[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Cinnamic Acids from Tetrahydroisoquinoline Carboxylic Acids

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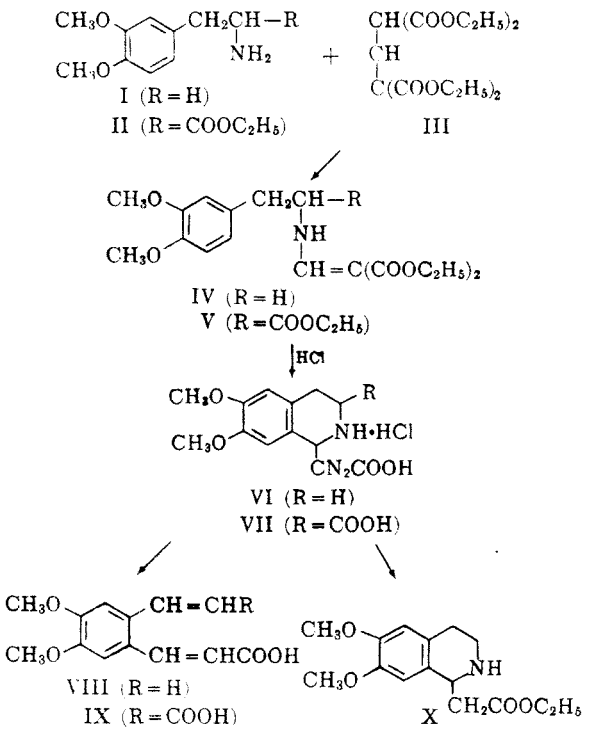
Hydrochloric acid cyclizes the condensation product of 3,4-dimethoxyphenylethylamine and dicarbethoxyglutaconic ester to 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid. This with excess dimethyl sulfate and alkali yields 2-vinyl-4,5-dimethoxycinnamic acid. The ethyl ester of 3,4-dimethoxyphenylalanine condenses smoothly with dicarbethoxyglutaconic ester, but cyclization is not straightforward. Bischler-Napieralski cyclization of N-formyl-3,4-dimethoxyphenylalanine gives the fully aromatized isoquinoline product.

Ethyl 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline-3-carboxylate on treatment with excess dimethyl sulfate and alkali gives a 2-acylcinnamic acid.[1] In a related process, appropriately substituted 1,2,3,4-tetrahydroisoquinolines (*e.g.*, VI or VII) might be expected to give 2-vinylcinnamic acids. The present paper describes work directed to the preparation in this way of 2-vinyl-4,5-dimethoxycinnamic acid (VIII) and of 4,5-dimethoxy-*o*-phenylenediacrylic acid (IX).

While both 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (VI) and 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid could serve as precursors to 2-vinyl-4,5-dimethoxycinnamic acid (VIII), only 3-carboxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (VII) could give diacrylic acid IX. From the preparative standpoint, compound VII appeared to be more closely related to compound VI than to the 1-methyl-3-carboxy derivative. Accordingly, for experience in forming compound VII, we directed our attention to VI. 3,4-Dimethoxyphenylethylamine (I) condensed with dicarbethoxyglutaconic ester (III)[2] in the expected manner[3] to give 3,4-dimethoxyphenylethylaminomethylenemalonic ester (IV). Hot hydrochloric acid, by cyclization, ester hydrolysis, and decarboxylation, converted IV to the hydrochloride of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (VI).[4] Formulation VI received support from the fact that the melting point of derived ethyl ester X compared well with the melting point of the same compound prepared in a different way.[7] Application of the multi-step, single-operation exhaustive methylation process to tetrahydroisoquinoline VI led to 2-vinyl-4,5-dimethoxycinnamic acid (VIII) without difficulty.



3,4-Dimethoxyphenylalanine, the starting material for the synthesis of diacrylic acid IX, was obtained from the N-benzoyl derivative,[1] or by methylation and deacetylation of N-acetyl-3,4-dihydroxyphenylalanine. The ester (II) of 3,4-dimethoxyphenylalanine combined smoothly with glutaconic ester III to yield the aminomethylenemalonic derivative V. An uncomplicated cyclization with hydrochloric acid was not realized, for although appreciable amounts of crude water-soluble product VII was obtained, only a small amount of sharp melting product could be isolated. Experiments in which the crude cyclization product was exposed directly to dimethyl sulfate and alkali gave only

(1) W. J. Gensler, E. M. Healy, I. Onshuus, and A. L. Bluhm, *J. Am. Chem. Soc.*, **78**, in press (1956).

(2) M. Conrad and M. Guthzeit, *Ann.*, **222**, 249 (1884).

(3) *Cf.* S. I. Levy, *J. Chem. Soc.*, **105**, 27 (1914), for examples and for earlier references, particularly to the work of Ruhemann.

(4) A standard Pictet-Spengler synthesis[5] of tetrahydroisoquinoline VI by cyclization of 3,4-dimethoxyphenylethylaminomethyleneacetic acid was not tried although a number of reagents (*e.g.*, formylacetic ester, propiolic ester,[6] 3,3-dimethoxypropionic ester,[6] etc.) might be expected to react with amine I to give the precursor compound. Attractive, but also not tried, was substitution of ethoxymethylenemalonic ester for dicarbethoxyglutaconic ester (III) in the preparation of VI.

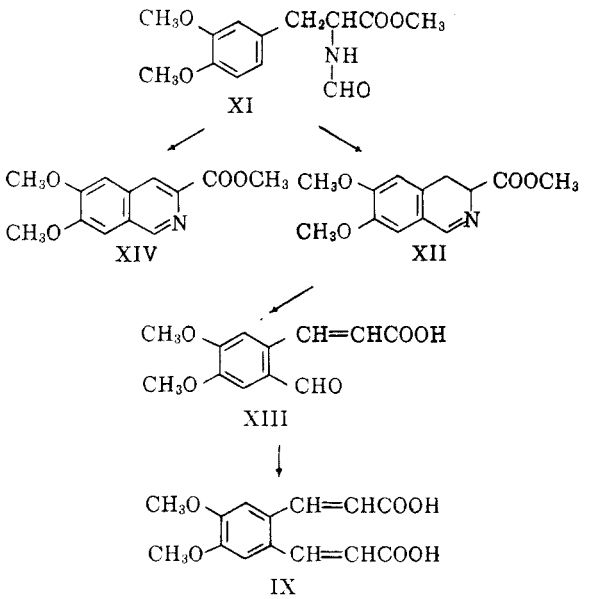
(5) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 6, 151 (1951).

(6) *Cf.* F. W. Gray, H. S. Mosher, F. C. Whitmore, and T. S. Oakwood, *J. Am. Chem. Soc.*, **73**, 3577 (1951).

(7) A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953).

minor amounts of materials of uncertain structure. Tetrahydroisoquinoline VII can exist in two stereoisomeric forms; diacrylic acid IX can exist in three stereoisomeric forms. Difficulty in isolating pure materials may in part be attributable to this feature of VII and of IX.

An alternate approach to diacrylic acid IX proceeds by a Bischler-Napieralski cyclization of N-formyl-3,4-dimethoxyphenylalanine methyl ester (XI) to methyl 6,7-dimethoxy-3,4-dihydroisoquinoline-3-carboxylate (XII), ring opening by the



process described before[1] to form 2-formyl-4,5-dimethoxycinnamic acid (XIII), and condensation of XIII with malonic acid to give IX. Formylation of 3,4-dimethoxyphenylalanine with acetic anhydride and formic acid[8] followed by esterification gave the starting material XI. The product of the Bischler-Napieralski cyclization of this compound, however, instead of the anticipated dihydroisoquinoline XII, proved to be the completely aromatic isoquinoline XIV. This assignment was based on the hydrogen content, and on comparison of the carbonyl infrared absorption frequency (1706 cm.$^{-1}$) with that of the non-aromatic ester, methyl 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline-3-carboxylate (1733 cm.$^{-1}$)[1,9] and was borne out by the fact that treatment with excess alkali and dimethyl sulfate gave no volatile amine and no sign of formyl derivative XIII.

The dehydrogenation was not anticipated, since other similarly constituted amido-esters[1,10,11] have been converted to 3,4-dihydroisoquinolines. However, it may be significant that no formamido-esters have been cyclized.[12] The difficulty in getting at the 2-formyl compound XIII, together with a report that came to our attention to the effect that phthalaldehyde under Doebner conditions combines with only *one* mole of malonic acid[13] discouraged further attempts in this direction.

EXPERIMENTAL[14]

3,4-Dimethoxyphenylethylaminomethylenemalonic ester (IV). 3,4-Dimethoxyphenylethylamine hydrochloride was prepared by treating an alcohol solution of the amine (I),[15] b.p. 140–143° (4 mm.), with gaseous or aqueous hydrogen chloride. The precipitated hydrochloride was crystallized from alcohol-acetone to a melting point of 152–153°.[16]

To a hot solution of 21.12 g. (0.060 mole) of sodio-dicarbethoxyglutaconic ester[2] in 150 ml. of absolute alcohol was added 13.05 g. (0.060 mole) of the hydrochloride in one portion. The yellow color faded, and a white precipitate of sodium chloride formed quickly. After 15 minutes of heating, the mixture was cooled and filtered. The filtrate was concentrated at 65° under the pressure of a water aspirator, and the residual sirup was taken up in ether. The pale yellow ethereal solution, after one wash with water, was dried over magnesium sulfate, and the dry solution was decolorized with carbon at room temperature. The residue from the ether solution was distilled in a wide-bore, short-path apparatus fitted with a capillary through which nitrogen was passed. The recovery of colorless ethyl malonate, n^{21}_D 1.4139, b.p. (bath temperature) 60–123° (0.012–0.013 mm.), was 8.39 g. or 88% of the stoichiometric amount. The desired product IV remained in the distilling flask as a residual, colorless, viscous sirup, n^{25}_D 1.5510, weighing 18.8 g. (89%).

Anal. Calc'd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17. Found: C, 61.4; H, 7.1.

Attempts at distilling this material, even under a high vacuum, resulted only in decomposition.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid hydrochloride (VI) *from 3,4-dimethoxyphenylethylaminomethylenemalonic ester* (IV). A mixture of 4.48 g. (0.0128 mole) of the aminomethylenemalonic ester IV and 122 ml. of

(8) *Cf.* V. du Vigneaud, R. Dorfmann, and H. S. Loring, *J. Biol. Chem.*, **98**, 577 (1932).

(9) Conjugated carbonyls absorb at a lower frequency than non-conjugated carbonyls. See L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, John Wiley and Sons, New York, 1954.

(10) A. Galat, *J. Am. Chem. Soc.*, **73**, 3654 (1951).

(11) T. Hosono, *J. Pharm. Soc. Japan*, **65**, No. 7/8A, 11 (1945) [*Chem. Abstr.*, **46**, 115 (1952)].

(12) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950), discuss related problems of Bischler-Napieralski cyclization and dehydrogenation. Hosono[11] noted dehydrogenation in Bischler-Napieralski cyclization with phosphorus oxychloride, but only after long reaction periods. An observation, curiously parallel to ours, and of possible interest in connection with the preparation of dihydroisoquinoline XII, was reported by G. R. Clemo and M. Hoggarth, *J. Chem. Soc.*, 95 (1954), who found that 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid on boiling in alcohol containing sulfuric acid dehydrogenated to give 3,4-dihydroisoquinoline-3-carboxylic ester.

(13) R. H. Wiley and P. H. Hobson, *J. Am. Chem. Soc.*, **71**, 2429 (1949). The Perkin process with phthalaldehyde gives *o*-phenylenediacrylic acid in low yield [J. Thiele and K. G. Falk, *Ann.*, **347**, 112 (1906)].

(14) Temperatures are uncorrected. Analyses were performed by Dr. Carol K. Fitz, 115 Lexington Avenue, Needham Heights, Mass., and Dr. Stephen M. Nagy and his assistants at Massachusetts Institute of Technology, Microchemical Laboratory, Cambridge.

(15) Generous samples of 3,4-dimethoxyphenylethylamine were very kindly provided by Professor Gilbert Stork and by Monsanto Chemical Company, St. Louis, Missouri.

(16) C. Mannich and W. Jacobsohn, *Ber.*, **43**, 189 (1910), reported m.p. 154–155°.

24% hydrochloric acid was warmed on the steam-bath for one to three hours, or until carbon dioxide was no longer given off. All material volatile at water aspirator pressure at temperatures no higher than 100° then was removed by distillation. The solid residue was dissolved in hot glacial acetic acid, the solution was filtered to remove some insoluble material, and the filtrate was cooled. The white precipitate was collected, washed with cold acetic acid, and air-dried. Crystallization of this material (2.74 g.; m.p. 218–220° with effervescence) from glacial acetic acid furnished 2.49 g. (68%) of hydrochloride VI, m.p. 218–218.5° (effervescence).

Anal. Calc'd for $C_{13}H_{18}NO_4Cl$: C, 54.25; H, 6.30. Found: C, 54.1; H, 6.4.

Attempted cyclization of compound IV with hydrogen chloride in alcohol or in benzene failed to give useful product.

Ethyl ester of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (X). Hydrochloride VI (0.50 g. or 0.0017 mole) was boiled with 1 ml. of thionyl chloride for 30 minutes under a condenser provided with a calcium chloride drying tube. The initial yellow suspension gradually changed to an orange-red solution. Absolute alcohol (10 ml.) was added to the cooled solution, and, when the vigorous reaction had subsided, the mixture was boiled for 15 minutes. Excess alcohol was removed by distillation on the steam bath under reduced pressures, aqueous bicarbonate was added, and the mixture was extracted first with ether and then with chloroform. The extracts were washed with water, were combined, and were dried over magnesium sulfate. Evaporation of solvent by blowing air over the solution on the steam-bath left an amber sirup. Two crystallizations from ligroin (b.p. 66–75°) gave 0.09 g. of product X, m.p. 77.5–78.0°. The value found before[7] for the ethyl ester of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid was 77–78°.

2-Vinyl-4,5-dimethoxycinnamic acid (VIII). A mixture of 0.50 g. (0.0017 mole) of hydrochloride VI, 1.4 ml. of dimethyl sulfate, and 18 ml. of 20% sodium hydroxide solution was heated on the steam-bath for three hours. Acidification of the cold solution with dilute hydrochloric acid deposited a pale yellow solid, which was washed with cold water and dried in a vacuum desiccator. This material (0.44 g.; m.p. 172–177°) was dissolved in aqueous bicarbonate, treated with decolorizing carbon, and reprecipitated with acetic acid. Repetition of the process gave product melting at 179–180°. Two additional treatments as before, followed by two crystallizations from dilute aqueous alcohol furnished cream-colored 2-vinyl-4,5-dimethoxycinnamic acid (VIII), m.p. 177–178°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.5; H, 6.1.

3,4-Dimethoxyphenylalanine. 3,4-Dimethoxyphenylalanine was obtained from its N-benzoyl derivative[1] by hydrolysis with barium hydroxide essentially according to Deulofeu and Mendivelzua.[17] 3,4-Dimethoxyphenylalanine was also obtained from 3,4-dihydroxyphenylalanine[18] by N-acetylation, O-methylation, and deacetylation. Directions for the latter preparation follow.

To a suspension of 10 g. (0.508 mole) of 3,4-dihydroxyphenylalanine in 50 ml. of water was added 36.2 ml. of acetic anhydride. The acetic anhydride was added in eight portions over a 15-minute period while the mixture was warmed on the steam-bath under a condenser. After the addition was complete the mixture was kept hot for an additional 15 minutes, and then was distilled from a Claisen flask at steam temperatures and under reduced pressures until no further distillate appeared. The residue, neutralized with barium carbonate, was mixed with 38.4 g. of hydrated barium hydroxide and treated slowly and with stirring with 19.0 ml. of dimethyl sulfate. Intermittent cooling kept the temperature at 30–40°. After the addition the solution was stirred at room temperature for two hours, was filtered, and the clear dark-amber filtrate was poured into a hot solution of 11.2 ml. of concentrated sulfuric acid in 55 ml. of water. The cooled mixture was filtered to remove barium sulfate, and the filtrate was held on the steam-bath under a condenser for 66 hours.

The solution was adjusted to *p*H 2 by addition of barium carbonate, the mixture was filtered, and the filtrate was concentrated to a pasty mass by distillation on the steam-bath at reduced pressure. This was cooled for two hours before filtering to collect the product. The light gray 3,4-dimethoxyphenylalanine, after washing on the funnel with a little cold water and air-drying, weighed 4.7 g. and melted at 252–253° (dec.). An additional 2.1 g. with m.p. 244–246° (dec.) was obtained by concentrating the mother liquors.

Hydrochloride of 3,4-dimethoxyphenylalanine ester (II). Dry hydrogen chloride was passed into a suspension of 16.4 g. (0.073 mole) of 3,4-dimethoxyphenylalanine in 350 ml. of absolute ethanol for one hour. The resulting clear solution was boiled for three hours under a condenser fitted with a calcium chloride drying tube. The solution then was concentrated to 100 ml. by distillation *in vacuo*, cooled, diluted with 100 ml. of acetone, and chilled overnight. The white solid, after collection, washing with acetone, and air-drying, weighed 13.4 g. (64%) and melted at 158.5–160°. A sample of this 3,4-dimethoxyphenylalanine ester hydrochloride recrystallized three times from alcohol-acetone melted at 162–163.5°.

Anal. Calc'd for $C_{13}H_{20}NO_4Cl$: C, 53.86; H, 6.96. Found: C, 53.6; H, 7.0.

Ethyl ester of 3,4-dimethoxyphenylalaninomethylenemalonic ester (V). Sodio-dicarbethoxyglutaconic ester (III) (9.1 g. or 0.026 mole) was added in one portion to a hot solution of the hydrochloride of ester II (7.5 g. or 0.026 mole) in 80 ml. of absolute alcohol. The yellow color was discharged immediately, and a white precipitate of sodium chloride appeared shortly thereafter. The mixture was boiled 15 minutes, then cooled 15 minutes in the ice-bath, and filtered. The filtrate was distilled on the steam-bath under reduced pressure, and the residual sirup was dissolved in ether and washed with four 5-ml. portions of water. After the ether solution was dried (magnesium sulfate) and treated with decolorizing carbon, solvent was removed on the steam-bath. Distillation of the pale yellow viscous oil in a wide-bore short-path apparatus at bath temperatures of 90–135° (3 mm.) afforded 2.8 g. of recovered ethyl malonate, $n^{24.5}_D$ 1.4121. The non-volatile pale yellow viscous product V weighed 9.3 g. (84%) and showed $n^{24.8}_D$ 1.5328.

Anal. Calc'd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90. Found: C, 59.4; H, 7.0.

Attempts at converting aminomethylenemalonic derivative V *to tetrahydroisoquinoline* VII *and to diacrylic acid* IX. (*A.*) Hydrochloric acid (100 ml. of 24%) containing 2.61 g. (0.0062 mole) of compound V was boiled for three hours, and then was allowed to stand at room temperature overnight. Carbon dioxide in copious quantity was evolved initially from the hot solution. Volatile material was removed from the solution, after filtration, by distillation on the steam-bath under a water-pump vacuum. The residue (2.45 g.) an amphorous, pale yellow, water-soluble material, was dried for two days in a vacuum desiccator containing potassium hydroxide pellets.

Anal. Calc'd for $C_{14}H_{18}NO_6Cl$ as a tribasic acid: neut. equiv., 110.5. Found: neut. equiv., 113.5.

Silver nitrate with an aqueous solution of this product gave a white precipitate, which dissolved in aqueous ammonia and reprecipitated on acidification with nitric acid.

(*B.*) In another similar experiment, the hydrochloric acid cyclization mixture was extracted with ether before concentrating. The residue, crystallized several times from glacial acetic acid, furnished a small amount of white product, m.p. 254–255° (dec.).

(17) V. Deulofeu and G. Mendivelzua, *Z. physiol. Chem.*, 219, 233 (1933).

(18) We wish to thank Dow Chemical Company, Midland, Michigan, for providing this material.

Anal. Calc'd for $C_{14}H_{18}NO_6Cl$: C, 50.68; H, 5.47. Calc'd for $C_{14}H_{18}ClNO_6 \cdot 1.5H_2O$: C, 46.86; H, 5.90. Found: C, 46.4; H, 5.9.

(*C.*) In other experiments the crude hydrochloric acid cyclization product was treated directly with excess alkali and dimethyl sulfate. In one case a base-soluble acid-insoluble solid was obtained, which after recrystallization from aqueous alcohol showed m.p. 273–274° (dec.). In another case the product was crystallized from aqueous alcohol to a constant melting point of 173–175°.

Anal. Calc'd for $C_{14}H_{14}O_6$ (IX): C, 60.43; H, 5.07. Calc'd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.36; H, 5.83.

N-Formyl-3,4-dimethoxyphenylalanine. Acetic anhydride (33.3 ml.) was added dropwise to a stirred solution of 10.0 g. (0.045 mole) of 3,4-dimethoxyphenylalanine in 107 ml. of 90% formic acid. The rate of addition was adjusted to maintain the temperature at 60°. After the addition the mixture was cooled, and 16 ml. of ice-water was added. Concentration *in vacuo* left a sirupy residue which, after crystallization (including treatment with decolorizing charcoal) from water, afforded 9.29 g. (82%) of the N-formyl derivative, m.p. 132–132.5°. A sample for analysis, m.p. 133–134°, was prepared by several crystallizations from water.

Anal. Calc'd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97. Found: C, 56.5; H, 6.0.

Methyl ester of n-formyl-3,4-dimethoxyphenylalanine (XI). (*A.*) *Fischer esterification.* Dry hydrogen chloride was bubbled into an ice-cold solution of 1 g. of the N-formyl derivative (0.0039 mole) in 16 ml. of dry methanol for 30 minutes. The resulting mixture was boiled for two hours under a condenser provided with a drying tube, and then was concentrated to a sirup. Water was added, and the product was extracted with chloroform. The extract was dried over magnesium sulfate, the solvent was removed, and the crude product was decolorized in aqueous methanol and crystallized from the same solvent. The methyl ester XI so obtained weighed 0.40 g. (38%) and melted at 103–105°. Four additional crystallizations brought the melting point to 110.8–111°.

Anal. Calc'd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41. Found: C, 58.2; H, 6.4.

Use of concentrated sulfuric acid in place of hydrogen chloride was less satisfactory.

(*B.*) *Esterification with diazomethane.* Diazomethane was generated in the cold from nitrosomethylurea using 2 ml. of 50% aqueous potassium hydroxide and 10–20 ml. of chloroform per gram of nitrosomethylurea. The yellow chloroform solution was decanted onto potassium hydroxide pellets, swirled, and used without delay.

A suspension of 6.98 g. (0.0276 mole) of the N-formyl derivative was treated at ice-bath temperatures with a cold chloroform solution of diazomethane derived from 7 g. of nitrosomethylurea. The suspension was swirled frequently during the addition. The insoluble starting material disappeared as the soluble ester formed. After one hour in the cold and $1^1/_2$ hours at room temperature, chloroform and excess diazomethane were removed by distillation, and the residual methyl ester was crystallized from aqueous methanol. Product XI so obtained weighed 6.75 g. (92%) and melted at 109–111°.

Ether could be used satisfactorily as the solvent in place of chloroform.

Methyl 6,7-Dimethoxyisoquinoline-3-carboxylate (XIV). A solution of 1 g. of N-formyl-3,4-dimethoxyphenylalanine methyl ester (0.0037 mole) in 4 ml. of freshly distilled phosphorus oxychloride was boiled for 30 minutes under a moisture-protected condenser. The cooled mixture was quenched on ice and water, made basic with aqueous ammonia, and extracted with chloroform. The chloroform solution, after drying with magnesium sulfate and removing solvent, left 0.31 g. of cream-colored crystals, m.p. 200–202°. Crystallization from methanol gave 0.28 g. (30%) of white feathery crystals, m.p. 209–210°.

Anal. Calc'd for $C_{13}H_{15}NO_4$ (XII): C, 62.64; H, 6.07. Calc'd for $C_{13}H_{13}NO_4$ (XIV): C, 63.15; H, 5.30. Found for material melting at 209.7–210.1°: C, 62.8; H, 5.3. Found for material melting at 210–211°: C, 62.8, 62.9; H, 5.4; 5.4.

Cyclization of XI with phosphorus pentoxide in boiling toluene, with phosphorus oxychloride and phosphorus pentoxide in boiling toluene, or with phosphorus oxychloride in boiling naphthalene or in boiling xylene gave isoquinoline XIV melting at, or just below, 210°.

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