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# APORPHINES 10. APPROACHES TO THE SYNTHESIS OF 7-HYDROXYAPORPHINES

## STEREOSELECTIVE SYNTHESIS OF (±)-10,11-DIMETHOXY-7-OXOAPORPHINE, (±)-7-HYDROXYAPORPHINE AND (±)-7-HYDROXYNORAPORPHINE[a]

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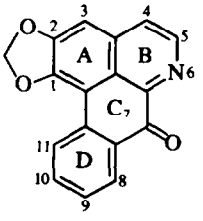
**Abstract**—A new method for the stereoselective synthesis of 7-hydroxyaporphine (**3a**) and 7-hydroxynoraporphine (**3b**) via the 4-oxazolin-2-one **20** as a protecting group has been developed. Pschorr cyclization of **20** and hydrolysis of the oxazoloaporphine **21** with trifluoroacetic acid led exclusively to the dehydronoraporphine **22**. Reduction of **21** with LAH gave **3a** and treatment of **21** with methyllithium gave **3b**. The synthesis of 10,11-dimethoxy-7-oxoaporphine (**2**) involving a Reissert alkylation-Pschorr cyclization sequence has been achieved.

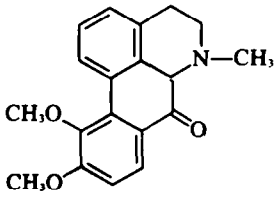
The synthesis of aporphines functionally substituted in the 7-position with an O atom is of interest because of their occurrence in naturally occurring alkaloids. Typical of such oxoaporphines are liriodenine (**1**) and atheroline.[1a] Surprisingly, no studies have been reported on 7-oxoaporphines (ring B saturated) since Schlittler's[2] synthesis of 1,2,9,10 - bis(methylenedioxy) - 7 - oxoaporphine and 7 - oxo - 1,2,9,10 - tetramethoxyaporphine.

[a]Abstracted in part from the thesis of F. E. G. submitted in partial fulfillment of the Ph.D. degree, Northeastern University, June, 1972.

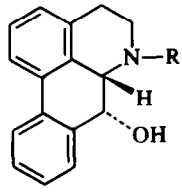
Several 7-hydroxyaporphines such as ushinsunine (micheline) (**4a**), norushinsunine (michelalbine) (**4b**) and guatterine (**4c**) have been described[3-6] and contain a *trans* configuration of the 7-OH group relative to the 6a proton. More recently the absolute configuration of **4a** was reported[7] on the basis of its reduction to the known alkaloid D-roemerine. The synthesis of (±)-**4b** was also described.[7] The 7-hydroxyaporphines are of considerable interest to us not only because of their natural occurrence,[1b] but also because of their potential pharmacological interest as possible metabolites of such catecholamines as apomor-



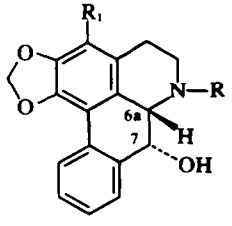
**1**
liriodenine



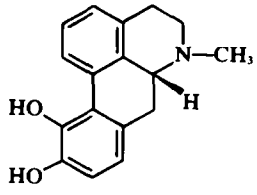
**2**



**3a**: R = $CH_3$
**b**: R = H



**4a**: R = $CH_3$, R' = H
**b**: R = H, R' = H
**c**: R = $CH_3$, R' = $OCH_3$



**5**
Apomorphine

phine (5).[8] In our continuing study of the chemistry and pharmacological effects of aporphines it was thus of interest to us to develop methods for the elaboration of 7-hydroxyaporphines. The biological activity of **3a** and **b** has been described elsewhere.[9]

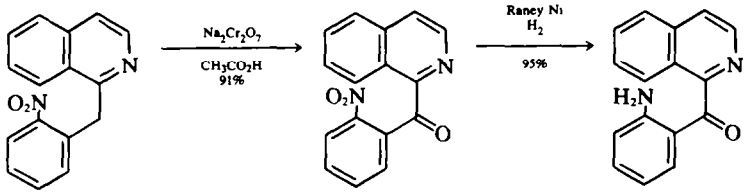
In a preliminary communication[10] from this laboratory we reported the preparation of **3a**, **3b** and **22** via the 4 - oxa - zolin - 2 - one as a protecting group for the carbinolamine backbone of such aporphines. The elaboration of C - (α) - hydroxylated tetrahydrobenzylisoquinolines[11] via the 4 - oxazolin - 2 - one ring system led to the application of this method to the synthesis of such 7-hydroxyaporphines. In this communication we shall present a detailed account of our efforts to prepare such 7-oxoaporphines as **2** and the 7-hydroxyaporphines **3a** and **b**.

Our first approach (Scheme 1) was to prepare the prototype 7-oxodehydroaporphine (**9**) by the dichromate oxidation of 1 - (2 - nitrobenzyl)-isoquinoline (**6**)[12] to give the ketone **7** followed by Raney Ni/$H_2$ reduction to **8**. Several attempts to cyclize **8** to **9** by Pschorr-type conditions[13] failed, however. In a closely related reaction the Pschorr procedure has been successfully utilized for the synthesis of liriodenine (**1**) when applied to the 6'-aminobenzoylisoquinoline precursor.[14] It is not unreasonable to assume that the aromatic ring in the isoquinoline ring in **8** was sufficiently deactivated by the charge delocalization on the nitrogen to prevent ring closure to **9**.

loride salt, by its UV and mass spectra, and by elemental analyses. The hygroscopic character, sensitivity to light, and low overall yield of **2** obtained by this sequence necessitated the investigation of alternative approaches to the 7-hydroxyaporphines.

The procedure shown in Scheme 3 was successful for the preparation of (±) - 7 - hydroxyaporphine (**3a**) and (±) - 7 - hydroxynoraporphine (**3b**).[10] This method has several unique and important advantages. It allows for the reduction of the isoquinoline ring prior to Pschorr cyclization, eliminating the deactivating influence of the heterocyclic ring; the 4 - oxazolin - 2 - one system provided a dual protective role (i.e., for a secondary amino function and the hydroxyl group) during the diazotization reaction; a stereospecific synthesis of the *cis* - (±) - 7 - hydroxyaporphine (**3a**) was assured by this procedure. Molecular models of (±) - oxazoloaporphine, (**21**), showed excessive steric strain in a *trans* arrangement of the 6a and 7 protons. The NMR spectrum of **3b** further confirms the *cis* assignment of the 6a and 7 protons. The coupling constant for the C-7 proton at δ 4·56 ($J_{6a,7}$ = 3·5 Hz) is in agreement with the NMR data reported by Harris and Geissman[6] in support of the *cis* arrangement of the 6a, 7 protons in ushinsunine (**4a**).

Reduction of **21** with lithium aluminum hydride yielded 7-hydroxyaporphine (**3a**), while reaction of **21** with methyl lithium gave 7-




**6** **7** **8**

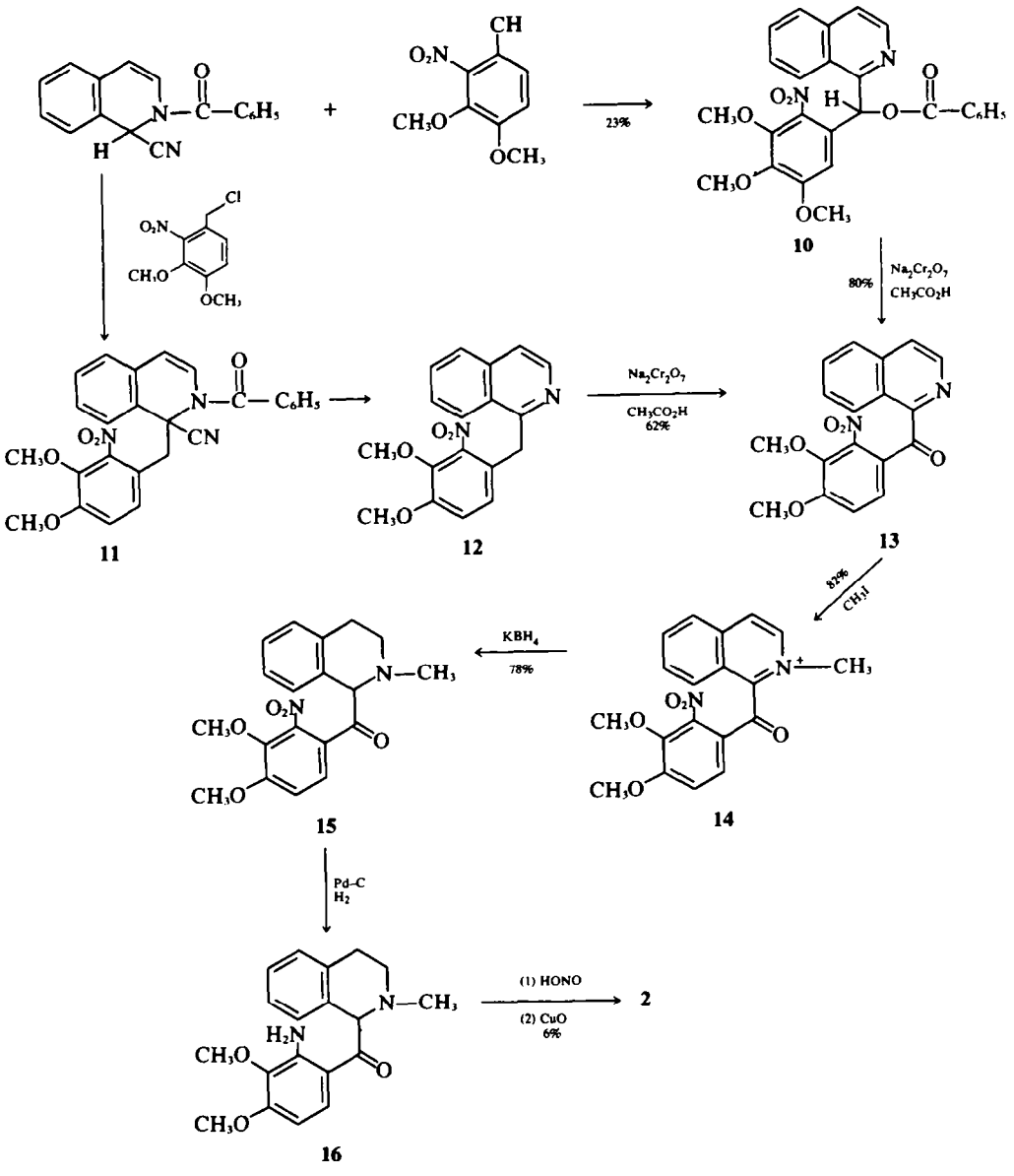
SCHEME 1.

Failure of this method prompted us to investigate modifications of the sequence used by Schlittler[2] for the synthesis of 7-oxoaporphines. Reduction of the isoquinoline ring to the 2 - aminobenzoyltetrahydroisoquinoline (as in **16**) prior to cyclization led to the successful synthesis of **2** shown in Scheme 2. We anticipated that the reduction of the 7-ketoaporphine to the 7-hydroxyaporphine would present no difficulties. Sufficient quantities of **2** were not available for such experiments, however.

The demonstrated utility of the Reissert alkylation procedure for the generation of substituted nitrobenzyl–isoquinolines[8,12,15] led to the synthesis of **10** and **11**. The benzoate ester **10** or isoquinoline **12**[8] upon oxidation with dichromate gave the benzoyl derivative **13**.

The product was characterized as its hydrochhydroxynoraporphine (**3b**). A similar sequence (**17** → **18b** → **20b**) was followed in the attempted synthesis of 7 - hydroxy - 10,11 - dimethoxyaporphine. Treatment of **21** with acid or base caused elimination to form the novel dehydronoraporphine system **22**.

Surprisingly, the Pschorr cyclization of **20b** failed to give the desired aporphine. Deaminated products were isolated, but no evidence of the aporphine ring structure was observed. A comparison of the NMR spectra of the aminooxazolones **20a** and **20b** showed that the coupling constants (8·5 Hz) between the proton attached to the 1-position and the benzylic proton are the same in both cases. Therefore, the dihedral angle between these two carbons in both compounds **20a** and **20b** are presumably alike. On this basis the NMR



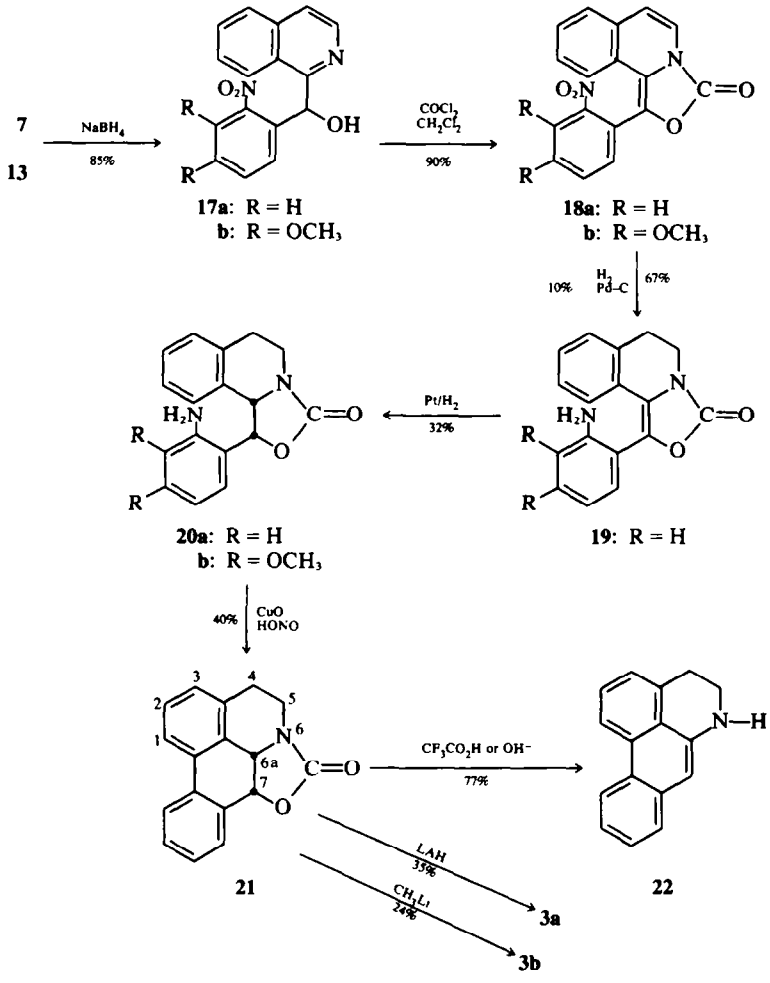
SCHEME 2.

spectrum offers no evidence that the aminodimethoxyphenyl group in **20b** was in a sterically unfavorable position for ring closure to the aporphine.

## EXPERIMENTAL

M.ps were obtained on Gallenkamp and Fisher-Johns apparatus. IR spectra were recorded on a Perkin-Elmer 521 and 237 grating spectrophotometer. UV spectra were recorded on a Beckman DK recording spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer. Mass spectra were recorded on a Dupont Consolidated Electrodynamics Corporation 21-110B high resolution spectrometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Galbraith Laboratories. Inc., Knoxville, Tennessee.

1-(2-*Nitrobenzoyl*)*isoquinoline* (**7**). A suspension of **6**[12] (8 g; 0·03 mole) in 40 ml glacial AcOH was heated on the steam bath until complete soln was obtained. A soln of sodium dichromate (9 g; 0·03 mole) in 40 ml AcOH was added all at once and the mixture heated on the steam bath with stirring for 2 h. Then 16 ml formic acid was added carefully to the hot soln again heating on the steam bath for another 10–15 min followed by the addition of 50 ml water. The soln was cooled in ice and the product filtered under suction. The yellow solid was washed with




SCHEME 3.

water on the funnel until the washings were neutral and dried to give 7·7 g (91%), m.p. 170–172°. No further purification was required; $\nu_{max}^{Nujol}$ 1680, 1520, 1330, 920 cm$^{-1}$. (Found: C, 68·92; H, 3·72; N, 9·96. Calcd for $C_{16}H_{10}N_2O_3$: C, 69·06; H, 3·62; N, 10·07%).

1 - (2 - *Aminobenzoyl*)*isoquinoline* (**8**). A suspension of **7** (2 g, 0·0072 mole) in 100 ml absolute alcohol was shaken with 2 g of Raney Ni aqueous suspension in a Parr hydrogenator under 50 lbs $H_2$ pressure. After 16 h the mixture was filtered and evaporated to dryness to give 1·7 g (95%) of a yellow solid, m.p. 153–157°. Recrystallization from EtOH raised the m.p. to 161–164°; $\nu_{max}^{Nujol}$ 3430, 3330, 3200, 1630, 1490, 1380, 1000, 825, 750 cm$^{-1}$; NMR δ ($CDCl_3$) 8·61 (d, J = 5·5 Hz), 7·84 (m), 7·25 (m), 6·65 (br, $D_2O$ exchanges), 6·56 (m). (Found: C, 76·99; H, 5·60; N, 11·15. Calcd for $C_{16}H_{12}N_2O$: C, 77·40; H, 4·87; N, 11·28%).

1 - *Isoquinolyl* - 2 - *nitro* - 3,4 - *dimethoxyphenylcarbinol benzoate* (**10**). A mixture of 2 - benzoyl - 1,2 - dihydroisoquinaldonitrile (19·7 g; 0·075 mole), 3,4 - dimethoxy - 2 - nitrobenzaldehyde[8] (15·6 g; 0·075 mole) and 250 ml DMF was stirred vigorously as 3·2 g (0·076 mole) of 57% sodium hydride (mineral oil suspension) was added all at once at −40°. The temp was held at −20° to −30° for 1 h and then allowed to slowly increase to room temp. The mixture was stirred for 16 h at ambient temps, poured into 500 ml of ice water and extracted with ether. The ether extract was washed with water concentrated to ⅓ its volume and filtered. The benzoate ester was dried to give 8 g (23%), m.p. 187–190°. Recrystallization from EtOH raised the m.p. slightly, m.p. 188–189°; $\nu_{max}^{KBr}$ 1715, 1525, 1500, 1450, 1365, 1290, 1270, 1250, 1090, 1050, 710 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm (ε × 10$^{-3}$) 320 (5·49), 308 (5·02), 282 (7·10), 272 (8·36), 220 (76·0); NMR δ ($CDCl_3$), 3·79 (s, 3), 3·90 (s, 3), 6·85 (d, J = 9 Hz, 1), 7·13 (d, J = 9 Hz, 1), 7·25–8·3 (m, 10), 8·45 (d, J = 5·5 Hz, 1). (Found: C, 67·63; H, 4·47; N, 6·24. Calcd for $C_{25}H_{20}N_2O_6$: C, 67·56; H, 4·54; N, 6·30%).

1-(3,4-*Dimethoxy*-2-*nitrobenzoyl*)*isoquinoline* (**13**)

*Method A: Oxidation of* 1 - *isoquinolyl* - 2 - *nitro* - 3,4 - *dimethoxyphenylcarbinol benzoate* (**10**). To a soln of **10** (9·8 g; 0·022 mole) in 51 ml glacial AcOH at 110° was added a soln of sodium dichromate (10·3 g; 0·035 mole) in 51 ml glacial AcOH. After refluxing for 1 h the soln was cooled slightly and 25·5 ml formic acid was added dropwise. When the addition was over (about 5 min) the

soln was heated on the steam bath for 15 min and water was added to the cloud point. The mixture was cooled and the product filtered to yield 6 g (80%), m.p. 139–143°. Recrystallization from EtOH did not raise the m.p., m.p. 138–139·5°; $\nu_{max}^{KBr}$ 1660, 1525, 1350, 1270 $cm^{-1}$; NMR $\delta$ ($CDCl_3$), 3·92 (s, 3), 3·96 (s, 3), 6·97 (d, J = 9 Hz, 1), 7·45 (d, J = 9 Hz, 1), 7·68 (m, 3), 7·75 (d, J = 5·5 Hz, 1), 8·45 (d, J = 5·5 Hz, 1), 8·5 (m, 1). (Found: C, 63·75; H, 4·23; N, 8·16. Calcd for $C_{18}H_{14}N_2O_5$: C, 63·90; H, 4·17; N, 8·28%).

*Method B*: *Oxidation of* 1 - (3,4 - *dimethoxy* - 2 - *nitrobenzyl*) - *isoquinoline*[8] (**12**). A soln of sodium dichromate (29 g; 0·1 mole) in 120 ml glacial AcOH was added rapidly to a soln of 1 - (3,4 - dimethoxy - 2 - nitrobenzyl)isoquinoline[3] (20 g; 0·089 mole) in 120 ml glacial AcOH. The soln was heated at 70° for 20 min and at 95° for 1 h. Then 60 ml formic acid was added carefully to the hot soln which was then diluted with water until precipitation ceased. After cooling in ice the mixture was filtered, the product washed with water and dried to yield 21 g (62%), m.p. 134–138°. No further purification was carried out with this sample.

1 - (3,4 - *dimethosy* - 2 - *nitrobenzoyl*)*isoquinoline methiodide* (**14**). A mixture of **13** (2 g; 5·9 mmoles) and MeI (14 ml; 21·4 g; 0·15 mole) was heated in a sealed tube at 130–140° for 5 h and allowed to stand overnight at room temp. The contents was filtered and the yellow solid washed with ether and dried to give 2·3 g (82%), m.p. 200–202° dec. No further purification was required. (Found: C, 47·33; H, 3·49; N, 5·68. Calcd for $C_{19}H_{17}IN_2O_5$: C, 47·52; H, 3·57; N, 5·83%).

1 - (3,4 - *Dimethoxy* - 2 - *nitrobenzoyl*) - 2 - *methyl* - 1,2,3,4 - *tetrahydroisoquinoline* (**15**). Potassium borohydride (26 mg) was added to a suspension of **14** (480 mg; 0·001 mole) in 5 ml abs EtOH. Then 13 mg of additional borohydride was added every 30 min for 90 min. After the second increment of reducing agent had been added the mixture became homogeneous while vigorous stirring was continued. At the end of a total elapsed time of 2 h, 0·25 ml of water was added and a ppt was obtained. After stirring for another h the soln was filtered and the filtrate was diluted with water yielding a brown, gummy material. The mixture was extracted with ether, the extract was washed, dried, and evaporated. The residue was dissolved in a small volume of EtOH and made acidic with ethanolic HCl to give 142 mg (36%) of a near colorless solid, m.p. 160–163°; NMR $\delta$ (DMSO-$d_6$) 2·88 (s, 3), 3·89 (s, 3), 4·1 (s, 3), 3·5 (br, 4), 7·25 (br, 6). (Found: C, 57·82; H, 5·37; N, 7·08. Calcd for $C_{19}H_{21}ClN_2O_5$: C, 58·09; H, 5·39; N, 7·13%).

The reaction was repeated on a large scale (2·3 g; 0·00475 mole) of **14** to give 1·32 g (78%) of the crude product as the free base. No further characterization was made of this material.

10,11 - *Dimethoxy* - 7 - *oxoaporphine* (**2**). A mixture of **15** (300 mg; 0·0008 mole), 35 ml EtOH and 75 mg of 10% Pd-C was shaken in a Parr hydrogenator under 50 psi of $H_2$. The soln was filtered and the filtrate was evaporated to dryness to give 262 mg (100%) of a yellow, viscous oil. A TLC on a silica gel plate revealed an intense spot at $R_f$ = 0·40 ($CHCl_3$) while the nitro precursor (**15**) on the same plate had an $R_f$ of 0·53. Without further characterization the oil was dissolved in 4 ml of 10% $H_2SO_4$ and diazotized with 1 ml of 2N $NaNO_2$ at 0–5°. After stirring for 15 min at −5° to 0° the red soln was treated with a small quantity of sulfamic acid to destroy excess nitrous acid (negative starch iodide paper test) and the soln of diazonium salt was added dropwise to a vigorously stirred mixture of 0·85 g of cuprous oxide in 15 ml of 10% $H_2SO_4$ at −5° to 0°. Considerable foaming occurred and in 15 min the catalyst agglomerated and adhered to the walls of the flask. After an h the mixture was made basic with conc $NH_4OH$ and extracted with ether. The ether soln was washed, dried, and evaporated to give a dark oil. The oil was dissolved in 2–3 ml of EtOH And acidified with alcoholic HCl. The soln was diluted with ether until a brown, flocculent ppt was obtained (16 mg; 5·8%), m.p. 170–175° dec; $\nu_{max}^{KBr}$ 1665, 1630, 1610, 1580, 1280 $cm^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 283 (12·2), 255 (18·3), 225 (26·4); mass spectrum (70 ev) *m/e* (309 $M^+$), 165, 146. (Found: N, 4·10; Cl, 10·74. Calcd for $C_{19}H_{20}ClNO_3$: N, 4·05; Cl, 10·25%).

$\alpha$ - (1 - *Isoquinolyl*) - 2 - *nitrobenzyl alcohol* (**17a**). A mixture of **7** (1 g; 0·0036 mole) and $NaBH_4$ (0·5 g; 0·013 mole) in 30 ml abs EtOH was stirred overnight at room temp. The mixture was cooled, poured into 70 ml of water and allowed to stand in an ice bath until crystallization occurred. The product was filtered, washed with cold water and dried to give 0·8 g (79%), m.p. 144–147°.

A 5-g run provided **17a** (4·3 g; 85%) by the same procedure. A small sample was recrystallized from EtOH for elemental analysis, m.p. 145–146°; $\nu_{max}^{Nujol}$ 3200, 1520, 1330 $cm^{-1}$. (Found: C, 68·50; H, 4·28; N, 10·02. Calcd for $C_{16}H_{12}N_2O_3$: C, 68·56; H, 4·32; N, 10·00%).

1 - (2 - *Nitrophenyl*)*oxazolo*[4,3-*a*]*isoquinoline* - 3 - *one* (**18a**). To a rapidly stirred soln of **17a** (0·7 g; 0·0025 mole) in a mixture of 10 ml dichloromethane and 4 ml triethylamine at 0–5° was added dropwise 4 ml of a soln of phosgene in dichloromethane (26%). A dark, red solid precipitated from the soln during the addition. When the addition was complete the ice bath was removed and the mixture was stirred at room temp for 15 min. The soln was then poured into cold water and the organic layer was separated. The dichloromethane soln was washed with water, $KHCO_3$ aq, satd NaCl aq and finally dried over $MgSO_4$. The solvent was evaporated and the residue triturated with cold MeOH. The maroon solid was collected to yield 0·53 g (70%), m.p. 195–198°; $\nu_{max}^{KBr}$ 1750, 1665, 1520, 1370, 1275, 1230 $cm^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 335 (7·33), 259 (23·8), 252 (23·2).

The reaction on a slightly larger scale, 4 g (0·014 mole) of the carbinol provided 3·9 g (90%) of **18a**. The product was submitted for analysis without further purification. (Found: C, 66·0; H, 3·37; N, 9·22. Calcd for $C_{17}H_{10}N_2O_4$: C, 66·66; H, 3·28; N, 9·15%).

1 - (2 - *Aminophenyl*)*oxazolo*[4,3-a]*isoquinoline* - 3 - *one* (**19a**). To a soln of **18a** (400 mg; 1·3 mmoles) in a mixture of 10 ml glacial AcOH and 60 ml dry THF was added 200 mg of 10% Pd-C. The mixture was hydrogenated at 50 lbs of pressure for 17 h. Concentration of the filtered soln and careful addition of water to the point of cloudiness gave yellow crystals (247 mg; 67%), m.p. 148–151°. Recrystallization from 95% EtOH provided an analytical sample containing 1/2 mole of water, m.p. 158–161°; $\nu_{max}^{KBr}$ 3350, 3270, 3230, 1755, 1650 $cm^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 345 (8·85), 260 (20·0), 250 (22·0); NMR $\delta$ (acetone, d-6) 3·15 (s, $2NH_2$, $D_2O$ exchanges), 6·4 (m, 1), 6·87 (m, 1), 7·3 (m, 8). (Found: C, 71·09; H, 4·35; N, 9·79. Calcd for $C_{17}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$: C, 71·57; H, 4·59; N, 9·82%).

1 - (2 - *Aminophenyl*) - 1,5,6,10b - *tetrahydrooxazolo* [-4,3-a] - *isoquinoline* - 3 - *one* (**20a**). To a soln of **19a** (100 mg; 0·00036 mole) in a mixture of 3 ml glacial AcOH and 30 ml dry THF was added 50 mg of $PtO_2$. The mixture was hydrogenated at 50 lbs of pressure for 17 h and the filtered soln was concentrated. Dilution of the concentrate

with water provided a crude product **20a** which was recrystallized from EtOH to give 33 mg (32%) of colorless needles, m.p. 211–213°; $\nu_{max}^{KBr}$ 3460, 3355, 1730, 1490, 1450, 1410, 750, 740 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 290 (5·83), 230 (sh, 1635); NMR $\delta$ (DMSO-$d_6$) 2·6–3·3 (m, 3), 3·99 (m, 1), 5·3 (s, 2, $NH_2$, $D_2O$ exchanges), 5·53 (d, J = 8·5 Hz, 1), 6·22 (d, J = 8·5 Hz, 1), 6·3–7·1 (m, 8). (Found: C, 72·61; H, 5·59; N, 9·93. Calcd for $C_{17}H_{16}N_2O_2$: C, 72·84; H, 5·75; N, 9·99%).

In subsequent runs the aminoisoquinoline intermediate was not isolated. After reduction with Pd-C the filtered soln was then shaken with $PtO_2$ for the required time and **20a** was obtained directly. On the average these runs gave yields in the order of 50–60% from **18a**.

(±)-*Oxazoloaporphine* (**21**). A soln of **20a** (1·12 g; 0·004 mole) in 250 ml 10% $H_2SO_4$ was cooled to −5° and treated with 5 ml of 2N $NaNO_2$. After 15 min elapsed the excess nitrous acid was destroyed with the addition of small portions of sulfamic acid. Then 8 g of cuprous oxide was added in one portion and the mixture stirred vigorously for 1·5–2 h at −5° to 0°. The soln was filtered and the mixture of organic and inorganic solids was extracted with methylene chloride. After extracting the aqueous phase with methylene chloride the extract was washed with water and saturated brine. The dried soln was filtered and evaporated to dryness to give 800 mg of a foamy orange solid. Trituration of the material with acetonitrile followed by filtration and drying gave 409 mg (40%) of the crude **21**, m.p. 225° dec. Recrystallization of a small sample from EtOH for analyses gave light orange crystals, m.p. 255–260° dec; $\nu_{max}^{KBr}$ 1740, 1380, 1190 cm$^{-1}$; $\lambda_{max}^{EtOH}$ 285 (sh, 14·67), 270 (19·85); mass spectrum (70 ev) *m/e* 263 (M$^+$). (Found: C, 77·21, 77·32; H, 5·10, 5·04; N, 5·27. Calcd for $C_{17}H_{13}NO_2$: C, 77·55; H, 4·98; N, 5·32%).

6a,7-*Dehydronoraporphine hydroiodide* (**22**)

*A. Acid hydrolysis.* A soln of **21** (350 mg; 0·0013 mole) in 3 ml of trifluoroacetic acid with several drops of water added was heated on the steam bath for 15–20 min. Water was added to the hot soln dropwise until precipitation ceased. An oil settled out which solidified on scratching. The mixture was extracted with chloroform and the organic soln shaken successively with water, $KHCO_3$ aq, water and sat brine. After drying, the chloroform soln was filtered, and evaporated to give a light tan solid. The product was dissolved in about 5 ml of acetone and 3–4 drops of 58% HI were added. The soln was cooled in ice with the gradual precipitation of the dehydroaporphine hydroiodide. After 10 or 15 min in an ice bath the product was filtered under nitrogen, washed with cold acetone and dried to yield 345 mg (77%) of **22**, m.p. 250° dec; $\nu_{max}^{KBr}$ 3360, 1610, 1590, 1470, 1325, 1310, 820, 750, 730 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 325 (11·15), 255 (41·0), 239 (34·9); NMR $\delta$ (DMSO-$d_6$) 3·45–3·7 (m, 4), 7·5–8·15 (m, 5), 8·77 (m, 2), 10·2 (s, 1, NH, $D_2O$ exchanges), 7·72 (s, 1, $D_2O$ exchanges); mass spectrum (70 ev) *m/e* 219 (M$^+$), 189, 162. (Found: C, 55·18, 55·11; H, 4·01, 4·00; N, 3·83, 3·79. Calcd for $C_{16}H_{14}IN$: C, 55·35; H, 4·06; N, 4·04%).

*B. Alkaline hydrolysis.* A soln of **21** (5 mg) in 10% alcoholic KOH was heated at 60–70° for 15 min. The soln was cooled, diluted with water and extracted with ether. The ether soln was washed with water until neutral, dried, filtered, and evaporated. The UV spectrum of the residue was identical with the product derived from acid hydrolysis.

(±) - 7 - *Hydroxyaporphine hydroiodide* (**3a**). A mixture of **21** (26 mg; 0·1 mmole), 25 ml dry THF and LAH (37 mg; 0·1 mole) was refluxed with stirring for 16 h. The mixture was cooled and the excess LAH was decomposed carefully with water. The mixture was filtered and the inorganic ppt was washed with methylene chloride. The organic soln was washed with water, dried, filtered, and evaporated to dryness. The residue was dissolved in about 2–3 ml of acetone, made acidic with 2 drops of 58% HI and the soln cooled in ice. The yellow salt was filtered under $N_2$ and dried, m.p. 205° dec; $\nu_{max}^{KBr}$ 3370, 3010, 2950, 2910, 2850, 2790, 1450, 740 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 270 (16·85); mass spectrum (70 ev) *m/e* 251 (M$^+$), 233.

A similar reaction from **21** (100 mg; 0·00038 mole) provided 50 mg (34·7%) of (**3a**) hydroiodide. (Found: C, 53·49; H, 4·82; N, 3·74. Calcd for $C_{17}H_{16}INO$: C, 53·84; H, 4·78; N, 3·69%).

(±) - 7 - *Hydroxynoraporphine* (**3b**). A soln of **21** (300 mg; 0·00114 mole) in 250 ml dry ether was stirred at room temp with 40 ml of 2·2M MeLi for 16 h. The soln was cooled and decomposed with water. The mixture was filtered and the inorganics were extracted with methylene chloride. The extracts were combined with the ether soln, dried, filtered, and evaporated to give a near colorless solid. The residue was triturated with ether, filtered, and the product dried, yielding 66 mg (24·5%) of **3b**, m.p. 188–190°, as the free base. Recrystallization from EtOH gave light tan crystals, m.p. 198–200° dec; $\nu_{max}^{KBr}$ 3300, 3010, 2930, 1560, 1450, 740 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 270 (18·15); NMR $\delta$ (DMSO-$d_6$) 4·56 (d, 1, J = 3–4 Hz), 2·6–4·1 (m, 4), 6·9–7·98 (m, 7); mass spectrum (70 ev) *m/e* 237 (M$^+$), 219. (Found: C, 80·63; H, 6·64; N, 5·79. Calcd for $C_{16}H_{15}NO$: C, 80·98; H, 6·37; N, 5·90%).

3,4 - *Dimethoxy* - $\alpha$ - (1 - *isoquinolyl*) - 2 - *nitrobenzyl alcohol* (**17b**). To $NaBH_4$ (6 g, 0·16 mole) in 240 ml abs alcohol was added a soln of **13** (20 g; 0·059 mole) in 60 ml DMF dropwise. After stirring for 2 h at room temp the mixture was diluted with water until precipitation ceased and the gummy product separated. The crude material was triturated with 100 ml of warm EtOH, cooled, and filtered to give 15 g (73%), m.p. 135–139°. A small sample was recrystallized from EtOH, m.p. 142–143°; $\nu_{max}^{Nujol}$ 3330, 1525, 1490, 1325, 1280, 1250, 1050, 1030 cm$^{-1}$; NMR $\delta$ ($CDCl_3$) 3·78 (s, 3), 3·94 (s, 3), 5·63 (br, 1), 6·33 (s, 1), 6·4 (d, J = 9 Hz, 1), 6·72 (d, J = 9 Hz, 1), 7·7 (m, 1), 8·5 (d, J = 5 Hz, 1) (Found: C, 63·38; H, 4·74; N, 8·01. Calcd for $C_{18}H_{16}N_2O_5$: C, 63·52; H, 4·74; N, 8·23%).

1 - (3,4 - *Dimethoxy* - 2 - *nitrophenyl*)*oxazolo*[4,3-a]*isoquinoline* - 3 - *one* (**18b**). A soln of phosgene (19·8 g; 0·2 mole) in 110 ml dichloromethane was added dropwise to a mixture of **17b** (14 g; 0·041 mole) in 202 ml dichloromethane and $Et_3N$ (81 ml, 0·58 mole) at 0–5°. The mixture was allowed to stir at room temp for 1 h, poured into ice water, and the organic layer separated. The dichloromethane soln was washed with water, saturated brine, dried, filtered, and evaporated. The residue was triturated with 15 ml EtOAc, filtered, and the crystalline orange solid washed with ether to give 13·5 g (90%), m.p. 192° dec; $\nu_{max}^{KBr}$ 1755, 1525, 1360, 1340, 1290, 1260, 775 cm$^{-1}$; $\lambda_{max}^{EtOH}$ nm ($\epsilon \times 10^{-3}$) 340 (6·8), 260 (14·8), 250 (14·5); NMR $\delta$ ($CDCl_3$) 4·0 (s, 6), 6·32 (d, J = 7·5, 1), 7·3 (m, 7). (Found: C, 61·68; H, 4·04; N, 7·64. Calcd for $C_{19}H_{14}N_2O_6$: C, 62·29; H, 3·85; N, 7·65%).

1 - (2 - *Amino* - 3,4 - *dimethoxyphenyl*) - 1,5,6,10b - *tetrahydrooxazolo*[4,3-a]*isoquinoline* - 3 - *one* (**20b**). A suspension of **18b** (13 g; 0·0356 mole) in 200 ml dry THF and 30 ml glacial AcOH was shaken with 4 g of 10% Pd-C under 50 lbs $H_2$ for 18 h. The mixture was filtered, concentrated, and the concentrate diluted with 150 ml of fresh THF. The soln was shaken with 4 g of platinum

oxide under 50 lbs of $H_2$ for 16 h, filtered, concentrated under reduced pressure. The AcOH concentrate was diluted with water, precipitating a gum. The aqueous phase was decanted and the crude material was washed with water, triturated with cold ethanol, and filtered to yield 4·5 g (37%) of **20b**, m.p. 163–167°. A small sample was recrystallized from EtOH to give colorless crystals, m.p. 169–170°; $\nu_{max}^{KBr}$ 3470, 3380, 1730, 1620, 1600, 1490, 1450, 1415, 1280, 1085, 985, 740 $cm^{-1}$; $\lambda_{max}^{EtOH}$ 295 nm ($\epsilon$ = 6960); NMR $\delta$ ($CDCl_3$) 2·35–3·44 (m, 3), 3·57 (s, 3), 3·74 (s, 2), 3·74 (s, 3), 4·18 (m, 1), 5·3 (d, J = 8·5 Hz, 1), 5·94 (d, J = 8·5 Hz, 1), 6·15 (d, J = 8 Hz, 1), 6·6 (d, J = 8 Hz, 1), 6·9 (m, 4). (Found: C, 67·10; H, 5·87; N, 8·14. Calcd for $C_{19}H_{20}N_2O_4$: C, 67·04; H, 5·92; N, 8·23%).

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