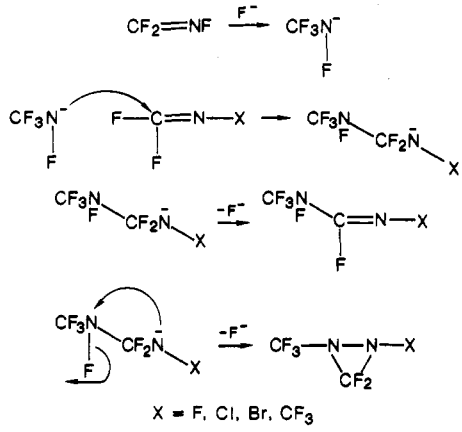
Scheme VI



A comparison of the spectral properties of the *N*-halodiaziridines prepared from CF_2=NF, CF_2=NCl, and CF_2=NBr and an analogous (trifluoromethyl)oxaziridine is provided in Table I. The characteristic ring vibration for small heterocyclic rings is observed between 1400 and 1440 cm^{-1} for each diaziridine and at 1458 cm^{-1} for the oxaziridine.[3,5,24] These frequencies are within the range expected for analogous fluorinated heterocycles.[25,26]

The ^{19}F NMR spectra are instructive regarding the probable structures of these rings. The *N*-fluorodiaziridine serves as a model from which the other structures can be reasonably assigned. As discussed in a previous report,[3] the fluorine on nitrogen provides a probe into the relative position of the other fluorines above and below the ring plane in the *N*-fluorodiaziridine. Since two distinct signals are observed for the geminal fluorines on the ring carbon, the inversion of the ring can be assumed to be slow on the NMR time scale. Likewise, the geminal fluorines are nonequivalent in the *N*-chloro- and *N*-bromodiaziridines.

Assignment of the position of the trifluoromethyl group in the N–F ring was deduced according to the relative coupling constants, since each coupling constant is measurable and distinct in this system. Close proximity in space generally renders a large coupling in rigid systems in the ^{19}F NMR.[27] According to this tenet, the trifluoromethyl group and the ring N–F were assigned as trans.[3] A cis orientation would show a large coupling constant, which is consistent with the coupling of the CF_3 group with the upper geminal fluorine (J_{MY} = 9.5 Hz) and the N–F with the lower geminal fluorine (J_{AX} = 17.5 Hz).

Diaziridines generally favor a trans arrangement of nitrogen substituents to alleviate repulsion of the two neighboring lone pairs.[28] Some diaziridines as well as triaziridines have been synthesized that can be isolated either as a cis isomer or as a mixture of isomers.[29,30] The NMR evidence favors a locked trans geometry for the *N*-fluorodiaziridine and it is reasonable to assume that the *N*-chloro- and *N*-bromodiaziridines have similar geometries in the absence of more definitive structure determinations.

In summary, CF_2=NBr provides many possibilities for additions in thermal and photochemical reactions as evidenced by its additions to fluoroolefins and carbon monoxide and its pyrolysis. Reaction with CF_2=NF over KF and CsF affirms the nucleophilicity of the CF_3NF^- anion on terminal difluoromethylene centers while indicating the poor nucleophilicity of the CF_3NBr^- anion. These two modes of reactivity make CF_2=NBr an attractive starting material for the synthesis of novel small molecules with potentially reactive centers.

Acknowledgment. The support of the U.S. Army Research Office and the National Science Foundation is gratefully acknowledged.

Registry No. I, 60247-20-3; II, 115031-89-5; III, 115031-90-8; IV, 115031-91-9; FCN, 1495-50-7; CF_3CN, 353-85-5; $(CN)_2$, 460-19-5; CF_2=NBr, 90624-74-1; CF_2=NN=CF_2, 692-73-9; CO, 630-08-0; $BrCF_2NCO$, 115031-92-0; C_2F_4, 116-14-3; CF_2=N(CF_2)$_2$Br, 115031-93-1; CF_2=CFBr, 598-73-2; CF_2=NCF_2CFBr_2, 115031-94-2; CF_3N=$CFCF_2Br$, 115031-95-3; CF_3N=$CFCFBr_2$, 115031-96-4; CF_2=NF, 338-66-9; $CF_3N(F)CF$=NBr, 115046-73-6; CF_3N=CF_2, 371-71-1; cyanuric fluoride, 675-14-9.

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Synthesis of 7-Oxygenated Aporphine Alkaloids from a 1-Benzylideneisoquinoline Enamide

George R. Lenz*

Department of Medicinal Chemistry, G. D. Searle and Company, Skokie, Illinois 60680

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A synthesis of 7-oxygenated aporphine alkaloids is described which proceeds from readily available benzylideneisoquinoline enamides. Photocyclization of a β-acetoxy enamide leads to a protected 7-hydroxydehydronoraporphine, which can be converted into both the *cis*- and *trans*-7-hydroxyaporphines in both the nor and parent series and also the *cis*-7-methoxyaporphines in both the nor and parent series.

The aporphine alkaloids constitute a large family of benzylisoquinoline-derived alkaloids with over 300 variations isolated and identified from natural sources.[1-3] In recent years, as isolation procedures have improved, new types of aporphines have been identified. These have included the dehydro- and didehydroaporphines,[3] the 7-

* Address correspondence to author at: Health Care Research and Development, The BOC Group Technical Center, 100 Mountain Avenue, Murray Hill, NJ 07974.

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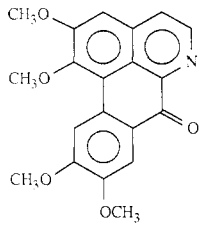
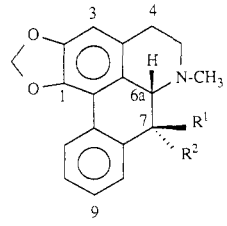
methyl deriatives,[3] an aporphine with an oxazine ring fused across the 6,7-positions,[4,5] and the entire family of 7-oxygenated aporphines. The members of this family range from the relatively simple 7-oxoaporphines (e.g. oxoglaucine (**1**)) to the more complex 7-hydroxy (e.g. ushinsunine **2** and oliveroline **3**) and 7-methoxy aporphines. Recently, the equivalent of a 7-methoxydehydro derivative **4** has been identified in the benzylisoquinoline-derived aristolactams.[6] The distribution[7] and biogenesis[8] of the

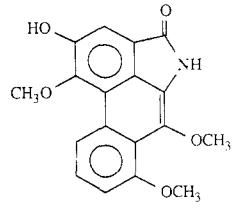


(1)



(2) (R^1=H, R^2=OH)

(3) (R^1=OH, R^2=H)



(4)

7-oxygenated aporphines have been described. There is currently interest in these alkaloids because of their structural relationship to such sympathomimetic amines as pseudoephedrine and ephedrine.[9,10] A limited number of synthetic approaches to the 7-hydroxyaporphines have been described,[11-15] but none for the 7-methoxyaporphines. This report describes our synthetic approach to the preparation of the 7-hydroxy- and 7-methoxyaporphines in the parent and nor series, and the 7-methoxydehydronoraporphines, all proceeding from a 1-benzylideneisoquinoline enamide and occurring through a common intermediate.

Originally it was envisaged that the functionality in a dehydroaporphine, containing an oxazolone ring fused across the 6,7-positions, could result in the various types of 7-substituted aporphines (cf. **16** → **17**). This approach was conceived and carried out by Ninomiya and co-workers 10 years ago.[16] It fails because sterically this stilbene–phenanthrene photocyclization does not occur, an observation we have confirmed. The solution to this problem is to use the precursor to the oxazolone, a β-acetoxybenzylideneisoquinoline enamide, which is readily prepared by using methodology we developed.[17]

Scheme I shows the successful realization of this approach. The enamide **5**, readily prepared from dihydropapaverine and ethyl chloroformate or diethyl pyrocarbonate,[5,18] is converted to its β-acetoxy derivative **6** by lead tetraacetate[19] by an improved procedure. The acetoxy enamide **6** readily undergoes stilbene → phenanthrene photocyclization; analogous to that of the nonacetoxylated parent **5**,[18] with the regiochemistry illustrated.[20] Although the yield of **7** is only 40–45%, it is average for this type of photocyclization, and the product can be readily isolated from the reaction mixture by crystallization from methanol, thus avoiding chromatography. The acetate can be readily removed with base. Hydride reduction of the phenol (**8**) gave only a noncharacterizable tar. As a result, the phenol was protected as its benzyl ether (**9**). Hydride reduction of **9** apparently stops at the methanol stage because the nor compound **10** was isolated in excellent yield. Hydrogenation of benzyl ether **10** over Adams' catalyst[21] smoothly and unexpectedly consumed 5 mol of hydrogen, with an inflection point after 4 mol. Two products were apparent from TLC and were separable by chromatography. The major product (**12**) was isolated in 52% yield and identified as the *trans*-7-hydroxynoraporphine.[22] This stereochemistry was assigned because of the large characteristic coupling constant (J = 12 Hz) of the 7-hydrogen (δ 4.81). The minor product (**13**) was isolated in 30% yield and identified as the *cis*-7-hydroxynoraporphine also because of the characteristically small coupling constant (J = 3 Hz) for the 7-hydrogen (δ 4.73).[1-3] The nor compounds **12** and **13** were then smoothly converted to the known 7-hydroxyaporphine alkaloids **14** and **15**[12] by using a modified Eschweiler–Clark reaction.[23] This synthetic pathway allows the stereoselective preparation of the more commonly occurring stereochemistry, trans, in both the nor and *N*-methyl-7-hydroxyaporphines.

The isolation of **12** from the hydrogenation of **10** was unexpected especially since it is the product of formal trans addition of hydrogen in a catalytic reaction. It is unlikely that this is occurring. The benzyl ether in **10** is catalytically cleaved to form the 7-hydroxynoraporphine (**11**), which possesses weak enamine properties, analogous to the dehydroaporphines.[24,25] Protonation of **11** at C-7 in acetic acid generates the 7-hydroxyiminium intermediate (A). Subsequently, the hydroxyl group in A can coordinate with the catalyst surface enabling hydrogen to add from the same side as the hydroxyl group, thus resulting in net trans addition. The usual cis addition observed with **13** can occur either through hydrogenation of **11** itself or inter-

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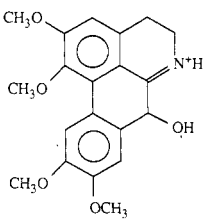

(A)

mediate A, provided that the hydroxyl group is not strongly coordinating. The 5 mol of hydrogen consumed in the reaction are the result of (i) cleavage of the benzyl ether, (ii) hydrogenation of the toluene thus formed to methylcyclohexane, and (iii) reduction of **11** to the 7-hydroxynoraporphines. A control experiment demonstrated that toluene was reduced to methylcyclohexane under these conditions.

The formation of the 6,7-oxazolone-fused nordehydroaporphine (**17**) was investigated both photochemically and thermally (Scheme II). The oxazolone **16** does not photocyclize to **17** under a variety of conditions.[16,17] However, the phenol **8** can be induced to form **17** upon prolonged refluxing in 4-picoline. The phenol **8** is very strongly hydrogen bonded and can actually undergo molecular distillation at 210 °C without cyclizing. In picoline, the deep burgundy anion is formed, which slowly cyclizes to **17**.

The 7-methoxyaporphines were prepared from the phenol **8** as illustrated in Scheme III. The phenol **8** is readily converted to its methyl ether **18**, which undergoes hydride reduction, again stopping at the methanol stage, to form the sensitive 7-methoxynordehydroaporphine (**19**). Reduction with Adams' catalyst, in this case, stops at 1 mol of hydrogen, and the *cis*-methoxynoraporphine (**20**) was isolated exclusively in 72% yield. The stereochemistry in **20** is again assigned because of the small coupling constant between the 6a- and 7-hydrogens. If this hydrogenation is proceeding through an intermediate like A, then the methyl ether would be expected to shield that side of the molecule from the catalyst surface, thus forming the cis adduct. Methylation of **20** to the *cis*-7-methoxyaporphine (**21**) proceeded uneventfully.

In summary, the protected 7-hydroxydehydronoraporphine (**8**), readily obtainable from dihydropapaverine in three steps, can be converted into the majority of the 7-oxygenated aporphines: (i) *cis*- and *trans*-7-hydroxynoraporphines, (ii) *cis*- and *trans*-7-hydroxyaporphines, (iii) *cis*-7-methoxynoraporphines, and (iv) *cis*-7-methoxyaporphines. The missing *trans*-7-methoxyaporphine is potentially available by O-methylation of the *trans*-7-hydroxyaporphines, although this experiment has not been conducted.

Experimental Section

General Methods. General conditions and apparatus have been previously described.[5]

Preparation of the (*Z*)-Acetoxy Enamide (6) of Ethyl 1-(3′4′-Dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (5). The enamide **5** (10.0 g, 24.2 mmol) is dissolved in 550 mL of benzene, containing 5 mL of pyridine, and dried by refluxing and using a Dean–Stark trap. The solution was placed under argon, and 15 g of lead tetraacetate, dried under vacuum over refluxing acetone, was added. After the mixture was stirred for 18 h, any excess lead(IV) was reduced with excess glycerine. After being stirred for an additional 4 h, the mixture was washed three times with water (250 mL). The benzene solution was dried with sodium sulfate and diluted with 100 mL of pyridine before being refluxed under argon, for 17 h. The faintly yellow solution was cooled, washed three times with water (250 mL), dried with sodium sulfate, and evaporated to a semisolid. This residue was triturated with ether (75 mL), filtered, and washed with mixed hexanes (bp 40–60 °C) to yield 7.10 g of the acetoxy enamide **6**. The mother liquor deposited an additional 1.1 g of **6** for a total of 8.2 g (72%), mp 146–8 °C.[17]

Photocyclization of the Acetoxy Enamide to Ethyl 7-Acetoxy-1,2,9,10-tetramethoxy-6a,7-didehydronoraporphine-6-carboxylate (7). A solution of acetoxy enamide **6** (1.5 g, 3.18 mmol) in benzene (165 mL), containing iodine (0.25 g), was irradiated, under argon, with a 450-W medium-pressure mercury arc through a Pyrex filter for 9.5 h. Three separate equivalent runs were combined and washed with 5% aqueous sodium hydrogen sulfite, and then the benzene solution was dried with sodium sulfate. After drying, the solution was treated with decolorizing charcoal, filtered through filter-aid, and evaporated to an oil. The oil was taken up in methanol, whereupon the photoproduct **7** crystallized (1.93 g, 43%): mp 194–197 °C; ν_{max} 1770, 1700, 1600, and 1515 cm^{-1}; λ_{max} 235 (17 900), 258 (40 300), 268 (52 200), 285 (20 200), 315 (12 400), 327 (12 800), 350 (3200), and 369 nm (1400); λ_{min} 226 (16 500), 296 nm (8700); ^{1}H NMR δ 9.22 (1 H, s, 11-H), 7.22 (1 H, s), 7.03 (1 H, s), 4.18 (2 H, q), 4.05 (3 H, s), 4.02 (3 H, s), 3.99 (3 H, s), 3.90 (3 H, s), 3.15 (2 H, broad s), 1.89 (3 H, s), and 1.27 (3 H, t). The signal(s) for the C5-methylene protons are buried under the methoxy methyl signals. Anal. Calcd for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 64.29; H, 5.96; N, 3.07.

Ethyl 7-Hydroxy-1,2,9,10-tetramethoxy-6a,7-didehydronoraporphine-6-carboxylate (8). (a) Acid-Catalyzed Hydrolysis. The acetate **7** (184 mg, 0.39 mmol) was suspended in 25 mL of ethanol, containing *p*-toluenesulfonic acid monohydrate (293 mg), and brought to reflux. TLC (1:1 ethyl acetate/toluene) on silica indicated a less polar product. After 26 h of reflux, the solution was cooled and diluted with a small amount of water (5 mL), and the crystalline product was collected to yield the strongly hydrogen bonded phenol **8** (117 mg, 85%): mp 189.5–190.5 °C; ν_{max} 3440, 3180, 1695 (w), 1655 (s), 1615, 1600, and 1510 cm^{-1}; λ_{max} 265.5 (57 800), 285 (25,000), 312 (11 300), and 325 nm (12 000); λ_{min} 304 (9200) and 317 nm (10 300); ^{1}H NMR δ 9.17 (1 H, s, 11-H), 7.86 (1 H, s), 7.00 (1 H, s), 4.35 (2 H, q), 4.07 (3 H, s), 4.04 (3 H, s), 3.98 (3 H, s), 3.87 (3 H, s), 3.17 (2 H, t), 1.39 (3 H, t). The C5-methylene protons resonances are burried underneath the methoxy methyl signals. Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90; N, 3.28. Found: C, 64.19; H, 5.98; N, 3.39.

(b) Based-Catalyzed Transesterification. A solution of the acetate **7** (2.20 g, 4.68 mmol) in tetrahydrofuran (80 mL) was diluted with anhydrous methanol (80 mL) and placed under argon. Sodium methoxide (2.0 g) was added, and the mixture was stirred magnetically for 1.5 h, at which time citric acid (2 g) in water (40 mL) was added. The majority of the organic solvents was removed by evaporation, and the precipitate was filtered and dried to yield the free phenol **8** (1.91 g, 95%).

Ethyl 7-(Benzyloxy)-1,2,9,10-tetramethoxy-6a,7-didehydronoraporphine-6-carboxylate (9). A solution of the phenol **8** (620 mg, 1.45 mmol) in acetone (40 mL) was placed under argon, and benzyl bromide (500 mg, 2.9 mmol) and potassium carbonate (400 mg, 2.9 mmol) were added before the mixture was refluxed for 6 h. The reaction mixture was evaporated to a solid, stirred with methylene chloride (20 mL), and extract flash chromatographed.[26] Elution with 5% ethyl acetate in methylene chloride yielded the protected phenol **9** (616 mg, 82%), crystallized from methanol and water: mp 147.5–150.5 °C; ν_{max} 1700 cm^{-1}; λ_{max} 238 (20 400), 258 (50 200), 268 (62 900), 288 (27 000), 315 (12 200), 328 (12 800), 353 (2600), and 372 nm (2100); λ_{min} 228 (16 300), 304 (9200), 320 (11 400), and 364 nm (1500); ^{1}H NMR δ 9.21 (1 H, s, 11-H), 7.61 (1 H, s), 7.34 (5 H, m), 7.03 (1 H, s), 5.00 (2 H, s), 4.19 (2 H, q), 4.05 (3 H, s), 4.00 (3 H, s), 3.94 (3 H, s), 3.16 (2 H, br s), and 1.21 (3 H, t). The signal(s) for the protons at C5 are under the methoxyl signals. Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.04; N, 2.71. Found: C, 69.63; H, 6.03; N, 2.83.

7-(Benzyloxy)-1,2,9,10-tetramethoxy-6a,7-didehydronoraporphine (10). A solution of the protected phenol **9** (776 mg, 1.50 mmol) in benzene (125 mL), under argon, was dried by refluxing and using a Dean–Stark trap. The dry solution was cooled, and a 70% solution of sodium bis(methoxyethoxy)alu-

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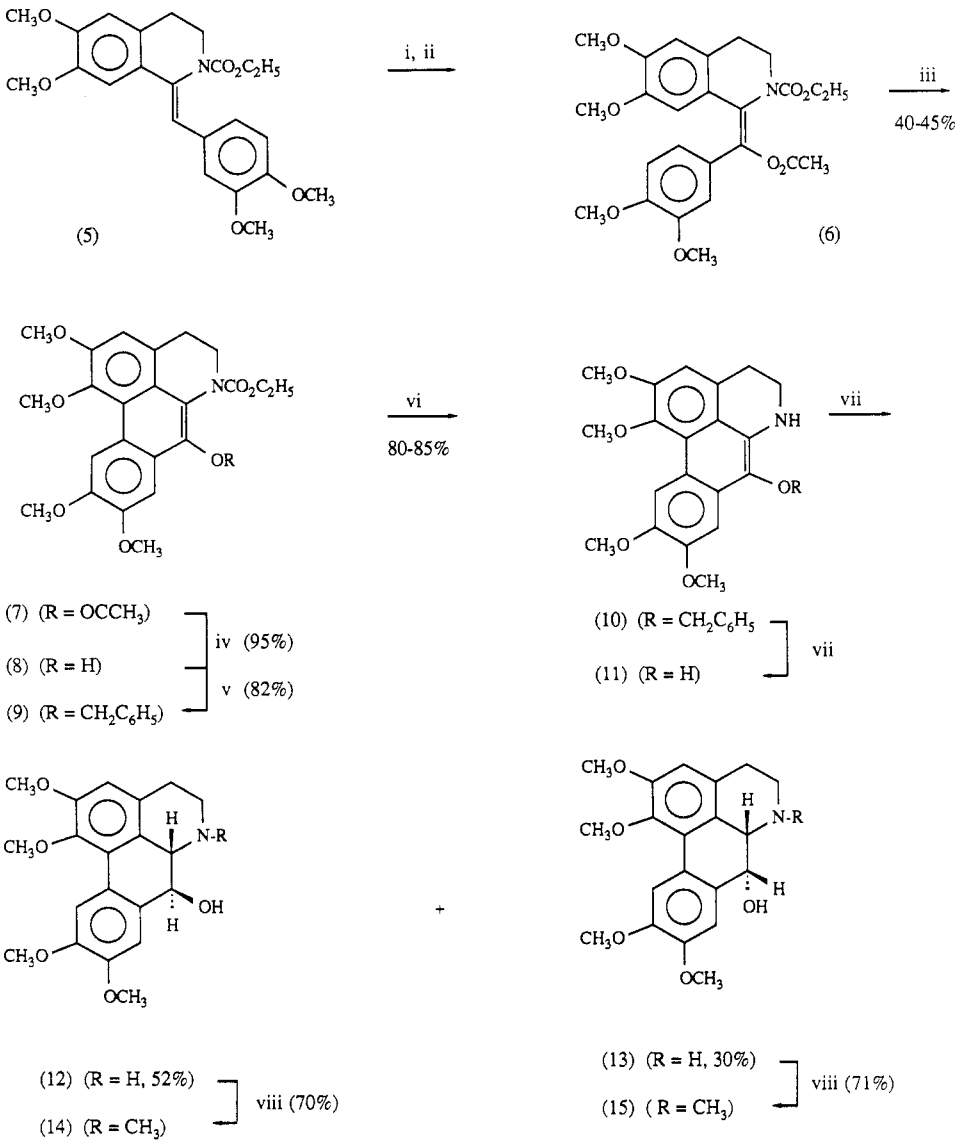
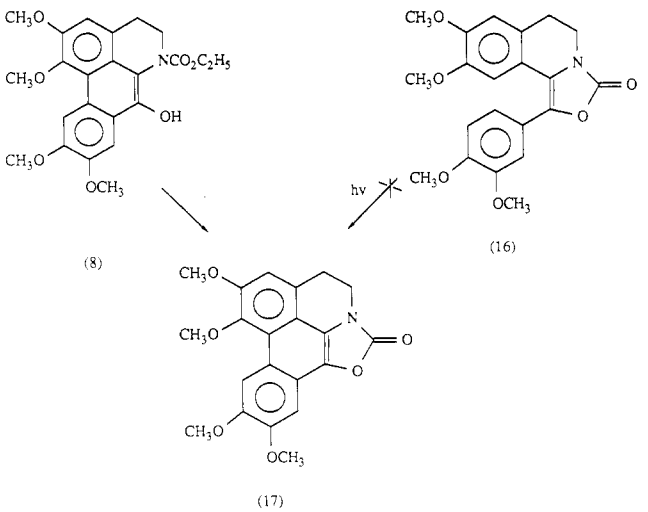
Scheme I[a]



[a] Reagents: (i) lead tetraacetate, benzene; (ii) pyridine, Δ; (iii) $h\nu$, iodine, benzene; (iv) sodium methoxide, methanol; (v) benzyl bromide, potassium carbonate, acetone; (vi) $NaH_2Al(OCH_2CH_2OCH_3)_2$; (vii) H_2/Pt, acetic acid; (viii) HCHO (aq), $NaCNBH_3$.

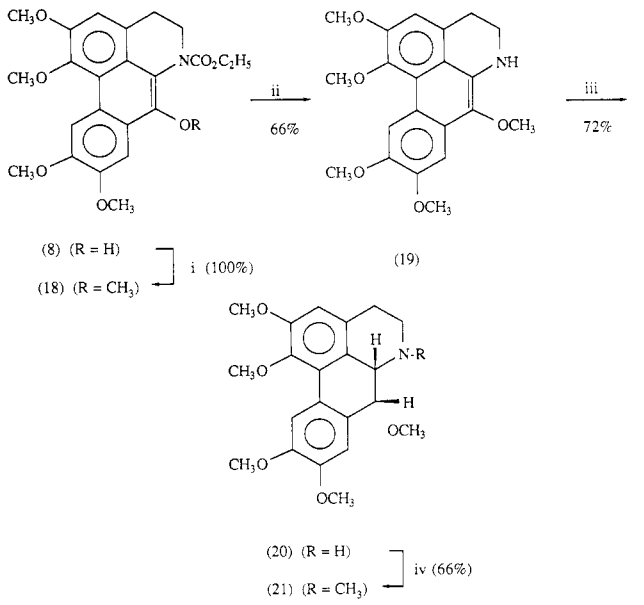
Scheme II



minum hydride in benzene (6 mL) was added. After the mixture was stirred at room temperature for 18 h, excess hydride reagent was quenched with a saturated Rochelle salt solution (50 mL). The organic layer was separated, dried with sodium sulfate, and evaporated to an oil. The oil was immediately placed under nitrogen, methanol (15 mL) was added, and the mixture was cooled to −15 °C. The product crystallized and was filtered under nitrogen to yield **10** (536 mg, 80%): mp 127–128 °C; ν_{max} 3440 (broad), 1630, 1605, and 1510 cm^{-1}; λ_{max} 240 (ϵ 24 500), 270 (43 600), 333 (11 400), and 338 nm (3200); λ_{min} 227 (17 900) and 306 nm (6100); ^1H NMR δ 9.15 (1 H, s, 11-H), 7.25–8.10 (6 H, m), 6.98 (1 H, s), 5.01 (2 H, s), 4.03 (3 H, s), 4.01 (3 H, s), 3.93 (6 H, s), and 2.75–3.0 (4 H, m). Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.91; H, 6.16; N, 3.19.

***cis*- and *trans*-7-Hydroxy-1,2,9,10-tetramethoxynoraporphines (13 and 12).** The benzyl derivative **10** (532 mg, 1.19 mmol) was added to a prereduced suspension of Adams' catalyst, prepared from PtO_2 (220 mg), in acetic acid (125 mL). The hydrogen reduction was conducted at room temperature and pressure for 24 h. During this period, 5 equiv of hydrogen were consumed, four rapidly and the fifth slower. After filtration and washing of the catalyst, the acetic acid solution was condensed to a small volume, taken up in methylene chloride (25 mL), and washed with 5% sodium bicarbonate solution (3 × 50 mL). The organic solution was dried with 5% sodium sulfate, evaporated, and flash chromatographed. Colored impurities were removed with 5% methanol in methylene chloride. Elution with 10% methanol in methylene chloride furnished the *trans*-7-hydroxynoraporphine **12** (220 mg, 52%): mp 152–153 °C; ν_{max} 3420, 2840,

Scheme III[a]



[a] Reagents: (i) Methyl iodide, potassium carbonate, acetone; (ii) $NaH_2Al(OCH_2CH_2OCH_3)_2$; (iii) H_2/Pt, acetic acid; (iv) HCHO-(aq), $NaCNBH_3$.

1517, and 1120 cm^{-1}; λ_{max} 237 (sh) (ϵ 20700), 274 (sh) (9900), 282.5 (12200), 300.5 (12100), and 315 (sh) nm (8000); λ_{min} 255 (3500) and 291 nm (10500); ^1H NMR 8.02 (1 H, s), 7.27 (1 H, s), 6.57 (1 H, s), 4.81 (1 H, d, J = 12 Hz), 3.92 (3 H, s), 3.88 (6 H, s) and 3.65 (3 H, s). The remaining aliphatic hydrogens are spread out under the methoxyl group resonances from δ 2.6–4.0; m/z 357.1577 (M^+, calcd 357.1577, 26), 356 (21), 355 (32), 340 (30, M – OH), 339 (25, M – H_2O), 327 (46, M – CH_2O), 326 (39), 324 (25, M – CH_3 – H_2O), and 45 (100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.26; H, 6.51; N, 4.07.

Continued elution with 17–20% methanol in methylene chloride furnished the *cis*-7-hydroxynoraporphine **13** (130 mg, 30%): mp 130 °C dec; ν_{max} 3430, 1515, and 1115 cm^{-1}; λ_{max} 237 (sh) (ϵ 22100), 285 (13400), 298 (12800) and 310 (sh) nm (9800); λ_{min} 256.5 (3900) and 293 nm (12600); ^1H NMR δ 8.17 (1 H, s), 6.89 (1 H, s), 6.57 (1 H, s), 4.73 (1 H, d, J = 3 Hz), 3.91 (6 H, s), 3.87 (3 H, s), and 3.68 (3 H, s). The remaining aliphatic hydrogens are spread out between δ 2.1–4.1; m/z 357.1559 (M^+, calcd 357.1577, 39.5), 356 (26), 355 (19.5), 340 (37.5), 339 (41), 368 (26), 327 (37), 326 (48), 325 (22), 60 (82), and 45 (100). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.92; H, 6.35; N, 3.71.

***cis*-7-Hydroxy-1,2,9,10-tetramethoxyaporphine (15).** The *cis*-noraporphine **13** (130 mg, 0.36 mmol) was dissolved in acetonitrile (5 mL), containing aqueous formaldehyde (0.28 mL of a 37% solution) and sodium cyanoborohydride (72 mg). After 1.5 h, the pH of the solution was adjusted to pH 8 with 15% aqueous acetic acid. The solution was then poured into 5% sodium bicarbonate solution (100 mL) and extracted with methylene chloride (3 × 25 mL). After drying with sodium sulfate, the residue was flash chromatographed. Elution with 5% methanol in methylene chloride yielded **15** as an oil. Crystallization from ether yielded **15** (95 mg, 71%): mp 139–145 °C; ν_{max} 3510, 1605, 1585, and 1520 cm^{-1}; λ_{max} 219 (ϵ 36800), 237 (sh) (21300), 284 (14800), 296 (14000), and 307 (sh) nm (11100); λ_{min} 254 nm (ϵ 3500); ^1H NMR δ 8.17 (1 H, s), 6.91 (1 H, s), 6.57 (1 H, s), 4.63 (1 H, d, J = 3 Hz), 3.94 (3 H, s), 3.91 (3 H, s), 3.87 (3 H, s), 3.67 (3 H, s), 2.58 (3 H, s, NCH_3), and 2.0–4.0 (5 H, m); m/z 371 (M^+, 47), 370 (31), 369 (87), 354 (100), 340 (82), 206 (55). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.80; H, 6.65; N, 3.70.

***trans*-7-Hydroxy-1,2,9,10-tetramethoxyaporphine (14).** The *trans*-noraporphine **12** (200 mg, 0.56 mmol) was dissolved in acetonitrile (8 mL), and water (2 mL) was then added. After addition of sodium cyanoborohydride (111 mg) to the stirred solution, 37% aqueous formaldehyde (0.43 mL) was added. After 2 h, the solution was poured into water (50 mL) and extracted with methylene chloride (4 × 25 mL). The organic extracts were dried with sodium sulfate and evaporated, and the residue was flash chromatographed. Elution with 7.5% methanol in methylene chloride yielded **14** as an oil. Crystallization from ether yielded the aporphine **14** (145 mg, 70%): mp 136.5–138.5 °C; ν_{max} 3450, 1585, 1515, and 1120 cm^{-1}; λ_{max} 218 (ϵ 33900), 238 (sh) (20400), 281.5 (13200), 300 (13700), and 314 (sh) nm (9600); λ_{min} 250 (ϵ 4000) and 290 nm (11500); ^1H NMR δ 8.04 (1 H, s), 7.25 (1 H, s), 6.57 (1 H, s), 4.51 (1 H, d, J = 12 Hz), 3.97 (3 H, s), 3.91 (3 H, s), 3.88 (3 H, s), 3.67 (3 H, s), 3.33 (1 H, d, J = 12 Hz), 2.57 (3 H, s, NCH_3), 2.5–3.5 (4 H, m); m/z 371 (M^+, 44), 370 (17), 369 (5), 341 (22), 340 (100), 206 (62). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.80; H, 6.84; N, 3.81.

Cyclization of the 6-Carbethoxy-7-hydroxydehydronoraporphine to the Oxazolone (17). The phenol **8** (246 mg, 0.58 mmol) was dissolved in 3-picoline (15 mL, bp 143 °C), placed under argon, and refluxed for 21 h. The deep burgundy solution was cooled and poured in 6 N HCl (200 mL) and extracted with chloroform (3 × 35 mL). The lightly colored solution was dried with sodium sulfate and evaporated. The residue was recrystallized by dissolving in methylene chloride, adding methanol, and evaporating the methylene chloride to yield **17** (144 mg, 65%): mp 268.5–273.5 °C dec; ν_{max} 1765 cm^{-1}; λ_{max} (CH_2Cl_2) 265 (sh) (ϵ 51400), 272 (58300), 289 (19300), 319 (11700), 333 (14900), 367 (2900), and 383 nm (3300); λ_{min} (CH_2Cl_2) 286 (18900), 301 (6300), 324 (10800), 355 (1940), and 376 nm (2500); ^1H NMR δ 8.59 (1 H, s), 7.28 (1 H, s), 7.17 (1 H, s), 4.11 (2 H, t), 4.06 (3 H, s), 4.03 (6 H, s), 3.99 (3 H, s), 2.89 (2 H, t). Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.08; H, 4.95; N, 3.93.

Ethyl 1,2,7,9,10-Pentamethoxydehydronoraporphine-6-carboxylate (18). The phenol **8** (350 mg, 0.82 mmol) was dissolved in acetone (25 mL), containing methyl iodide (2 mL) and potassium carbonate (350 mg). The mixture was refluxed under nitrogen for 2 h, cooled, and diluted with distilled water (25 mL), and the organic solvents were evaporated to yield crystals of methyl ether **18** (362 mg, 100%): mp 186–188 °C; ν_{max} 1700, 1630, 1620, 1605, and 1510 cm^{-1}; λ_{max} 258 (sh) (ϵ 49000), 268 (62000), 285 sh (23000), 313 (11600), 326 (12200), 353 (1800), and 371 nm (1400); λ_{min} 302 (ϵ 9000) and 319 nm (11000); ^1H NMR δ 9.20 (1 H, s), 7.63 (1 H, s), 7.03 (1 H, s), 4.22 (2 H, q), 4.06 (6 H, s), 3.99 (3 H, s), 3.91 (3 H, s), 3.89 (3 H, s), 3.18 (2 H, t), and 1.24 (3 H, t). The C5 hydrogens are under the methoxyl resonances; m/z 441 (M^+, 23), 354 (34), 426 (9), 382 (8), and 28 (100). Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 64.95; H, 6.37; N, 3.03.

1,2,7,9,10-Pentamethoxydehydronoraporphine (19). The carbethoxy derivative **18** (327 mg, 0.74 mmol) was dissolved in 50 mL of dry benzene, placed under argon, and reduced with a 70% solution of sodium bis(methoxyethoxy)aluminum hydride in benzene (2.5 mL). After 16 h, the light orange solution was quenched with saturated ammonium chloride solution (50 mL), whereupon it turned light yellow. After the solution was dried with sodium sulfate, the solvent was evaporated and the residue was flash chromatographed. Elution with 10% ethyl acetate in methylene chloride gave the sensitive dehydronoraporphine **19**, which was crystallized from methanol at –78 °C (184 mg 66%): mp 114 °C dec; ν_{max} 3390, 1620, 1600, and 1510 cm^{-1}; ^1H NMR δ 9.13 (1 H, s), 7.30 (1 H, s), 6.97 (1 H, s), 4.11 (3 H, s), 4.07 (3 H, s), 4.01 (3 H, s), 3.92 (3 H, s), 3.88 (3 H, s), 3.45 (2 H, m), and 3.22 (2 H, t). Anal. Calcd for $C_{21}H_{23}NO_5 \cdot 0.5\ H_2O$: C, 66.65; H, 6.39; N, 3.70. Found: C, 66.25; H, 6.37; N, 3.44.

***cis*-1,2,7,9,10-Pentamethoxynoraporphine (20).** The dehydronoraporphine **19** (151 mg, 0.40 mmol) was hydrogenated at room temperature and atmospheric pressure in acetic acid (35 mL) over prereduced platinum oxide (79 mg) for 3 h. After filtering the catalyst, the solvent was evaporated and the residue was dissolved in chloroform (25 mL). After washing with 5% sodium bicarbonate solution (25 mL), the solution was dried with sodium sulfate, the solvent was evaporated, and the residue was flash chromatographed. Elution with 5% methanol in chloroform yielded an oil, which was crystallized from ether to yield the aporphine **20** (107 mg, 72%): mp 169–173 °C; ν_{max} 3460, 1520, and 1115 cm^{-1}; λ_{max} 219 (ϵ 35600), 235.5 (sh) (25000), 286 (15300), and 297 nm (15000); λ_{min} 255.5 nm (ϵ 3900); ^1H NMR δ 8.19 (1 H, s), 6.77 (1 H, s), 6.57 (1 H, s), 4.08 (1 H, d, J = 3.5 Hz), 3.95 (3 H, s), 3.91 (3 H, s), 3.86 (3 H, s), 3.70 (3 H, s), 3.23 (3 H, s),

2.15-4.0 (5 H, m); m/z 371 (M^+, 6), 356 (18), 340 (2.6), 327 (4.6), 43 (100). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.85; H, 6.93; N, 3.52.

***cis*-1,2,7,9,10-Pentamethoxyaporphine (21).** The noraporphine **20** (255 mg, 0.69 mmol) was dissolved in acetonitrile (10 mL) containing water (2.5 mL). Sodium cyanoborohydride (178 mg), followed by 37% aqueous formaldehyde solution (0.55 mL), was added to this magnetically stirred solution. After 2 h the mixture was diluted with water and extracted with methylene chloride (4 × 30 mL). After treatment with decolorizing carbon, the organic solution was filtered through filter-aid to give a light yellow solution. After removal of the solvent, the residue was crystallized from ether, containing a small amount of methanol, to yield the aporphine **21** (175 mg, 66%): mp 186-191 °C; ν_{max} 1605, 1520 and 1115 cm^{-1}; λ_{max} 218 (ϵ 40 500), 236 (sh) (24 000), 285 (16 000), and 298 nm (15 000); λ_{min} 255 nm (ϵ 4000); ^1H NMR δ 8.15 (1 H, s), 6.78 (1 H, s), 6.55 (1 H, s), 4.30 (1 H, d, J = 3 Hz), 3.95 (3 H, s), 3.91 (3 H, s), 3.86 (3 H, s), 3.68 (3 H, s), 3.18 (3 H, s, $CHOCH_3$), 2.85-3.45 (2 H, m), 2.3-2.75 (2 H, m), 2.57 (3 H, s, NCH_3); m/z 385 (M^+, 21), 383 (26), 370 (100, $M^+ - CH_3$), 368 (78, $M^+ - CH_3 - H_2$). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.48; H, 7.06; N, 3.95.

Synthesis and Conformational Analysis of Two Chiral (Nonracemic) 4-Substituted Quinolizidines

John M. McIntosh* and Luca C. Matassa

Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada N9B 3P4

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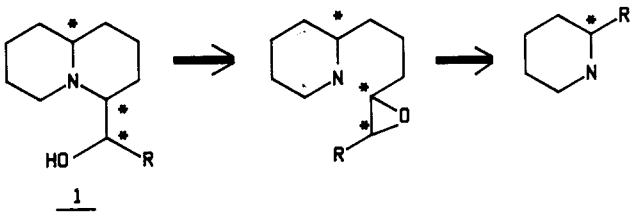
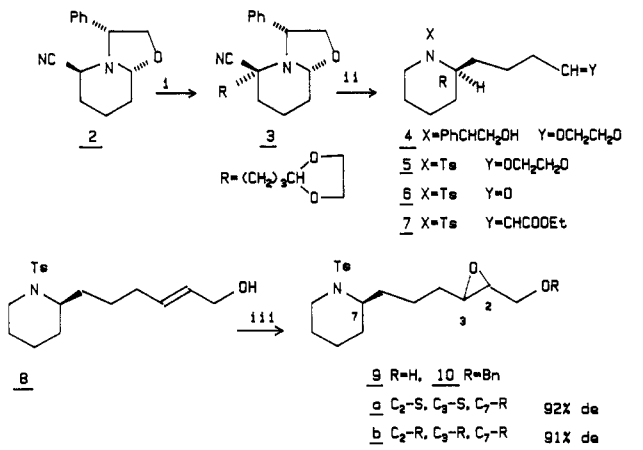
The synthesis of (4*R*,10*R*,11*R*)- and (4*S*,10*R*,11*S*)-4-(1,2-dihydroxyethyl)quinolizidine (**13a** and **13b**) in enantiomerically pure form has been carried out. The chiral centers were established by formation of a chiral 2-substituted piperidine and cyclization of optically active epoxides. The solution conformations of these molecules have been determined by 300-MHz proton NMR measurements.

Chiral β-amino alcohols are interesting molecules from several points of view. Many exhibit potent biological activity (e.g., ephedrine, quinine). Their use as chiral directing agents in organic synthesis has been widely exploited.[1] More importantly from a synthetic organic viewpoint, they appear to possess the capability of functioning as catalysts in a number of situations. For example, derivatives in which the nitrogen has been quaternized are useful phase-transfer catalysts, capable of inducing asymmetry.[2] The hydroxy group appears to be obligatory for significant chirality transfer in these reactions.[3] Also, chiral amino alcohols (frequently obtained from amino acids) have been used successfully as chiral catalysts in a number of reactions.[4] Some time ago, we set out to examine the effect of small stereochemical differences on such chirality transfers. To achieve this, we required a set of stereoisomers in which the spatial arrangement of the heteroatoms was well defined and easily determined. To simplify the synthetic plan, it was necessary that such molecules be derived by small changes, late in a general synthetic route. The choice of the target molecules was influenced strongly by our previous experience[5] with the

Scheme I



Scheme II[a]



[a] (i) LDA/THF/-78 °C, 4-iodobutanal ethylene ketal (84%); (ii) $NaBH_4$/EtOH (82%); H_2/Pd/C; TsCl/Et_3N/CH_2Cl_2; H_3O^+ (74%); $(EtO)_2P(O)CH_2COOEt$/BuLi (92%); Dibal (88%); (iii) Ti(O-iPr)$_4$/DET/BuOOH.

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