

TOTAL SYNTHESIS OF PERUVIANINE, A PHENOLIC
7-OXOAPORPHINE ALKALOID OF TELITOXICUM PERUVIANUM

Keith T. Buck*

Fries and Fries Division, Mallinckrodt, Inc.,

110 East 70th Street, Cincinnati, Ohio 45216, U.S.A.

Denise L. Edgren, Geoffrey W. Blake, and Mary D. Menachery*

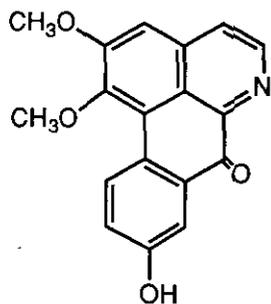
Penn State Altoona, 3000 Ivyside Park, Altoona, PA 16601-3760, U.S.A.

Abstract – Peruvianine, a phenolic 7-oxoaporphine alkaloid from Telotoxicum peruvianum, has been synthesized *via* photo-Pschorr cyclization of an aminophenol precursor.

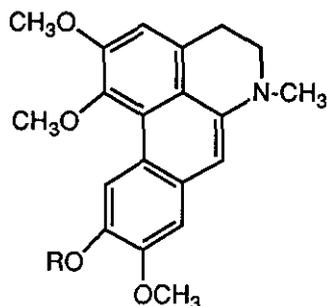
Peruvianine, isolated from Telotoxicum peruvianum (Menispermaceae), was assigned structure (1) on spectral grounds in 1981.¹ The alkaloid is therefore one of the small family of phenolic 7-oxoaporphines.² We now report confirmation of structure (1) by total synthesis of peruvianine.

Syntheses of only a few phenolic 7-oxoaporphine alkaloids have been reported, using three approaches:

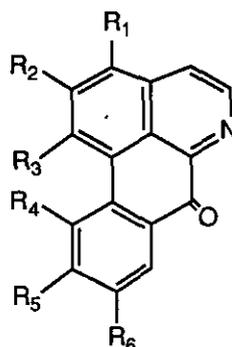
A) oxidation/selective demethylation of nonphenolic aporphine alkaloids; thus photooxidation and hydrolysis of the acetyl group converted 2 [from selective demethylation of dehydroglauicine (3)] to oxolirioferine (4),³ and arosine (5) and arosinine (6) were produced by thermolysis of 7;⁴ B) photocyclization of phenolic *o*-bromobenzylisoquinolines or oxidized derivatives, as in the syntheses of atheroline (8) and glauanine (9) from 10,^{5,6} and of oxolirioferine (4) by photocyclization of 11;³ C) Pschorr ring closure, with autoxidation if necessary, of *O*-benzyl-protected *o*-aminobenzyl-(or *o*-aminobenzoyl)isoquinolines, as in the synthesis of atheroline (8) from 12⁷ and of subessiline (13) from 14.⁸



1



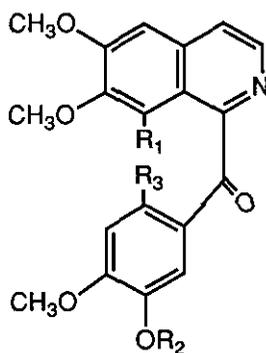
2. R = Ac
3. R = Me



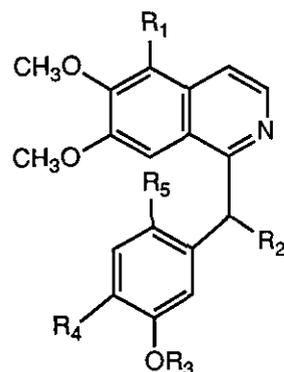
4. R₂ = R₃ = R₆ = OMe; R₅ = OH; R₁ = R₄ = H
7. R₂ = R₃ = R₄ = R₅ = OMe; R₁ = R₆ = H
8. R₂ = R₃ = R₅ = OMe; R₆ = OH; R₁ = R₄ = H
9. R₂ = R₃ = R₅ = OMe; R₄ = OH; R₁ = R₆ = H
13. R₁ = R₂ = R₃ = OMe; R₆ = OH; R₄ = R₅ = H



5. R = CH₃
6. R = H



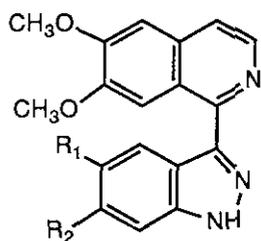
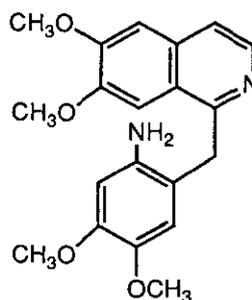
10. R₁ = Br; R₂ = R₃ = H
12. R₂ = CH₂Ph
R₁ = H; R₃ = NH₂



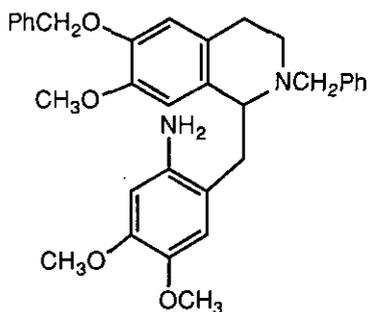
11. R₂ = R₄ = OH; R₅ = Br; R₃ = Me; R₁ = H
14. R₁ = OMe; R₃ = CH₂Ph; R₅ = NH₂; R₂ = R₄ = H

The present synthesis of peruvianine (1) was patterned after that of subessiline (13),⁸ except for novel variation in the final steps (Scheme I). Accordingly, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (15)⁹ was converted to the free base,⁹ which was aromatized to 16 in 79% yield by refluxing with 10% Pd/C in *p*-cymene. The Reissert compound (17) was prepared as described⁷ and alkylated in 51% yield with 18⁸ under phase-transfer conditions (50% NaOH, benzene, benzyltrimethylammonium hydroxide).⁸ The resulting 19 was treated with Triton B under nitrogen⁸ giving 20 (72%). The expected byproducts, analogous to those obtained in the synthesis of subessiline,⁸ were detected in the supernate.¹¹

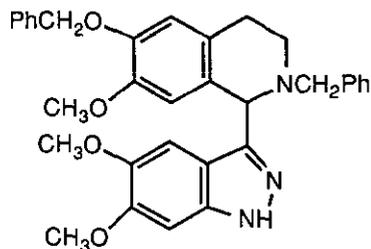
Originally, we had planned to retain the benzyl protecting group until the final step of the synthesis, as had been done in the cases of atheroline (8) and subessiline (13). However, we were prompted to change our strategy when hydrogenation of 20 over 5% Pd/C in ethanol afforded the aminophenol 21 in 43% yield.¹² Diazotization of 21 in 1 N sulfuric acid and adjustment of the reaction to pH 6-7 with NaOH gave as the major product (65% yield) the indazole 23. Formation of 23 was not unexpected since an analogous transformation was known to take place in the diazotization of 6'-aminopapaverine (24), affording 25,¹³ and in the attempted photo-Pschorr reaction of the benzyltetrahydroisoquinoline (26), giving 27.¹⁴

23. R₁ = OH ; R₂ = H25. R₁ = R₂ = OMe

24



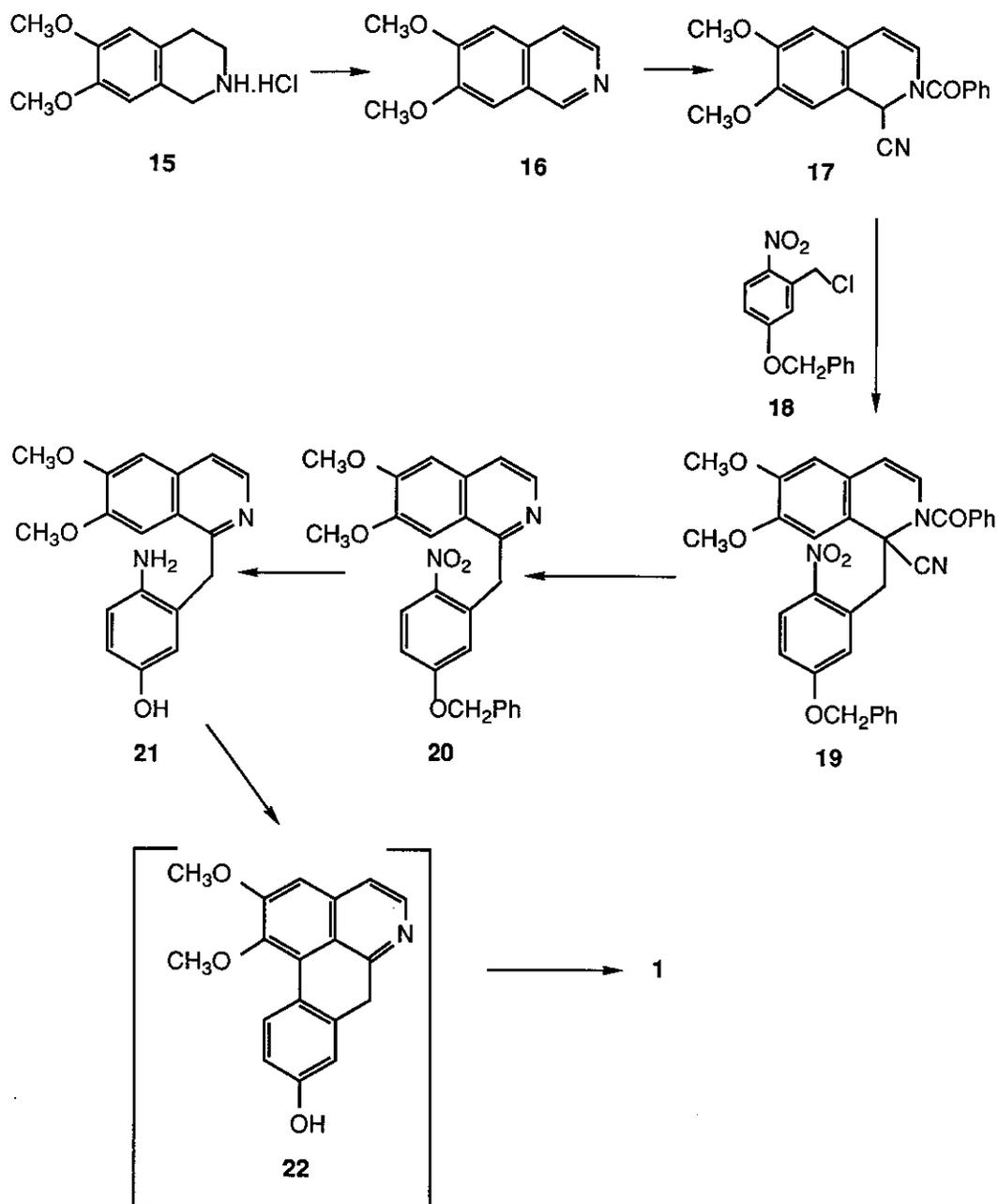
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27

In contrast to the above result, diazotization of 21 in 1 N sulfuric acid at 0° C, adjustment of the reaction to pH 12 and photo-Pschorr cyclization by irradiation under nitrogen with a medium pressure 450 Watt lamp for 22 h gave, after acidification to pH 5-6, exposure to air and workup by column chromatography, a 2.7% yield of material identical (uv, nmr, ms and tlc) to an isolated sample (1) of peruvianine. Formation of 1 presumably occurs *via* autoxidation of 22. Although the direct photo-Pschorr reaction of aminophenols has been used in the

synthesis of phenolic aporphine alkaloids,¹⁵ the present report is the first example of the synthesis of a phenolic 7-oxoaporphine by direct ring closure of a diazotized aminophenol.



Scheme 1

EXPERIMENTAL

2-Benzoyl-1-[5-benzyloxy-2-nitrobenzyl]-1,2-dihydro-6,7-dimethoxyisoquinaldonitrile (19).

A solution of Reissert compound (17) (1.6 g, 5.00 mmol) and nitrobenzyloxybenzyl chloride (18) (1.6 g, 5.77 mmol) in benzene (50 ml) was stirred and a solution of benzyltrimethylammonium chloride (0.1 g) in water (0.5 ml) was added. The reaction was flushed with nitrogen for 10 min. A 50% sodium hydroxide solution (7 ml) was added through a septum and stirring was continued for 90 min at room temperature, while flushing with nitrogen. The reaction gradually darkened and NaCl precipitated. The mixture was then cooled in an ice bath and 5% sulfuric acid was added dropwise to pH 6. A solid separated and after cooling in the refrigerator the product was filtered, washed with cold water and dried in air to afford yellow crystals of 19 (1.42 g, 51%); mp 213°C (decomp.). ¹H Nmr (360 MHz, CDCl₃): δ 7.73 (d, J = 9.1 Hz, H-3'), 7.29-7.69 (m, 10 H, benzyl and benzoyl), 7.19 (d, J = 2.7 Hz, H-6'), 6.93 (dd, J = 2.7 and 9.1 Hz, H-4'), 6.54 (s, H-5), 6.41 (s, H-8), 6.34 and 5.68 (d, J = 7.8 Hz, 1 H each, H-3 and H-4), 4.56 and 3.82 (d, J = 13.0 Hz, 1H each, benzylic), 3.90 and 3.58 (s, 3H each, OMe). FAB- ms (m/z): 562 (40, MH⁺), 535 (MH⁺ - HCN), 319 (100).

1-[2-Nitro-5-benzyloxybenzyl]-6,7-dimethoxyisoquinoline(20).

The Reissert alkylation compound (19) (1.26 g, 2.25 mmol) was suspended in DMF (8 ml, dried by passage through a neutral alumina column) and the mixture was flushed with nitrogen through a septum. Through a hypodermic needle was added in one slug 0.67 ml of Triton B (40% methanolic benzyltrimethylammonium hydroxide). A deep blue color developed and all solids dissolved. The mixture was stirred 45 min under nitrogen. The deep blue mixture was cooled in an ice bath and diluted with water (50 ml). The product was extracted several times into chloroform. The combined extract was washed with water, dried over sodium sulfate and the solvent was evaporated to yield an oil which solidified on cooling in the freezer. The mixture was triturated with hexane-ether, filtered and the yellow solid was recrystallized from chloroform - ether to give chromatographically pure 20 (0.697 g, 72%), mp 132-134 °C. ¹H Nmr (360 MHz, CDCl₃): δ 8.28 and 7.41 (d, J = 5.6 Hz, H-3 and H-4), 8.09 (d, J = 9.1 Hz, H-3'), 7.25-7.31(m, 6H, benzyl + H-5), 7.06 (s, H-8), 6.88 (dd, J = 2.7 and 9.1 Hz, H-4'), 6.74 (d, J = 2.7 Hz, H-6'), 4.97 and 4.94 (s, 2H each, CH₂), 4.02, 3.93 (s, 3H each, OMe). ms (m/z): 430 (M⁺, 0.17), 385 (24), 384(85), 293 (38), 91(100). Hrms: 430.1523 calcd for C₂₅H₂₂N₂O₅; found 430.1527.

4-Amino- α -(6,7-dimethoxy-1-isoquinolinyl)-*m*-cresol (21).

To a solution of nitrobenzylisoquinoline (**20**) (0.400 g, 0.930 mmol) in 95% ethanol (75 ml) was added potassium carbonate (0.050 g) and 5% Pd on carbon (0.2 g). The mixture was hydrogenated at 57 psi for 3 h. Solids were filtered off, solvent was evaporated and the residue was extracted with chloroform. The chloroform extract was filtered through a short column of neutral alumina and the solvent was evaporated, yielding a tan-green gum (280 mg). Purification by column chromatography gave **21** as an amorphous powder (125 mg, 43%). $^1\text{H Nmr}$ ((360 MHz, CDCl_3): δ 8.19 and 7.36 (d, $J = 5.7$ Hz, 1 H each, H-3 and H-4), 7.50 (s, H-8), 7.04 (s, H-5), 6.67 (d, $J = 2.4$ Hz, H-6'), 6.56 (d, $J = 8.4$ Hz, H-3'), 6.52 (dd, $J = 8.4$ and 2.4 Hz, H-4'), 4.40 (s, CH_2), 4.01, 3.99 (s, 3H each, OMe). Decoupling at δ 6.67 gave doublets at 6.56, 6.52; at δ 8.19 gave a singlet at 7.36; at δ 6.52-6.56 gave a singlet at 6.67. Ms (m/z): 310 (M^+ , 43), 294 (100), 278 (20), 264 (7), 250 (12). Hrms: 310.1313 calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$; found 310.1311. Uv (95% EtOH): 326 nm ($\log \epsilon$ 3.66), 313(3.68), 238(4.73).

1-[3'-(5'-Hydroxyindazolyl)]-6,7-dimethoxyisoquinoline(23).

To a solution of aminophenol (**21**) (51 mg, 0.164 mmol) in 1N H_2SO_4 (5 ml) at 0°C was added NaNO_2 (24 mg, 0.348 mmol). After adjusting the pH to about 6-7, the product was extracted into CH_2Cl_2 and further purified by column chromatography to afford the indazole **23** (34.5 mg, 65%). $^1\text{H Nmr}$ (360 MHz, $\text{C}_3\text{D}_6\text{O}$): δ 9.15(s, H-8), 8.48 and 7.58 (d, $J = 5.5$ Hz, 1H each, H-3 and H-4), 8.10 (d, $J = 2.4$ Hz, H-4'), 7.50 (d, $J = 8.9$ Hz, H-7'), 7.33 (s, H-5), 7.06 (dd, $J = 8.9$ and 2.4 Hz, H-6'), 4.00, 3.96 (s, 3H each, OMe); Decoupling at δ 7.06 (H-6') gave singlets at 7.50 (H-7') and 8.10 (H-4'). NOE experiments were in accordance with the assignments. Ms (m/z): 321(M^+ , 100), 307(15), 306(67), 305(36), 304(50), 291(30), 290(34), 288(22), 276(13), 275(29), 260(11). Hrms: 321.1110 calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3$; found 321.1100.

9-Hydroxy-1,2-dimethoxy-7H-dibenzo[de,g]quinolin-7-one (1).

The aminophenol (**21**) (31 mg, 0.100 mmol) in 1N H_2SO_4 (1 ml) was cooled to 0°C and diazotized using NaNO_2 (7.0 mg, 0.101 mmol). 2.5 M NaOH (0.65 ml) was added and the solution was diluted to 100 ml. Photolysis of the solution was carried out using medium pressure 450 watt lamp under nitrogen for 22 h. The solution was acidified to pH 5-6 and allowed to undergo air oxidation. The product was extracted into CHCl_3 , washed, dried and evaporated to dryness. Purification by column chromatography gave peruvianine (**1**) (0.84 mg, 2.7% yield), which was identical to natural alkaloid by nmr, tlc, ms, and uv. Decoupling at δ 7.32 (H-10) gave singlets at 9.13 (H-11) and 7.89 (H-8).

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