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A New Synthesis of 3,4-Dihydroxyphenylalanine (Dopa)[1a]

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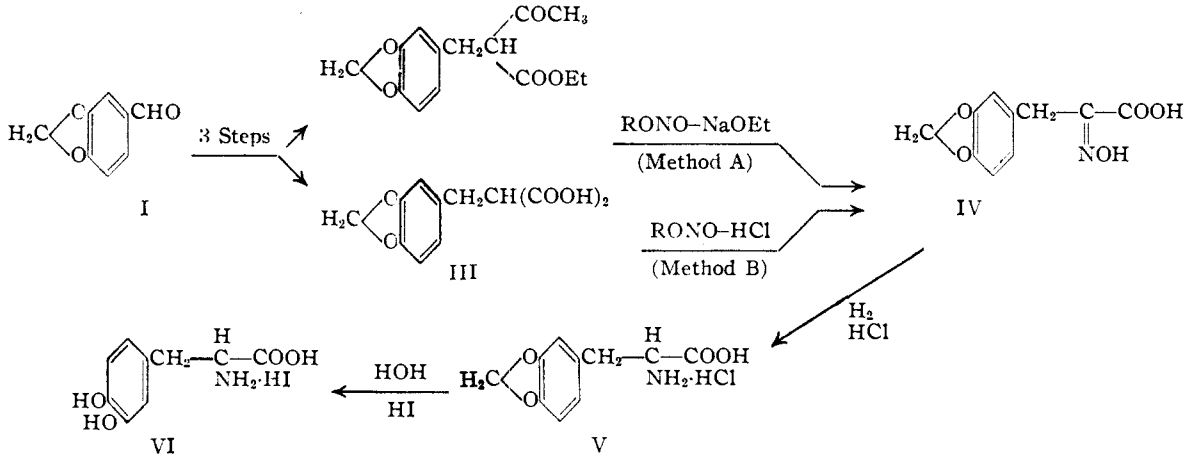
3,4-Dihydroxyphenylalanine (dopa) has been postulated as an intermediate in the biological synthesis of melanin[2] and epinephrine.[3,4] The *levo*-isomer may be isolated from the velvet bean[5] or prepared synthetically from *l*-tyrosine.[6] Many of the syntheses of *dl*-dopa and its derivatives[3,7a-c] are tedious and often give an impure product. Improvements in the azlactone synthesis from vanillin have been made by Harington and McCartney[7c] but the method is not entirely suitable for large scale preparations.

Previous work in this Laboratory has shown that α-amino acids can be conveniently prepared by the reduction of α-oximino acids.[8] The preparation of α-oximino acids from substituted acetoacetic and malonic esters and from substituted malonic acids[9] offered methods for preparing intermediates leading to the synthesis of dopa. It has been shown[9] that 3,4-substituted benzylacetoacetic esters, *e. g.*, 3,4-methylenedioxybenzylacetoacetic ester, are sensitive to a high concentration of acids and therefore cannot be nitrosated by the usual acid-catalyzed procedure.[8] When the nitrosation of 3,4-methylenedioxybenzylacetoacetic ester II was carried out in ethanolic sodium ethoxide with alkyl nitrite, a 60% yield of α-oximino β-(3,4-methylenedioxyphenyl)-propionic acid IV was obtained (Method A). A more satisfactory method for the preparation of IV is the nitrosation of 3,4-methylenedioxybenzylmalonic acid III with alkyl nitrite in the presence of hydrogen chloride (Method B). Yields from 85 to 90% were obtained consistently. Catalytic reduction of IV produced 3,4-methylenedioxyphenylalanine V, which was hydrolyzed with hydriodic acid to dopa-HI, VI. Slight discoloration of the dopa salt was noted after five or six days. 3,4-Methylenedioxyphenylalanine V, on the other hand, is quite stable over long periods and it is suggested that this intermediate amino acid be kept and converted into dopa as needed. Equations for the synthesis of dopa-HI, starting with piperonal[10] are shown



Experimental

3,4-Methylenedioxybenzylacetoacetic Ester (II).—This ester, b. p. 160–161 (4 mm.), was prepared in 61% yield in the usual manner from sodioacetoacetic ester and piperonyl chloride.[11]

3,4-Methylenedioxybenzylidenmalonic Ester.—Prepared according to the directions of Knoevenagel,[12] the ester distilled at 215–225 (8–10 mm.). The yield was 50%; if allowance was made for recovered piperonal, the yield was 87%.

3,4-Methylenedioxybenzylmalonic Acid (III).—A solution of 73 g. (0.25 mole) of 3,4-methylenedioxybenzylidenmalonic ester in 250 ml. of ethanol was shaken with 3 g. of 10% palladium-charcoal catalyst[13] in an atmosphere of hydrogen for three hours, when the theoretical quantity of hydrogen was taken up. The catalyst was removed by filtration, the 3,4-methylenedioxybenzylmalonic ester was not isolated but was converted into the acid by adding to the clear alcoholic filtrate 56 g. (1 mole) of potassium

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(2) H. S. Raper, *Biochem. J.*, **20**, 735 (1926).

(3) C. Funk, *J. Chem. Soc.*, **99**, 55 (1911).

(4) A. Vinet, *Bull. soc. chim. biol.*, **22**, 559 (1940); *Compt. rend.*, **210**, 552 (1940).

(5) T. Torquati, *Arch. farmacol. sper.*, **15**, 213, 308 (1913).

(6) E. Waser and N. Lewandowski, *Helv. Chim. Acta*, **4**, 657 (1921).

(7) (a) H. Stephen and C. Welzmann, *J. Chem. Soc.*, **105**, 1152 (1914); (b) C. Granacher, *Helv. Chim. Acta*, **6**, 458 (1923); (c) C. R. Harington and W. McCartney, *Biochem. J.*, **21**, 852 (1927)

(8) K. E. Hamlin, Jr., and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).

(9) R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947).

(10) Veratraldehyde or other 3,4-dialkoxybenzaldehydes may be employed with equally good results.

(11) H. Decker and O. Koch, *Ber.*, **38**, 1741 (1905).

(12) E. Knoevenagel, *Ber.*, **31**, 2594 (1898).

(13) W. H. Hartung, THIS JOURNAL, **50**, 3370 (1928).

hydroxide, refluxing and stirring for one hour. Distilled water (100 ml.) was then added, and the alcohol was removed by distillation. The resulting aqueous solution of the potassium salt was cooled to 0° by means of crushed ice, and dilute hydrochloric acid was added until the mixture was acid to congo red. The malonic acid was extracted with ether, the ether solution dried over anhydrous sodium sulfate, and 100 ml. of dry toluene was added. The ether was removed over a steam-bath and the residual toluene solution was cooled overnight. Fifty-three grams (89.5% yield) of 3,4-methylenedioxybenzylmalonic acid was removed by filtration. The colorless product melted[14] with evolution of gas at 143°. The previously reported melting point is 142–143°.[15]

α-Oximino-β-(3,4-methylenedioxyphenyl)-propionic Acid (IV): Method A.—In a 250-ml. 3-neck flask fitted with mechanical stirrer, reflux condenser and dropping funnel was placed 60 ml. of absolute ethanol in which was dissolved 2.3 g. of sodium. To the cooled and stirred solution was added 20.4 g. (0.1 mole) of 3,4-methylenedioxybenzylacetoacetic ester. To the flask, surrounded by a cold (10°) water-bath was added, with rapid stirring, 9.8 g. (0.11 mole) of isopropyl nitrite over a period of fifteen minutes. Stirring was continued for thirty minutes after addition of the nitrite, then the ethanol and isopropanol were removed under reduced pressure at 50°. Crushed ice (35 g.) was added to the residue and the mixture carefully acidified with 6 *N* sulfuric acid, then extracted with ether. The ether solution was then thoroughly extracted with cold 10% sodium hydroxide solution. The alkaline extract was warmed on the steam-bath for fifteen minutes, then chilled and carefully acidified with dilute hydrochloric acid. The α-oximino acid was filtered off, decolorized in hot 30% ethanol with Nuchar and recrystallized from dilute ethanol. The colorless crystalline product melted at 160°. The yield was 62%.

Anal. Calcd. for $C_{10}H_9O_5N$: N, 6.2. Found: N, 6.3 (Kjeldahl).

Method B.—In a beaker surrounded by an ice–salt mixture was placed a solution of 5.6 g. (0.024 mole) of piperonylmalonic acid in 100 ml. of ether, and to it was added 2.2 g. (0.025 mole) of isopropyl nitrite. Dry hydrogen chloride was passed into the stirred mixture at the rate of two to three bubbles per second for about one hour. The reaction mixture, now yellow in color, was allowed to stand at room temperature for four hours, then warmed on the steam-bath until the solvents had evaporated. The residue was dissolved in hot toluene, and the solution was allowed to cool in the ice-box. The colorless crystals of the oxime were collected and dried over sulfuric acid *in vacuo*. A yield of 4.7 g. (89%) of product melting at 160° was obtained.

3,4-Methylenedioxyphenylalanine Hydrochloride (V).—To 7 g. (0.031 mole) of the oxime IV, dissolved in 100 ml. of absolute alcohol containing 2 g. of hydrogen chloride, was added 3 g. of 10% palladium catalyst. The mixture was hydrogenated at atmospheric pressure, the theoretical quantity of hydrogen being taken up in two and one-half hours. The catalyst was removed, the filtrate was concentrated to about 50 ml. under reduced pressure, and 200 ml. of dry ether was added with stirring. Cooling of the ether–alcohol solution produced 6.4 g. (92%) of colorless crystals of 3,4-methylenedioxyphenylalanine hydrochloride which melted at 284° with decomposition.

Anal. Calcd. for $C_{10}H_{11}O_4N{\cdot}HCl$: N, 5.38. Found: N, 5.30 (Kjeldahl).

3,4-Dihydroxyphenylalanine Hydriodide (VI).—In fifty milliliters of hydriodic acid (sp. gr. 1.49) was dissolved 7.4 g. (0.03 mole) of 3,4-methylenedioxyphenylalanine hydrochloride, and the mixture was refluxed for two hours. Toluene (200 ml.) was then added, a Dean–Stark trap equipped with stopcock outlet for removal of the water was inserted between the flask and reflux condenser and the mixture refluxed until no more water collected in the trap (three to four hours). The toluene solution of the dopa-hydriodide was allowed to cool overnight in the ice-box and the amino acid filtered off. The crystals were colorless and did not darken while being dried *in vacuo* over sulfuric acid. The acid melted at 201° (d.)[16] and gave a dark green color with ferric chloride. The yield of dopa-hydriodide was 4.1 g. (88%).

Anal. Calcd. for $C_9H_{11}O_4N{\cdot}HI$: N, 4.32. Found: N, 4.27 (Kjeldahl).

Summary

1. A practical synthesis of *dl*-3,4-dihydroxyphenylalanine (dopa) has been developed.

2. 3,4-Methylenedioxybenzylacetoacetic ester and 3,4-methylenedioxybenzylmalonic acid were nitrosated to give α-oximino β-(3,4-methylenedioxyphenyl)-propionic acid, which was reduced catalytically to give 3,4-methylenedioxyphenylalanine in good yield. The latter was converted into *dl*-dopa by hydrolysis with hydriodic acid.

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(14) All melting points obtained are uncorrected.

(15) "Beilstein," Vol. 19, p. 287.

(16) No constant has been previously reported for the hydriodide of dopa. Stephen and Weizmann (7a) reported the hydrochloride, m. p. 246° (d.) and the hydrobromide, m. p. 212° (d.).