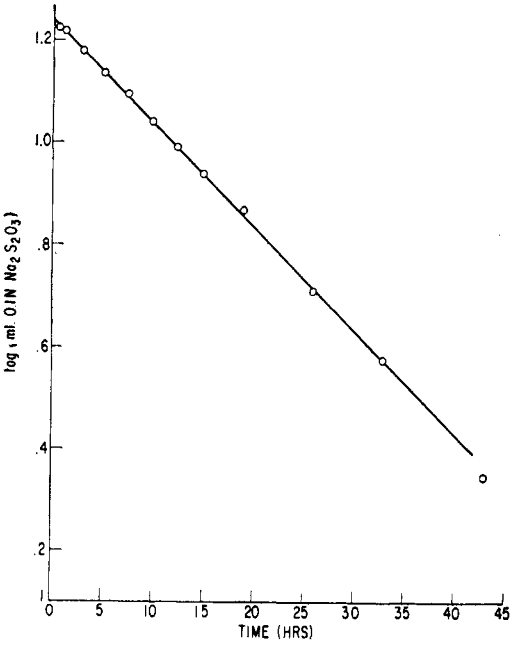

Fig. 3.—Hydrolysis of diphenyl carbonate in 1:1 dioxane–water at 100°.

ion to ester was used, so that the reaction could be treated as pseudo first order. In a typical experiment a solution of diphenyl carbonate (1.5×10^{-4} M) in 1:1 dioxane–water and a solution of sodium hydroxide (2×10^{-2} M) in the same solvent were immersed in a constant-temperature bath at 20°. After 30 min. equal volumes of the two solutions were mixed and the resulting solution was quickly transferred to a quartz cell in a Beckman Model DU spectrophotometer equipped with a jacket through which water was circulated from the constant temperature bath. The absorbance was measured at 291 μ. By using fast-draining pipets for the transfers the first measurement could be made within 30 seconds after the solutions were mixed. Subsequent measurements were made as fast as the instrument could be balanced (approximately every 10 sec.) until there was no further change in absorbance. Second-order rate constants were determined by dividing the pseudo-first-order rate constants (determined graphically from a plot of log ($A_\infty - A$) against time by hydroxide ion concentration. The calculated second-order constants for reaction of diphenyl carbonate were not affected by changes in the initial concentration of the two reagents:

Diphenyl carbonate	Sodium hydroxide	k (l. mole^{-1} sec.$^{-1}$)
3.75×10^{-5}	10^{-2} M	0.87
7.5×10^{-5}	10^{-2} M	.84
1.5×10^{-4}	10^{-2} M	.88
7.5×10^{-5}	5×10^{-3} M	.84
1.5×10^{-4}	5×10^{-3} M	.85

Synthesis of 5-Ethyl-8-methoxycorydaldine

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In connection with another problem it became necessary to synthesize 5-ethyl-8-methoxycorydaldine and some of its derivatives. Initial efforts to ethylate or acetylate 8-methoxycorydaldine[2] directly failed and consequently the ethyl group had to be introduced at an earlier stage. The synthetic sequence used is outlined in Chart I. Mescaline, the starting material of this synthesis, was prepared from gallic acid[3] and converted to the urethane I.[2] Acylation with acetic anhydride in polyphosphoric acid proceeded with excellent yield and the resulting ketone II exhibited infrared absorption at 1710 ($—NH\overset{\overset{O}{\|}}{C}—OC_2H_5$) and 1680 cm.$^{-1}$ ($—\overset{\overset{O}{\|}}{C}CH_3$). The nuclear magnetic resonance (n.m.r.) spectrum[4] exhibited singlets due to methyl groups at 6.14, 6.15, 6.21 ($—OCH_3$), and 7.6 τ ($\overset{\overset{O}{\|}}{C}CH_3$) as well as the usual signals for an ethyl group. The presence of a single aromatic proton was confirmed

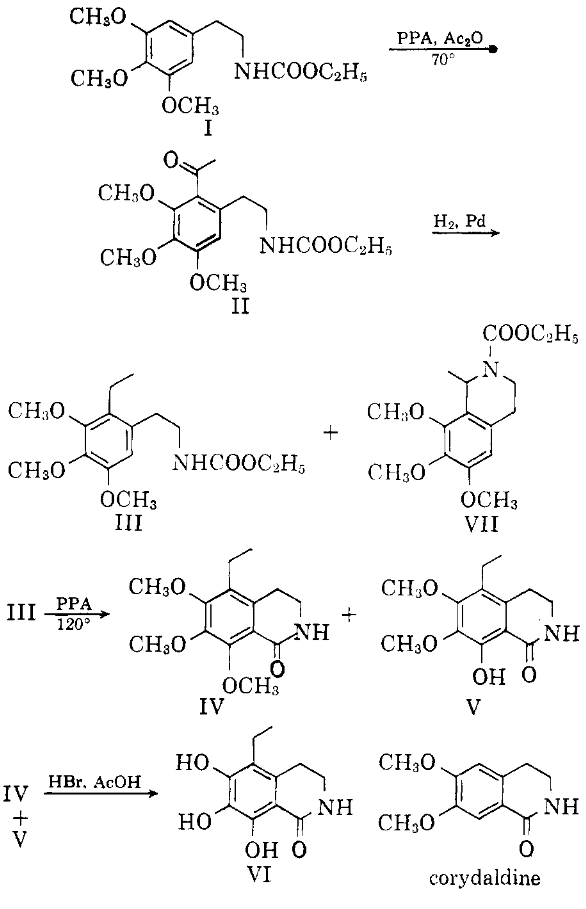

Chart I

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[1] National Institutes of Health Predoctoral Fellow, 1960–1961.

[2] R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945).

[3] F. Bennington, *ibid.*, **73**, 1353 (1951).

[4] All n.m.r. spectra were determined on a Varian A-60 spectrometer in carbon tetrachloride unless specified otherwise.

by a peak at 3.5 τ; the methylene groups gave rise to an unsymmetrical quartet centered at 6.7 τ (N—CH_2—) and a triplet at 7.4 τ (Ar—CH_2—).

Reduction of the hindered ketone II was effected by hydrogenation in acetic acid at 80°. It was necessary to use equal weights of 10% palladium on powdered charcoal as catalyst in order to obtain a fair yield of the desired N-carbethoxy-2-(2-ethyl-3,4,5-trimethoxyphenyl)ethylamine (III). The infrared spectrum of this oil possessed a single carbonyl band at 1730 cm.$^{-1}$. In the n.m.r. spectrum the methylenes gave rise to a multiplet (seven bands, 4H) centered at 7.3 τ, and the two methyl groups to an almost symmetrical quartet at 8.8 τ. This quartet is the result of overlap of two triplets with the same splitting constant (J = 7 c.p.s.). The other functional groups gave rise to bands similar to those of the corresponding groups in II. When hydrogen consumption was slow because of a smaller catalyst-to-product ratio or because of poisoning, the product was 2-carbethoxy-1-methyl-1,2,3,4-tetrahydro-6,7,8-trimethoxyisoquinoline (VII) or a mixture of III and VII.

Structure VII for this by-product was assigned on the basis of elemental analysis and the physical properties of the material. The infrared spectrum showed carbonyl absorption at 1700 cm.$^{-1}$ but no bands attributable to an N—H group. Ultraviolet absorption indicated the same chromophore as in I and III and the n.m.r. spectrum showed a singlet at 3.7 τ due to the aromatic proton and three bands attributed to methoxy groups at 6.08, 6.24, and 6.26 τ. A group of four non symmetrical bands centered at 9.3 τ is considered to result from partial overlap of a triplet (urethane methyl group) and a doublet from spin–spin coupling of the 1-methyl group and the hydrogen atom adjacent to it (J = 8 c.p.s.). Finally, structure VII was confirmed by synthesis as outlined in Chart II.

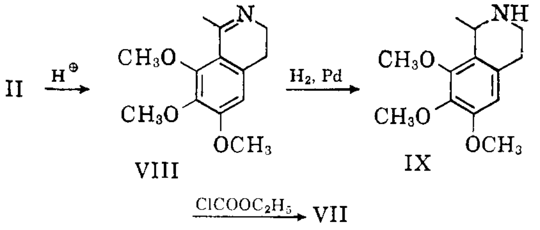

Chart II

Prolonged treatment of II with hydrochloric acid gave the Schiff base VIII isolated as its hydrochloride, which was hydrogenated smoothly to 1-methyl-1,2,3,4-tetrahydro-6,7,8-trimethoxyisoquinoline (IX). Treatment of this compound with ethyl chloroformate gave VII as a colorless oil, identical with that obtained from hydrogenation of III.

Treatment of the urethane III with polyphosphoric acid at 120° gave 5-ethyl-8-methoxycorydaldine (IV) and 5-ethyl-8-hydroxycorydaldine (V).

The former compound (IV) exhibited infrared bands at 1680 (C=O) and 1580 cm.$^{-1}$ (C=C). The n.m.r. spectrum (in $CDCl_3$) showed singlets at 6.05 (6H) and 6.10 τ (3 H) (OCH_3), and a triplet at 8.9 τ (J = 7 c.p.s.) (CH_3 in C_2H_5). The methylene groups gave a complex pattern similar to that found in the spectrum of III. The phenolic product V gave a strong blue color with ferric chloride and exhibited infrared bands at 3500, 3300, 1660, and 1580 cm.$^{-1}$. The n.m.r. spectrum was similar to that of IV except there was a sharp peak at 3.4 τ (OH) and the methoxy groups gave rise to two equally intense bands between 6 and 6.1 τ.

Both compounds IV and V were converted to the same trihydroxyisoquinolone (VI) when treated with hydrogen bromide in acetic acid.

Experimental[5]

N-Carbethoxy-2-(2-acetyl-3,4,5-trimethoxyphenyl)ethylamine (II).—N-Carbethoxy-2-(3,4,5-trimethoxyphenyl)-ethylamine (I) (140 mg.) was dissolved in acetic anhydride (0.05 ml.) with slight heating, mixed with polyphosphoric acid (0.7 g.) and the mixture heated in an open tube at 60–70° for 2.5 hr. At the end of this period 10 ml. of water and ice was added and the mixture extracted with two 20-ml. portions of methylene chloride. The extracts were washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent gave II as an oil (152 mg., yield: 95%), which, from its infrared spectrum and chromatographic behavior, appeared to be essentially pure. On standing for several months one sample crystallized; after recrystallization from cyclohexane it melted at 58–60°. An analytical sample was prepared by short-path distillation at 180° (0.05 mm.); $\nu_{max}^{CCl_4}$ 1710, 1680 (shoulder), and 1600 cm.$^{-1}$; λ_{max}^{EtOH} 225 and 257 mμ (ϵ 13,200 and 4400 resp.).

Anal. Calculated for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.00; H, 7.37; N, 4.31.

N-Carbethoxy-2-(2-ethyl-3,4,5-trimethoxyphenyl)ethylamine (III).—A mixture of 10% palladium on charcoal catalyst (3 g.) and acetic acid (50 ml.) was saturated with hydrogen at 80° and atmospheric pressure, then 3 g. of ketone II in 50 ml. of acetic acid was added, and the hydrogenation was continued. The first mole of hydrogen was consumed rapidly, while the second mole took 10–20 hr. When the hydrogen consumption stopped, the mixture was cooled and filtered, the catalyst washed with warm methanol, and the combined filtrates evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml. of chloroform and washed with 50-ml. portions of dilute hydrochloric acid and saturated sodium bicarbonate solution, then dried over magnesium sulfate, and the solvent evaporated, yielding an oil (2.8 g.) which was chromatographed on 100 g. of acid-washed alumina (Merck). The first fractions eluted with pentane–benzene (1:1) contained 340 mg. of an oil which proved to be VII (see below). Further elution with benzene yielded the desired product (III) (1.33 g., yield 49%) as an oil.

An analytical sample was prepared by short-path distillation at 160° and 0.05 mm.; $\nu_{max}^{CCl_4}$ 3600, 1730, 1600 cm.$^{-1}$, λ_{max}^{EtOH} 255 and 280 mμ (ϵ 10,500 and 1,340 respectively).

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(5) Microanalyses are by S. M. Nagy and associates, Massachusetts Institute of Technology Microanalytical Laboratory, and the Scandinavian Microanalytical Laboratory, Denmark. Melting points were observed on a Kofler hot-stage microscope and are uncorrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model II, and infrared spectra were taken on a Perkin-Elmer Infracord with a sodium chloride prism. The listing of infrared bands includes only those which are relevent to structural arguments.

Anal. Calculated for $C_{16}H_{25}NO_5$: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.73; H, 8.30; N, 4.44.

As a further proof of structure the urethane moiety in III was hydrolyzed to the primary amine in the following way: A solution of III (150 mg.) in ethanol (3 ml.) and 2 *N* sodium hydroxide (2 ml.) was heated at reflux overnight, then diluted with water and extracted with chloroform. The combined extracts were dried (sodium sulfate) and evaporated. The residue, 67 mg. of oil, was dissolved in ether and saturated with hydrogen chloride gas. The precipitated salt was purified by recrystallization from ethanol to yield pure 2(2-ethyl-3,4,5-trimethoxyphenyl)ethylamine hydrochloride, m.p. 148–150°.

Anal. Calculated for $C_{13}H_{22}ClNO_3$: C, 56.62; H, 8.04; N, 4.94. Found: C, 56.60; H, 8.25; N, 5.15.

5-Ethyl-8-methoxycorydaldine (3,4-Dihydro-5-ethyl-6,7,8-trimethoxy-1-(2H)-isoquinolone) (IV).—A mixture of III (1.33 g.) and polyphosphoric acid (13 g.) was heated at 120° for 1.5 hr., then ice and water (50 ml.) was added and the mixture extracted with five 50-ml. portions of chloroform. The extracts were washed with saturated sodium chloride solution, combined, and dried over magnesium sulfate. After the solvent was evaporated, the residue, 230 mg. of yellow oil, was chromatographed on 15 g. of Woelm alumina (activity IV). Benzene, followed by chloroform eluted 154 mg. (14%) of crystalline IV, which after recrystallization from ethyl acetate melted at 127–129°.

An analytical sample was prepared by short-path distillation at 160° and 0.05 mm., $\nu_{max}^{CCl_4}$ 3300, 1680, and 1580 cm.$^{-1}$, λ_{max}^{EtOH} 217, 255, and 292 mμ (ϵ 43,000, 8,550, and 1,720 respectively).

Anal. Calculated for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.47; H, 7.27; N, 5.22.

5-Ethyl-8-hydroxycorydaldine (3,4-Dihydro-6,7-dimethoxy 5-ethyl-8-hydroxy-1-(2H)-isoquinolone (V).—Elution with chloroform–methanol (50:1) gave crystalline V (54 mg.), which, after recrystallization from ethyl acetate, melted at 177–179°. A sample sublimed at 0.05 mm. (170° bath) showed infrared bands at $\nu_{max}^{CCl_4}$ 3600, 3500, 1660, and 1580 cm.$^{-1}$ and ultraviolet absorption at λ_{max}^{EtOH} 220, 266 mμ (ϵ 37,500, 10,900 respectively) and gave a deep blue color with ferric chloride solution.

Anal. Calculated for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: 62.09; H, 6.84; N, 5.72.

3,4-Dihydro-5-ethyl-6,7,8-trihydroxy-1-(2H)-isoquinolone (VI).—5-Ethyl-8-methoxycorydaldine (IV) (375 mg.) was heated to reflux under nitrogen with 8 ml. of acetic acid and 2 ml. of 40% aqueous hydrogen bromide solution for 4 hr., and the solution evaporated to dryness *in vacuo*. The crystalline residue was triturated with ether and chloroform and recrystallized from 4 ml. of ethanol yielding 217 mg. (72%) VI, as colorless needles, m.p. 215–217°. An analytical sample was prepared by repeated recrystallization rom ethanol, m.p. 222–223°; ν_{max}^{KBr} 1640, 1615, 1600, 1510, cm.$^{-1}$, λ_{max}^{EtOH} 278 and 320 mμ (ϵ 9,900 and 3,100 respectively) dark blue color with alcoholic ferric chloride.

Anal. Calculated for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: 59.16; H, 5.96; N, 6.20.

3,4-Dihydro-1-methyl-6,7,8-trimethoxyisoquinoline Hydrochloride (VIII).—N-Carbethoxy-2-(2-acetyl-3,4,5-trimethoxyphenyl)ethylamine (II) (1 g.) was heated to reflux with 6 *N* hydrochloric acid (3 ml.) and ethanol (3 ml.) for 6 hr. The ethanol was evaporated and the residue diluted with water (10 ml.) and extracted with six 10-ml. portions of chloroform. After drying (sodium sulfate) the solvent was evaporated and the residue leached with ether. The insoluble part, VIII (375 mg.), melted at 156–158° after recrystallization from a mixture of acetonitrile and ethyl acetate and showed infrared bands at $\nu_{max}^{CHCl_3}$ 1650, 1600, and 1570 cm.$^{-1}$. The ether-soluble part was mostly unchanged starting material (II).

1-Methyl-1,2,3,4-tetrahydro-6,7,8-trimethoxyisoquinoline Hydrochloride (IX).—A mixture of VIII (160 mg.) and platinum oxide (50 mg.) in 5 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure. After one molecular equivalent of hydrogen was consumed (1 hr.), the reaction stopped; the catalyst was filtered off, and the solvent evaporated. The residue was recrystallized from ethyl acetate and gave 80 mg. of IX as colorless crystals melting at 148–150°. $\nu_{max}^{CHCl_3}$ 1600 and 1500 cm.$^{-1}$.

N-Carbethoxy-1-methyl-1,2,3,4-tetrahydro-6,7,8-trimethoxyisoquinoline (VII).—To a solution of IX (80 mg.) in 2 ml. of water was added ethyl chloroformate (0.05 ml.) and a few drops of 2 *N* sodium hydroxide. The mixture was shaken in a test tube for 30 min. and then extracted with chloroform. After drying over magnesium sulfate the solvent was evaporated to yield 90 mg. of VII as a colorless oil. The purity of the sample was substantiated by a single spot on a thin-layer chromatogram. The R_f value and the infrared spectrum were identical with those of VII, the less polar hydrogenation product of N-carbethoxy-2-(2-acetyl-3,4,5-trimethoxyphenyl)ethylamine (II) (see below).

When the hydrogenation of II was conducted in such a way that the reaction was slow, VII was the major product as exemplified by the following example: 10% palladium-on-charcoal catalyst (100 mg.) in acetic acid (5 ml.) was saturated with hydrogen at room temperature and a solution of II (300 mg.) was then added in 5 ml. of acetic acid and the hydrogenation continued for 3 days. Only 1 equivalent of hydrogen was consumed. The catalyst was removed by filtration and the solution evaporated under reduced pressure. After partitioning the residue between chloroform and saturated sodium bicarbonate solution, the organic layer was dried (magnesium sulfate) and the solvent evaporated. The crude product was chromatographed on 6 g. of acid-washed alumina (Merck). Benzene–pentane (1:1) mixture eluted pure XII. (240 mg.) as a colorless oil.

An analytical sample was prepared by short-path distillation at 160° and 0.05 mm.; $\nu_{max}^{CCl_4}$ 1700, 1600 cm.$^{-1}$.

Anal. Calculated for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.86; H, 7.58; N, 4.46.

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Migration of Terminal Double Bond in the Course of Huang-Minlon Reduction

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A synthesis of the hitherto unknown 16-heptadecenoic acid (VII) was attempted, because this acid was regarded as a potential intermediate for the preparation of several lipide materials. The reaction sequence is illustrated in the flow sheet. However, the unexpected 15-heptadecenoic acid (V) was obtained as a result of double bond migration in the Huang-Minlon reduction.[1]

The 2-acylcyclohexanone (III) was prepared from 10-undecenoyl chloride (I) and *N*-(1-cyclohexenyl)morpholine (II) according to the pro-

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[1] Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).