The Synthesis of Imenine. A Route to 4-Oxygenated Oxoaporphines

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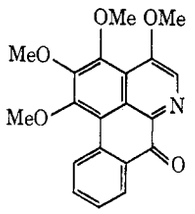
The alkaloid imenine (1) has been synthesized. This work represents the first synthesis of an oxoaporphine base containing a 4-oxygenated function.

The yellow alkaloid imenine occurs in the woody stems of the Amazonian vines *Abuta imene*[1] and *A. rufescens*[2] (Menispermaceae). An X-ray crystallographic analysis has shown that imenine has structure **1**,



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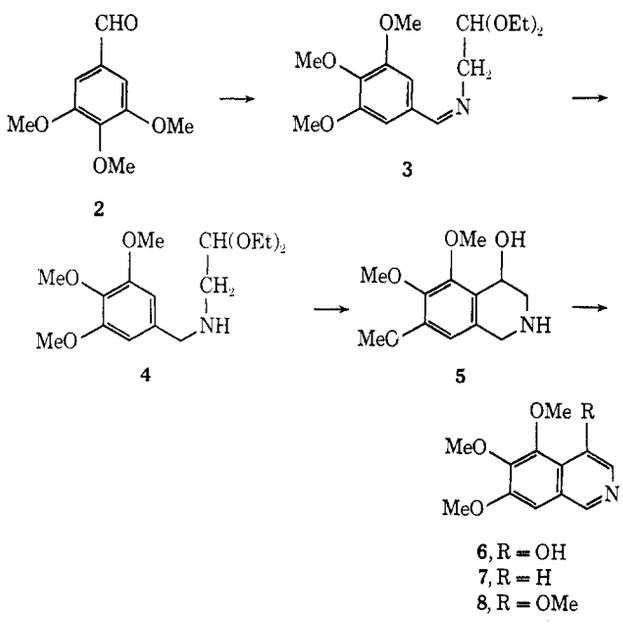
making it the first example of a 4-oxygenated oxoaporphine base.[1] We now report the first synthesis of imenine; this work represents also the only synthesis of any natural 4-oxygenated aporphine.[3]

Results

Condensation of 3,4,5-trimethoxybenzaldehyde (**2**) with aminoacetaldehyde diethyl acetal gave the Schiff base **3**, which was directly hydrogenated to *N*-(3,4,5-trimethoxybenzyl)aminoacetaldehyde diethyl acetal (**4**). Hydrolytic cyclization of **4** by aqueous hydrochloric acid was carried out according to the general procedure of Bobbitt[4] to give 4-hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**5**), mp 138–139.5°, in 61% yield based on aldehyde **2**. When the alcohol **5** was heated with 10% palladium on charcoal in *p*-cymene at 140–145°, a fair yield (23%) of the phenolic dehydrogenation product, 4-hydroxy-5,6,7-trimethoxyisoquinoline (**6**), mp 116–117°, was obtained; 5,6,7-trimethoxyisoquinoline (**7**)[5] was also isolated in 18% yield. Methylation of phenol **6** with diazomethane gave 4,5,6,7-tetramethoxyisoquinoline (**8**), mp 96°.

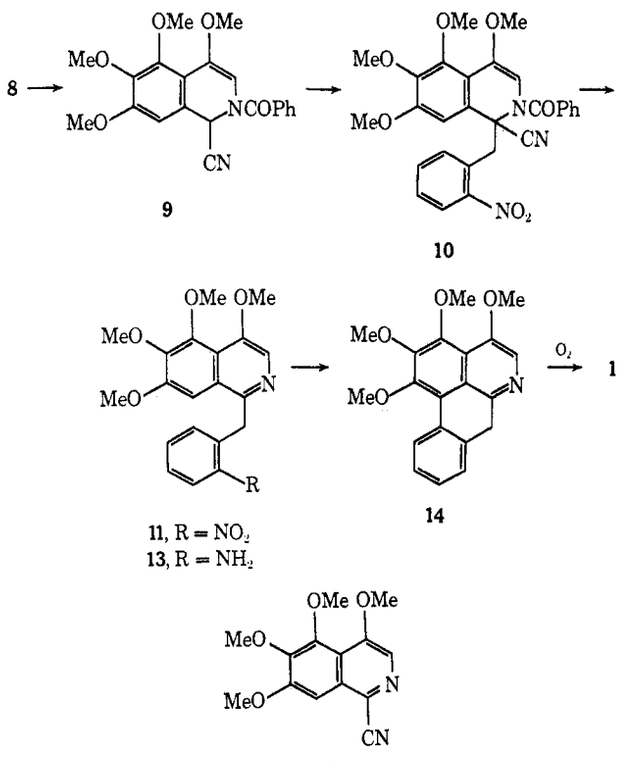


2 **3** **4** **5**

6, R = OH
7, R = H
8, R = OMe

Elaboration of **8** to imenine was effected by use of the Reissert method.[6] Thus, treatment of **8** with benzoyl chloride and potassium cyanide afforded the Reissert compound **9**, mp 136–137°, in 51% yield. Alkylation of **9** by *o*-nitrobenzyl chloride, followed by direct Triton B hydrolysis[5,7] of the intermediate **10**, afforded 1-(2-nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (**11**), mp 118–119°, in 38% yield; 1-cyano-4,5,6,7-tetramethoxyisoquinoline (**12**), mp 138–139°, was obtained as a by-product in this reaction.

The conventional approach to imenine from **11** required, as the next step, oxidation of **11** to the corresponding ketone. Attempts to carry out this oxidation using chromic acid under varied conditions led to failure; either **11** was recovered unchanged or overoxidation to highly polar products took place. The desired synthesis was completed, however, by reducing **11** to the corresponding amine **13**, and then subjecting **13** to the usual Pschorr cyclization conditions. The product directly isolated from the Pschorr reaction was not the expected bisdehydroaporphine **14**, but rather imenine



9 **10** **14**

11, R = NO_2
13, R = NH_2

12

(1) M. D. Glick, R. E. Cook, M. P. Cava, M. Srinivasan, J. Kunitomo, and A. I. daRocha, *Chem. Commun.*, 1217 (1969).

(2) K. T. Buck, unpublished observations.

(3) Only two other natural bases of this type have been reported: (a) J. Kunitomo, Y. Okamoto, E. Yuge, and Y. Nagai, *Tetrahedron Lett.*, 3287 (1969); (b) I. Ribas, J. Sueiras, and L. Castedo, *ibid.*, 2033 (1972).

(4) J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, **33**, 856 (1968).

(5) M. P. Cava and M. V. Lakshmikantham, *ibid.*, **35**, 1867 (1970).

(6) F. D. Popp and W. E. McEwen, *J. Amer. Chem. Soc.*, **79**, 3773 (1957).

(7) M. P. Cava and M. Srinivasan, *Tetrahedron*, **26**, 4649 (1970).

(1), identical in all respects with the natural alkaloid. The yield of imenine based upon nitro compound **11** was remarkably good (35%).

Discussion

The imenine synthesis described above contains several novel steps which are worthy of comment.

The direct dehydrogenation of alcohol **5** to phenol **6** illustrates the simplest and most direct synthesis of a 4-hydroxyisoquinoline yet recorded. In view of the ease of preparation of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines,[4] the use of our procedure should make available many hitherto inaccessible 4-hydroxyisoquinolines.

The formation of imenine (1) from the amine **13** represents the first successful example of the Pschorr cyclization starting from a 1-(2-aminobenzyl)isoquinoline. The direct isolation of imenine rather than the expected cyclization product **14** indicates that **14** is extremely susceptible to attack by oxygen. This is not too surprising, since abstraction of a hydrogen from the methylene carbon of ring C would afford a highly delocalized and *planar* radical. The ease of oxidation of **14** to imenine offers a reasonable explanation for the fact that ring B aromatic aporphines related to **14** have neither yet been encountered synthetically nor in nature except as their stable oxidation products, the oxoaporphines.

Experimental Section

Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. All melting points are uncorrected. Nmr spectra were measured on Varian A-60 and Varian A-100 instruments in $CDCl_3$ using tetramethylsilane as an internal standard unless noted. Mass spectra were measured on a Perkin-Elmer Model 270 instrument. Ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer.

4-Hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (5).—A mixture of 3,4,5-trimethoxybenzaldehyde (**2**, 100.0 g), aminoacetaldehyde diethyl acetal (120 ml), and dry benzene (1000 ml) was kept at room temperature for 20 hr, and then refluxed for 6 hr using a Dean-Stark to collect the water which was formed. Evaporation of the solvent afforded the syrupy Schiff base **3**, which was dissolved in EtOH (200 ml) and hydrogenated in the presence of platinum at room temperature (45 psi H_2 pressure) for 20 hr. After filtration of the catalyst, evaporation of solvent left the syrupy amino acetal **4**, which was dissolved in EtOH (250 ml). Aqueous 6 *N* HCl (2275 ml) was added dropwise to the stirred and cooled (0–5°) solution of **4**, after which the mixture was stirred at room temperature for an additional 20 hr. Basification with ammonia, followed by $CHCl_3$ extraction and solvent removal, gave, after crystallization from Et_2O, pale yellow needles of 4-hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**5**, 73.9 g, 61%): mp 138–139°; ir (KBr) 3.05 μ (OH); uv λ_{max}^{EtOH} 290 nm (log ϵ 2.95).

Anal. Calcd for $C_{12}N_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.23; H, 7.40; N, 5.69.

Dehydrogenation of Alcohol 5.—A mixture of 2.80 g of alcohol **5**, 10% Pd on charcoal (3.0 g), and *p*-cymene (200 ml) was heated at 140–145° for 5 hr in an atmosphere of N_2. The catalyst was removed by filtration, and Et_2O saturated with dry HCl was added. A yellow precipitate formed, which was filtered off and partitioned between 10% aqueous NaOH and $CHCl_3$ (50 ml). The aqueous phase was neutralized with NH_4Cl and extracted with $CHCl_3$. The evaporated extract crystallized from CH_2Cl_2–hexane to give colorless needles of 4-hydroxy-5,6,7-trimethoxyisoquinoline (**6**, 0.613 g, 23%): mp 116–117°; *m/e* 235 (M^+); uv λ_{max}^{EtOH} (log ϵ) 248 (4.53), 287 (3.77), 298 (3.74), 330 (3.74), 343 nm (3.77).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.55; H, 5.65; N, 5.90.

The $CHCl_3$ phase from the separation of **6** was dried and evaporated, and the residue was purified by chromatography on alumina (C_6H_6 eluent) to give 5,6,7-trimethoxyisoquinoline (**7**) as a yellow syrup[5] (0.503 g, 18%): nmr δ 9.10 (1 H, s, C_1 H), 8.43 (1 H, d, J = 6.0 Hz, C_3 H), 7.85 (1 H, d, J = 6.0 Hz, C_4 H), 7.07 (1 H, s, C_8 H), 4.03, 3.99, 3.97 (each 3 H, s, 3 OCH_3); uv λ_{max}^{EtOH} (log ϵ) 240 (4.73), 320 (3.72), 335 nm (sh) (3.66). The hydrochloride of **7** formed needles, mp 179–180°, from MeOH–Et_2O.

Anal. Calcd for $C_{12}H_{13}NO_3 \cdot HCl$: N, 5.47. Found: N, 5.30.

4,5,6,7-Tetramethoxyisoquinoline (8).—An excess of ethereal diazomethane was added to a solution of phenol **6** (2.50 g) in a mixture of MeOH (25 ml), dioxane (15 ml), and ether (10 ml). After 3 days at room temperature, excess diazomethane was destroyed by adding acetic acid. The usual work-up, followed by crystallization from hexane, gave pale yellow needles of 4,5,6,7-tetramethoxyisoquinoline (**8**, 2.40 g): mp 96°; nmr δ 8.68, 7.97 (each 1 H, s, C_1 and C_3 H), 7.02 (1 H, s, C_8 H), 4.03, 3.90 (each 3 H, s, 2 OCH_3), 3.98 (6 H, s, 2 OCH_3); *m/e* 249 (M^+); uv λ_{max}^{EtOH} (log ϵ) 246 (4.61), 285 (3.87), 325 (3.79), 338 nm (3.83).

The hydrochloride of **8** crystallized from EtOAc as colorless prisms, mp 148–150°.

Anal. Calcd for $C_{13}H_{15}NO_4 \cdot HCl$; C, 54.64; H, 5.64; N, 4.90. Found: C, 54.72; H, 5.63; N, 5.13.

2-Benzoyl-1-cyano-4,5,6,7-tetramethoxy-1,2-dihydroisoquinoline (9).—To a vigorously stirred mixture of 4,5,6,7-tetramethoxyisoquinoline (**8**, 3.865 g), CH_2Cl_2 (40 ml), potassium cyanide (1.98 g), and water (10 ml) was added dropwise at 0–5° a solution of benzoyl chloride (4.0 g) in CH_2Cl_2 (10 ml). After the solution was stirred for an additional 3 hr at 0–5°, CH_2Cl_2 (200 ml) and water (100 ml) were added, and the organic layer was separated. The washed (H_2O) and dried (Na_2SO_4) solvent was evaporated to afford a gum which, after silica chromatography ($CHCl_3$ eluent), crystallized from *i*-PrOH to give the Reissert compound **9** (2.93 g, 51%) as colorless prisms: mp 136–137°; nmr δ 7.72–7.33 (5 H, m, C_6H_5), 6.72 (1 H, s, C_8 H), 6.52, 5.98 (each 1 H, s, C_1 and C_3 H), 3.88 (9 H, s, 3 OCH_3), 3.67 (3 H, s, OCH_3); uv λ_{max}^{EtOH} (log ϵ) 240 (4.38), 299 (4.13), 317 nm (4.07).

Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.21; H, 5.28; N, 7.54.

1-(2-Nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (11).—Sodium hydride (57% in mineral oil, 0.057 g) was added at 0–5° to a stirred mixture of Reissert compound **9** (0.540 g), *o*-nitrobenzyl chloride (0.270 g), sodium iodide (0.010 g), and dry benzene (50 ml). After the solution was stirred for 1.5 hr at 5–10° (N_2 atmosphere), NH_4Cl (0.200 g) and a solution of Triton B (30% in MeOH, 6 ml) in MeOH (10 ml) was added. After the solution was stirred for 20 hr at room temperature, benzene (100 ml) and water (20 ml) were added. The usual work-up of the organic phase gave a gum which was subjected to preparative tlc on silica ($CHCl_3$–Et_2O, 2:3, as developer) to give two major bands. Elution of the more polar band, followed by crystallization from $CHCl_3$–hexane, gave 1-(2-nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (**11**, 0.202 g, 38%): mp 118–119°; uv λ_{max}^{EtOH} (log ϵ) 248 (4.46), 296 (3.80), 300 (3.78), 330 (3.65), 340 nm (3.68).

Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.73; H, 5.35; N, 7.37.

Elution of the less polar band, followed by crystallization from $CHCl_3$–hexane, gave 1-cyano-4,5,6,7-tetramethoxyisoquinoline (**12**, 0.064 g): mp 138–139°; ir (KBr) 4.45 μ (CN); nmr δ 8.12 (1 H, s, C_3 H), 7.38 (1 H, s, C_8 H), 4.17, 4.08, 4.03, 3.95 (each 3 H, s, 4 OCH_3); uv λ_{max}^{EtOH} (log ϵ) 260 (4.57), 303 (3.73), 314 (3.75), 353 nm (3.85).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.50; H, 5.35; N, 10.27.

Hydrogenation of 11 and Pschorr Reaction of 13.—The isoquinoline **11** (0.100 g) was dissolved in tetrahydrofuran (30 ml) and hydrogenated in the presence of Raney nickel (W-2) at atmospheric pressure for 20 hr. The catalyst was removed and the solvent was then evaporated to afford a gum, which was dissolved in ether (30 ml). Ether saturated with HCl gas was added to the solution to give the hydrochloride of amine **13** (0.088 g) as a colorless powder. This hydrochloride was dissolved in a mixture of methanol (12 ml) and 2 *N* H_2SO_4 (0.7 ml) and then diazotized by the dropwise addition of 10% sodium nitrite (0.48 ml) at 0–5°. After the solution was stirred for a further 20 min at 0–5°, copper powder (0.020 g) was added to the reaction mixture. The mixture was gradually warmed to 40°, stirred at 40–45° for 40 min, basified with ammonia and extracted with $CHCl_3$. The usual work-up afforded a brown residue, which was purified by preparative tlc on silica ($CHCl_3$–Et_2O, 1:2, developer) to give, after

crystallization from methanol, yellow needles of imenine (1, 0.032 g, 35%): mp 206–207°; nmr δ 9.12 (1 H, pair of doublets, J = 8.0 and 2.0 Hz, C_{11} H), 8.57 (1 H, s, C_5 H), 8.56 and 7.80–7.35 (3 H, m, C_{10}, C_9, and C_8 H), 4.22, 4.12, 4.07, 4.02 (each 3 H, s, 4 OCH_3); m/e 351 (M^+), 336 (M − 15), 321 (M − 30); uv λ_{max}^{EtOH} (log ε) 240 (4.30), 275 (4.38), 335 (3.71), 345 (3.71), 434 nm (4.03); $\lambda_{max}^{EtOH-HCl}$ (log ε) 244 (4.07), 290 (4.11), 360 (3.77), 484 nm (3.67). Its ir (KBr) was superimposible upon that of natural imenine and a mixture melting point (206–207°) with the natural base showed no depression.

Registry No.—**1**, 24268-94-8; **5**, 36982-69-1; **6**, 36982-70-4; **7**, 36982-71-5; **7** HCl, 36982-72-6; **8**, 36982-73-7; **8** HCl, 36982-74-8; **9**, 36982-75-9; **11**, 36982-76-0; **12**, 36982-77-1; **13**, 36982-78-2.

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The Reaction of Iodobenzene with Nickel Carbonyl in the Presence of *N*-Benzylidene Alkylamine

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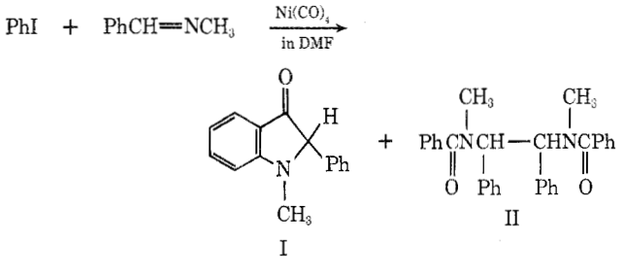
The intermediate benzoylnickel carbonyl iodide, derived from iodobenzene and nickel carbonyl, was reactive toward *N*-benzylidene alkylamine to give 1-alkyl-2-phenylindolin-3-one in *N*,*N*-dimethylformamide (DMF). On the other hand, the similar reaction in benzene solution proceeded *via* a different course to give coupling products of two of the benzoyl groups to an intervening imine double bond.

Organomonohalides react with metal carbonyls to form unstable acyl or alkyl metal carbonyl derivatives, which exhibit unique reactivities toward unsaturated compounds;[1,2] *i.e.*, the addition of the acyl or alkyl group to carbon–carbon double bonds, carbon–carbon triple bonds, and carbon–oxygen double bonds. Herein, although the carbonation and ring closure reactions of Schiff bases or aromatic ketoximes using dicobalt octacarbonyl had been established as a synthetic reaction of phthalimidine derivatives,[3] the reaction of alkyl or acyl metal carbonyl derivatives with imines which contain carbon–nitrogen double bond has not yet been reported.

In this paper we wish to report two types of novel and synthetically useful reactions, *i.e.*, the benzoylation and cyclization of imines to 1-alkyl-2-phenylindolin-3-one (in DMF) and the coupling reaction of two of the benzoyl groups to an intervening imine double bond (in benzene).

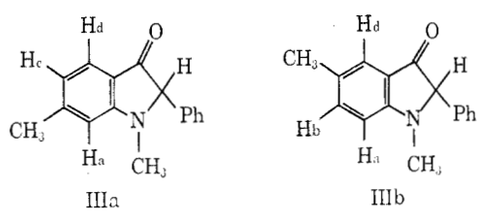
Results and Discussion

Iodobenzene reacted with nickel carbonyl in DMF at 75° in the presence of *N*-benzylidenemethylamine to give 1-methyl-2-phenylindolin-3-one (I) and *N*,*N*′-



dibenzoyl-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine (II) in 28 and 13% yields, respectively.

To determine whether the initial reaction for the formation of I is C attack of the benzoyl group or N attack of the phenyl group, a similar reaction was carried out using *p*-methyliodobenzene instead of iodobenzene. The isolated product (60% yield) was determined to be 1,6-dimethyl-2-phenylindolin-3-one (IIIa)



by the elemental analysis and ir, mass, and nmr spectra. The nmr spectrum showed the proton H_a signal at τ 3.07 (singlet), the characteristic proton on the α-substituted aromatic nucleus with amine nitrogen, and the proton H_d signal at τ 2.3 (doublet). Herein in the case of the product by the N attack of the *p*-tolyl group to the imine double bond, 1,5-dimethyl-2-phenylindolin-3-one (IIIb), the H_a proton signal should be a doublet and the H_d proton signal a singlet. The formation of IIa strongly suggests that the attack of benzoyl group to the carbon site of the imine double bond occurs first, followed by cyclization, to give the indolinone derivatives as shown in Scheme I. The 1,2-diphenylethylenediamine derivative VI might be formed by the N-attack of benzoyl group to the imine double bond.

This reaction underwent a remarkable solvent effect. When benzene was used as a solvent instead of DMF, the main product was not the indolinone derivative but the coupling product of two of benzoyl group to an intervening imine double bond, *N*-methyl-*N*-(α-phenylphenacyl)benzamide (VII) (53% yield). Similarly the reaction using *N*-benzylideneethylamine gave *N*-ethyl-*N*-(α-phenylphenacyl)benzamide (VIII) in 59% yield. This remarkable solvent effect was considered to be due to the difference of the structure of the intermediate benzoylnickel carbonyl iodide; that is, the benzoylnickel complex was assumed to be monomeric in DMF solution and dimeric in benzene

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