Aporphines 24. The Synthesis of *N*-Alkylderivatives of Bulbocapnine and Isocorydine

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The synthesis of three new racemic aporphine alkaloids (**1b**, **1c** and **2**) is reported and these alkaloids are fully characterized. The method of synthesis involved either a Bischler-Napieralski-Pschorr sequence or a Reissert alkylation-Pschorr cyclization route. The Pschorr cyclization also gave the morphinandienones **7a** and **7b**, respectively.

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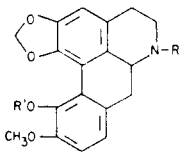
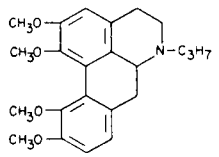
The current interest in the aporphine alkaloids centers on their potential therapeutic application in the treatment of neuropathological disorders such as Parkinson's Disease, as neuroleptic agents, and in cancer chemotherapy (1,2). The finding that apomorphine (10,11-dihydroxyaporphine) is a potent direct agonist of central dopamine receptors in mammals stimulated investigations of its role and that of dopamine in physiological and pathological states. Replacement of the methyl group on the nitrogen of apomorphine (3,4) and related monohydroxyaporphines (5) with a *n*-propyl group considerably increased the pharmacological activity of these aporphines. The antagonistic activity of (+)-bulbocapnine (**1a**) to dopamine in the production of cyclic-AMP when added to adenylate cyclase from rat brain prompted the synthesis of *N*-*n*-propylnorbulbocapnine (**1c**) (6), the corresponding *O*-methyl derivative **1b** and *N*-*n*-propylnorisocorydine (**2**) for biological evaluation.

As a logical first approach we considered the *N*-demethylation of (+)-bulbocapnine followed by alkylation with the appropriate alkyl function. An unsuccessful attempt to prepare norbulbocapnine with cyanogen bromide in chloroform (7) led to ring cleavage to give a phenanthrene. Conditions for the *N*-demethylation of an aporphine have been developed (8) but ring cleavage was also an ever present side reaction. It thus seemed most expeditious to undertake the more tedious total synthesis of the racemic aporphine alkaloids **1b**, **1c** and **2** employing either a Bischler-Napieralski-Pschorr sequence (Scheme 1) or a Reissert alkylation-Pschorr cyclization route (Scheme 3). The total synthesis of these aporphine alkaloids is the subject of this report.



1a, R = CH_3; R' = H (Bulbocapnine)
b, R = *n*-C_3H_7; R' = CH_3
c, R = *n*-C_3H_7; R' = H



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An Arndt-Eistert homologation has been applied to produce the amides **3a**,**b** (Scheme 1) required for the Bischler-Napieralski cyclization in the synthesis of the racemic forms of the alkaloids pukateine (9) and bulbocapnine (10). Alternatively, the amides **3a** and **3b** were prepared by the treatment of the appropriate acid with the desired amine at 170-180° (11) using a slight excess of the amine. The amides **3a** and **3b** could be converted into the dihydroisoquinolines **4a** and **4b** with phosphorus oxychloride in refluxing acetonitrile. Quarternization with *n*-propyl iodide gave the quaternary salts **5a** and **5b**. Reduction of **5a** with potassium borohydride gave the tetrahydroisoquinoline **6a**. It should be noted that carbon-carbon cleavage reported for analogous nitrobenzyl isoquinolinium salts would not be expected to occur with such 3,4-dihydroisoquinolinium salts on the basis of the mechanism previously proposed (12). Further reduction of **6a** or **6b** over 10% palladium on carbon or platinum oxide in methanol or the direct reduction of **5a** over platinum oxide in absolute methanol (the reduction of **4a** to **8a** was carried out under similar conditions), followed by a Pschorr cyclization in 10% sulfuric acid over cuprous oxide gave a complex mixture of products. The aporphines **1b** (16%), **2** (6%) and the morphinandienones **7a** (3%) and **7b** (1%), respectively, were separated by preparative tlc and characterized by their uv, nmr, ir and mass spectra, as detailed in the Experimental. The formation of dienone-type compounds as well as aporphines from such Pschorr reactions has previously been reported (13). A mechanism has been proposed by Kametani, *et al.*, (14), which accounts for the formation of such morphinandienones.

When the Pschorr cyclization was carried out on the reduction product of **6b** in 20% sulfuric acid and glacial acetic acid (1:1) over copper/cuprous oxide, the yield of the corresponding products was slightly improved (20% for **1b** and 2% for **7b**). The separation of products was carried out on a silica gel column developed with ethyl acetate/methanol (99:1). In this case an additional product, veratryl acetate was also isolated. This product requires a carbon-carbon cleavage that is not mechanistically related to the previous borohydride cleavage referred to above (12).

The reduction of **4a** to **8a** was carried out under similar conditions to the reduction of **6**. An attempt to prepare the amine precursor **8b** of the desired bulbocapnine deriva-

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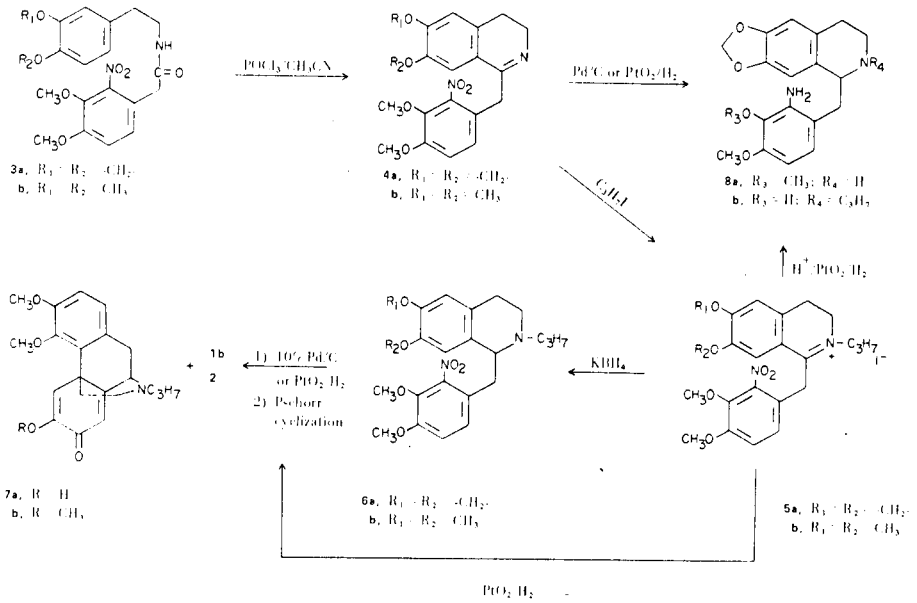
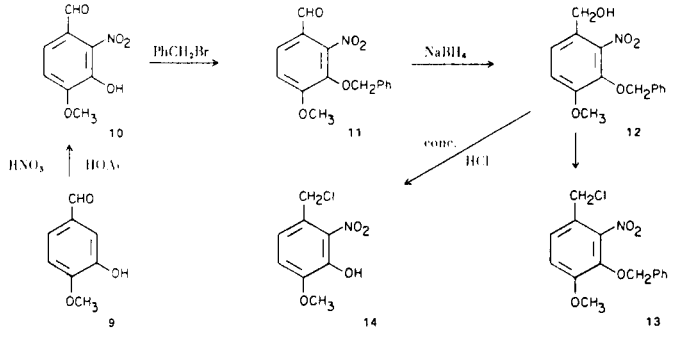
Scheme 1



tive **1c** using the acid catalyzed *O*-demethylation procedure used successfully for the synthesis of apocodeine (4) gave the amine obtained from reduction of **6a** (45%) and only minor amounts of **8b**. The complex mixture of products obtained from the acid catalyzed reduction of **5a** to **8b** forced us to abandon this route for the synthesis of **1c** and to employ a scheme in which the 11-hydroxy group was protected by a benzyl group which could be removed in the final stages of synthesis. Thus, the chloride **13** was prepared from isovanillin (**9**) in a sequence of reactions shown in Scheme 2.

Scheme 2



An attempt to convert **12** to the chloride **13** with concentrated hydrochloric acid gave the phenol **14** as the major product. However, **13** could be prepared in 86% yield by treating the alcohol **12** with thionyl chloride in dry acetonitrile at room temperature for several hours. 6,7-Methylenedioxyisoquinoline **15** (Scheme 3) was converted to the benzoyl Reissert compound **16** according to the method of Popp and Blount (15). The Reissert adduct **17** was prepared (78% yield) from **13** and **16** in sodium hydride/dimethylformamide and hydrolyzed with Triton-B to the benzylisoquinoline **18** (59%). Conversion to the quaternary salts **19a** and **19b** and reduction of **19b** over platinum oxide in methanol gave a mixture of the amines **20** and **21** which could be converted to **1c** (9%) along with a complex mixture of products, *via* a Pschorr cyclization. The identification of **1c** was confirmed by elemental analysis and by nmr, uv and mass spectra.

We conclude that the Reissert alkylation-Pschorr cyclization route for the synthesis of such aporphines is superior to the Bischler-Napieralski-Pschorr cyclization sequence.

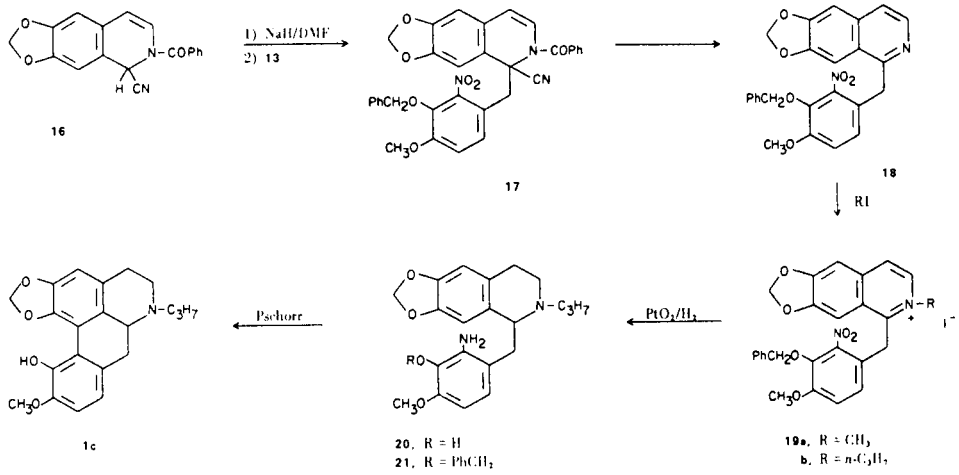
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were recorded on a Perkin-Elmer 700 spectrophotometer. Mass spectra were recorded on a Nuclide mass spectrometer 12-90-G. Nmr spectra were recorded on a Varian T-60 spectrometer, with TMS as the internal standard.

3,4-Dimethoxy-2-nitro-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-phenylacetamide (**3a**).

2-Nitrohomoveratric acid (16) (20 g., 0.083 mole) was added to a solution of 16.7 g. (0.01 mole) of homopiperonylamine (17) in 250 ml. of dry xylene. The mixture was allowed to reflux for 18 hours (with a Dean-Stark trap). The xylene was evaporated under reduced pressure and the solid residue was dissolved in chloroform, washed with 10% hydrochloric acid followed with 5% sodium bicarbonate. The chloroform layer was washed with water, dried and evaporated to give 29.9 g. (93%) of **3a**. Crystallization from ethanol gave a colorless solid, m.p. 156-157° (lit. (18) m.p. 158°).

Scheme 3



3,4-Dimethoxy-2-nitro-*N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide (**3b**).

Under identical conditions as above for **3a**, 12 g. (0.05 mole) of the acid and 10 g. (0.555 mole) of homoveratrylamine (Aldrich) gave 18.8 g. (94%) of **3b**, m.p. 88-90° (lit. (18) m.p. 64-65°); nmr (deuteriochloroform): δ aromatic, 7.0 (bs, 2H), 6.7 (bs, 3H), CH_2CO, 3.35 (s, 2H), CH_2CH_2, 3.40 (t, 2H), 2.70 (t, 2H), OMe, 3.95 (2s, 6H), 3.85 (s, 6H).

1-(3,4-Dimethoxy-2-nitrobenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (**4a**).

Freshly distilled phosphorus oxychloride (70 g.) was added dropwise to a well stirred solution of 28 g. (0.072 mole) of **3a** in 600 ml. of acetonitrile (dried over molecular sieves). The mixture was allowed to reflux for 1 hour, cooled, and the solvent removed under reduced pressure at 40°. The frothy dark residue was dissolved in hot water (80°) and filtered to remove the dark gummy residue. The salt of **4a** precipitated from the cooled aqueous solution. The solid was filtered (m.p. 220-225°), stirred in water/chloroform, made basic with ammonium hydroxide, and the chloroform layer was separated, washed, dried and evaporated to give 17.1 g. (64%) of **4a**, m.p. 163-165° (lit. (18) m.p. 164°); nmr (deuteriochloroform): δ aromatic, 6.95, 6.70 (2s, 4H), OCH_2O, 5.95 (s, 2H), $ArCH_2$, 4.10 (s, 2H), OCH_3, 3.85, 3.90 (2s, 6H).

1-(3,4-Dimethoxy-2-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**4b**).

Under identical conditions as described above for **4a**, 18.8 g. (0.047 mole) of **3b** and 27 ml. of phosphorus oxychloride gave 13.8 g. (76%) of **4b**, m.p. 158-159° (lit. (19) m.p. 159-160°); nmr (deuteriochloroform): δ aromatic, 6.95, 6.70 (2bs, 4H), CH_2CH_2, 3.75, 2.70 (2t, 4H), OCH_3 and $ArCH_2$, 3.90 (4s, 14H).

1-(3,4-Dimethoxy-2-nitrobenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline Propiodide (**5a**).

A solution of 10 g. (0.027 mole) of **4a** in 80 ml. of *n*-propyl iodide was allowed to reflux with stirring for 24 hours. The resulting precipitate was filtered while hot and the yellow crystals were washed with ether and dried to give 12.6 g. (86%), m.p. 165-170° dec.; nmr (deuteriochloroform): δ aromatic, 7.20, 7.25, 7.10, 6.85 (4s, 4H), OCH_2O, 6.10 (s, 2H), $ArCH_2$, 4.40 (s, 2H), N^+-CH_2, 4.25 (m, 4H), CH_2, 3.25 (t, 2H), 1.80 (m, 2H), $NC_2H_4CH_3$, 1.00 (t, 3H); ir (deuteriochloroform): ν max 1590, 1540, 1510, 1470, 1410, 1400, 1350, 1290, 1260, 1230, 1200 cm^{-1}.

Anal. Calcd. for $C_{22}H_{25}IN_2O_6$: C, 48.90; H, 4.66; N, 5.18; I, 23.48. Found: C, 48.82; H, 4.73; N, 5.09; I, 23.56.

1-(3,4-Dimethoxy-2-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Propiodide (**5b**).

Under identical conditions as for **5a**, 13.8 g. (0.036 mole) of **4b** in 80 ml. of *n*-propyl iodide gave 18.2 g. (92%) of **5b**, yellow crystals, m.p. 186-188°.

Anal. Calcd. for $C_{23}H_{29}IN_2O_6$: C, 49.65; H, 5.25; N, 5.03; I, 22.80. Found: C, 49.63; H, 5.20; N, 5.01; I, 22.79.

1-(2-Nitro-3,4-dimethoxybenzyl)-2-*n*-propyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**6a**).

An aqueous solution of 3.8 g. (0.072 mole) of potassium borohydride was added dropwise to a well stirred solution of 14 g. (0.026 mole) of **5a** in 1000 ml. of ethanol and 700 ml. of water. The bright yellow mixture was stirred for an additional 50 minutes at room temperature. The mixture was slowly heated and finally allowed to reflux for 1 hour. Solid potassium borohydride (1.75 g.) was added in small portions to the boiling reaction mixture. The mixture was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure and water/chloroform was added. The heterogenous solution was treated with 20% sodium hydroxide, the chloroform layer was separated, washed, dried and evaporated to give **6a** as an oil (9.48 g.) (88%); nmr (deuteriochloroform): δ aromatic, 6.90 (s, 2H), 6.40, 6.50 (2s, 2H), OCH_2O, 5.85 (s, 2H), OCH_3, 3.90, 3.95 (2s, 6H), $C_2H_4CH_3$, 0.65 (t, 2H); ir (carbon tetrachloride): ν max 1640, 1500, 1480, 1380, 1290 cm^{-1}. The hydrochloride salt of **6a** was prepared as a colorless solid, m.p. 112-115°.

Anal. Calcd. for $C_{22}H_{27}ClN_2O_6 \cdot \frac{1}{2}H_2O$: C, 57.46; H, 6.13; N, 6.09. Found: C, 57.60; H, 6.28; N, 6.04.

(±)-*O*-Methyl-*N*-*n*-propylnorbulbocapnine (**1b**).

Reduction Method A.

A solution of 8.4 g. (0.020 mole) of **6a** in 100 ml. of absolute methanol was hydrogenated with 0.3 g. of platinum oxide at 30 psi for 2 hours. The mixture was filtered and the solvent was

removed under reduced pressure. The residue (frothy solid: 7.22 g.) was dissolved in chloroform and washed with ammonium hydroxide solution, water, dried, and evaporated to give 6.7 g. (87%) of an oil: nmr (deuteriochloroform): δ aromatic, 6.45 (q, 2H, J = 8 Hz), 6.50 (s, 2H), OCH_3, 3.80 (2s, 6H), $C_2H_4CH_3$, 0.75 (t, 3H), NH_2, 4.90 (bs, 2H). The oil was used in the next step without further purification.

Reduction Method B.

Compound **5a** (5.3 g., 0.0098 mole) in 100 ml. of absolute methanol was hydrogenated over 0.3 g. of platinum oxide at 45 psi overnight and worked up as in Method A resulting in 3.74 g. (98%) of the oily amine. A solution of 4.9 g. (0.0128 mole) of this amine in 26 ml. of 10% aqueous sulfuric acid and 5 ml. of methanol was stirred at -5-0° and 9.2 ml. of 2*M* sodium nitrite (0.0186 mole) was added over a period of 5 minutes. Stirring of the cold deep red solution was continued an additional 20 minutes, then the excess nitrous acid was destroyed by the addition of sulfamic acid until a starch-iodide test was negative. The diazo solution was added dropwise (under nitrogen atmosphere) to a well stirred mixture of 5.2 g. of cuprous oxide in 190 ml. of 10% sulfuric acid. The reaction mixture was stirred at room temperature overnight. The mixture was filtered to give a brown solution whose *p*H was adjusted to about 6 with concentrated ammonium hydroxide. The cloudy green mixture was then stirred for 30 minutes, and was made strongly basic by the addition of more ammonium hydroxide (the mixture was cooled in an ice-bath during the addition). The deep blue solution was extracted with 150 ml. of chloroform by stirring the mixture for 20 minutes, and the aqueous solution was extracted further with 3 x 50 ml. of chloroform. The chloroform layers were combined, washed, dried over magnesium sulfate and evaporated, the dark residue was dissolved in ether and the insoluble solid produced was filtered (0.565 g.). The ether filtrate was evaporated to yield 2.41 g. of frothy solid. This mixture of products was separated on 12 plates (Analtec, 20 x 20, 2000 μ, silica gel) developed with ethyl acetate/methanol (9:1), the blue fluorescent band (in uv light) at R_f = 0.73 gave 770 mg. (16%) of **1b** as an oil: nmr (deuteriochloroform): δ aromatic, 6.90 (q, 2H, J = 8 Hz), 6.60 (s, 1H), OCH_2O, 6.05, 5.85 (2d, 2H), OCH_3, 3.75, 3.85 (2s, 6H), $NC_2H_4CH_3$, 0.95 (t, 3H). The hydrochloride of **1b** was prepared to yield 550 mg. (65%) of a colorless solid, m.p. 144-146° dec., ir (potassium bromide): λ max 2300, 1470, 1440, 1380, 1300, 1270, 1240 cm^{-1}; uv (ethanol): λ max mμ 306 (3.78), 272 (4.06), 224 (4.43); ms: m/e (%) the molecular ion 367 was not observed but the principal fragmentation peaks were observed $(M-CH_3)^+$, 352 (81), $(M-C_2H_5)^+$, 338 (37), 337 (34), 336 (14), retro Diels-Adler, 296 (16).

Anal. Calcd. for $C_{22}H_{26}ClNO_4 \cdot \frac{1}{2}H_2O$: C, 63.99; H, 6.59; N, 3.39; Cl, 8.58. Found: C, 63.90; H, 6.69; N, 3.35; Cl, 8.71.

Morphinanedienone (**7a**).

The dark brown band (in uv light) at R_f = 0.60 gave 305 mg. of an oil that was a mixture of products. Five ml. of dry ether was added and the mixture was cooled for a day resulting in a colorless solid that was filtered, washed with a small amount of ether and dried to give the morphinandienone **7a**, 132 mg. (3%), m.p. 146-148°; nmr (deuteriochloroform): δ aromatic, 6.80 (s, 2H), vinylic, 7.45, 6.35 (2s, 2H), OCH_3, 3.90 (2s, 6H), $NC_2H_4CH_3$, 0.90 (t, 3H); ir (deuteriochloroform): ν max 1665, 1640, 1615, 1480, 1460, 1420, 1410, 1400, 1380, 1350 cm^{-1}; uv (ethanol): λ max mμ 282 (3.73), 238 (4.28); ms: m/e M^+, 355 (100), $(M-1)^+$, 354 (19), $(M-CH_3)^+$, 340 (24.5), $(M-C_2H_5)^+$, 326 (73), $(M-OCH_3)^+$, 324 (20.4).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.86; H, 7.11; N, 3.79.

1-(2-Amino-3,4-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**8a**).

The nitro compound **4a** (2.3 g., 0.0062 mole) was hydrogenated over 0.15 g. of platinum oxide as described above to give 2.02 g. (95%) of **8a** (glassy solid); nmr (deuteriochloroform): δ aromatic, 6.45 (q, 2H, J = 8 Hz), 6.50 (s, 2H), OCH_2O, 5.90 (s, 2H), NH_2, 4.90 (bs, 2H), OCH_3, 3.80, 3.85 (2s, 6H), $NC_2H_4CH_3$, 0.80 (t, 3H); R_f = 0.39 (ethyl acetate/methanol, 9:1). The hydrochloride of **8a** was prepared, m.p. 195-200° dec.

Anal. Calcd. for $C_{19}H_{24}Cl_2N_2O_4$: C, 54.95; H, 5.82; N, 6.75; Cl, 17.07. Found: C, 54.69; H, 6.05; N, 6.53; Cl, 17.37.

(±)-*O*-Methyl-*N*-*n*-propylnorisocorydine (**2**).

Under identical conditions as described for the reduction Method B above, 16 g. (0.029 mole) of **5b** was reduced over 0.5 g. of platinum oxide to give 10.8 g. (94%) of an oil. This amine was reacted in the next step without further purification.

Method A.

Using the procedure described above, 6.6 g. (0.0165 mole) of the amine gave 1.1 g. of an ether insoluble material that was washed with ether and dried to give an unidentified greenish powder, m.p. 100-104° (*Anal.* Found: C, 65.61; H, 7.50; N, 3.93), and 3.9 g. of an oil that was separated on 20 tlc plates (Analtec, 20 x 20 cm, 2000 μ silica gel), developed with ethyl acetate/methanol (9:1). The blue fluorescent band at R_f = 0.74 gave 810 mg. of an oil that on cooling gave 0.380 mg. (6%) of off-white crystals of **2** free base, m.p. 145-146°; nmr (deuteriochloroform): δ aromatic, 6.90, 6.85, 6.65 (3s, 3H), OCH_3, 3.90 (s, 6H), 3.75, 3.65 (2s, 6H), $NC_2H_4CH_3$, 0.95 (t, 3H); ir: (deuteriochloroform): ν max 1470, 1420, 1380, 1320, 1260, 1220 cm^{-1}; uv (ethanol): λ max mμ (3.76), 272 (4.12), 222 (4.59); ms: m/e (%) M^+, 383 (47), $(M-1)^+$, 382 (11), $(M-CH_3)^+$, 368 (84), $(M-OCH_3)^+$, 352 (100).

Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.54. Found: C, 71.33; H, 7.57; N, 3.54.

Morphinanedienone (**7b**).

The dark brown band (in uv light) at R_f = 0.56 gave 1.06 g. of a brown oil that was a mixture of products. Treatment with ether in the cold gave 49 mg. (1%) of the morphinandienone **7b** as a colorless solid, m.p. 105-106°; nmr (deuteriochloroform): δ aromatic 6.80 (s, 2H), vinylic, 7.25, 6.25 (2s, 2H), OCH_3, 3.92, 3.85, 3.78 (3s, 9H), $NC_2H_4CH_3$, 0.90 (t, 3H); ir (deuteriochloroform): ν max 1660, 1640, 1615, 1510, 1480, 1460, 1420, 1410, 1400, 1380, 1350 cm^{-1}; uv (ethanol): λ max mμ 283 (3.89), 239 (4.33); ms: m/e (%) M^+, 369 (100), $(M-CH_3)^+$, 354 (52.5), $(M-C_2H_5)^+$, 340 (12), $(M-OCH_3)^+$, 338 (55).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.71; H, 7.11; N, 3.80. Found: C, 71.58; H, 7.27; N, 3.97.

Method B.

The procedure above was modified by using 5.8 g. (0.0145 mole) of the amine in 50 ml. of glacial acetic acid and 50 ml. of 20% sulfuric acid. The diazonium salt was produced in the cold with 6 ml. of 2*M* sodium nitrite and then added to a well-stirred mixture of 5 g. of copper (powder), and 5 g. of cuprous oxide in 200 ml. of glacial acetic acid and 200 ml. of 20% sulfuric acid. The workup was as above resulting in 0.55 g. of the ether insoluble material and 4.21 g. of an oily mixture that on cooling overnight gave 0.71 g. (13%) of **2**. The remaining oil, about 3 g., was separated on 200 g. silica gel column with ethyl acetate/methanol

(99:1). The first fraction gave 0.5 g. of veratryl acetate. The second fraction gave an additional 0.345 g. (6.4%) of **2** (overall yield, 19.4%), and the third fraction was a mixture of products that were not identified. The last fraction gave 108 mg. (2%) of **7b**.

2-Nitroisovanillin (**10**).

This compound was prepared from isovanillin (**9**) by the procedure described in the literature (20) and converted to *O*-benzyl-2-nitroisovanillin (**11**) by published procedures (21).

2-Nitro-3-*O*-benzyl-4-methoxybenzylalcohol (**12**).

Seventy g. (0.244 mole) of **11** was reduced with 3 g. (0.35 mole) of sodium borohydride as described for the reduction of 2-nitroveratraldehyde (5) to give 62 g. (85%) of **12**, a brown oil, which was used in the next step without further purification.

2-Nitro-3-benzyloxy-4-methoxybenzylchloride (**13**).

To a solution of 2.9 g. (0.001 mole) of **12** in 15 ml. of acetonitrile (dried over molecular seives) was added 1 ml. (1.67 g., 0.014 mole) of thionyl chloride and the mixture was allowed to stir overnight. The solvent was evaporated, chloroform was added and the excess of thionylchloride was removed by evaporation. The residue was dissolved in chloroform, washed with 2% sodium hydroxide, water, dried and evaporated to give 2.5 g. of an oil that was passed through 50 g. silica gel developed with hexanes/ethyl acetate (70:30), to give 2.22 g. (72%) of **13**.

1-Cyano-2-benzoyl-1,2-dihydro-6,7-methylenedioxyisoquinoline (**16**).

This compound was prepared according to the method reported by Popp and Blount (15). Compound **15** (20 g., 0.116 mole) gave 12.25 g. (35%) of **16**, m.p. 135-136°; nmr (deuteriochloroform): δ aromatic, 7.55 (s, 5H), 6.65, 6.80 (2s, 2H), vinylic, 6.55, 5.90 (2s, 2H), OCH_2O, 6.00 (s, 2H).

Anal. Calcd. for $C_{18}H_{12}N_2O_3$: C, 71.04; H, 3.97; N, 9.20. Found: C, 70.82; H, 4.08; N, 9.15.

1-Cyano-2-benzoyl-1-(2-nitro-3-benzyloxy-4-methoxy)benzyl-6,7-methylenedioxyisoquinoline (**17**).

A solution of 1.7 g. (0.0055 mole) of **13** in 2 ml. of dimethylformamide was added (under nitrogen atomsphere) to a cooled mixture (-10-5°) of 1.6 g. (0.0053 mole) of **16** and 0.240 g. (50% mineral oil) of sodium hydride in 5 ml. of dimethylformamide (dry). The mixture was stirred for 0.5 hour and at room temperature for an additional 3 hours, and then was poured into 100 ml. of crushed ice and stirred producing a precipitate that was filtered and washed with water. After trituration with ethanol and air drying, 2.4 g. (79%) of yellow solid (m.p. 176-177°) were isolated. A small portion of this solid was recrystallized from ethanol to give pure **17**, m.p. 178-180°; nmr (deuteriochloroform): δ aromatic, 7.55 (m, 5H), 7.35 (s, 5H), 7.05 (q, 2H, J = 8 Hz), 6.80, 6.58 (2s, 2H), vinylic, 6.20, 5.45 (2d, 2H, J = 8 Hz), OCH_2O, 6.00 (s, 2H), CH_2PH, 5.05 (s, 2H), OCH_3, 3.90 (s, 3H), $ArCH_2$, 3.55 (q, 2H, J = 8 Hz); ir (deuteriochloroform): ν max 2250, 1680, 1640, 1600, 1540, 1500, 1480, 1455, 1370, 1260 cm^{-1}.

Anal. Calcd. for $C_{33}H_{25}N_3O_7$: C, 68.86; H, 4.37; N, 7.30. Found: C, 68.62; H, 4.62; N, 7.09.

1-(2-Nitro-3-benzyloxy-4-methoxybenzyl)-6,7-methylenedioxyisoquinoline (**18**).

A solution of 9.4 g. (0.0163 mole) of **17** in 100 ml. of dimethylformamide was cooled in ice and 4 ml. of triton-B was added. The mixture was stirred in the cold for an hour, an additional 2 ml. of triton-B was added after the second and fourth hour and stirred at room temperature until tlc showed major conversion from R_f = 0.73 to R_f = 0.55 (ethyl acetate/hexanes, 30:70) about 5 hours. The dark solution was poured into ice. The mixture was extracted with chloroform, washed twice with 500 ml. of water, dried and evaporated to dryness. The residue was crystallized from ethanol to give 4.3 g. (59%) of **18**, m.p. 142°.

Anal. Calcd. for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.53; N, 6.30. Found: C, 67.46; H, 4.87; N, 6.29.

1-(2-Nitro-3-benzyloxy-4-methoxybenzyl)-6,7-methylenedioxyisoquinoline Propiodide (**19b**).

This compound was prepared from 1-iodopropane and **18**, m.p. 209° dec.

Anal. Calcd. for $C_{28}H_{28}IN_2O_6$: C, 54.64; H, 4.58; N, 4.55; I, 20.62. Found: C, 54.75; H, 4.47; N, 4.51; I, 20.74.

1-(2-Nitro-3-benzyloxy-4-methoxybenzyl)-6,7-methylenedioxyisoquinoline Methiodide (**19a**).

This compound was prepared similarly from **18** and methyl iodide, m.p. 200-203° dec. (yellow crystals).

Anal. Calcd. for $C_{26}H_{23}IN_2O_6$: C, 53.25; H, 3.95; N, 4.77; I, 21.64. Found: C, 53.05; H, 3.96; N, 4.78; I, 21.68.

A solution of 4.3 g. (0.007 mole) of **19b** in 250 ml. of absolute methanol was reduced over 0.5 g. of platinum oxide at 47 psi for 48 hours. The workup as described for the reduction of **6** gave 1.9 g. (73%) of a dark, glossy solid R_f = 0.47 (ethyl acetate). This solid (1.4 g.) was purified on 30 g. of silica gel column developed with ethyl acetate to give 1.26 g. of **20** as a brown, glassy solid; nmr (deuteriochloroform): δ aromatic, 6.35 (q, 2H, J = 8 Hz), 6.45, 6.50 (2s, 2H), OCH_2O, 6.85 (s, 2H), NH_2OH, 4.85 (bs, 3H), OCH_3, 3.80 (s, 3H), $C_2H_4CH_3$, 0.90 (t, 3H); ir (deuteriochloroform): ν max 3500, 3400, 1730, 1630, 1500, 1480, 1380, 1260, 1240 cm^{-1}. This compound was reacted in the next step without further purification.

(±)-*N*-*n*-propylnorbulbocapnine (**1c**).

The procedure for the preparation of **2** (Method B), was used for the preparation of **1c**. Thus, 1.26 g. (0.0034 mole) of the amine **20** gave 0.32 g. of an ether insoluble material, and 570 mg. of an oily mixture that was separated on 5 plates, and developed with ethyl acetate/methanol (9:1). The blue fluorescent band (in uv light) at R_f = 0.79 gave 110 mg. (9%) of an oil; nmr (deuteriochloroform): δ aromatic, 6.80, 6.60 (2s, 3H), OCH_2O, 6.05, 5.90 (2d, 2H), OCH_3, 3.95 (s, 3H), $NC_2H_4CH_3$, 0.95 (t, 3H). The hydrochloride salt was prepared (75 mg.) giving a light green solid, m.p. 151-158° dec.; ir (deuteriochloroform): ν max 1505, 1485, 1470, 1440, 1420, 1380, 1350, 1320, 1280, 1240, 1230 cm^{-1}; uv (ethanol): λ max mμ 306 (3.72), 275 (3.97), 228 (4.39); ms: m/e (%) M^+, 353 (39), $(M-1)^+$, 352 (21), $(M-CH_3)^+$, 338 (42), $(M-OH)^+$, 336 (20), $(M-C_2H_5)^+$, 324 (16), retro diels alder 282 (8.4).

Anal. Calcd. for $C_{21}H_{24}ClNO_4$: C, 64.69; H, 6.21; N, 3.59. Found: C, 64.19; H, 6.57; N, 3.82.

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