1943, soon to be followed by the collapse of the monarchy, Bruni retired to strictly private life, but the writer received many demonstrations of his sympathy for the new birth of democracy in his country. Bruni's last concern and last working effort in the summer of 1945 were for his book, a treatise on general and inorganic chemistry for student use. In the foreword of the last edition, Bruni had written:

I give this book to the printer not without emotion because, thus enlarged and completed, it represents my scientific legacy.

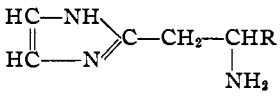
INSTITUTE OF GENERAL CHEMISTRY
OF THE POLYTECHNIC SCHOOL OF MILAN

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazole Compounds. I. A Synthesis of Imidazoles with Functional Groups in the 2-Position

BY REUBEN G. JONES

In connection with a broad study of possible relationships of chemical structure to biological activity, it was of interest to prepare the isomer (I) of histamine and the isomer (II) of histidine in which the side chains were attached to the 2-position of the imidazole nucleus.



I, R = H
II, R = COOH

These compounds have been synthesized by a method which appears to be generally applicable to the preparation of a variety of 2-substituted imidazoles. A number of other new members of this little-known class of compounds are also reported at this time.

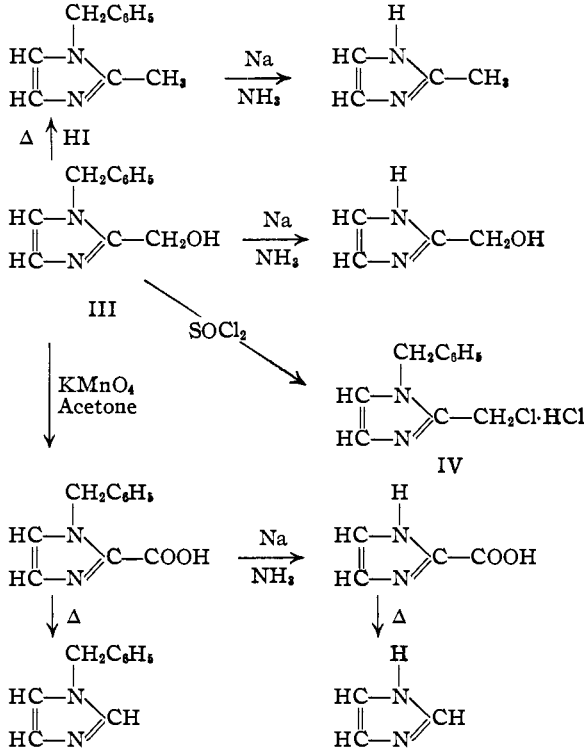
It has been shown[1a,b,c] that certain imidazoles having a methyl group in the 1-position will condense with formaldehyde to yield the corresponding 2-hydroxymethylimidazoles. These compounds can then be converted to a variety of other derivatives.[1b] In the present investigation 1-benzylimidazole has been used as the starting material. When heated with an excess of aqueous formaldehyde, 1-benzylimidazole gave an almost quantitative yield of 1-benzyl-2-hydroxymethylimidazole (III) which was isolated easily as the crystalline hydrochloride. Proof that the hydroxymethyl group entered the 2-position was provided by hydriodic acid reduction of the compound to yield 1-benzyl-2-methylimidazole. This was dissolved in liquid ammonia and treated with sodium to remove the benzyl group according to the method of du Vigneaud and Behrens.[2] The known 2-methylimidazole was thus obtained. It was found that in general these 1-benzylimidazoles are easily debenzylated by the sodium–liquid ammonia method. On the other hand one attempt to cleave the benzyl group by catalytic hydrogenolysis[3] did not meet with success.

(1) (a) Sarasin, *Helv. Chim. Acta*, **6**, 377 (1923). (b) Sonn, Hotes and Sieg, *Ber.*, **57**, 953 (1924). (c) Grindley and Pyman, *J. Chem. Soc.*, 3128 (1927).

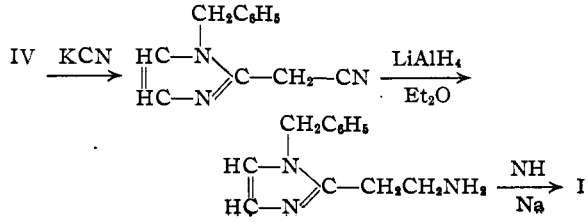
(2) du Vigneaud and Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(3) Cirkofer, *Ber.*, **75**, 429 (1942).

A number of transformations of 1-benzyl-2-hydroxymethylimidazole (III) are outlined in the reactions

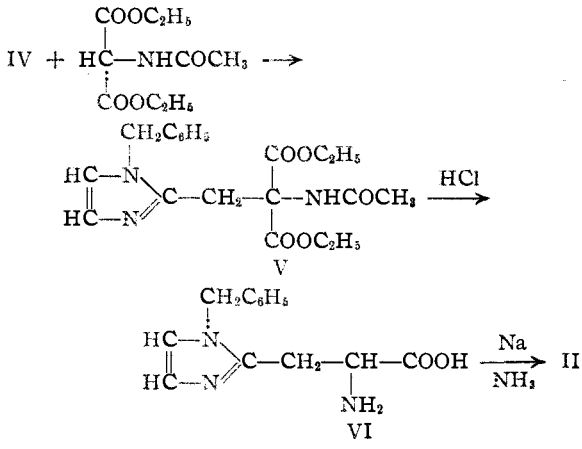


For the synthesis of 2-β-aminoethylimidazole (I), 1-benzyl-2-chloromethylimidazole (IV) was converted to 1-benzyl-2-cyanomethylimidazole. This compound underwent smooth reduction with



lithium aluminum hydride[4] to give 1-benzyl-2-β-aminoethylimidazole which was debenzylated to yield (I).

The amino acid (II) was prepared from (IV) *via* acetamidomalonic ester.[5] The substituted malonic ester (V) was obtained as a sirup which was hydrolyzed directly with hydrochloric acid to form 1-benzyl-2-imidazolealanine (VI). Debenzylation of (VI) with sodium and liquid ammonia led to the desired 2-imidazolealanine (II).



1-Benzyl-2-chloromethylimidazole (IV) underwent normal condensation with sodium malonic ester. The resulting product was converted to 1-benzyl-2-β-carbethoxyethylimidazole which was debenzylated to yield 2-β-carbethoxyethylimidazole.

Experimental

1-Benzyl-2-mercaptoimidazole.—N-Benzylaminoacetal was prepared in 80–85% yield by heating benzylamine with chloroacetal according to the method of Rügheimer and Schön[6] except that a threefold excess of benzylamine was used.

To a mixture of 223 g. (1.0 mole) of N-benzylaminoacetal, 95 g. (1.17 mole) of sodium thiocyanate and 500 ml. of 50% aqueous alcohol was added with stirring 100 ml. (1.2 mole) of 12 *N* hydrochloric acid. The resulting mixture in an open beaker was heated on the steam-bath for five hours during which time most of the alcohol evaporated leaving a violet colored, water insoluble, crystalline mass. The product was dissolved in sodium hydroxide solution. The solution was treated with carbon, filtered and acidified with hydrochloric acid to yield 165 g. (87%) of 1-benzyl-2-mercaptoimidazole. A sample for analysis was recrystallized from ethyl acetate; m. p. 144–145°.

Anal. Calcd. for $C_{10}H_{10}N_2S$: N, 14.74. Found: N, 14.75.

1-Benzylimidazole.—1-Benzyl-2-mercaptoimidazole (165 g., 0.87 mole) was added in portions to a stirred solution of 200 ml. of concentrated nitric acid in 500 ml. of water maintained at 40–50° by cooling in an ice-bath. When the reaction was complete, the solution was treated with 300 ml. of 12 *N* sodium hydroxide solution. The mixture was extracted with chloroform. The brown oil which remained after evaporation of the dried chloroform solution was distilled at reduced pressure to give 120 g. (87.5% yield) of 1-benzylimidazole; b. p. 187–189° (25 mm.), 166–167° (13 mm.); m. p. 71–72° (lit.[7] 70–71°). The picrate, recrystallized from water, melted at 75–76°.

Anal. Calcd. for $C_{16}H_{13}N_5O_7$: N, 18.20. Found: N, 18.00.

1-Benzyl-2-hydroxymethylimidazole (III).—A solution of 28 g. (0.177 mole) of 1-benzylimidazole in 45 g. of 40% formalin in a sealed Carius tube was heated at 140° for six hours. The tube was opened, and the colorless liquid was washed out with methanol. The methanol solution was evaporated *in vacuo* on the steam-bath leaving a viscous, colorless sirup which did not crystallize after standing for several days. The sirup was taken up in 100 ml. of alcohol, 25 ml. of 12 *N* hydrochloric acid was added, and the solution was evaporated to dryness in vacuum. The white crystalline residue was dissolved in 100 ml. of boiling absolute alcohol. The solution was cooled somewhat, 200 ml. of anhydrous ether added, then the mixture was chilled. The resulting crystalline product weighed 34.5 g. after air drying, and by working up the filtrate an additional 3.0 g. was obtained bringing the total yield of 1-benzyl-2-hydroxymethylimidazole hydrochloride to 37.5 g. (94.5%), m. p. 159–160°. A sample of the hydrochloride obtained from the picrate (see below) melted at 161.5–162°.

Anal. Calcd. for $C_{11}H_{12}N_2O\cdot HCl$: N, 12.47. Found: N, 12.55.

Equally good yields of the 2-hydroxymethyl compound were obtained by heating the 1-benzylimidazole–formalin mixture at 110–120° for fifteen hours instead of 140° for six hours.

1-Benzyl-2-hydroxymethylimidazole picrate obtained in 85% yield from the sirupy free base and hot aqueous picric acid melted at 132–133° after recrystallization from water.

Anal. Calcd. for $C_{17}H_{13}N_5O_8$: N, 16.78. Found: N, 16.72.

1-Benzyl-2-methylimidazole and 2-Methylimidazole.—A mixture of 10.0 g. (0.045 mole) of 1-benzyl-2-hydroxymethylimidazole hydrochloride, 1.3 g. of red phosphorus and 25 ml. of hydriodic acid (sp. gr. 1.7) in a sealed tube was heated at 160° for five hours. The contents of the tube were filtered, and the clear colorless filtrate was evaporated to a sirup. This was treated with excess 12 *N* sodium hydroxide solution and the mixture extracted with benzene. After drying over sodium carbonate the benzene was distilled and the residual product distilled *in vacuo* to yield 6.5 g. (85%) of 1-benzyl-2-methylimidazole as a colorless viscous liquid b. p. 125–127° (3 mm.). The picrate crystallized from water as bright yellow needles; m. p. 153–154°.

Anal. Calcd. for $C_{17}H_{15}N_5O_7$: N, 17.45. Found: N, 17.70.

To a solution of 6.0 g. (0.035 mole) of the above 1-benzyl-2-methylimidazole in 150 ml. of liquid ammonia was added sodium metal in small pieces until a permanent blue color was formed. This required 1.7 g. of sodium. The mixture was treated with 5 g. of ammonium chloride, and, after the ammonia had been removed by gentle warming, the residue was extracted with 200 ml. of hot benzene. Evaporation of this solution left 2.65 g. (92.5% yield) of 2-methylimidazole, m. p. 130–132°. The crude product was sublimed *in vacuo* and then recrystallized from benzene–petroleum ether to give white needles melting at 140–141°. Authentic 2-methylimidazole melted at 140.5–141.5° (lit.[8] 136–137°), and the mixed melting point was also 140.5–141.5°.

2-Hydroxymethylimidazole.—A solution of 19 g. (0.10 mole) of the crude sirupy 1-benzyl-2-hydroxymethylimidazole in 150 ml. of liquid ammonia was treated with small pieces of sodium metal until a permanent blue color was formed (6.8 g. of sodium). Then 25 g. of ammonium

(4) Nystrom and Brown, THIS JOURNAL, **69**, 1147 (1947). Private communication, Metal Hydrides Incorporated, Beverly, Massachusetts.

(5) Albertson and Archer, THIS JOURNAL, **67**, 308 (1945).

(6) Rügheimer and Schön, *Ber.*, **41**, 17 (1908).

(7) Wallach, *ibid.*, **16**, 539 (1883).

(8) Dedichen, *ibid.*, **39**, 1838 (1906).

chloride was added in small portions after which the mixture was allowed to evaporate to dryness. The residue was extracted with 200 ml. of boiling absolute alcohol. This solution was evaporated *in vacuo* to about 50 ml., filtered and the filtrate evaporated *in vacuo* to yield a sirup which could not be induced to crystallize. The sirup was dissolved in 25 ml. of water, and this solution was added to a hot solution of 25 g. of picric acid in one liter of boiling water. Nothing separated when the solution was cooled to room temperature, but after standing overnight 19 g. of large cubic crystals was deposited. This product, m. p. 144–145°, was recrystallized from 100 ml. of absolute alcohol to yield 15.5 g. (47.5%) of 2-hydroxymethylimidazole picrate as yellow needles, m. p. 151–152°.

Anal. Calcd. for $C_{10}H_9N_5O_8$: N, 21.41. Found: N, 21.42.

A mixture of 15.0 g. (0.046 mole) of the above picrate, 25 ml. of nitrobenzene and 25 ml. of 6 *N* hydrochloric acid in a small separatory funnel was shaken until all solid had dissolved. The nitrobenzene layer was drawn off, and the aqueous solution was washed with four 25-ml. portions of chloroform. The water solution was evaporated to dryness *in vacuo*. To the residue was added 50 ml. of absolute alcohol and again the mixture was evaporated to dryness *in vacuo* at 100°. The residue was dissolved in 25 ml. of hot absolute alcohol, and this solution was diluted with dry ether whereupon 6.1 g. (98% yield) of 2-hydroxymethylimidazole hydrochloride separated as white needles; m. p. 111–113°. The product was not hygroscopic.

Anal. Calcd. for $C_4H_6N_2O{\cdot}HCl$: N, 20.82. Found: N, 20.80.

1-Benzyl-2-imidazolecarboxylic Acid.—A solution of 19 g. (0.10 mole) of crude 1-benzyl-2-hydroxymethylimidazole in 200 ml. of acetone was cooled in an ice-bath and stirred while 22 g. (0.14 mole) of 100-mesh potassium permanganate was added in small portions during one-half hour. The temperature was maintained at 5–10°, and the mixture was stirred for one additional hour. The acetone was removed by evaporation at reduced pressure and the black residue was extracted with two one-liter portions of hot water. Evaporation *in vacuo* of the water solution left a white solid. The product was washed with chloroform and then recrystallized from absolute alcohol–ether to yield 13 g. of white crystalline solid which appeared to be a hydrated potassium salt; m. p. 94–96° with shrinking at 75–80°. No satisfactory analyses were obtained.

The above salt (12.0 g.) was dissolved in 20 ml. of water and the clear solution was treated with concentrated hydrochloric acid until the *p*H was about 2.0. The crystalline precipitate was collected on a filter and air dried. It weighed 9.5 (43% yield); m. p. 103–104° (dec.). A sample recrystallized from water melted at 106° (dec.). The analytical sample was dried *in vacuo* at 60° for one hour.

Anal. Calcd. for $C_{11}H_{10}N_2O_2.H_2O$: N, 12.72; neut. equiv., 220.2. Found: N, 12.54; neut. equiv., 213.

The acid decarboxylated very readily at the melting point, and even in hot water it slowly evolved carbon dioxide. A 1.0 g. portion was decarboxylated by melting, and the resulting product was sublimed *in vacuo* to yield 0.79 g. (99%) of 1-benzylimidazole, m. p. 72–73°; mixed with an authentic sample, m. p. 72–73°.

2-Imidazolecarboxylic Acid.—In 50 ml. of liquid ammonia was suspended 4.4 g. (0.02 mole) of 1-benzyl-2-imidazolecarboxylic acid monohydrate. Sodium in small pieces was added until a permanent blue color resulted (1.0 g. of sodium). The blue color was discharged with a little ammonium chloride, and the solution was evaporated to dryness, finally by gentle warming *in vacuo*. The residue was taken up in 25 ml. of water. The cloudy solution was stirred with a little carbon, filtered and acidified to *p*H 2.0 with concentrated hydrochloric acid. Soon the 2-imidazolecarboxylic acid separated as silvery platelets which, after cooling the mixture for one hour in an ice-bath, were collected on a filter and air dried. The yield was 1.95 g. (87%). A sample recrystallized from 80% alcohol melted at 163–164° (dec.).

Anal. Calcd. for $C_4H_4N_2O_2$: N, 25.00; neut. equiv., 112.09. Found: N, 24.53; neut. equiv., 113.5.

A 0.2 g. sample of the acid in a sublimation apparatus was heated until decarboxylation was complete, and the resulting imidazole was sublimed *in vacuo*. The yield was 0.1 g., m. p. 85–86°. A mixture with authentic imidazole melted at 87–88°.

1-Benzyl-2-chloromethylimidazole (IV).—To 60 ml. of thionyl chloride was added in small portions 68 g. (0.30 mole) of 1-benzyl-2-hydroxymethylimidazole hydrochloride. Reaction took place immmediately with heat evolution, and a clear solution resulted. The solution was heated on the steam-bath for fifteen minutes, and then the excess thionyl chloride was distilled under reduced pressure on the steam-bath. The residual crystalline 1-benzyl-2-chloromethylimidazole hydrochloride was washed with dry ether and air dried. It weighed 73 g. (100% yield), m. p. 181–182°.

Anal. Calcd. for $C_{11}H_{11}N_2Cl{\cdot}HCl$: N, 11.53; Cl, 29.17. Found: N, 11.76; Cl, 28.86.

1-Benzyl-2-cyanomethylimidazole.—A solution of 90 g. of potassium cyanide in 100 ml. of water was cooled to 5° and with continuous stirring a solution of 37 g. (0.15 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride in 250 ml. of absolute alcohol was added during a period of one hour. The mixture was stirred at room temperature for three hours, then filtered and the salt washed with two 200-ml. portions of alcohol. The total filtrate was evaporated *in vacuo* to small volume and extracted with three 300-ml. portions of chloroform. The chloroform solution was washed with dilute sodium hydroxide solution, dried over magnesium sulfate and evaporated to dryness *in vacuo*. A brown oil remained which quickly crystallized. This crude product which melted over the range 65–80° was dissolved in 150 ml. of hot absolute alcohol and to it was added a solution of 35 g. of picric acid in 150 ml. of hot absolute alcohol. A brown oil separated which soon crystallized. The mixture was cooled to 70°, and the 1-benzyl-2-cyanomethylimidazole picrate was collected on a filter. It was washed by suspension in 100 ml. of warm absolute alcohol and air dried. The yield was 17.5 g. (27.5%), m. p. 160–162°.

In other runs lower temperatures and longer reaction periods were employed, but the yield could not be improved.

The above picrate was soluble in acetone or chloroform, sparingly soluble in absolute alcohol, insoluble in boiling water. A sample recrystallized from absolute alcohol melted at 166–167°.

Anal. Calcd. for $C_{18}H_{14}N_6O_7$: N, 19.72. Found: N, 19.48.

The picrate (23 g., 0.054 mole) was rubbed to a fine powder and placed in a separatory funnel with 160 ml. of nitrobenzene and 100 ml. of cold 6 *N* hydrochloric acid. The mixture was vigorously shaken until all solid had disappeared. After the nitrobenzene layer had been separated the aqueous solution was washed with three 75-ml. portions of chloroform. The nitrobenzene and chloroform solutions were then extracted with another 50 ml. portion of cold 6 *N* hydrochloric acid. The combined hydrochloric acid solution was immediately neutralized with excess sodium carbonate. The resulting mixture was extracted with four 50-ml. portions of chloroform. This chloroform extract was dried with magnesium sulfate and evaporated to dryness *in vacuo* leaving 10.3 g. (97% yield) of 1-benzyl-2-cyanomethylimidazole as a white, hard, crystalline solid, m. p. 114–115°. It was readily soluble in benzene, moderately soluble in hot petroleum ether.

Anal. Calcd. for $C_{12}H_{11}N_3$: N, 21.31. Found: N, 21.04.

1-Benzyl-2-β-aminoethylimidazole.—Eleven grams (0.056 mole) of powdered 1-benzyl-2-cyanomethylimidazole was placed in the thimble of a Soxhlet extractor above a boiling solution of 5 g. (0.13 mole) of lithium aluminum

hydride[4,9] in 500 ml. of dry ether. After about three hours, when all of the cyano compound had been dissolved and carried down into the lithium aluminum hydride solution, the latter was treated with 10 ml. of water, added dropwise, followed by 50 ml. of 12.5 *N* sodium hydroxide solution. The mixture was vigorously stirred for about one hour and then the ether was decanted into a clean flask. The mixture was extracted twice more by vigorously stirring with 300 ml. portions of ether. The total ether solution was dried with potassium carbonate and concentrated. Distillation of the residual liquid *in vacuo* gave 9.7 g. (88% yield) of 1-benzyl-2-β-aminoethylimidazole as a viscous colorless liquid, b. p. 161–163° (0.7 mm.), which crystallized to a hard, white, hygroscopic solid, m. p. 59–60°. The dipicrate, prepared in absolute alcohol, melted at 185–186°.

Anal. Calcd. for $C_{24}H_{21}N_9O_{14}$: N, 19.14. Found: N, 19.26.

The dihydrochloride, m. p. 224–225°, was soluble in water, absolute alcohol, insoluble in ether, and it was not hygroscopic.

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot 2HCl$: N, 15.33. Found: N, 14.97.

2-β-Aminoethylimidazole (I).—A solution of 9.2 g. (0.046 mole) of 1-benzyl-2-β-aminoethylimidazole in 100 ml. of liquid ammonia was treated with 2.15 g. of sodium metal. Then 2.7 g. (0.05 mole) of ammonium chloride was added, and the ammonia was allowed to evaporate. Sodium carbonate (3 g.) and 25 ml. of water were added. The solution was evaporated to dryness *in vacuo* on the steam-bath, and the residue was extracted with two 100-ml. portions of hot absolute alcohol. This was evaporated *in vacuo* leaving a viscous oil which was dissolved in 25 ml. of water and the resulting solution was added to a solution of 30 g. of picric acid in 800 ml. of hot water. After the mixture had cooled to room temperature, the crystalline picrate was collected on a filter and recrystallized in two portions from 500 ml. of water. There was thus obtained 21 g. (80% yield) of 2-β-aminoethylimidazole dipicrate, m. p. 213–214° (dec.).

Anal. Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.14. Found: N, 22.18.

The above picrate (21 g., 0.037 mole) was decomposed with 6 *N* hydrochloric acid using nitrobenzene in the usual manner, and there was obtained 6.7 g. (98% yield) of 2-β-aminoethylimidazole dihydrochloride, m. p. 229–230°. It was very sparingly soluble in hot absolute alcohol.

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83. Found: N, 22.46.

1-Benzyl-2-imidazolealanine (VI).—A solution was prepared by adding 87 g. (0.40 mole) of acetamidomalonic ester to 250 ml. of absolute alcohol in which had been dissolved 13.8 g. (0.60 g. atom) of sodium. This solution was cooled in an ice-bath and to it was added during one-half hour 49 g. (0.20 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride dissolved in 350 ml. of absolute alcohol. The mixture was stirred for two hours at room temperature and then evaporated *in vacuo* on the steam-bath to remove most of the alcohol. The residue was dissolved in 400 ml. of ice-cold 2 *N* hydrochloric acid. This solution was extracted with four 200-ml. portions of ethyl acetate to remove the unchanged acetaminomalonic ester. The water solution was neutralized with excess sodium carbonate and extracted with three 200-ml. portions of ether. The ether solution was dried and evaporated leaving the 1-benzyl-2-imidazolemethylacetaminomalonic ester as a glass which did not crystallize.

The product was dissolved in 200 ml. of 12 *N* hydrochloric acid and the solution heated on the steam-bath for sixteen hours. Evaporation of this solution left a glass-like product which could not be induced to crystallize. It was dissolved in 200 ml. of water and the solution was brought to *p*H 8.15 with sodium hydroxide. This solution was evaporated *in vacuo* almost to dryness, and the residue was extracted with 500 ml. of hot 90% alcohol. The alcohol extract was evaporated in an open beaker to a volume of about 200 ml. After standing and cooling it deposited 24 g. of white crystalline solid; m. p. 203–204°. The solid was washed by suspension in 100 ml. of absolute alcohol and then in 25 ml. of water in which it was somewhat soluble. It was recrystallized from 140 ml. of 70% alcohol to yield 19.5 g. (38.4%) of 1-benzyl-2-imidazolealanine hemihydrate, m. p. 216–217° (dec.).

Anal. Calcd. for $C_{13}H_{15}N_3O_2 \cdot {}^1/_2H_2O$: C, 61.40; H, 6.34. Found: C, 61.27; H, 6.68.

2-Imidazolealanine (II).—A solution of 12.7 g. (0.05 mole) of 1-benzyl-2-imidazolealanine in 100 ml. of liquid ammonia was treated with sodium as described above. The residue, after evaporation of the ammonia, was dissolved in 50 ml. of water, and the solution was brought to *p*H 8.0 by the careful addition of concentrated hydrochloric acid. The white crystalline precipitate, 5.3 g. (68.5% yield crude), was recrystallized from 70 ml. of water using carbon to decolorize the solution. There was obtained 4.4 g. (57% yield) of pure 2-imidazolealanine, m. p. 254–255° (dec.).

Anal. Calcd. for $C_6H_9N_3O_2$: N, 27.05. Found: N, 26.81.

1-Benzyl-2-β-carbethoxyethylimidazole.—1-Benzyl-2-chloromethylimidazole hydrochloride was caused to condense with sodiomalonic ester in a manner similar to that described above for the condensation with sodioacetamidomalonic ester. The resulting crude 1-benzyl-2-imidazolemethylmalonic ester was heated with concentrated hydrochloric acid, and the sirupy 1-benzyl-2-β-carboxyethylimidazole hydrochloride thus obtained was esterified with absolute alcoholic hydrogen chloride to give 1-benzyl-2-β-carbethoxyethylimidazole in an over-all yield of 83%. It distilled at 164–166° (0.3 mm.) $n^{25}D$ 1.5352.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: N, 10.85. Found: N, 10.60.

2-β-Carbethoxyethylimidazole.—1-Benzyl-2-β-carbethoxyethylimidazole (20.8 g., 0.08 mole) in 300 ml. of liquid ammonia was debenzylated with sodium. After evaporation of the ammonia the product was extracted from the residue with chloroform. There was obtained 9.5 g. of crude product which was recrystallized from benzene–petroleum ether to yield 8.1 g. (60%) of 2-β-carbethoxyethylimidazole, m. p. 103–104°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: N, 16.66. Found: N, 16.94.

An attempt to remove the benzyl group from 1-benzyl-2-β-carbethoxyethylimidazole by hydrogenolysis in glacial acetic acid using Adams catalyst was not successful. Although the theoretical quantity of hydrogen was absorbed no toluene was split off. Presumably the material underwent partial hydrogenation.

Acknowledgment.—The author is grateful to K. C. McLaughlin for valuable assistance and to W. L. Brown and H. L. Hunter for the microanalyses reported herein.

Summary

A method for the preparation of 2-substituted imidazoles has been described.

The isomers of histamine and histidine and a number of other 2-substituted imidazole compounds have been prepared and characterized.

(9) Obtained from Metal Hydrides, Inc., Beverly, Massachusetts.

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