitated solid removed by filtration, giving 0.5 g. of a white powder. The infrared spectrum (Nujol) showed the presence of hydroxyl and carboxyl groups. The polymer was insoluble in water.

The benzene extract obtained above was precipitated into hexane, giving 4.0 g. (36%) of a hard, brittle, white solid. The vinyl acetate:methyl acrylate content of the polymer was estimated to be 70:30 by a comparison of the intensities of the infrared absorptions at 8.0 and 8.55 $\mu$, respectively.

*Anal.* Calcd. for $(C_5H_6N_2)_{5.2}(C_4H_6O_2)_{94.8}$: C, 57.60; H, 7.10; N, 1.73. Found: C, 55.76; H, 7.24; N, 1.69.

**Hydrolysis of Terpolymer.**—To 1.0 g. of the polymer prepared above in 100 ml. of water was added 1.0 g. of potassium hydroxide and the mixture heated on a steam-bath with stirring until the polymer completely dissolved (30 min.), then for 1 hour more. The solution was neutralized with 2 *N* hydrochloric acid, dialyzed against tap water for 72 hours, and lyophilized, giving 0.65 g. of a fluffy, white solid; [$\eta$] 1.40 in 0.1 *N* potassium bromide. The infrared spectrum (Nujol) showed only very weak ester carbonyl absorption compared to the starting material. The spectrum also had strong absorptions in the hydroxyl and carboxylate regions.

*Anal.* Found: N, 2.32 (0.08 mole of imidazole per 100 g. of polymer).

**Terpolymerization of Vinyl Acetate, Acrylic Acid and 4-Vinylimidazole.**—A degassed mixture of 25.5 g. (0.3 mole) of freshly distilled vinyl acetate, 1.6 g. (0.02 mole) of distilled acrylic acid, 0.5 g. (0.005 mole) of vinylimidazole and 0.02 g. (0.05 mole %) of azo-bisisobutyronitrile in a polymerization tube was heated at 75° for 1 hour. The polymer formed was fractionated by extraction with benzene. The benzene-soluble polymer was precipitated into hexane, giving 9.2 g. (33%) of a white powder. This polymer contained no nitrogen and its infrared spectrum (film) was practically identical with that of pure poly-(vinyl acetate).

The benzene-insoluble polymer was dissolved in 3% aqueous ammonia and the solution neutralized with 2 *N* hydrochloric acid, dialyzed against tap water for 72 hours and lyophilized, giving 2.4 g. (9%) of a brittle solid. The infrared spectrum (KBr) showed ester and carboxylate absorptions. The acrylic acid: vinyl acetate content was estimated to be 2:1 by comparison of

(30) H. C. Miller and H. S. Rothrock, U. S. Patent 2,657,192, Oct. 27, 1953.

the relative intensities of the ester (1730 cm.$^{-1}$) and carboxylate (1565 cm.$^{-1}$) absorptions with synthetic mixtures of poly-(vinyl acetate) and poly-(sodium acrylate).

*Anal.* Found: N, 6.85 (0.24 mole of imidazole per 100 g. of polymer).

**Hydrolysis of Terpolymer.**—To a solution of 0.5 g. of the terpolymer prepared above in 200 ml. of 50% aqueous methanol was added 2.0 g. (0.04 mole) of potassium hydroxide. The solution was refluxed, with stirring, for 5 hours, stirred at room temperature overnight, neutralized with 2 *N* hydrochloric acid, dialyzed against tap water for 24 hours, and lyophilized, giving 0.4 g. of a fluffy, white solid; $[\eta]$ 3.33 in 0.2 *N* potassium bromide. The infrared spectrum (Nujol) showed hydroxyl and carboxylate absorptions and was very similar to the spectrum of the hydrolyzed terpolymer prepared from vinyl acetate, methyl acrylate and 4-vinylimidazole.

*Anal.* Found: N, 5.63 (0.20 mole of imidazole per 100 g. of polymer).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

# A New Method for the Conversion of Glycidic Esters to Aldehydes and Ketones

BY E. P. BLANCHARD, JR., AND G. BÜCHI

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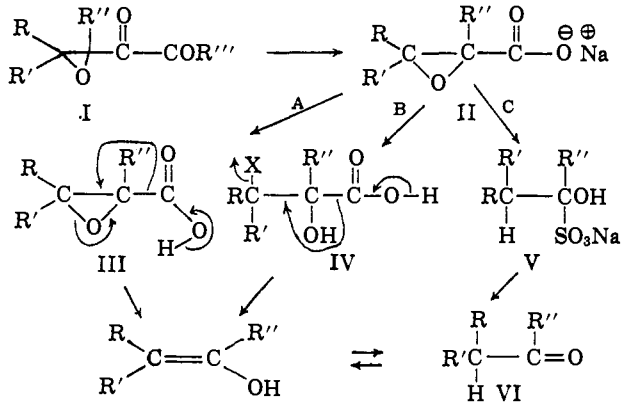
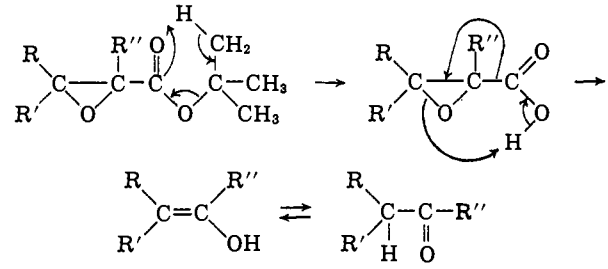
Pyrolysis of *tert*-butyl glycidic esters is shown to be a useful method for the preparation of aldehydes and ketones, particularly those containing acid sensitive substituents. Seven examples serve to illustrate the utility of this procedure.

One of the more useful transformations of glycidic esters concerns their conversion to aldehydes and ketones. Three methods for effecting this change have been in fairly general use. The first step in each of these methods is the saponification of the glycidic ester I to the corresponding alkali glycidate II, a reaction which is best achieved by the procedure of Claisen.[1] Hydrolysis with *aqueous* alkali results in the appearance of carbonyl compounds presumably formed by "retro-aldol cleavage" of initially produced $\alpha,\beta$-dihydroxy-ester.[2] Path A represents the most commonly used sequence for effecting decarboxylation. The alkali glycidate II is transformed to the glycidic acid III which is pyrolyzed. Path B is based on the observation of Darzens[3] that addition of hydrogen chloride or hydrogen bromide to glycidic acids produces $\alpha$-hydroxy-$\beta$-halocarboxylic acids. Later investigators utilized this reaction and treated the $\alpha$-hydroxy-$\beta$-halo-acid (IV) with alkali. Decarboxylation with concomitant loss of hydrogen halide furnishes the desired aldehydes or ketones (VI) in fair to good yields.[4,5] Path C[5] consists of heating the alkali glycidate II with a saturated aqueous solution of sodium bisulfite. This mild, presumably acid-catalyzed decarboxylation, is followed by formation of the sodium bisulfite adduct



V of the aldehyde and certain ketones, thus protecting the desired products from further transformations.

In each of these methods an intermediate is exposed to an acidic medium at one stage. For certain syntheses it is advantageous to effect the conversion without recourse to acidic reagents. A procedure which meets this requirement is the direct pyrolysis of *t*-butyl glycidic esters to isobutylene, carbon dioxide and the desired carbonyl compounds. Examination of the pertinent literature revealed that Johnson and his



co-workers[5] had already attempted such a pyrolysis without success, but in deference to current journal practice did not report experimental conditions. Fortunately, at the time we learned about this earlier study we had already pyrolyzed *t*-butyl $\beta$-methyl-$\beta$-(3-methylene-4-methylamyl)-glycidate (XIII) to 2,6-dimethyl-3-methyleneheptanal-1 (XXII) in 56% yield. A product analysis by gas liquid partition chromatography indicated the absence of double bond isomers, while a sample of this aldehyde prepared by the "bisulfite procedure" (method C) was grossly contaminated with substances whose infrared spectra indicated absence of a methylene group. Isomerization undoubtedly had occurred during prolonged heating in the presence of the acidic sodium bisulfite. Encouraged by the successful pyrolysis just mentioned we decided to investigate the thermal decomposition of other *t*-butyl glycidic esters and the results are presented in this report.

Seven *t*-butyl glycidic esters listed in Table I were prepared by condensation of the appropriate ketone with either *t*-butyl chloroacetate or *t*-butyl $\alpha$-chloropropionate following the reliable procedure of Johnson, *et al.*[5] In agreement with earlier observations, the infrared spectra of all esters exhibited two bands in the carbonyl region.[2,6] Five of these glycidic esters can exist in diastereomeric forms and the products actually isolated may well have represented mixtures of such isomers. The esters listed in Table I were then pyro-

(1) L. Claisen, *Ber.*, **38**, 693 (1905).

(2) H. O. House, J. W. Blaker and D. A. Madden, *J. Am. Chem. Soc.*, **80**, 6386 (1958).

(3) G. Darzens, *Compt. rend.*, **150**, 1243 (1910). The preparation and reactions of glycidic esters were reviewed by M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949), and by O. Bayer, Houben-Weyl, "Methoden der Organischen Chemie," Vol. VII, G. Thieme Verlag, Stuttgart, 1954, p. 326. A critical discussion of the mechanism of the Darzens synthesis was presented by M. Ballester, *Chem. Rev.*, **55**, 283 (1955).

(4) W. A. Yarnall and E. S. Wallis, *J. Org. Chem.*, **4**, 270 (1939).

(5) W. S. Johnson, J. C. Belew, L. J. Chinn and R. A. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).

(6) H. O. House and J. W. Blaker, *ibid.*, **80**, 6389 (1958).