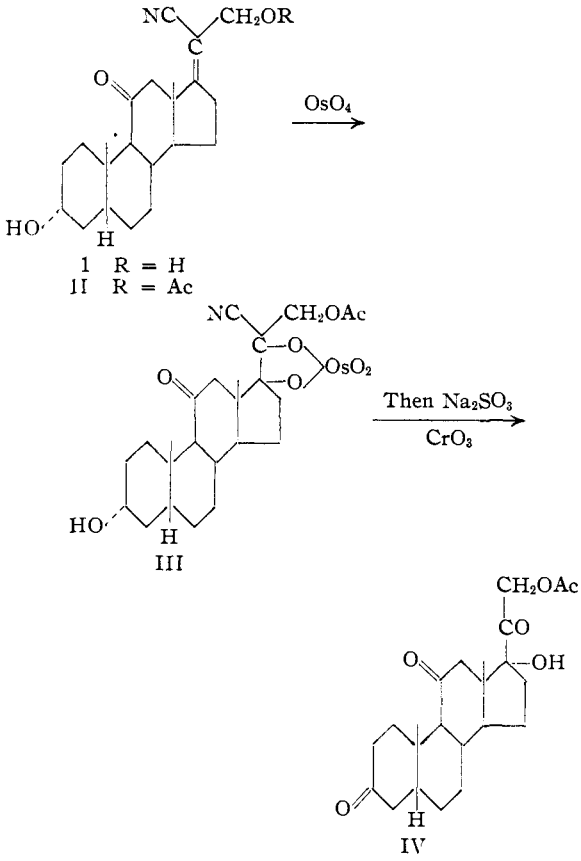


zene gave 479 mg. of the monoacetate, m. p. 151–152° (cor.), $[\alpha]^{25}D$ + 16° (acetone). A solvated form which melted with decomposition at about 130–140° was obtained by crystallization from dilute alcohol. Saponification of the mother liquors gave a nearly quantitative yield of the free diol, m. p. 256–258°. For analysis a sample was heated at 120° *in vacuo* for two hours.

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.14; H, 8.33. Found: C, 71.77; H, 8.42.

Pregnane-17α,21-diol-3,11,20-trione Acetate (IV).—To a solution of 429 mg. of Δ^{20}-20-cyanopregnene-3α,21-diol-11-one 21-acetate in 4 cc. of benzene was added 600 mg. of osmium tetroxide followed by 0.30 cc. of pyridine. After sixteen hours the mixture was concentrated nearly to dryness *in vacuo* at 35°. To the residue was added 5 cc. of 90% acetic acid and 1.05 cc. of acetic acid containing 3.70 milliequivalents of sulfuric acid. The solution was cooled to 0° and treated dropwise with 4.4 cc. of a 90% acetic acid solution containing 200 mg. of chromic acid. The mixture was permitted to stand at 15° for forty-five minutes, then poured into 20 cc. of water containing 15 g. of potassium bicarbonate (partly in solution), the flask being rinsed with a little dilute methanol. The mixture was stirred until evolution of carbon dioxide ceased, and the remaining carbon dioxide was removed from solution *in vacuo* at 30°. Ten cc. of an aqueous solution containing 2.0 g. of sodium sulfite and 2.0 g. of potassium bicarbonate was added followed by 20 cc. of benzene and 20 cc. of methanol. The mixture was stirred overnight, filtered, acidified to *p*H 6 with acetic acid, concentrated *in vacuo* until the organic solvents were removed and the aqueous suspension then extracted with four 50-cc. portions of chloroform. The washed chloroform extracts were combined and concentrated to dryness giving 323 mg. of crystalline residue consisting mostly of the dioldione acetate (IV) but containing a small amount of the free dioldione. The latter was converted to the acetate by dissolving the residue in 2 cc. of a pyridine–acetic anhydride mixture and warming at 50° for five minutes. The addition of water precipitated the crystalline acetate; after recrystallization from alcohol it melted at 227–229°. A mixed melting point with pregnane-17α,21-diol-3,11,20-trione acetate (m. p. 229–231°) was 228–231°; yield, 200 mg.

Acknowledgment.—The author is indebted to Dr. Karl Folkers for various suggestions and to Miss Jean E. Andrews for assistance.

Summary

A more efficient method for the preparation of pregnane-17α,21-diol-3,11,20-trione acetate is described. The method is based upon the stability of the addition product of osmium tetroxide and Δ^{17}-20-cyanopregnenes toward chromic acid.

RAHWAY, NEW JERSEY RECEIVED MARCH 11, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. III. 1-Substituted Analogs of Histidine and Histamine

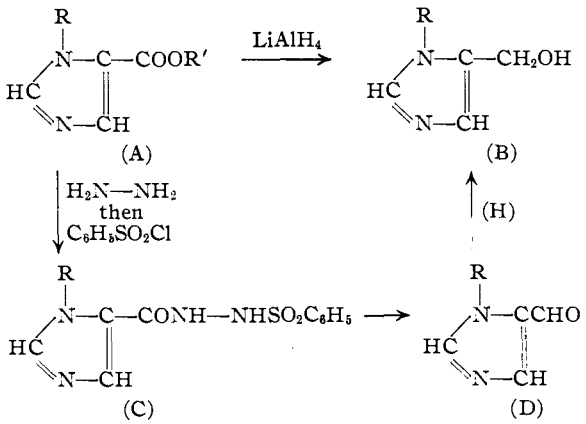
BY REUBEN G. JONES AND KEITH C. McLAUGHLIN

In the preceding paper of this series[1] there was described a convenient method for the synthesis of 4(or 5)-imidazolecarboxylic acid esters and 1-substituted-5-imidazolecarboxylic acid esters. It has been found that the ester group in these compounds can be converted readily to aldehyde and to hydroxymethyl. This has now made it possible to synthesize a series of analogs of histidine and histamine having substituents in the 1-position of the imidazole ring. Five such analogs of histidine and one analog of histamine have been prepared and are described at this time. This work constitutes part of a study concerned with possible relationships of chemical structure to biological activity of α-amino acids and amines.

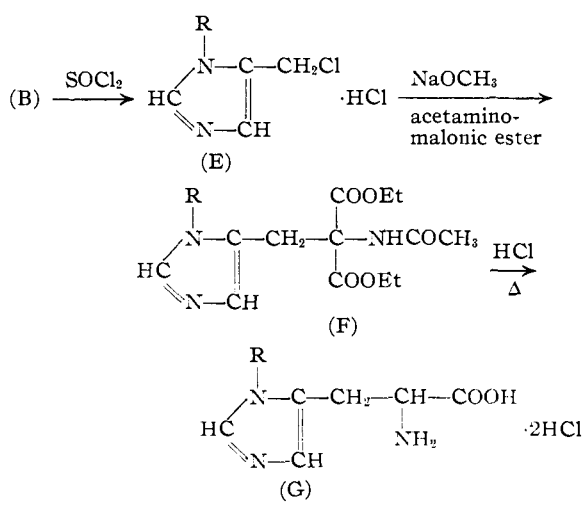
The 5-imidazolecarboxylic acid esters (A) were smoothly reduced with lithium aluminum hydride in ether solution to the corresponding 5-hydroxymethyl compounds (B). The imidazole ring was not attacked by the reducing agent. The 1-substituted-5-imidazole aldehydes (D) were obtained in satisfactory yields through the benzenesulfonhydrazides (C) according to the procedure of McFadyen and Stevens.[2] The aldehydes were readily hydrogenated to the hydroxymethyl compounds.

(1) Jones, THIS JOURNAL, **71**, 644 (1949).

(2) McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).



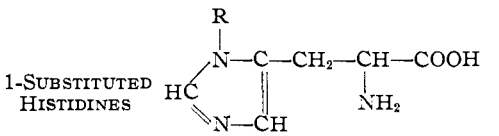
1-Methyl-5-imidazolalanine (1-methylhistidine) occurs naturally. It has been synthesized previously by Sakami and Wilson[3] who obtained it in over-all yield of 7% starting from fructose. As a key intermediate in their synthesis, Sakami and Wilson used 1-methyl-5-imidazolealdehyde. In our hands this method using the now easily available 1-methyl-5-imidazolealdehyde gave poor yields. Therefore, 1-methylhistidine as well as the other 1-substituted histidine analogs of Table I were synthesized through the condensation of the 1-substituted-5-chloromethylimidazoles with acetaminomalonic ester following the general method elaborated by Albertson and Archer[4] and by Snyder and co-workers.[5] The 1-substituted-5-chloromethylimidazoles (E) were obtained by the reaction of the corresponding hydroxymethyl compounds (B) with thionyl chloride.



The amino acids presented in Table I were obtained from the hydrochlorides (G) by removing the chloride ion with silver carbonate in the usual way. Our sample of *dl*-1-methylhistidine melted with decomposition at 269–270° which is about 20° higher than the melting point reported for the natural product[6] or the synthetic product of Sakami and Wilson.[3]

TABLE I

1-SUBSTITUTED HISTIDINES



R	Empirical formula	Yield, %[a]	M. p., °C.[b]	N Anal., % Calcd.	Found
CH_3	$C_7H_{11}N_3O_2$	67	269–270	[c]	
$(CH_3)_2CH$	$C_9H_{15}N_3O_2$	44	223–224	21.31	21.54
C_6H_5	$C_{12}H_{13}N_3O_2$	49	241–242	18.16	18.00
C_6H_{11}[d]	$C_{12}H_{19}N_3O_2$	49	235–237	17.71	17.71
$C_6H_5CH_2$	$C_{13}H_{15}N_3O_2$	45	239–240	17.17	17.32

[a] Yields are for the over-all process and are based upon the chloromethyl compounds. [b] Corrected for stem exposure. The melting points reported here are actually decomposition points. [c] *Anal.* Calcd. for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.56. Found: C, 49.63; H, 6.64. Sample dried in vacuum at 150°. When the sample was dried in vacuum at 100° the compound retained one molecule of water of crystallization. *Anal.* Calcd. for $C_7H_{11}N_3O_2 \cdot H_2O$: N, 22.45; loss on drying, 9.6. Found: N, 22.54; loss on drying at 150° *in vacuo*, 9.1. [d] Cyclohexyl.

1-Methyl-4-β-aminoethylimidazole dihydrochloride was synthesized in accordance with the directions of Pyman.[7] At the same time there was isolated a small quantity of 1-methyl-5-β-aminoethylimidazole as the dipicrate.[7] This latter compound was more satisfactorily obtained from 1-methyl-5-chloromethylimidazole by allowing it to react with potassium cyanide followed by reduction of the resulting nitrile. It was isolated also as the dihydrochloride. Both of these isomeric 1-methylated analogs of histamine were tested for histamine-like activity. The results of these tests have been reported elsewhere.[8] It is interesting to note, however, that 1-methyl-5-β-aminoethylimidazole, which may be regarded as the decarboxylation product of the naturally occurring 1-methylhistidine, showed no histamine-like activity or other observable physiological activity. On the other hand, 1-methyl-4-β-aminoethylimidazole had typical histamine activity although of a low order.

Methyl 1-methyl-5-imidazolecarboxylate underwent normal condensation with acetophenone under the influence of sodium methylate in hot toluene to yield benzoyl-(1-methyl-5-imidazoyl)-methane. The reaction of 1-methyl-5-imidazolealdehyde with malonic acid in water solution gave α-carboxy-β-(1-methyl-5-imidazole)-acrylic acid. This compound was not decarboxylated in boiling pyridine solution. It took up no hydrogen when an aqueous solution of the sodium salt was shaken with Adams catalyst under 60 lb. hydrogen pressure.

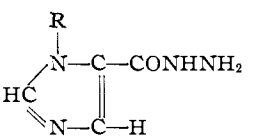
(3) Sakami and Wilson, *J. Biol. Chem.*, **154**, 215 (1944).
(4) Albertson and Archer, THIS JOURNAL, **67**, 308 (1945).
(5) Snyder, Shekleton and Lewis, *ibid.*, **67**, 310 (1945).
(6) Linneweh, Keil and Hoppe-Seyler, *Z. physiol. Chem.*, **183**, 11 (1929); Linneweh and Linneweh, *ibid.*, **189**, 80 (1930).
(7) Pyman, *J. Chem. Soc.*, **99**, 2172 (1911).
(8) Lee and Jones, *J. Pharmacol.*, **95**, 71 (1949).

Experimental[9]

1-Substituted-5-imidazolecarboxyhydrazides (Table II).—The methyl or ethyl ester of the 1-substituted-5-imidazolecarboxylic acid[1] was dissolved in the minimum quantity of warm alcohol and treated with an equal weight of 100% hydrazine hydrate. After warming for one hour on the steam-bath the reaction mixture was evaporated to dryness in vacuum. The residue of practically pure hydrazide was washed with a little dry ether and air dried. Samples for analyses were recrystallized from aqueous alcohol.

TABLE II

5-IMIDAZOLECARBOXYHYDRAZIDES

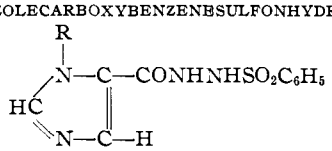


R[a]	Empirical formula	Yield, %	M. p., °C.[b]	N Analyses, % Calcd.	Found
H[c]	$C_4H_6N_4O$	100	203–204	...	...
CH_3	$C_5H_8N_4O$	99	188–189	39.98	39.76
$(CH_3)_2CH$	$C_7H_{12}N_4O$	98	99–100	33.31	33.36
C_6H_5	$C_{10}H_{10}N_4O$	100	159–160	27.71	27.48
C_6H_{11}[d]	$C_{10}H_{16}N_4O$	95	175–176	26.90	26.63

[a] Samples were recrystallized from alcohol. [b] Corrected for stem exposure. [c] Previously prepared by Balaban, *J. Chem. Soc.*, 268 (1930), who reports a melting point of 213°. [d] Cyclohexyl.

TABLE III

5-IMIDAZOLECARBOXYBENZENESULFONHYDRAZIDES



R[a]	Empirical formula	Yield, %	M. p., °C.[b]	N Analyses, % Calcd.	Found
H	$C_{10}H_{10}N_4O_3S$	75	237–238	21.04	20.99
CH_3	$C_{11}H_{12}N_4O_3S$	92	212–213	19.99	20.25
$(CH_3)_2CH$	$C_{13}H_{16}N_4O_3S$	90	180–181	18.17	18.13
C_6H_5	$C_{16}H_{14}N_4O_3S$	85	184–185	16.37	16.60
C_6H_{11}[c]	$C_{16}H_{20}N_4O_3S$	98	165–166	16.08	16.15

[a] Samples were recrystallized from alcohol. [b] Corrected for stem exposure. These compounds all decomposed at the melting point. [c] Cyclohexyl.

1-Substituted-5-imidazolecarboxybenzenesulfonhydrazides (Table III).—The hydrazide (Table II) was dissolved or suspended in four or five parts of pyridine and, with stirring, 1.1 equivalents of benzenesulfonyl chloride was added in small portions. The mixture was stirred for an additional fifteen minutes and then diluted with ten parts of water. The crystalline precipitate was collected, washed with a little water and air-dried. Samples for analysis were recrystallized from alcohol or alcohol-water mixtures.

The above procedure was used for the preparation of the compounds of Table III with the exception of the unsubstituted 5-imidazolecarboxybenzenesulfonhydrazide. This was obtained as follows: 14.5 g. (0.10 mole) of 4(5)-imidazole carboxyhydrazide (Table II) was dissolved in 60 ml. (0.24 mole) of cold 4 *N* sodium hydroxide solution. Twenty grams (0.113 mole) of benzenesulfonyl chloride was added. The mixture was vigorously shaken and cooled for about twenty minutes. It was then filtered, and the filtrate was acidified with 10 ml. (0.12 mole) of 12 *N* hydrochloric acid to precipitate the desired compound.

1-Substituted-5-imidazolealdehydes (Table IV).—The following typical example illustrates the procedure: In a one-liter three-necked flask equipped with a stirrer and a reflux condenser were placed 75 g. (0.27 mole) of 1-methyl-5-imidazolecarboxybenzenesulfonhydrazide, 75 g. of anhydrous sodium carbonate and 225 ml. of glycerol. The flask was immersed in an oil-bath at 170° and the contents stirred rapidly. After seven minutes the foaming had stopped, and the reaction was considered to be complete. The flask was quickly removed from the oil-bath and cooled in ice-water. The mixture was diluted with 225 ml. of water and extracted with five 200-ml. portions of chloroform. The chloroform solution was dried, the solvent removed and the residual aldehyde distilled in vacuum.

The decomposition of 4(5)-imidazolecarboxybenzenesulfonhydrazide by the above procedure failed to yield 4(5)-imidazolealdehyde.

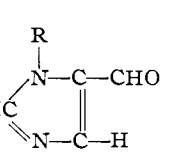
The phenylhydrazones were prepared by heating together 0.5 g. of the aldehyde with 0.5 g. of phenylhydrazine. The resulting product was washed with ether and recrystallized from absolute alcohol or ethyl acetate-petroleum ether mixtures.

5-Hydroxymethylimidazoles (Table V).—These compounds were obtained in two ways. The aldehydes (Table IV) were reduced quantitatively to the desired hydroxymethyl compounds with hydrogen at 50 lb. pressure using Adams platinum catalyst and a trace of ferric chloride with alcohol as solvent. A more convenient method was the direct reduction of the methyl or ethyl esters of the 5-imidazolecarboxylic acids[1] with lithium aluminum hydride. The following example illustrates this method.

Crude, solid lithium aluminum hydride,[10] 10 g., was crushed in a mortar and added to 300 ml. of anhydrous ether in a one-liter, three-necked flask provided with a stirrer and reflux condenser. With stirring 28.0 g. (0.20 mole) of ethyl 4(5)-imidazolecarboxylate[1] was added in small portions during one-half hour. The mixture was

TABLE IV

5-IMIDAZOLEALDEHYDES, HC



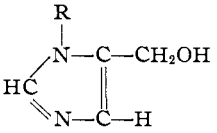
R	Empirical formula	Yield, %	M. p., °C.	B. p., mm.	N Analyses, % Calcd.	Found	Phenylhydrazones M. p., °C.	N Analyses, % Calcd.	Found
CH_3[a]	$C_5H_6N_2O$	60–66	53–54	109–110 (12)					
$(CH_3)_2CH$[b]	$C_7H_{10}N_2O$	58	Liquid	115–116 (12)	20.28	19.97	116–118	24.54	24.69
C_6H_5[c]	$C_{10}H_8N_2O$	51	120–121	157–160 (2)	16.27	16.40	207–209	21.36	21.50
C_6H_{11}[d]	$C_{10}H_{14}N_2O$	61	70–71	170–172 (19)	15.72	15.12	186–188	20.88	20.81

[a] Previously prepared by a different method, see Hubball and Pyman, *J. Chem. Soc.*, 21 (1928); see also ref. 3. [b] $n^{25}D$ 1.5218. [c] Recrystallized from alcohol. [d] Cyclohexyl; sample for analysis sublimed in vacuum.

(9) All melting points are corrected for stem exposure of the thermometer.

(10) Obtained from Metal Hydrides, Inc., Beverly, Mass.

TABLE V

5-HYDROXYMETHYLIMIDAZOLES, 

R	Empirical formula	Yield, %[a]	M. p., °C.	N Analyses, % Calcd.	Found
H[b]	$C_4H_6N_2O$	92	91–92[c]		
CH_3[d]	$C_5H_8N_2O$	88	113–114	24.99	24.67
$(CH_3)_2CH$[d]	$C_7H_{12}N_2O$		85–86	[e]	
C_6H_5[d]	$C_{10}H_{10}N_2O$	84	83–85	16.09	15.45
C_6H_{11}[d,f]	$C_{10}H_{16}N_2O$		134–135	15.55	15.37
$C_6H_5CH_2$	$C_{11}H_{12}N_2O$	82	139–140	14.89	14.90

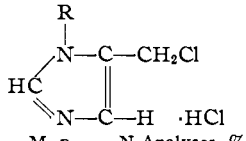
[a] Yields are for the products obtained by reduction of the corresponding esters with lithium aluminum hydride. [b] Previously prepared by different methods, see Pyman, *J. Chem. Soc.*, 99, 668 (1911); Weidenhagen and Hermann, *Ber.*, 68, 1953 (1935); Darby, Lewis and Totter, THIS JOURNAL, 64, 463 (1942). [c] M. p. picrate, 205–207°. [d] Obtained in quantitative yield by catalytic hydrogenation of the aldehyde. [e] Calcd.: C, 59.97; H, 8.63. Found: C, 59.72; H, 8.35. [f] Cyclohexyl.

stirred for an additional one-half hour and then 25 ml. of water was very carefully added dropwise. The resulting suspension of white granular solid in ether was filtered, and the solid was suspended in 300 ml. of hot methanol. The mixture was saturated with carbon dioxide and then filtered. The solid was extracted again by suspension in hot methanol. The combined ether and methanol filtrates were evaporated to dryness in vacuum, and the residue was taken up in 300 ml. of hot absolute alcohol. Evaporation of the filtered ethanol solution left practically pure 4(5)-hydroxymethylimidazole which was dried in vacuum over calcium chloride.

The other compounds of Table V were prepared in essentially the same way except that ether solutions of the 1-substituted 5-carboxyimidazole esters were added to the lithium aluminum hydride solutions, and the final hydroxymethyl compounds were sometimes extracted from the aluminum hydroxide with chloroform instead of methanol.

1-Substituted-5-chloromethylimidazole Hydrochlorides (Table VI).—These were prepared by adding the hydroxymethyl compound (Table V) in small portions to two parts of thionyl chloride. The resulting solution was warmed on the steam-bath for fifteen minutes and then the excess thionyl chloride was removed by evaporation in vacuum. The residue was dissolved in the minimum quantity of hot absolute alcohol, and dry ether was added to precipitate the 1-substituted-5-chloromethylimidazole hydrochloride as a crystalline solid. Samples for analysis were recrystallized from absolute ethanol–ether mixtures.

TABLE VI

5-CHLOROMETHYLIMIDAZOLE HYDROCHLORIDES 

R	Empirical formula	Yield, %	M. p., °C.[a]	N Analyses, % Calcd.	Found
CH_3	$C_5H_7N_2Cl\cdot HCl$	94	166–167	16.75	16.34
$(CH_3)_2CH$	$C_7H_{11}N_2Cl\cdot HCl$	92	178–179	14.36	14.33
C_6H_5	$C_{10}H_9N_2Cl\cdot HCl$	95	173–174	12.23	12.43
C_6H_{11}[b]	$C_{10}H_{15}N_2Cl\cdot HCl$	92	199–200	11.92	11.91
$C_6H_5CH_2$	$C_{11}H_{11}N_2Cl\cdot HCl$	99	185–187	11.52	11.49

[a] Corrected for stem exposure. [b] Cyclohexyl.

1-Substituted-5-imidazolealanines (Table I).—The preparation of 1-methylhistidine is illustrative of the method used for the synthesis of the compounds in Table I.

Tweny-one grams (0.90 g. atom) of sodium was dissolved in 350 ml. of absolute alcohol, and then 130 g. (0.60 mole) of acetaminomalonic ester was added. The solution was cooled in an ice-bath, and with stirring a solution of 46 g. (0.28 mole) of 1-methyl-5-chloromethylimidazole hydrochloride in 500 ml. of absolute alcohol was added over a period of one-half hour. The cooling bath was removed and the mixture was stirred at room temperature for two hours. Finally the mixture was heated on the steam-bath and most of the alcohol was removed by evaporation in vacuum. The solid residue was taken up in 600 ml. of ice-cold 2 *N* hydrochloric acid, and this solution was extracted with three 300-ml. portions of ethyl acetate. From the ethyl acetate extracts there was recovered 70 g. of acetaminomalonic ester. The aqueous solution was made basic with excess sodium carbonate and extracted with three 200-ml. portions of chloroform. Evaporation of the chloroform solution left 66 g. of solid. This was twice recrystallized from a benzene–petroleum ether mixture, and 59 g. (68% yield) of pure ethyl α-acetamino-α-carbethoxy-β-(1-methyl-5-imidazole)-propionate was obtained; m. p. 120–121°.

Anal. Calcd. for $C_{14}H_{21}N_3O_5$: N, 13.50. Found: N, 13.58.

The above compound (59 g., 0.19 mole) was dissolved in 100 ml. of 12 *N* hydrochloric acid and the solution was heated on a steam-bath for sixteen hours. The solution was evaporated in vacuum to a sirup which slowly crystallized. This solid (1-methylhistidine dihydrochloride) was dissolved in 200 ml. of hot water, and 70 g. of silver carbonate was added in portions. The hot mixture was filtered and the filtrate saturated with hydrogen sulfide. Decolorizing carbon was added, the mixture was filtered, and the colorless filtrate was evaporated in vacuum until crystallization began. Precipitation was completed by adding 100 ml. of absolute alcohol to the mixture. The yield of white crystalline 1-methylhistidine was 31.3 g.

The intermediate ethyl α-acetamino-α-carbethoxy-β-(1-substituted-5-imidazole)-propionates, in the preparation of the other compounds of Table I, were obtained only as sirups which were not analyzed but were hydrolyzed directly.

1-Methyl-5-cyanomethylimidazole Picrate.—A solution of 13.5 g. (0.08 mole) of 1-methyl-5-chloromethylimidazole hydrochloride in 60 ml. of absolute alcohol was added dropwise during one-half hour to a stirred solution of 45 g. (0.7 mole) of potassium cyanide in 50 ml. of water cooled in an ice-salt-bath. The resulting mixture was stirred at room temperature for one hour, and then it was filtered, and the solids were washed with three 100-ml. portions of 95% alcohol. The combined filtrates were mixed with 50 ml. of water containing 10 g. of sodium carbonate, and the solution was evaporated to dryness in vacuum on the steam-bath. The residue was extracted with three 200-ml. portions of boiling ethyl acetate. This extract was evaporated in vacuum leaving a brown oil which was dissolved in 50 ml. of water and added to a hot solution of 20 g. of picric acid in 800 ml. of water. The mixture was evaporated in vacuum to about 400 ml. and cooled to yield 21 g. of crude 1-methyl-5-cyanomethylimidazole picrate. Recrystallization from water gave 18 g. (24.5% yield) of pure product, m. p. 156–157°.

Anal. Calcd. for $C_{12}H_{10}N_6O_7$: N, 24.00. Found: N, 24.20.

1-Methyl-5-cyanomethylimidazole picrate was also prepared in a yield of 17%, m. p. 150–152°, from 4(5)-cyanomethylimidazole by the method of Pyman.[7]

1-Methyl-5-β-aminoethylimidazole Dihydrochloride.—1-Methyl-5-cyanomethylimidazole was reduced with sodium and alcohol to 1-methyl-5-β-aminoethylimidazole which was isolated as the dipicrate, m. p. 199–201°, according to the directions of Pyman.[7] The dipicrate was converted to the dihydrochloride in the usual way. It was deliquescent but only very sparingly soluble in hot absolute alcohol; m. p. 265–266°.

Anal. Calcd. for $C_6H_{11}N_3\cdot 2HCl$: N, 21.21. Found: N, 21.00.

α-Carboxy-β-(1-methyl-5-imidazole)-acrylic Acid.—A solution of 5.5 g. (0.05 mole) of 1-methyl-5-imidazolealdehyde and 6.1 g. (0.05 mole) of malonic acid monohydrate in 25 ml. of water was heated on the steam-bath for one-half hour. The mixture was cooled and the white crystalline precipitate was collected and air dried. It weighed 9.4 g. (96% yield); m. p. 224–226° dec.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.90; H, 4.06; N, 14.28; neut. equiv., 98.09. Found: C, 49.02; H, 4.28; N, 14.14; neut. equiv., 97.95.

The compound failed to take up any hydrogen when the sodium salt in aqueous solution was shaken with Adams platinum catalyst under 60 lb. hydrogen pressure.

Benzoyl-(1-methyl-5-imidazoyl)-methane.—To a solution of 28 g. (0.20 mole) of methyl 1-methyl-5-imidazolecarboxylate in 200 ml. of dry toluene was added 17.2 g (0.30 mole) of sodium methylate followed by 36 g. (0.30 mole) of acetophenone. The thick mixture was heated on the steam-bath for two hours and then allowed to stand overnight at room temperature. The mixture was shaken with 500 ml. of cold water, and the aqueous layer was separated and acidified with 18 ml. of glacial acetic acid. This mixture was extracted with ether, and the ether solution was dried and evaporated leaving a pale yellow crystalline solid which was washed with petroleum ether and air-dried; yield, 35.5 g. (78%). A sample recrystallized from ethyl acetate–petroleum ether melted at 116.5–117.5°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: N, 12.28. Found: N, 12.14.

Summary

A number of 1-substituted-5-imidazolecarboxylic acid esters have been converted to the aldehydes by the McFadyen–Stevens method.

1-Substituted-5-hydroxymethylimidazoles have been synthesized by catalytic hydrogenation of the corresponding aldehydes, and also by reduction of the corresponding esters with lithium aluminum hydride.

Five 1-substituted analogs of histidine have been synthesized and characterized.

1-Methyl-5-(β-aminoethyl)-imidazole dihydrochloride has been prepared.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Studies in the Structure of Colchicine. The Structure of Ring C[1,2]

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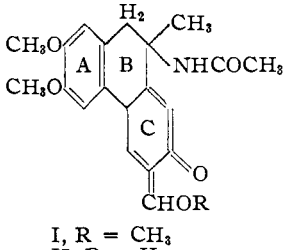
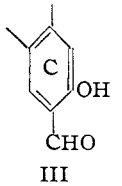
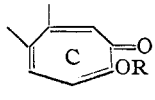
The structure suggested for ring C of colchicine (I) by Windaus[5] has not been completely satisfactory in accounting for the unusual properties of colchicine and its hydrolysis product, colchiceine (II). Neither colchicine nor colchiceine give any



I, R = CH_3
II, R = H



III



IV, R = CH_3
V, R = H

carbonyl derivatives; furthermore, the structure II makes colchiceine a tautomeric form of an ortho-hydroxyaldehyde (III). The latter would be expected to be the stable form, rather than II, but the properties of colchiceine differ significantly from those of an ortho-hydroxyaldehyde. Dewar[6] proposed that colchicine and colchiceine had structures IV and V, respectively, and pointed out that V would be chelated, which would allow resonance stabilization between two nearly equivalent bond structures. The present paper records results which give strong support to the Dewar structure for ring C.[7]

Catalytic reduction of ring C in colchiceine (assuming that no rearrangement occurred) would lead to a 1,2-diol (VI) on the basis of structure V, whereas on the Windaus formulation (II), a 1,3-diol (VII) would be obtained. The diol, hexahydrocolchiceine, actually obtained by catalytic reduction of colchiceine with Raney nickel has been found to be a 1,2-diol, because it reacted with exactly one mole of periodate to form an aldehydic product. The same behavior toward periodate was shown by several derivatives of hexahydrocolchiceine.[8]

Reduction of pure colchiceine with hydrogen and Raney nickel in methanol at room temperature and atmospheric pressure resulted in an uptake of three moles of hydrogen, with the formation of hexahydrocolchiceine (VI) which could be

(1) This work was aided by a grant from the National Institute of Health.

(2) For the previous paper in this series, see Huang, Tarbell and Arnstein, THIS JOURNAL, **70**, 3183 (1948). Part of the material in the present paper has been reported in preliminary form (Arnstein, Tarbell, Huang and Scott, *ibid.*, **70**, 1669 (1948)).

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(5) Windaus, *Ann.*, **439**, 59 (1924).

(6) Dewar, *Nature*, **155**, 141, 479 (1945). The suggestion of Lettre, *Angew. Chem.*, **59**, 223 (1947), that ring C has a pyrone structure seems to be incompatible with the results of the present paper. The interesting observations of Santavy, *Helv. Chim. Acta*, **31**, 821 (1948), on the formation of colchicic acid from colchicine and sodium methoxide are more readily explained on the basis of structure IV than I.

(7) The presence of the same seven-numbered ring as in IV and V, has recently been demonstrated conclusively in purpurogallin ((a) Haworth, Moore and Pauson, *J. Chem. Soc.*, 1045 (1948); Barltrop and Nicholson, *ibid.*, 116 (1948)), and in γ-thujaplicin ((b) Erdtmann and Gripenburg, *Nature*, **161**, 719 (1948)).

(8) No evidence is so far available as to the position of the oxygen functions in ring C with respect to ring B, and hence structures such as IV, V and VI are uncertain in this respect; work is in progress on this point.