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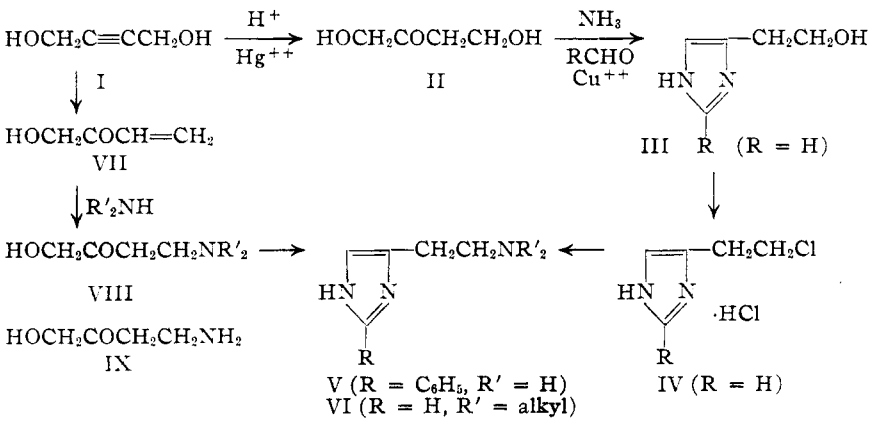
Studies of Imidazole Compounds. V. A New and Improved Synthesis of 4-(2-Substituted Aminoethyl)-imidazoles

BY CHARLES F. HUEBNER

A new and improved method of synthesis of 4-(2-substituted ethyl)-imidazoles has been described. The starting material is the inexpensive 1,4-butynediol which is transformed to 1,4-dihydroxybutanone-2 or hydroxymethylvinyl ketone. The former by the Weidenhagen reaction with formaldehyde and ammonia yields 4-(2-hydroxyethyl)-imidazole. The latter is treated with a secondary amine and followed by the Weidenhagen reaction to give a 4-(2-substituted aminoethyl)-imidazole. A 2-substituent may be introduced into the imidazole through use of an aldehyde other than formaldehyde.

This paper describes a new and improved synthesis of 4-(2-substituted aminoethyl)-imidazoles and related 4-(2-substituted ethyl)-imidazoles, a family which includes the physiologically important substance histamine. Even the best of previous methods have been long and tedious.[1,2] The synthesis described here may be carried out in a single reaction vessel by a number of consecutive steps without the isolation of intermediates. The starting material is the readily available, inexpensive 1,4-butynediol (I). It is hydrated in the presence of a mercury catalyst as described by Reppe and co-workers[3] to 1,4-dihydroxybutanone-2 (II). The latter substance, containing a ketol grouping, will react with formaldehyde, ammonia and cupric acetate according to the general method discovered by Weidenhagen[4] to form 4-(2-hydroxyethyl)-imidazole (III), which is isolated as its insoluble cuprous salt. The free imidazole (III) obtained by decomposition with hydrogen sulfide is converted by thionyl chloride to the useful intermediate 4-(2-chloroethyl)-imidazole hydrochloride (IV) which by appropriate reaction can be converted into 4-(2-substituted N, O and S ethyl)-imidazoles.[5] Histamine is available through this route. The use of benzaldehyde in the Weidenhagen reaction leading to the hitherto undescribed 2-phenylhistamine (V) *via* the substituted hydroxy and chloroethyl imidazoles illustrates the extension of the method to 2-substituted-imidazoles. Only one example of this type of imidazole bearing the 4-(2-aminoethyl)-side chain has been described[6] and it was prepared by a long series of reactions.



In a simplified variation of the method, 4-(2-substituted aminoethyl)-imidazoles (VI) can be prepared directly. In this case I is rearranged to hydroxymethyl vinyl ketone (VII) again as described by Reppe. The latter, either in pure form[7] or as the crude aqueous reaction mixture[8] resulting from rearrangement of I rapidly adds a secondary amine. The amino-hydroxy ketone (VIII), without isolation, is treated with an aldehyde, ammonia and cupric acetate to form directly 2-substituted-4-(2-substituted aminoethyl)-imidazoles. Dimethylamine and piperidine have been used as the amines and formaldehyde, acetaldehyde, propionaldehyde and benzaldehyde as the aldehydes to illustrate the generality of the method.

Attempts were made to synthesize histamine by using ammonia in the reaction with VII. After reaction for a short period (*ca.* 15 sec.), in the hope that the amino ketone (IX) had not completely self-condensed, the usual Weidenhagen reaction was carried out. An extremely small amount of an insoluble cuprous salt was obtained, which on decomposition with hydrogen sulfide was shown to contain histamine by both pharmacological assay and paper chromatography. Addition of VII directly to the hot solution of formaldehyde, ammonia and cupric acetate yielded a small amount of a condensation product whose structure is under investigation.

Of inestimable value in this work was the use of paper chromatography to identify the imidazole reaction products. This enabled one in the early part of the work to carry out reactions on a small scale and to ascertain simply the outcome by running comparative chromatograms of the crude reaction mixtures with authentic samples of the desired imidazoles. It may be of interest to describe briefly the chromatographic method used. These studies were under way in this Laboratory when Urbach's description[9] of the paper chromatographic identification of histamine, appeared.

(1) Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).
(2) Turner, THIS JOURNAL, **71**, 3476 (1949).
(3) Reppe and co-workers, "Acetylene and Carbon Monoxide Chemistry," Copenhaver and Bigelow, New York, N. Y., 1949, p. 138.
(4) Weidenhagen and Herrmann, *Ber.*, **68**, 1960 (1935).
(5) Huebner, Turner and Scholz, THIS JOURNAL, **71**, 3942 (1949).
(6) Y. Tamamushi, *J. Pharm. Soc. Japan*, **53**, 226 (1933).
(7) Reference 3, p. 136, example 1.
(8) *Ibid.*, p. 137, example 2.
(9) K. F. Urbach, *Proc. Soc. Exp. Biol.*, **68**, 430 (1948).

Of the various solvent systems tried by us, *n*-butanol saturated with 20% pyridine in water gives the best separation of closely related imidazoles.

The ascending technique is used and the color developed with diazotized *p*-bromoaniline.[10] Table I shows the R_f values of some representative imidazoles. The optimal amount of imidazole employed for a chromatogram is 5–10 γ. It should be pointed out that the pairs of homologs, 4-(2-ethylaminoethyl)-, 4-(2-*n*-propylaminoethyl)- and 4-(2-dimethylaminomethyl)- and 4-(2-dimethylaminoethyl)-imidazole can be separated as can the isomers 4-(2-diethylaminomethyl)- and 4-(2-*n*-propylaminoethyl)-imidazole. When the solvent front has migrated about 30 mm., differences in R_f value of 0.04 can be distinguished. It should be mentioned that these R_f values are not absolute, and certain uncontrollable variables cause a slight change in the value. Controls should be run when working with unknown imidazoles. In this system, the higher the number of carbon atoms in the imidazole, the higher is the R_f value. One may reverse this order using 1.5 *N* aqueous ammonia saturated with *n*-butanol as the developer, but this system gives considerable tailing of the spots.

There is variation in color of the azo dye produced, according to the nature and position of the substituent on the imidazole ring. Substituents in the 4- and 5-position give a red dye; an alkyl group in the 2-position, a yellow color and an SH group in the 2-position, an orange color. As is well known,[11] a substituent in the 1-position prevents coupling with a diazonium salt; hence no color is developed.

Of the new imidazoles described in this paper, 4-(2-aminoethyl)- and 4-(2-dimethylaminoethyl)-2-phenyl-imidazole have appreciable histamine-like action, as determined on the guinea pig ileum strip by Dr. B. N. Craver of these laboratories.

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TABLE I

R_f VALUES OF IMIDAZOLES IN THE SYSTEM: *n*-BUTANOL SATURATED WITH 20% AQUEOUS PYRIDINE

Imidazole substituent	R_f	Color
4-(2-Aminoethyl)-	0.30	Red
4-(2-Hydroxyethyl)-	.55	Red
4-(2-Ethylaminoethyl)-	.60	Red
Imidazole (no substituent)	.68	Red
4-(2-Dimethylaminomethyl)-	.75	Red
4-(2-*n*-Propylaminomethyl)-	.76	Red
4-(2-Dimethylaminoethyl)-	.79	Red
4-(2-Diethylaminomethyl)-	.82	Red
4-(2-Piperidinomethyl)-	.86	Red
4-(2-Piperidinoethyl)-	.90	Red
4-(2-Benzylmethylaminoethyl)-	.94	Red
2-Methyl-	.70	Yellow
2-Hydroxyethyl-4-phenyl-2-mercapto-	.83	Yellow
2-Mercapto-	.56	Orange
4-(2-Hydroxyethyl)-	.50	Orange

(10) K. F. Urbach, *Proc. Soc. Exp. Biol.*, **70**, 146 (1949).

(11) R. Burian, *Ber.*, **37**, 6961 (1904).

Experimental

A. 4-Ethylimidazoles from 1,4-Dihydroxybutanone-2 (II). 4-(2-Chloroethyl)-imidazole Hydrochloride (IV).—A crude solution of 1,4-dihydroxybutanone-2 (II) in 20 cc. of water, prepared from 2 g. of 1,4-butynediol (I), according to Reppe and co-workers, was added to a solution of 9 g. of cupric acetate and 3.2 cc. of 36% formaldehyde solution in 70 cc. of concd. ammonia (d. 0.90). After one-half hour on the steam-bath, the black cuprous salt of the imidazole was filtered, washed well with water, and suspended in 100 cc. of hot water. Hydrogen sulfide was passed through the solution while concd. hydrochloric acid was slowly added to keep the mixture acid to congo red. Decolorizing charcoal was added, and the solids were removed by filtration. The presence of 4-(2-hydroxyethyl)-imidazole in this mixture was shown by paper chromatography. The water was removed *in vacuo*, absolute ethanol added, and in turn distilled off. Thionyl chloride (3 cc.) was added to the sirupy residue and gently warmed for one-half hour. Twenty-five cc. of dry benzene was added and the solvent and excess reagent removed *in vacuo*. The residue was dissolved in about 10 cc. of absolute ethanol and enough dry ether added to precipitate a black tarry by-product. This was filtered with the aid of carbon, and further slow addition of dry ether brought the crystalline chloroimidazole out of solution. This was recrystallized three times from ethanol–ether to free it of sirupy impurities; weight 0.5 g., m.p. 121–123°. The m.p. of a mixture with a sample of authentic 4-(2-chloroethyl) imidazole[2] was 122–124°. No extensive attempts were made to work out reaction conditions for optimum yield.

Anal. Calcd. for $C_5H_7N_2Cl\cdot HCl$: C, 35.95; H, 4.82; Cl, 42.45. Found: C, 36.17; H, 5.17; Cl, 42.44.

2-Phenyl-4-(2-hydroxyethyl)-imidazole.—A solution of II in 200 cc. of water, derived from 20 g. of I, was added to a mixture of 90 g. of cupric acetate and 30 cc. of benzaldehyde in 1000 cc. of concd. ammonia. The reaction mixture was heated for one hour on the steam-bath with frequent shaking. The tan cuprous salt was filtered and decomposed with hydrogen sulfide as described above. The solution of the imidazole hydrochloride was added to a hot saturated solution of 32 g. of picric acid. The crystalline picrate which separated on cooling was recrystallized from water; m.p. 149–150°; yield 25 g.

Anal. Calcd. for $C_{11}H_{12}N_2O\cdot C_6H_3N_3O_7$: N, 16.79. Found: N, 16.72.

The picrate was converted to the hydrochloride by decomposition with dilute hydrochloric acid and extraction of the picric acid with ether. On concentration to dryness and recrystallization of the residue from ethanol–ether, 12 g. of the hydrochloride resulted, m.p. 173–175°.

Anal. Calcd. for $C_{11}H_{12}N_2O\cdot HCl$: N, 12.47. Found: N, 12.77.

The free base, which was obtained by adding ammonia to an aqueous solution of the hydrochloric acid, was recrystallized from water, m.p. 52–53°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: N, 14.89. Found: N, 14.98.

2-Phenyl-4-(2-chloroethyl)-imidazole Hydrochloride.—Ten cc. of thionyl chloride was warmed on the steam-bath with 6 g. of the imidazole hydrochloride for one-half hour. The excess reagent was distilled off *in vacuo* and the residue recrystallized from ethanol–ether; yield 5 g., m.p. 167–168°.

Anal. Calcd. for $C_{11}H_{11}N_2Cl\cdot HCl$: N, 11.52; Cl, 29.17. Found: N, 11.40; Cl, 29.76.

2-Phenyl-4-(2-aminoethyl)-imidazole Dihydrochloride (2-Phenylhistamine) (V).—Two grams of 2-phenyl-4-(2-chloroethyl)-imidazole hydrochloride was heated in a bomb tube with 20 cc. of a saturated solution of dry ammonia in ethanol at 110° for 12 hours. One gram of sodium carbonate in 10 cc. of water was added and the solvent removed *in vacuo*. The imidazole was extracted from the inorganic salts by hot ethanol. The remaining sirup after removal of the ethanol was converted to the dipicrate as described above and recrystallized from water, m.p. 256–257°.

Anal. Calcd. for $C_{11}H_{13}N_3\cdot 2C_6H_3N_3O_7$: N, 19.53. Found: N, 19.42.

The dihydrochloride prepared from the picrate (0.9 g.) was recrystallized from a hot ethanol–water (4:1) solution,

to which ether was added to the point of turbidity, m.p. 305–307°.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot 2HCl$: N, 16.15. Found: N, 16.09.

2-Phenyl-4-(2-dimethylaminoethyl)-imidazole dihydrochloride.—Two grams of the chloroethyl imidazole was heated at 110° for 12 hours in a bomb tube with 20 cc. of a 30% solution of dimethylamine in ethanol. The reaction mixture was worked up as described above. The **dipicrate** melted at 218–220°.

Anal. Calcd. for $C_{13}H_{17}N_3 \cdot 2C_6H_3N_3O_7$: N, 18.73. Found: N, 19.00.

One gram of the dihydrochloride was obtained from the picrate, m.p. 270–275°.

Anal. Calcd. for $C_{13}H_{17}N_3 \cdot 2HCl$: N, 14.59; Cl, 24.65. Found: N, 14.61; Cl, 24.53.

B. **4-Ethylimidazoles from Hydroxymethyl Vinyl Ketone (VII). 4-(2-Piperidinoethyl)-imidazole Dihydrochloride.**—To 2 g. of freshly distilled hydroxymethyl vinyl ketone[7] (VII) was added 2 g. of piperidine in 10 cc. of ethanol with rapid mixing. A spontaneous reaction took place with evolution of heat. After two minutes this mixture was added to a solution of 10 g. of cupric acetate and 5 cc. of formaldehyde solution (36%) in 75 cc. of concd. ammonia, and heated on the steam-bath for one hour. The insoluble cuprous salt was collected and decomposed with hydrogen sulfide in the manner described above. The aqueous solution of the hydrochloride was concentrated to a sirup *in vacuo*. Crystallization occurred on scratching. On recrystallization from ethanol–methyl ethyl ketone, 3.1 g. (47%) of the imidazole hydrochloride, m.p. 275–278°, was obtained. The m.p. of the mixture with an authentic sample of 4-(2-piperidinoethyl)-imidazole dihydrochloride prepared by an independent method[5] was undepressed.

Anal. Calcd. for $C_{10}H_{17}N_3 \cdot 2HCl$: N, 16.66; Cl, 28.17. Found: N, 16.64; Cl, 28.29.

The dipicrate melted at 188–191°, and the mixture with an authentic sample[5] showed no depression.

Anal. Calcd. for $C_{10}H_{17}N_3 \cdot 2C_6H_3N_3O_7$: N, 19.78. Found: N, 19.74.

2-Ethyl-4-(2-piperidinoethyl)-imidazole Dihydrochloride.—The product from 2 g. VII and 2 g. of piperidine was reacted with the same mixture described above with the exception of the use of 2.5 g. of propionaldehyde in place of the formaldehyde. The hydrochloride could not be crystallized so the dipicrylsulfonate was prepared and recrystallized twice from water; yield 3 g., m.p. 253°.

Anal. Calcd. for $C_{12}H_{21}N_3 \cdot 2C_6H_3N_3SO_9$: N, 15.89. Found: N, 15.79.

The sirupy hydrochloride was obtained by decomposition of the picryl sulfonate with aqueous hydrochloric acid and extraction of the picrylsulfonic acid liberated with *n*-butanol.

2-Phenyl-4-(2-piperidinoethyl)-imidazole.—The product from 2 g. of VII and 2 g. of piperidine reacted with the same mixture as described above except that as the aldehyde, 3 g. of benzaldehyde was used. After decomposition of the cuprous salt, ammonia was added to the solution of the imidazole hydrochloride. The crystalline imidazole base was collected and recrystallized from ethanol–water; yield 0.8 g., m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{21}N_3$: N, 16.47. Found: N, 16.45.

C. **4-Ethylimidazoles from Crude Aqueous Hydroxymethyl Vinyl Ketone (VII). 4-(2-Dimethylaminoethyl)-imidazole Dihydrochloride.**—I was converted to an aqueous solution of VII of an estimated concentration of 6% by the method described by Reppe and co-workers.[8] To 100 cc. of this solution was added 12 cc. of a 32% aqueous solution of dimethylamine. After 15 minutes standing at room temperature, during which time a slight warming occurred, this solution was added to a solution of 30 g. of cupric acetate and 15 cc. of formaldehyde solution (36%) in 225 cc. of concd. ammonia. The mixture was heated on the steam-bath for one hour, the cuprous salt decomposed with hydrogen sulfide, and the crystalline imidazole **dipicrate** prepared by the addition of a hot aqueous solution of 10 g. of picric acid. After recrystallization of the dipicrate from water, 3.8 g. was obtained; m.p. 230–232°.

Anal. Calcd. for $C_7H_{13}N_3 \cdot 2C_6H_3N_3O_7$: N, 21.11. Found: N, 21.13.

The dipicrate was converted to the crystalline dihydrochloride, m.p. 184–185°. No depression of the m.p. of a mixture with an authentic sample[5] was noted.

4-(2-Piperidinoethyl)-imidazole Dihydrochloride.—To 100 cc. of the 6% hydroxymethylvinyl ketone solution at room temperature, 6 cc. of piperidine was added. After 15 minutes, this solution was added to a solution of 30 g. of cupric acetate and 15 cc. of formaldehyde solution (36%) in 225 cc. of concd. ammonia. The mixture was heated on the steam-bath, the cuprous salt decomposed, and the imidazole dihydrochloride crystallized as previously described; wt. 4.1 g., m.p. 275–278°.

2-Methyl-4-(2-piperidinoethyl)-imidazole Dihydrochloride.—One hundred cc. of aqueous 6% hydroxymethyl vinyl ketone containing 6 cc. of piperidine was added to a solution of 30 g. of cupric acetate and 5 g. of acetaldehyde in 225 cc. of concd. ammonia. The hydrochloride obtained in the usual way was a sirupy, non-crystalline material. It was purified by conversion to a **dipicrate**, m.p. 153–154°.

Anal. Calcd. for $C_{11}H_{19}N_3 \cdot 2C_6H_3N_3O_7$: N, 19.35. Found: N, 19.78.

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