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A NEW SYNTHESIS OF DL-HISTIDINE AND DL-N-METHYLHISTIDINE AND SOME REACTIONS OF 4(5)-IMIDAZOLEALDEHYDE

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4(5)-Imidazolealdehyde was first prepared by Pyman (1) by oxidation of 4(5)-hydroxymethylimidazole. Several years later Pyman (2) condensed the aldehyde with hippuric acid and following the classical Erlenmeyer lines realized his second synthesis of histidine. The first one was also due to Pyman (3) who employed malonic ester and 4(5)-chloromethylimidazole.

Several condensation reactions of the aldehyde were described by Pyman (2) and with more detail and extension by Hubball and Pyman (4). Imidazolealdehyde does not react in all respects as a true aldehyde. It gives no Cannizzaro reaction, or Perkin condensation and is inert towards methylmagnesium iodide. It resists air oxidation quite well.

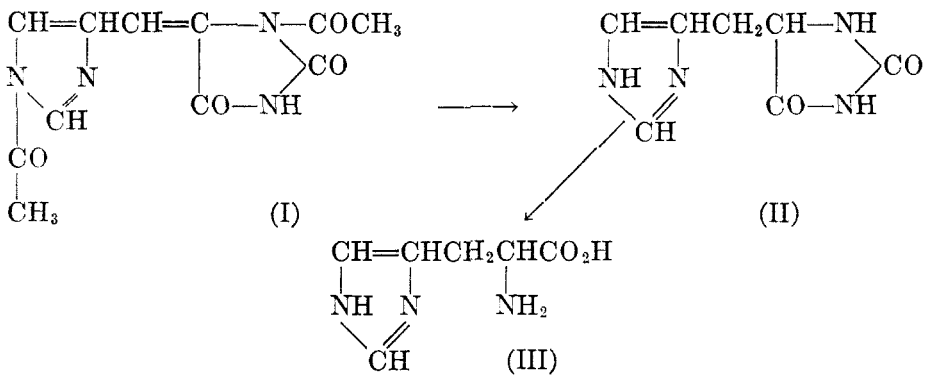
The improvement by Darby, Lewis, and Totter (5) of the primitive method of Girard and Parrod (6) of obtaining hydroxymethylimidazole from fructose, has made imidazolealdehyde accessible in large quantities and allowed the study of a series of condensations from which a new synthesis of DL-histidine and of DL-N-methylhistidine has resulted.

4(5)-Imidazolealdehyde condenses with thiohydantoin, hydantoin, and creatinine by the action of acetic anhydride–sodium acetate. Condensation with acetylthiohydantoin and hydantoin was also obtained with piperidine following the method of Boyd and Robson (7). The 5-imidazolyl-4(5)-methylenethiohydantoin could be desulfurized with monochloroacetic acid and transformed into 5-imidazolyl-4(5)-methylenehydantoin (8).

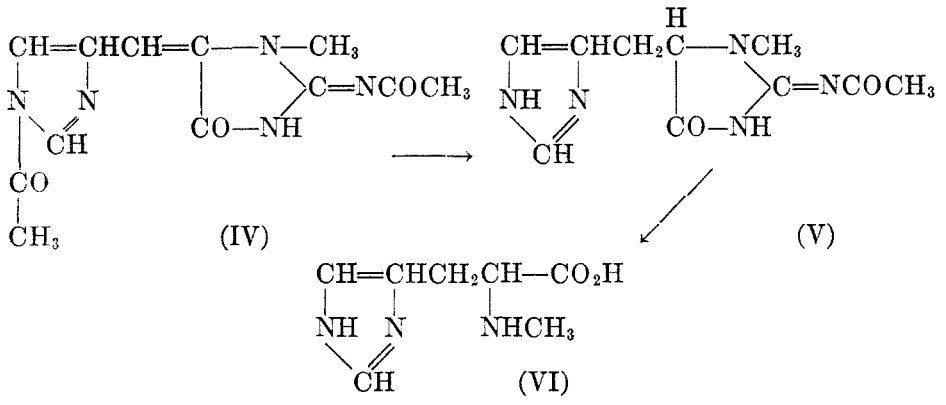
By condensing imidazolealdehyde with aceturic acid, an unstable azlactone was prepared, that on recrystallization from water yielded the corresponding acrylic acid. The 2,4-dinitrophenylhydrazone was also prepared in the usual way and obtained as the hydrochloride.

The reduction with sodium amalgam of 5-[1-acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (I) obtained by condensation of the imidazole aldehyde with hydantoin, yielded 5-[imidazolyl-4(5)-methyl]hydantoin (II) and upon hydrolysis DL-histidine (III) was produced. The racemic 5-[imidazolyl-4(5)-methyl]hydantoin (II) was obtained as a picrate, m.p. 211–212°, with almost the same melting point (209°) as the L isomer, described by Shchukina (9) who prepared it from L-histidine and urea.

This is a new synthesis of histidine (III) and besides the two syntheses of Pyman (2, 3) previously mentioned, two more methods have been described by Albertson and Archer (10) and Albertson and Tullar (11). In both cases they start with 4(5)-chloromethylimidazole and condense it with either ethyl acetamidomalonate or acetamidocyanoacetic ester.



The application to 5-[1-acetylimidazolyl-4(5)-methylene]-2-acetylcreatinine (IV) of the series of reactions described by Wheeler and Hoffman (12) and Deulofeu and Mendivelzua (13) for the synthesis of N-methylamino acids, gave through the 5-[imidazolyl-4(5)methyl]-2-acetylcreatinine (V), DL-N-methylhistidine (VI).



DL-N-Methylhistidine was synthetized by Fargher and Pyman (14) and many years later by Fishman and White (15) using the same method: condensation of *dl*-α-chloro-β-imidazolylpropionic acid with methylamine. The L isomer was prepared by du Vigneaud and Behrens (16) by methylation of N-*p*-toluenesulfonyl-1-benzyl-L-histidine and subsequent elimination of the *p*-toluenesulfonyl and benzyl groups.

EXPERIMENTAL

The *4(5)-imidazolealdehyde* employed in this work was prepared according to Pyman (2) by oxidation of 4(5)-hydroxymethylimidazole. This compound was obtained by the procedure described by Darby, Lewis, and Totter (5). The stated yields were obtained in both cases.

5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylthiohydantoin. Imidazolealdehyde (0.2 g.) and thiohydantoin (0.4 g.) were mixed and condensed by the action of 0.4 g. of sodium acetate and 1.6 ml. of acetic anhydride by heating 20 minutes at 135°. Water was added, the precipitate collected, and after drying, recrystallized from an acetic anhydride-acetic acid mixture as dark yellow crystals, m.p. 260–262°.

Anal. Calc'd for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.59; N, 20.14.
Found: C, 47.92; H, 3.85; N, 19.32.

5-[Imidazolyl-4(5)-methylene]thiohydantoin. Imidazolealdehyde (0.15 g.) was mixed with 0.15 g. of acetylthiohydantoin, 0.26 ml. of pyridine, and 0.15 ml. of piperidine and heated at 100° for two minutes. The condensation product separated during the reaction. Water was then added and then acetic acid to maximum precipitation. The solid was recrystallized from ethanol; yellow prisms, m.p. 320°.

Anal. Calc'd for $C_7H_6N_4OS$: C, 43.29; H, 3.09; N, 28.86.
Found: C, 43.82; H, 2.96; N, 27.99.

A sample boiled with acetic anhydride gave a compound of m.p. 257° that was identical with the *diacetyl* derivative already described. Mixed melting point, 257–259°.

5-[1-Acetylimidazolyl-4(5)-methylene]acetylhydantoin. (I). Imidazolealdehyde (2 g.), 4 g. of hydantoin, 4 g. of fused sodium acetate, and 16 ml. of acetic anhydride were heated for 30 minutes at 135° in an oil-bath. The substances dissolved and the condensation product precipitated in crystalline form during the reaction. The mixture was cooled and water added, when more precipitation took place. After 24 hours at 5° the precipitate was recrystallized from a mixture of acetic anhydride-acetic acid; dark yellow crystals, m.p. 246°, almost insoluble in acetic anhydride and water, very soluble in acetic acid; yield 2.9 g. (52 %).

Anal. Calc'd for $C_{11}H_{10}N_4O_4$: C, 50.39; H, 3.81; N, 21.37; CH_3CO-, 32.84.
Found: C, 50.42; H, 4.02; N, 20.81; CH_3CO-, 31.82.

5-Imidazolyl-4(5)-methylenehydantoin. Imidazolealdehyde (0.1 g.) was mixed with 0.15 g. of hydantoin, 0.26 ml. of pyridine, and one ml. of piperidine and heated at 100° for two minutes. The solids dissolved. After heating, water was added, and then acetic acid to maximum precipitation of the condensation product. The collected precipitate when recrystallized from water gave pale yellow prisms, m.p. 285–287°, very soluble in acetic acid, rather insoluble in ethanol, which can also be employed for recrystallization.

Anal. Calc'd for $C_7H_6N_4O_2$: C, 47.19; H, 3.37; N, 31.46.
Found: C, 47.96; H, 3.56; N, 31.26.

5-Imidazolyl-4(5)-methylenethiohydantoin (0.2 g.) was boiled with a solution of 1 g. of monochloroacetic acid in 3 ml. of water for one and one-half hours. After cooling ammonia was added to maximum precipitation. The precipitate was dried, and recrystallized from water; yellow prisms, m.p. 282–286°, that gave no depression when mixed with a sample of 5-imidazolyl-4(5)-methylenehydantoin.

A sample of 5-imidazolyl-4(5)-methylenehydantoin boiled for a few minutes with acetic anhydride gave a product, m.p. 245°, identical with the diacetyl derivative described above. Mixed melting point 245°.

α-Acetylamino-β-imidazolyl acrylic acid. Imidazolealdehyde (0.4 g.) was mixed with 1 g. of aceturic acid and condensed by heating 20 minutes at 100° with 0.8 g. of sodium acetate and 3.2 g. of acetic anhydride. Water was then added and a solid was collected melting at about 101°. Recrystallized from water, hydrolysis took place and small yellow prisms, m.p. 280°, were obtained, yield 0.45 g. (50 %).

Anal. Calc'd for $C_8H_9N_3O_3$: C, 49.23; H, 4.61; N, 21.53; CH_3CO-, 22.05.
Found: C, 49.91; H, 4.92; N, 21.33; CH_3CO-, 22.44.

Imidazolealdehyde 2,4-dinitrophenylhydrazone. A boiling solution of 0.4 g. of 2,4-dinitrophenylhydrazine in 80 ml. of ethanol was treated with 0.2 g. of imidazolealdehyde. After a few minutes 0.4 ml. of concentrated hydrochloric acid was added; the heating was continued for four minutes and the solution cooled. A precipitate was produced; recrystallized from 50 % acetic acid, it was obtained as orange yellow needles, m.p. 291–292°.

Anal. Calc'd for $C_{10}H_8N_6O_4 \cdot HCl$: C, 38.40; H, 2.88; N, 26.83.
Found: C, 38.72; H, 3.05; N, 26.85.

5-[1-Acetylimidazolyl-4(5)-methylene]-3-acetylcreatinine. (IV). Creatinine (6 g.), 3 g. of imidazolealdehyde, 6 g. of fused sodium acetate, and 24 ml. of acetic anhydride were heated at 135° for 30 minutes. Water was then added, the precipitate collected and recrystallized

from a mixture of acetic acid–acetic anhydride; dark yellow crystals, m.p. 262°, yield 5.2 g. (60%).

Anal. Calc'd for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.72; N, 26.41.
Found: C, 52.55; H, 4.87; N, 26.08.

5-[Imidazolyl-4(5)-methyl]hydantoin picrate. (II). 5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (0.7 g.) was suspended in 7 ml. of water and treated with 7 g. of 3 % sodium amalgam. Solution took place, and with the reduction the solution became almost colorless. After 30 minutes dilute hydrochloric acid was added to *p*H 5 but no precipitate was produced. The solution was then evaporated *in vacuo*, the residue extracted with absolute ethanol, the ethanol evaporated, and the residue dissolved in 7 ml. of water. The calculated amount of picric acid was then added and dissolved by heating. A dark yellow *picrate* was obtained that, upon recrystallization from water saturated with picric acid, had m.p. 210–212°.

Anal. Calc'd for $C_7H_8N_4O_2 \cdot C_6H_3N_3O_7$: C, 38.14; H, 2.68; N, 23.98; N (NO_2), 10.26 (17).
Found: C, 38.72; H, 3.01; N, 23.41; N (NO_2), 10.95.

DL-*Histidine* (III). 5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (6.6 g.) was suspended in 66 ml. of water and treated with 66 g. of sodium amalgam. After 30 minutes, when the solution was colorless, the mercury and remaining sodium amalgam were separated, the solution was diluted with 27 ml. of water, 60 g. of crystalline barium hydroxide was added, and the mixture was heated to boiling for 12 hours. The barium was then eliminated with sulfuric acid and the new filtrate brought to *p*H 4.4–4.6 with hydrochloric acid. The solution was diluted to 1500 ml. and a warm solution of 40 g. of mercuric chloride in 135 ml. of 96 % ethanol was added. By the addition of sodium carbonate to *p*H 7–7.5 a precipitate was produced that after 24 hours was washed well with water. It was then suspended in 300 ml. of water and the mercury eliminated with hydrogen sulfide. After separation of the mercuric sulfide, the filtrate was decolorized with Norit, concentrated to 15 ml., neutralized with sodium carbonate, and diluted to 100 ml. Then 10.4 g. of picric acid was added and the mixture heated to solution. Upon cooling, *histidine dipicrate* separated. A total of 10 grams (yield, 70%) was obtained, m.p. 105°. Pyman (3) gives m.p. 103°.

5-[Imidazolyl-4(5)methyl]-2-acetylcreatinine picrate. (V). 5-[1-Acetyl-imidazolyl-4(5)-methylene]2-acetylcreatinine (1 g.) was suspended in 10 ml. of water and reduced by the addition of 10 g. of 3% sodium amalgam. Solution of the compound took place and decoloration marked the end of the reaction. After separation of the mercury, the solution was neutralized, the amount of picric acid calculated for the formation of a dipicrate added, and dissolved by heating. Upon cooling, a yellow *picrate* was obtained that recrystallized from water had m.p. 207–210°.

Anal. Calc'd for $C_{10}H_{13}N_5O_2 \cdot C_6H_3N_3O_7$: C, 41.37; H, 3.45; N, 24.03; N (NO_2), 9.05 (17).
Found: C, 41.87; H, 3.59; N, 23.53; N (NO_2), 9.71.

DL-*N-Methylhistidine.* (VI). 5-[1-Acetylimidazolyl-4(5)-methylene]2-acetylcreatinine (5 g.) was suspended in 50 ml. of water and reduced as usual with 50 ml. of sodium amalgam. The solution containing the 5-[imidazolyl-4(5)-methyl]-2-acetylcreatinine was diluted with 20 ml. of water, 45 g. of crystalline barium hydroxide was added and the mixture boiled for 12 hours, keeping the volume constant. The barium was then separated quantitatively, and the washings of the barium sulfate added to the above solution. This solution was concentrated to 50 ml. and 2.25 g. of picric acid was added and dissolved by heating. On cooling, 8.2 g. (yield, 71 %) of a *dipicrate*, m.p. 128°, was obtained. By recrystallization from water a m.p. of 132° was attained. Fargher and Pyman (13) give m.p. 132°.

SUMMARY

1. A new synthesis of DL-histidine and of DL-N-methyl histidine starting from imidazolealdehyde has been described.

2. Some condensation reactions of imidazolealdehyde are described.

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