present study, it is concluded that a large proportion of the methyl groups, which are transferred from methionine, are transferred through a transmethylation process. This work, along with the finding[4,5] that the methoxyl groups of lignin can arise from the direct transfer of methyl groups from methionine, indicates the generality of the transmethylation reaction in higher plants.

The question as to whether this transmethylation actually represents a net biosynthesis of nicotine still remains unproved. Since it has been shown that nicotine is synthesized mainly in the roots,[12] one approach to this question would be to ascertain whether or not a net synthesis of nicotine could be obtained by incubating root enzyme preparations with methionine and nornicotine. Such a study is in progress at the present time in this Laboratory, and the results will be forthcoming at a later date.

(12) R. F. Dawson, *Am. J. Botany*, **29**, 66 (1942).

EAST LANSING, MICHIGAN

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Hypotensive Methoxyisoquinolines

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Dehydronorcoralydine iodide (II) was synthesized. Hydrochlorides of 3-(3′,4′-dimethoxyphenyl)-6,7-dimethoxyisoquinoline, 1-methyl-4-(3′,4′-dimethoxyphenyl)-6,7-dimethoxyisoquinoline, 1-methyl-4-phenyl-6,7-dimethoxyisoquinoline, 1-methyl-6,7-dimethoxyisoquinoline and 5-methyl-2,3,10,11-tetramethoxybenzo[a]phenanthridine (IX) were prepared by phosphorus oxychloride cyclization of appropriate amides, dehydrogenation and treatment with hydrogen chloride. These compounds elicited a lowering of blood pressure in normal dogs. Certain modified procedures for synthesis of the compounds and their precursors are described.

It has been reported[1] that the alkaloid palmatine (I) effects a lowering of blood pressure and at the same time paralyzes the central nervous system and respiratory center, upon intravenous administration in mammals. Two related monophenolic alkaloids, jateorhizine and columbamine,[2] also produce these effects to a lesser extent. These facts prompted an investigation of the chemistry and pharmacology of several related classes of compounds incorporating methoxyl groups and the isoquinoline ring system.

Dehydronorcoralydine iodide (II) which differs from palmatine only in the position of one methoxyl group, was synthesized by the method of Pictet and Chou,[3] consisting of dehydrogenation of norcoralydine with iodine. Norcoralydine was prepared by cyclization of tetrahydropapaverine with formaldehyde in the presence of hydrochloric acid, according to the directions of Craig and Tarbell.[4] This cyclic condensation gave, in our hands, two different forms of norcoralydine, both of which led to the same dehydroiodide when treated with iodine. In the preparation of tetrahydropapaverine, hydrogenation of the carbon–nitrogen double bond and hydrogenolysis of the carbonyl group of 3,4-dihydropapaveraldine were accomplished in one step by the use of palladium–charcoal catalyst in glacial acetic acid at 80°, a method apparently not used heretofore in obtaining tetrahydroisoquinolines.

Compound IV, a 3-arylisoquinoline closely related in structure to dehydronorcoralydine, was obtained by cyclization of the amide IIIa with phosphorus oxychloride, followed by dehydrogenation (palladium). The substituted formamide IIIa was prepared from 3,4,3′,4′-tetramethoxydesoxybenzoin by the Leuckart reaction. In contrast to the formamide, the corresponding acetamide IIIb did not cyclize when treated with phosphorus oxychloride under the same conditions, but instead appeared to undergo elimination of acetamide at least in part, with the formation of 3,4,3′,4′-tetramethoxystilbene. The difference in behavior of IIIa and IIIb in the presence of phosphorus oxychloride cannot be explained readily.

Two methoxylated 1-methyl-4-phenylisoquinolines, VIa and VIb, were prepared by a series of steps as follows: Reformatsky reaction of 3,4,3′,4′-tetramethoxybenzophenone and 3,4-dimethoxybenzophenone with ethyl bromoacetate and hydrogenolysis of the resulting hydroxyesters provided ethyl β,β-diarylpropionates, which were converted quantitatively to the corresponding acid hydrazides by means of anhydrous hydrazine. The corresponding acid azides were prepared from the acid hydrazides by reaction with nitrous acid. The acid azides rearranged smoothly in the presence of acetic acid and acetic anhydride and afforded the N-substituted acetamides Va and Vb, respectively. This procedure also was employed in preparing IIIb from ethyl α,β-di-(3,4-dimethoxyphenyl)-propionate. Cyclization of Va and Vb with phosphorus oxychloride and dehydrogenation (palladium) of the resulting 3,4-dihydroisoquinolines gave VIa and VIb, respectively. A methoxylated tetrahydrobenzophenanthridine VIII was prepared from 1-(3′,4′-dimethoxyphenyl)-2-carbethoxy-6,7-dimethoxytetralin by the same series of steps, involving Curtius rearrangement of the corresponding acid azide and cyclization of amide VII. Palladium dehydrogenation of VIII led to elimination of two molecules of hydrogen and the formation of the fully aromatic structure IX, while hydrogenation

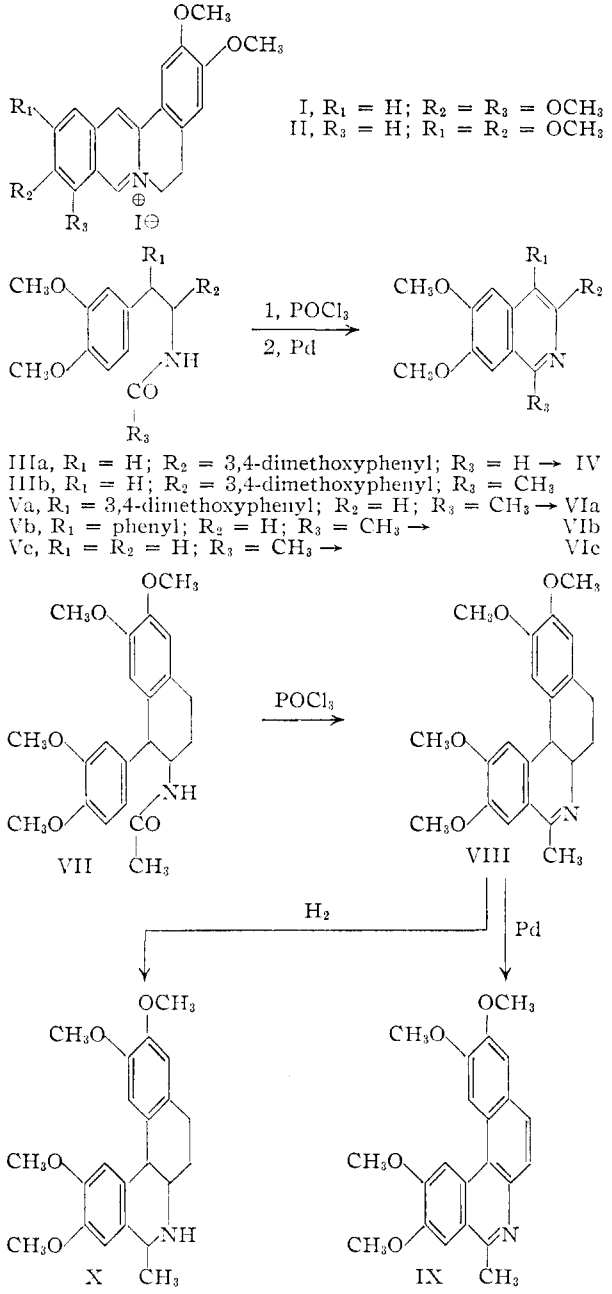
(1) J. Biberfeld, *Zeit. exp. Path. Pharm.*, **7**, 569 (1910).

(2) For the structures of these three alkaloids, *cf.* E. Späth and coworkers, *Ber.*, **58**, 1939, 2267 (1925); **59**, 1486 (1926), and earlier references.

(3) A. Pictet and T. Q. Chou, *Ber.*, **49**, 370 (1916).

(4) L. E. Craig and D. S. Tarbell, THIS JOURNAL, **70**, 2783 (1948).

CHART I



of VIII resulted in absorption of one molecule of hydrogen and formation of X. Thus it was apparent that no dehydrogenation accompanied the cyclization of VII.

The substituted isoquinolines, IV, VIa and VIb, the benzphenanthridine, IX, and the simple model pound, 1-methyl-6,7-dimethoxyisoquinoline, VIc (prepared as described in the Experimental part), were converted to hydrochlorides. An ethiodide was also prepared from VIa. In contrast with VIa, compound IV did not form an ethiodide when refluxed with ethyl iodide, probably because of steric effects. Compound IX gave an unstable ethiodide which decomposed upon attempted recrystallization.

The isoquinolinium salts were administered intravenously to anesthetized normal dogs in trial experiments, and their effects on blood pressure, acetylcholine, epinephrine, histamine and ganglionic function were observed. None of the compounds behaved as antihistamines, and only compound II affected acetylcholine, exerting a blocking action at a dose level of 7 mg. per kg. All the salts depressed blood pressure to some extent (see Table I). In this respect, the hydrochlorides of VIa and IX were more potent and had fewer side-effects and greater margins of safety than the other compounds which were studied. It is noteworthy that the hypotensive action of II and of the hydrochlorides of VIa and VIb appeared to be due in part to some mechanism, as yet not ascertained, other than adrenergic blockade, while the ethiodide of VIa was a strong adrenergic blocking agent. Ethiodides other than that of VIa were not administered, owing to low solubilities. Compounds II and IV appeared to act primarily as ganglionic blocking agents.

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Experimental[5]

1-(3′,4′-Dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (3,4-Dihydropapaveraldine).—Cyclization of 40 g. (0.111 mole) of N-(3,4-dimethoxyphenylacetyl)-homoveratrylamine with 100 ml. of phosphorus oxychloride in 800 ml. of toluene (3-hour reflux) and decomposition of the complex with excess potassium hydroxide in absolute ethanol gave, after dilution of the solution with water and trituration of the product with methanol, 30 g. (76%) of crystals, m.p. 185–189°. Recrystallization from ethyl acetate gave colorless crystals, m.p. 190–192° (reported[6] m.p. 190–191°).

The infrared spectrum (chloroform) had a peak at 6.03 μ and a multiplet in the region 6.25–6.40 μ, and thus it was apparent that oxidation of the methylene group of the initial product (dihydropapaverine) had occurred.

1,2,3,4-Tetrahydropapaverine Hydrochloride.—A mixture of 30 g. (0.0845 mole) of 3,4-dihydropapaveraldine, 4.5 g. of 10% palladium–charcoal catalyst, and 250 ml. of glacial acetic acid was shaken under hydrogen (40 lb.) at 80° for 5 hours. The catalyst was renewed twice during this period. Approximately two molecular equivalents of hydrogen (14 lb.) was absorbed in 40 minutes, and the remainder (4 lb.) was absorbed much more slowly. The catalyst was filtered and the acetic acid was evaporated. The residual viscous oil was dissolved in ether–methanol, and the solution was saturated at ice temperature with hydrogen chloride. The crystals were collected, triturated with absolute ethanol and air-dried. The yield of hydrochloride, m.p. 195–206°, was 22.2 g. (67%). Recrystallization from methanol afforded colorless crystals, m.p. 212–214° dec. (reported[4] m.p. 216°).

Norcoralydine.—A solution of 21 g. (0.054 mole) of tetrahydropapaverine hydrochloride in 300 ml. of water and 7 ml. of concentrated hydrochloric acid was treated with 20 ml. of formaldehyde and was heated on a steam-cone for an hour. The solution was diluted with 400 ml. of water, chilled and treated with excess potassium hydroxide. After the mixture had been refrigerated overnight, the solid material was collected, washed with cold water and pressed dry. The product was triturated with 150 ml. of warm methanol. The filtrate was evaporated, and the residue was recrystallized from 75 ml. of methanol. There was obtained 7.3 g. (37%) of crystals, m.p. 151–156°. Further recrystallization from methanol gave colorless crystals, m.p. 159–161° (reported m.p. 158–159°[4]; m.p. 157–158°[3]; m.p. 151.5–152.5°[7]).

(5) Melting points are corrected.

(6) J. S. Buck, R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 2184 (1924).

(7) E. Späth and R. Kruta, *Monatsh.*, **50**, 341 (1928).

TABLE I

Compound	Blood pressure fall, mg./kg.	Epinephrine block, mg./kg.	TMA block, mg./kg.	Fatal dose, mg./kg.	Other effects
II	Slight: 1.0 Marked: 31	15 (partial)	7 (partial)	63	Tachycardia
IV (HCl)	Slow: 50	None	15 (partial)	>50	.....
VIa (HCl)	Sustained: 3.0 and up	31	31	>63	Convulsions at 31; tachycardia
VIa[a] (EtI)	Slight: 7.0 Marked: 15	7 (rapid recovery)	7 (partial) 15 (complete)	76	Tachycardia
VIb (HCl)	Moderate, transient: 7.0	31 (partial)	31	>57	.....
VIc (HCl)	Slight: 3.0 Moderate, sustained: 31	53	53 (slight)	>53	.....
IX (HCl)	Moderate: 1.0 and up	7.0 and up (partial)	15 (partial)	>31	.....

[a] Injected as warm suspension, concn. 0.25%.

Anal. Calcd. for $C_{21}H_{25}O_4N \cdot {}^1/_2H_2O$: C, 69.21; H, 7.19; N, 3.84. Found: C, 69.48; H, 7.22; N, 3.79.

The crystals which remained insoluble in methanol weighed 8.0 g. (41%), and had m.p. 174–197° dec. Recrystallization from ethyl acetate gave 5.6 g. of slightly greenish crystals, m.p. 202–205°. Further recrystallization raised this m.p. to 203–206° (partial dec.).

Anal. Found: C, 68.27; H, 7.07; N, 3.78.

The infrared spectra of these products (chloroform) were devoid of absorption bands (other than C–H) below 6.2 μ, with the exception of a weak band at 2.82–2.85 μ (HOH). They were very similar in other respects, with minor differences in the 7.2 μ, 9.1 μ, and "fingerprint" regions. Both materials gave the same product when treated with iodine (see below).

Dehydronorcoralydine Iodide (II).—A solution of 2.0 g. of norcoralydine in 300 ml. of absolute ethanol was treated with 5.5 g. of iodine, and the mixture was refluxed for 4 hours. After chilling the mixture, the solid material was collected, and was triturated with several portions of warm ethyl acetate. The deep red, crystalline complex had a decomposition point at 223–226°, and could not be recrystallized successfully, owing to decomposition. When the complex was warmed with aqueous sodium bisulfite, the red color disappeared and yellow crystals were formed. These were collected, washed with dilute hydrochloric acid and water, air-dried, and recrystallized from methanol. The iodide (1.4 g.) consisted of yellow crystals, m.p. 253–255° dec. (varied with rate of heating), which appeared to be solvated (reported[8] for anhydrous salt, m.p. 252.5°). Attempts to recrystallize the compound from other solvents did not lead to pure, anhydrous material.

The higher-melting material obtained concomitantly with norcoralydine in the preceding experiment was treated with iodine in the same way. The red complex iodide, after trituration with ethyl acetate, had decomposition point 222.5–226°; the mixed d.p. with the complex obtained as described above was not depressed. Treatment of the complex with sodium bisulfite gave yellow crystals, m.p. 252–254° dec. from methanol; the mixed m.p. with the first sample of dehydroiodide was 252–255° dec. (undepressed).

3,4,3',4'-Tetramethoxydesoxybenzoin.—This ketone was prepared by the reaction of homoveratroyl chloride with veratrole in the presence of anhydrous aluminum chloride in carbon disulfide, and was purified by distillation *in vacuo*. The yield of ketone, b.p. 240–270° (1.0 mm.), was 31%. Further purification was effected by recrystallization from methanol; colorless crystals, m.p. 104–106° (reported[8] m.p. 107°).

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; red-orange crystals, m.p. 197–199°.

Anal. Calcd. for $C_{24}H_{24}O_8N_4$: C, 58.06; H, 4.87. Found: C, 58.12; H, 5.02.

The oxime was prepared by reaction of the ketone with hydroxylamine hydrochloride in pyridine, and was recrystallized from methanol; colorless crystals, m.p. 129–131° (reported[8] m.p. 128°). Attempts to reduce this oxime to an amine by hydrogenation in the presence of palladium–charcoal in ethanol and ethyl acetate gave products which were not identical with α,β-di-(3,4-dimethoxyphenyl)-ethylamine (see below).

α-(3,4-Dimethoxyphenyl)-3,4-dimethoxycinnamic Acid.—A mixture of 81 g. (0.49 mole) of veratraldehyde, 101 g. (0.52 mole) of homoveratric acid, 50.5 g. (0.52 mole) of potassium acetate and 230 ml. of acetic anhydride was refluxed for 2 hours. After dilution of the solution with 100 ml. of methanol and 2000 ml. of water, the product was collected, washed with water, pressed dry, and triturated with ether. The yield of crystals, m.p. 204–213°, was 98 g. (58%). Recrystallization from ethyl acetate gave colorless crystals, m.p. 216–217°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.86. Found: C, 65.82; H, 6.15.

α,β-Di-(3,4-dimethoxyphenyl)-propionic Acid and Ethyl Ester.—Hydrogenation of the acid from the preceding experiment in the presence of 5% palladium–charcoal catalyst in glacial acetic acid at 70° resulted, after filtration of the catalyst and evaporation of the solvent, in a quantitative yield of crude product, suitable for esterification. Recrystallization from methanol gave colorless crystals, m.p. 143–145°.

Anal. Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.98; H, 6.48.

Esterification of 83 g. of this acid with absolute ethanol in the presence of 5% of concentrated sulfuric acid in the usual way afforded 73 g. (81%) of crude ester, as an oil. This material was suitably pure for conversion to the acid hydrazide.

3,4-Dimethoxybenzophenone (4-Benzoylveratrole).—A condensation was carried out using 81.5 g. (0.58 mole) of benzoyl chloride, 69.5 g. (0.502 mole) of veratrole and 89 g. of anhydrous aluminum chloride in 300 ml. of carbon disulfide. After decomposition of the complex with ice and water, the neutral product was recrystallized from methanol in two crops. There was obtained 83 g. (68%) of crystals, m.p. 98–100° (reported[9] m.p. 99°).

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; red crystals, m.p. 256–257°.

Anal. Calcd. for $C_{21}H_{18}O_6N_4$: C, 59.71; H, 4.30. Found: C, 59.62; H, 4.29.

Ethyl β-Phenyl-β-(3,4-dimethoxyphenyl)-propionate.—A Reformatsky reaction was carried out in the usual way using 41.3 g. (0.171 mole) of 4-benzoylveratrole, 36 g. (0.216 mole) of ethyl bromoacetate and 50 g. of activated, 30-mesh zinc in 500 ml. of dry benzene, refluxing for 4 hours. The complex was decomposed with dilute acetic acid, and the neutral product was isolated as usual. Hydrogenation of this material, an oil, at 40 lb. in the presence of 10% palladium–charcoal catalyst in glacial acetic acid at 80° resulted in the absorption of one molecular equivalent of hydrogen, and gave, after filtration of the catalyst and evaporation of the solvent, a quantitative yield of orange oil, suitably pure for conversion to the acid hydrazide.

Ethyl β,β-Di-(3,4-dimethoxyphenyl)-propionate.—This ester was prepared as described previously.[10] The crude ester was used in the next step.

1-(3',4'-Dimethoxyphenyl)-2-carbethoxy-6,7-dimethoxytetralin.—This ester was prepared as described previously.[10]

N-Formyl-α,β-di-(3,4-dimethoxyphenyl)-ethylamine (IIIa).—A mixture of 23 g. (0.073 mole) of 3,4,3',4'-tetramethoxydesoxybenzoin, 200 ml. of formamide, 100 ml. of 90% formic acid and 50 g. of ammonium formate was distilled until the reflux temperature reached 165°, and was refluxed for 9 hours. The mixture was cooled and was diluted with 3000

(8) I. A. Allen and J. S. Buck, THIS JOURNAL, **52**, 310 (1930).

(9) F. Bruggemann, *J. prakt. Chem.*, [2] **53**, 253 (1896).

(10) G. N. Walker, THIS JOURNAL, **75**, 3387 (1953).

ml. of water. The crystals were collected, washed with water and recrystallized from methanol. The yield of crystals, m.p. 138–141°, was 14 g. (56%). Further recrystallization from methanol gave colorless crystals, m.p. 141–143°.

Anal. Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71. Found: C, 65.99; H, 6.87.

The infrared spectrum (chloroform) had peaks at 2.95 and 5.94 μ.

General Procedure in Preparation of Acid Hydrazides.—The four esters, obtained as described above, were refluxed in turn with two parts by weight of anhydrous hydrazine for 3 hours. The cooled solutions were poured into 20 volumes of ice-water. The crystals were collected in each case, washed with several portions of water and dried *in vacuo* at room temperature. Quantitative yields of the crude products were obtained, and it was not necessary to dry or further purify the hydrazides before proceeding to the next step. In each case a sample of the compound was recrystallized from methanol for analysis.

α,β-Di-(3,4-dimethoxyphenyl)-propionhydrazide: colorless crystals, m.p. 140–142°.

Anal. Calcd. for $C_{19}H_{24}O_5N_2$: C, 63.32; H, 6.71. Found: C, 63.12; H, 6.79.

β,β-Di-(3,4-dimethoxyphenyl)-propionhydrazide: colorless crystals, m.p. 240–242°.

Anal. Calcd. for $C_{19}H_{24}O_5N_2$: C, 63.32; H, 6.71. Found: C, 63.18; H, 6.78.

β-Phenyl-β-(3,4-dimethoxyphenyl)-propionhydrazide: colorless crystals, m.p. 113–115°.

Anal. Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71. Found: C, 68.15; H, 6.82.

1-(3′,4′-Dimethoxyphenyl)-2-carboxy-6,7-dimethoxytetralin hydrazide: colorless, hygroscopic crystals, m.p. 180–181° (dried at 100° *in vacuo*).

Anal. Calcd. for $C_{21}H_{26}O_5N_2 \cdot {}^1/_2H_2O$: C, 63.78; H, 6.88; N, 7.09. Found: C, 63.53; H, 6.96; N, 7.07.

Each of these acid hydrazides had infrared absorption bands at 2.94 and 5.98 μ (chloroform).

General Procedure in Preparation and Rearrangement of Acid Azides.—In each case, the acid hydrazide (0.10 mole) was dissolved in a solution consisting of 300 ml. of glacial acetic acid, 200 ml. of concentrated hydrochloric acid and 200 ml. of water. Ether (600 ml.) was added to form a second phase. The mixture was chilled to ice temperature and was stirred, while adding 20 g. of sodium nitrite gradually over a period of 30 minutes. The mixture was diluted with a liter of ice-water, and more ether (400 ml.) was added. After shaking the mixture, the layers were separated. The organic solution was washed with water (4 portions), 3% sodium hydroxide (until alkaline) and with successive portions of dilute acetic acid, sodium bicarbonate solution and water. The solution was dried over magnesium sulfate. Glacial acetic acid (75 ml.) and acetic anhydride (50 ml.) were added immediately, and the solution was distilled cautiously to remove the ether. The residual liquid was refluxed for 2 hours, and the excess reagents were evaporated. The product crystallized in each case after cooling and adding an equal volume of ether containing a little methanol, and was collected and weighed at this point.

N-Acetyl-α,β-di-(3,4-dimethoxyphenyl)-ethylamine (IIIb).—The yield of material, m.p. 148–165°, was 61% from α-(3,4-dimethoxyphenyl)-3,4-dimethoxycinnamic acid. Recrystallization from ethyl acetate gave colorless crystals, m.p. 160–163° (reported[8] m.p. 160–162°).

The infrared spectrum (chloroform) had bands at 2.94 and 6.00 μ.

Hydrolysis of the amide with potassium hydroxide in aqueous diethylene glycol for four hours gave **α,β-di-(3,4-dimethoxyphenyl)-ethylamine**; colorless crystals from ethyl acetate, m.p. 106–110° (reported[8] m.p. 107°).

N-Acetyl-β,β-di-3,4-dimethoxyphenyl)-ethylamine (Va).—The yield of material, m.p. 124–127°, was 52% from 3,4,-3′,4′-tetramethoxybenzophenone. Recrystallization from methanol gave colorless crystals, m.p. 129–131°.

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01. Found: C, 67.00; H, 6.96.

The infrared spectrum (chloroform) had peaks at 2.94 and 6.01 μ.

N-Acetyl-β-phenyl-β-(3,4-dimethoxyphenyl)-ethylamine (Vb).—The yield of material, m.p. 152–154°, was 46% from 4-benzoylveratrole. Recrystallization from methanol afforded colorless crystals, m.p. 154–156°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 72.19; H, 7.09.

1-(3′,4′-Dimethoxyphenyl)-2-acetylamino-6,7-dimethoxytetralin (VII).—The yield of compound, m.p. 217–220°, was 73% from the acid hydrazide. Recrystallization from methanol gave pale green crystals, m.p. 222–223.5°.

Anal. Calcd. for $C_{22}H_{27}O_5N$: C, 68.55; H, 7.06. Found: C, 68.37; H, 7.19.

The infrared spectrum (chloroform) had peaks at 2.90 and 6.00 μ.

General Procedure in Cyclization of Amides to 3,4-Dihydroisoquinolines.—In each case, a mixture of the amide and dry toluene (volume in ml. equal to 40 times the weight of the amide in grams) was boiled until the amide dissolved, the heating was discontinued and phosphorus oxychloride (volume in ml. equal to twice the weight of the amide) was added to the warm solution. After the spontaneous action subsided, the solution was refluxed for 2–3 hours, until hydrogen chloride was no longer evolved. The cooled solution was diluted with 15 volumes of pentane, and the complex which separated was collected and dissolved in the minimum amount of hot absolute ethanol. The hot solution was treated with solid potassium hydroxide until a strong alkaline reaction persisted, and was cooled and diluted with cold water until no further separation of material occurred. The product was extracted with ether–ethyl acetate (2–4 portions), and the organic solution was washed with two portions of water. After drying the solution, the solvents were evaporated at 70°.

General Procedure in Dehydrogenation of 3,4-Dihydroisoquinolines to Isoquinolines.—A mixture of the compound, an equal weight of 10% palladium–charcoal catalyst and *p*-cymene (volume in ml. equal to 100 times the weight of the compound) was distilled until the reflux temperature rose to 175°, and was refluxed for 2–4 hours. The mixture was filtered while hot, and the solution was recharged with catalyst. After refluxing for an additional 3 hours, and a second filtration, the cymene was removed by evaporation. At this point the isoquinoline crystallized in some cases, alone or with the aid of methanol. If the product failed to crystallize, it was converted directly to the hydrochloride, by dissolving it in methanol–ethyl acetate and introducing dry hydrogen chloride.

3-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline (IV).—Cyclization of 7.0 g. of N-formyl α,β-di-(3,4-dimethoxyphenyl)-ethylamine afforded 3.0 g. of crude material as a brown, viscous oil. Dehydrogenation gave, after trituration with methanol, 1.2 g. (18%) of material, m.p. 204–209°. Recrystallization from the same solvent led to brilliant, pale-yellow leaflets, m.p. 212–214°. The infrared spectrum (chloroform) had a peak at 6.15 μ.

Anal. Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.00; H, 5.96; N, 4.35.

The hydrochloride was recrystallized from methanol; yellow crystals, m.p. 232–235°, after drying at 80° *in vacuo*.

Anal. Calcd. for $C_{19}H_{20}O_4NCl \cdot {}^1/_4H_2O$: C, 62.38; H, 5.64; N, 3.83; Cl, 9.69. Found: C, 62.36; H, 5.72; N, 3.87; Cl, 9.41.

The isoquinoline did not form an ethiodide when refluxed with ethyl iodide for 3 hours.

1-Methyl-4-(3′,4′-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (VIa).—Cyclization of 4.5 g. of amide Va afforded, after trituration with methanol, 3.5 g. (82%) of the **3,4-dihydro**-compound as discolored crystals, m.p. 75–80°. Recrystallization from methanol gave colorless crystals, m.p. 87–89°. The infrared spectrum (chloroform) had a peak at 6.14 μ. The base was soluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.56; H, 6.77; N, 4.06.

Dehydrogenation of this dihydroisoquinoline (3.5 g.) gave, after trituration with methanol, 1.4 g. (40%) of crystals, m.p. 205–207°. Recrystallization from the same solvent led to pale greenish-yellow crystals, m.p. 206–208°. The infrared spectrum (chloroform) had a peak at 6.14 μ.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.52; H, 6.20; N, 4.14.

The hydrochloride was recrystallized from ethanol; pale yellow needles, m.p. 206–207° dec., after drying at 80° *in vacuo*.

Anal. Calcd. for $C_{20}H_{22}O_4NCl \cdot {}^1/_2H_2O$: C, 62.41; H, 6.02; N, 3.64; Cl, 9.21. Found: C, 62.62; H, 5.92; N, 3.58; Cl, 9.23.

The ethiodide was prepared by refluxing the isoquinoline with a large excess of ethyl iodide for 1.5 hours. The salt separated gradually as yellow crystals. Recrystallization from methanol gave bright yellow crystals, m.p. 219–223° dec., which could not be analyzed successfully due to their hygroscopic properties.

1-Methyl-4-phenyl-6,7-dimethoxyisoquinoline Hydrochloride (VIb·HCl).—Cyclization of 19.5 g. of amide Vb afforded 18 g. of viscous, red oil, the infrared spectrum of which had bands at 5.80 and 6.15 μ, the latter predominating. The oil was soluble in dilute hydrochloric acid. Aromatization of 17 g. of this crude material gave, after evaporation of the cymene, a greenish, glassy substance. This was dissolved in methanol–ethyl acetate and treated with hydrogen chloride at ice temperature. The crystals were collected and were recrystallized from ethyl acetate containing the minimum amount of methanol. The yield of material, m.p. 173–175° dec., was 6.5 g. (33%). Further recrystallization from the same solvents gave colorless needles, m.p. 183–185° dec., after drying at 80° *in vacuo*.

Anal. Calcd. for $C_{18}H_{18}O_2NCl \cdot {}^1/_2H_2O$: C, 66.50; H, 5.90; N, 4.31; Cl, 10.92. Found: C, 66.75; H, 6.03; N, 4.23; Cl, 10.72.

1-Methyl-6,7-dimethoxyisoquinoline (VIc).—Cyclization of 14.2 g. of N-acetyl-β-(3,4-dimethoxyphenyl)-ethylamine gave 3.6 g. (26%) of **1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline**, m.p. 85–96°. Recrystallization from cyclohexane raised the melting point to 102–104° (reported[11] m.p. 106–107°). The infrared spectrum (chloroform) had a peak at 6.15 μ. The base was moderately soluble in water.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.21; H, 7.54; N, 6.84.

Dehydrogenation of 3.2 g. of the dihydroisoquinoline gave green, glassy material, which was treated with hydrogen chloride in methanol–ethyl acetate. The hydrochloride was collected at ice temperature; 2.5 g. (67%) of crystals, m.p. 219–221° dec. Recrystallization from methanol–ethyl acetate led to colorless crystals having a green cast, m.p. 226–228° dec.

Anal. Calcd. for $C_{12}H_{14}O_2NCl$: C, 60.12; H, 5.89; N, 5.84; Cl, 14.79. Found: C, 60.28; H, 5.92; N, 5.85; Cl, 14.86.

5-Methyl-2,3,10-11-tetramethoxy-7,8,15,16-tetrahydrobenzo[a]phenanthridine (VIII) (R.I. 2743).—Cyclization of 7.2 g. of amide VII gave 6.2 g. (91%) of discolored crystals, m.p. 157–160°. Recrystallization from ethyl acetate led to colorless crystals having a green-yellow cast, m.p. 160–162°. The infrared spectrum (chloroform) had a peak at 6.21 μ with shoulders at 6.07 and 6.18 μ. The compound was soluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.05; H, 6.95; N, 3.75.

5-Methyl-2,3,10,11-tetramethoxybenzo[a]phenanthridine (IX) (R. I. 2743).—Dehydrogenation of 2.3 g. of crude VIII afforded, after trituration with methanol, 1.6 g. (70%) of crystals, m.p. 191–193°. Recrystallization from methanol did not raise this melting point. The infrared spectrum (chloroform) had a peak at 6.18 μ.

Anal. Calcd. for $C_{22}H_{21}O_4N$: C, 72.71; H, 5.83. Found: C, 72.48; H, 5.84.

The hydrochloride was recrystallized from methanol; yellow needles, m.p. 224–225°. It was readily soluble in water.

Anal. Calcd. for $C_{22}H_{22}O_4NCl$: C, 66.08; H, 5.55; N, 3.50; Cl, 8.87. Found: C, 65.86; H, 5.86; N, 3.48; Cl, 8.87.

The ethiodide, prepared by refluxing IX with ethyl iodide for three hours, returned to IX when warmed in methanol.

5-Methyl-2,3,10,11-tetramethoxy-5,6,7,8,15,16-hexahydrobenzo[a]phenanthridine (X).—Hydrogenation of VIII in glacial acetic acid in the presence of 5% palladium–charcoal catalyst at 40 lb. and 70° for an hour resulted in the formation of semi-crystalline, hygroscopic material. This material was triturated with ethyl acetate, and was converted to the **hydrochloride** by treatment with hydrogen chloride in methanol–ethyl acetate. Recrystallization from methanol gave colorless crystals, m.p. 263–265° dec.

Anal. Calcd. for $C_{21}H_{28}O_4NCl$: C, 65.09; H, 6.95; N, 3.45. Found: C, 64.70; H, 7.03; N, 3.34.

Attempted Cyclization of Amide IIIb.—When 22 g. of IIIb was refluxed with 40 ml. of phosphorus oxychloride in 500 ml. of dry toluene for 4 hours, and the product isolated as usual, there was obtained 11 g. of material which crystallized partially. The crystals were triturated with methanol and recrystallized from the same solvent. There was obtained 4.5 g. of colorless crystals, m.p. 157–159°. Neither this compound nor the glassy material remaining after evaporation of the filtrates was found to contain nitrogen. Melting points 155°[12] and 153°[13] have been recorded for 3,4,3′,4′-tetramethoxystilbene. The crystals obtained in this experiment appeared to contain a small amount of nonnitrogenous impurity which was difficult to remove by recrystallization. Further recrystallization from methanol did not raise the melting point.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.50; H, 6.65.

The infrared spectrum (chloroform) had a doublet at 6.22–6.27 μ. The compound did not react with 2,4-dinitrophenylhydrazine.

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