The Synthesis of Oconovine

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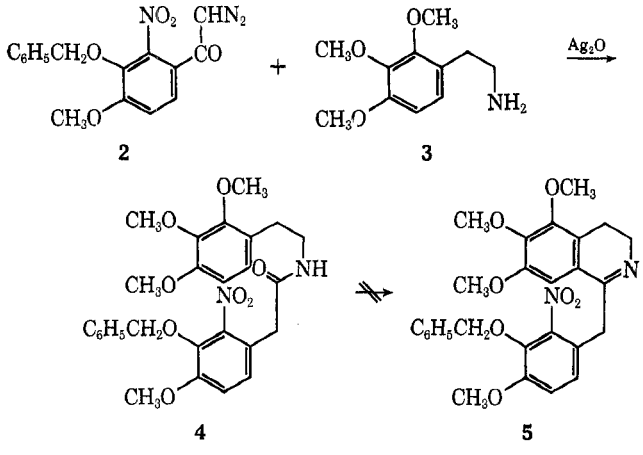
Received June 19, 1969

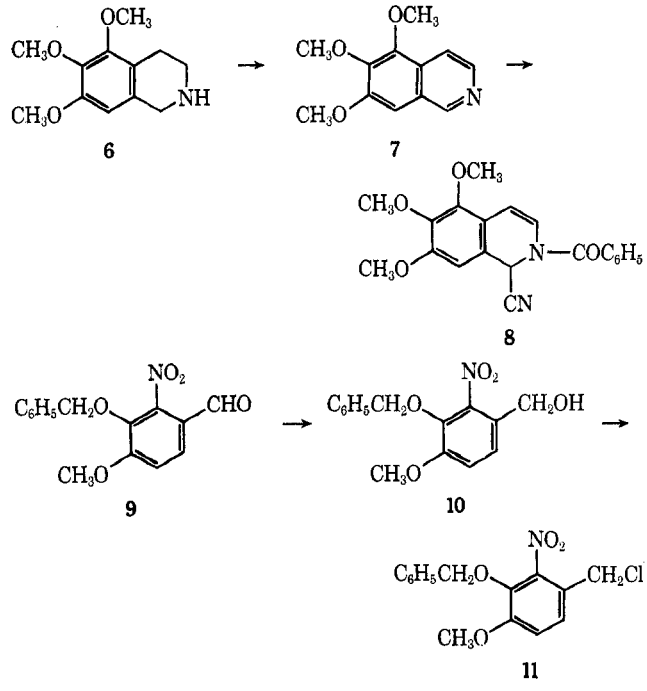
A synthesis is described for (±)-1,2,3,10-tetramethoxy-11-hydroxyaporphine (1). The latter proved to be the racemic form of the alkaloid (+)-oconovine, thus confirming the oconovine structure assigned earlier on the basis of spectroscopic evidence.

The amorphous base (+)-oconovine is one of two previously unreported alkaloids which have been found in an incompletely identified *Ocotea* species. Structure **1** was assigned to oconovine, primarily on the basis of spectroscopic evidence.[2] We now report the confirmation of this structure by a total synthesis of (±)-oconovine.

Since the proposed structure for oconovine (**1**) differs from that of isocorydine only by the presence of a 1-methoxy substituent, our first synthetic approach to oconovine was patterned after Kikkawa's successful isocorydine synthesis.[3] Thus decomposition of 2-nitro-3-benzyloxy-4-methoxy-ω-diazoacetophenone (**2**)[3] in the presence of 2,3,4-trimethoxy-β-phenylethylamine (**3**)[4] and silver oxide afforded an almost quantitative yield of the amorphous amide **4**, the nmr spectrum of which was fully in accord with the assigned structure. A number of attempts were made to cyclize this amide to the dihydroisoquinoline **5** under a variety of conditions; in all instances only nonbasic material was recovered.



In order to circumvent the use of the Bischler–Napieralski reaction, we turned to the alternate approach involving, as the key step, alkylation of the Reissert compound **8** by 2-nitro-3-benzyloxy-4-methoxybenzyl chloride (**11**). The latter halide was obtained by the sodium borohydride reduction of 2-nitroisovanillin benzyl ether[5] (**9**), followed by reaction of the resulting benzyl alcohol **10** with thionyl chloride. The Reissert compound **8** was prepared by the palladium dehydrogenation of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline[6] (**6**) to 5,6,7-trimethoxyisoquinoline (**7**), followed by treatment of the latter base with benzoyl chloride and potassium cyanide. Alkylation



of **8** by halide **11** proceeded smoothly, using the general alkylation conditions of Kershaw and Uff,[7] to give the crystalline alkylated derivative **12**. Attempted hydrolysis of the alkylated Reissert compound **12** by alcoholic alkali in the usual manner[8] gave an unexpected yellow substance, mp 95–98°, which was assigned the substituted anthranil structure **14** on the basis of spectral data and elemental analysis. Hydrolysis of the Reissert derivative **12** to the desired isoquinoline **13** was achieved in excellent yield, however, by a new procedure using Triton B in dimethylformamide at room temperature. As expected, the isoquinoline **13** was converted into the anthranil **14** in high yield on refluxing with alcoholic alkali. The isoquinoline **13** was converted into its amorphous methiodide **15** by heating with methyl iodide in dimethylformamide in a sealed tube. Sodium borohydride reduction of methiodide **15** gave the tetrahydro derivative **16**, which was reduced by zinc in acetic acid to the amino tetrahydroisoquinoline **17**. Both of the latter compounds (**16** and

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(2) M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell, A. I. daRocha, B. Hwang, B. Douglas, and J. A. Weisbach, *Tetrahedron Lett.*, 2437 (1968).

(3) I. Kikkawa, *J. Pharm. Soc. Jap.*, **78**, 1006 (1958).

(4) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

(5) D. H. Hey and J. C. Lobo, *J. Chem. Soc.*, 2246 (1954).

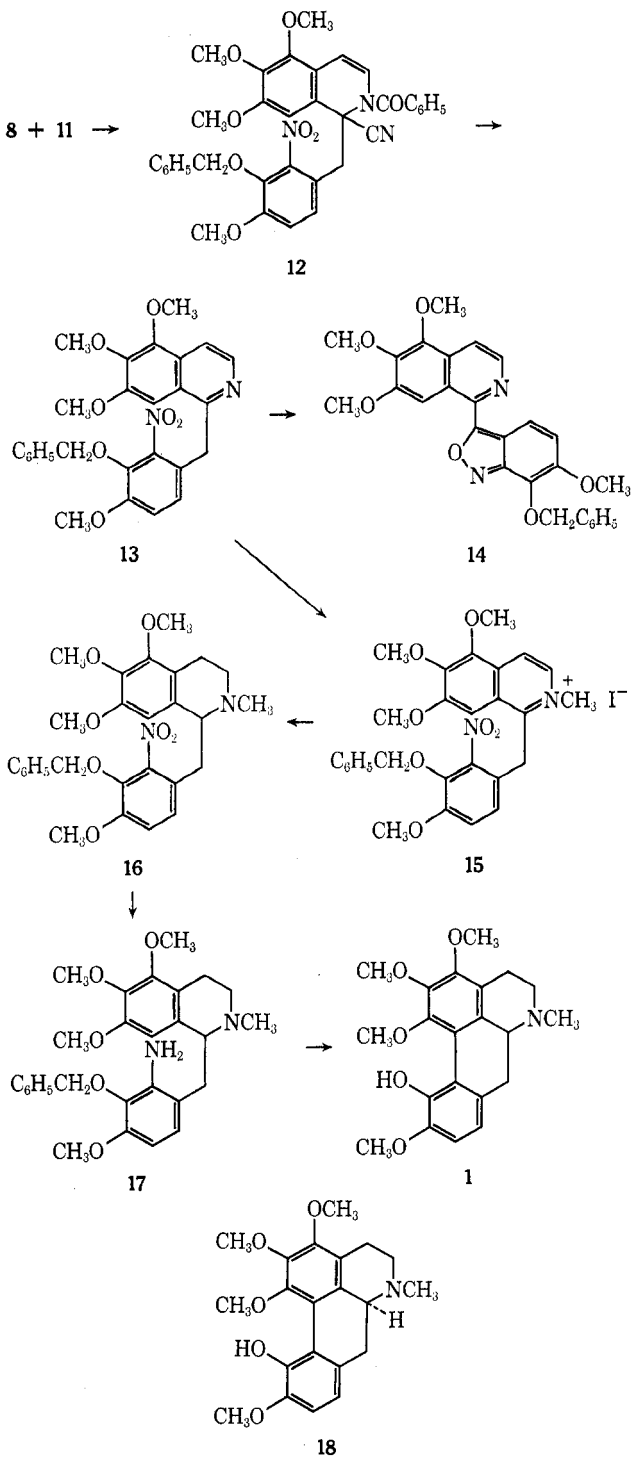
(6) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Eberman, *J. Org. Chem.*, **30**, 2248 (1965).

(7) B. C. Uff and J. R. Kershaw, *J. Chem. Soc., C*, 666 (1969).

(8) (a) F. D. Popp and W. E. McEwen, *J. Amer. Chem. Soc.*, **79**, 3776 (1957); (b) J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Lett.*, 3107 (1967). For a recent extensive review of the chemistry of Reissert compounds, see F. D. Popp *Advan. Heterocycl. Chem.*, **9**, 1 (1968).

17) were noncrystalline, but their nmr spectra were in accord with the assigned structures.

The Pschorr cyclization of amine **17** was effected by diazotization in dilute hydrochloric acid and slow decomposition of the resulting diazonium chloride at room temperature in the absence of a metal catalyst, followed by brief heating on the steam bath. Rather surprisingly, thin layer chromatography suggested that debenzylation had taken place during the Pschorr reaction with the direct formation of oconovine. Indeed, preparative chromatography led to the isolation of the amorphous base (±)-oconovine (**1**), which gave nmr, ultraviolet, and solution infrared spectra identical with those of the natural (+)-oconovine.



Like the natural base, racemic oconovine was further characterized as its crystalline methiodide.

No assignment of the absolute configuration of (+)-oconovine was made in the original publication describing its isolation.[2] It may be assumed to have the complete structure **18** on the apparently valid assumption that all dextrorotatory aporphines have the L (or *S*) configuration at the 6a carbon atom.[9]

Experimental Section[10]

2-Nitro-3-benzyloxy-4-methoxybenzyl Alcohol (10).—Sodium borohydride (0.15 g) was added in portions to a solution of 2-nitroisovanillin benzyl ether[5] (**9**, 2.0 g) in methanol (50 ml). When tlc indicated that the reduction was complete, the solvent was evaporated and the product was isolated in the usual manner to give alcohol **10** as a pale yellow gum which could not be crystallized: nmr δ 7.51 (s, 5 H, C_6H_5), 7.18 (AB q, 2 H, $\Delta\nu$ = 9 Hz, J = 9 Hz, aromatic), 5.20 (s, 2 H, $-OCH_2C_6H_5$), 4.58 (s, 2 H, $-CH_2OH$), 3.93 (s, 3 H, OCH_3), and 2.70 (s, 1 H, OH).

Alcohol **10** reacted with acetic anhydride in pyridine to give a crystalline O-acetyl derivative, mp 62° (ether–hexane).

Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.48; H, 5.30; N, 4.21.

2-Nitro-3-benzyloxy-4-methoxybenzyl Chloride (11).—Thionyl chloride (5 ml) was added to a solution of alcohol **10** (5.0 g) in benzene (50 ml) at room temperature. After 30 min, excess solvent and reagent were removed under reduced pressure and the residual oil was extracted with hexane. On cooling, the concentrated extract gave chloride **11** as a waxy solid (3.0 g, 56%), mp 41–45°. Analysis was not carried out because of the poor crystallization properties of the compound. The crude halide, however, was satisfactory for direct conversion into compound **12**.

5,6,7-Trimethoxyisoquinoline (7).—A solution of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline[6] (**6**, 8.0 g) in purified (Al_2O_3) decalin (300 ml) containing suspended 10% palladium on charcoal (2 g) was refluxed for 7 hr under a CO_2 atmosphere. Extraction of the cooled mixture with aqueous hydrochloric acid and work-up of the basic product in the usual manner afforded isoquinoline **7** (7.85 g) as an oil which did not crystallize. The base was characterized as its crystalline picrate, mp 179°.

Anal. Calcd for $C_{18}H_{16}N_4O_{10}$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.11; H, 3.49; N, 12.37.

1-Cyano-2-benzoyl-5,6,7-trimethoxy-1,2-dihydroisoquinoline (8).—Benzoyl chloride (7 ml) was added dropwise to a vigorously stirred mixture of isoquinoline **7** (7.8 g), methylene chloride (70 ml), potassium cyanide (8.39 g), and water (10 ml); external ice cooling was maintaned during the addition. After an additional 4 hr of stirring, the organic phase was separated, washed with water, and evaporated. Trituration of the residual solid with ethanol afforded Reissert compound **8** (6.5 g, 60.5%), mp 162°. The analytical sample, mp 165°, was crystallized from ethanol.

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.51; H, 5.22; N, 7.98.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-1-cyano-2-benzoyl-5,6,7-trimethoxy-1,2-dihydroisoquinoline (12).—Sodium hydride (1.07 g, 51% in mineral oil) was added to a solution of Reissert compound **8** (5.54 g) and chloride **11** (5.80 g) in dimethylformamide (130 ml) with external ice cooling. The mixture was stirred for 4 hr under nitrogen, diluted cautiously with water, and extracted with benzene. The usual work-up of the benzene layer, followed by crystallization of the residue from ethanol, afforded the alkylated Reissert compound **12** (6.86 g, 70%): mp 181°; nmr δ *ca.* 7.5–7.3 (m, 10 H, 2 C_6H_5), 7.08 (AB q, 2 H, $\Delta\nu$ = 9 Hz, J = 9 Hz, aromatic), 6.57 (s, 1 H, aromatic), 6.25 and 5.85 (vinylic doublets, 2 H, J = 8 Hz), 5.00 (s, 2 H, $-OCH_2C_6H_5$), 3.92 (s, 3 H, OCH_3), 3.90 (s, 6 H, 2 OCH_3), 3.72 (s, 3 H, OCH_3), and 3.6 (s, 2 H, CH_2Ar).

(9) M. Shamma and M. J. Hillman, *Experientia*, **25**, 544 (1969).

(10) Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected. Nmr spectra were run in $CDCl_3$ (TMS internal standard) using a Varian A-60 instrument; ultraviolet spectra were run in 95% EtOH unless otherwise stated, using a Perkin-Elmer Model 202 spectrophotometer.

Anal. Calcd for $C_{35}H_{31}N_3O_8$: C, 67.62; H, 5.03; N, 6.76. Found: C, 67.38; H, 5.28; N, 6.66.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-5,6,7-trimethoxyisoquinoline (13).—Triton B (7 ml, 40% methanolic benzyltrimethylammonium hydroxide) was added to a solution of compound **12** (5.78 g) in dimethylformamide (75 ml), and the mixture was kept at room temperature under nitrogen for 30 min. After dilution with ice and ether, concentrated hydrochloric acid was added until no further quantity of the hydrochloride of **13** separated. The salt was washed with ice–water and ether, and the free base **13** was liberated using ammonia. Crystallization from methanol gave **13** as white flakes (3.413 g, 75%): mp 120°; nmr δ 8.39 and 7.80 (d, 2 H, J = 6 Hz, aromatic), 7.4 (s, 5 H, C_6H_5), 7.10 (1 H), and 6.85 (2 H, both s, aromatic), 5.12 (s, 2 H, $-OCH_2C_6H_5$), 4.27 (s, 2 H, $-CH_2Ar$), and 4.02, 3.97, 3.93, and 3.83 (all s, OCH_3); uv λ_{max} 205 mμ (log ϵ 4.92), 245 (4.86), 283 (sh, 3.91), and 340 (3.72).

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.11; H, 5.34; N, 5.71. Found: C, 66.39; H, 5.35; N, 5.63.

The hydrochloride of **13**, mp 183°, crystallized from ether–ethanol.

Anal. Calcd for $C_{27}H_{27}N_2O_7Cl$: C, 61.65; H, 5.17; N, 5.31. Found: C, 61.81; H, 5.28; N, 5.47.

Alkali Transformation Product (14) of Base 13.—Base **13** (0.120 g) was refluxed for 4 hr under a N_2 atmosphere with a solution of potassium hydroxide (0.5 g) in ethanol (20 ml). Evaporation of the solvent, addition of water, and crystallization from ethanol gave fluffy yellow crystals of the anthranil derivative **14** (0.088 g, 76%): mp 95–98°; nmr δ 8.63 and 8.25 (d, 2 H, J = 5 Hz, aromatic), 8.17 (s, 1 H, aromatic), 8.0–6.9 (miscellaneous aromatics), 5.55 (s, 2 H, $-OCH_2C_6H_5$), and 4.20 (6 H), 4.10 (3 H), and 3.95 (3 H), (all s, OCH_3); uv λ_{max} 2.12 mμ (log ϵ 4.83), 269 (4.30), and 305 (sh, 3.94).

Anal. Calcd for $C_{27}H_{24}N_2O_6$: C, 68.63; H, 5.12; N, 5.93. Found: C, 68.55; H, 5.16; N, 6.19.

Compound **14** was also formed directly from compound **12** under the experimental conditions given above.

1-(2-Nitro-3-benzyloxy-4-methoxy)benzyl-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (16).—A solution of isoquinoline **13** (0.050 g) in a mixture of dimethylformamide (0.5 ml) and methyl iodide (1 ml) was heated for 4 hr on the steam bath. Evaporation of the solvent mixture *in vacuo* left a gummy residue of methiodide **15**, which was washed with ether. A sample of **15** (0.100 g) was dissolved in ethanol (10 ml), and sodium borohydride (0.030 g) was added at room temperature. After 3 hr, work-up in the usual manner gave base **16** as a gum (0.050 g, 55%) which moved as a single spot on a silica plate [$CHCl_3$–EtOH (5:1)]: nmr δ *ca.* 7.4 (s, 5 H, C_6H_5), 6.90 (s, 2 H, aromatic), 6.13 (s, 1 H, aromatic), 5.13 (s, 2 H, $-OCH_2C_6H_5$), 3.87, 3.83 (6 H), and 3.71 (all s, OCH_3), and 2.40 (s, 3 H, NCH_3).

1-(2-Amino-3-benzyloxy-4-methoxy)benzyl-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (17).—A solution of nitro compound **16** (0.127 g) in a mixture of acetic acid (20 ml) and ethanol (10 ml) was stirred at room temperature for several hours with excess zinc dust. The basic reaction product was isolated in the usual manner. The portion of this material (0.075 g, 63%) which was extractable into hot hexane showed an nmr spectrum in accord with structure **17**: δ *ca.* 7.4 (m, 5 H, C_6H_5), 6.50 (s, 1 H, aromatic), 6.38 (AB q, 2 H, $\Delta\nu$ = 19 Hz, J = 9 Hz, aromatic), 4.95 (s, 2 H, $-OCH_2C_6H_5$), 3.90, 3.85 (6 H), and 3.70 (all s, OCH_3), and 2.40 (3 H, NCH_3).

(±)-Oconovine (1).—A solution of amine **17** (0.500 g) in a mixture of concentrated hydrochloric acid (1 ml) and water (15 ml) was cooled well in an ice bath, and a solution of sodium nitrite (0.100 g) in a small amount of water was added dropwise. After 30 min, sulfamic acid was added to destroy excess nitrous acid and the solution was allowed to warm up to room temperature. After standing overnight, the solution was heated for 15 min on the steam bath. Zinc dust was added to reduce colored by-products and the solution was heated for a further 15 min. The cooled and filtered solution was made basic with aqueous sodium hydroxide and extracted with methylene chloride to give 0.15 g of alkali-insoluble base mixture. The initial fractions (0.070 g) obtained by chromatography on neutral alumina ($CHCl_3$ eluent) showed no benzyloxy group by nmr analysis and were shown by tlc to be mostly oconovine. Reaction with methyl iodide, followed by crystallization from ethanol–ether, gave pure (±)-oconovine methiodide (0.050 g, 12.5%): mp 228°; uv λ_{max} 220 mμ (log ϵ 4.12), 278 (3.90), and 315 (sh, 3.49).

Anal. Calcd for $C_{22}H_{28}NO_5I$: C, 51.47; H, 5.50; N, 2.73. Found: C, 51.50; H, 5.56; N, 2.66.

In another experiment, amine **17** (0.492 g) afforded a product which was subjected to a final purification by silica chromatography in chloroform [$CHCl_3$–EtOH (20:1) as eluent] to give pure (±)-oconovine (**1**, 0.058 g, 15%): uv λ_{max} 280 mμ (log ϵ 4.03) and 310 (sh, 3.77); λ_{max} [ethanolic KOH (0.075 *N*) 280 mμ (log ϵ 3.87) and 335 (3.98).

The nmr spectrum of **1** was identical with that recorded for the natural base,[2] and the solution ($CHCl_3$) infrared spectra of the two samples were superimposable.

Registry No.—**1**, 23740-41-2; **1** methiodide, 23740-42-3; **7** monopicrate, 23740-79-6; **8**, 23740-80-9; **10**, 23740-81-0; **10** O-acetyl derivative, 23740-82-1; **11**, 23740-83-2; **12**, 23740-84-3; **13**, 23740-85-4; **13** hydrochloride, 23740-86-5; **14**, 23740-87-6; **16**, 23740-43-4; **17**, 23740-44-5.

Acknowledgment.—We are grateful to Dr. M. J. Mitchell for samples of compounds **2** and **3**. We also thank the Smith Kline and French Laboratories, Philadelphia, Pa., for generous financial support of this investigation.