THE SYNTHESIS OF OXOAPORPHINES AND PHENANTHRENEDIONES FROM 7-HYDROXYDEHYDRONORAPORPHINES

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Abstract- Oxidation of 7-hydroxydehydronoraporphines with air over platinum or palladium yields oxoaporphines in high yield. When the nitrogen is acylated, oxidation with air in the presence of copper ions causes an oxidative ring fragmentation to form phenanthrenediones, also in high yield.

The aporphine alkaloids[1,2] are a broad class of tetracyclic isoquinoline alkaloids with wide distribution. Further metabolism of these secondary metabolites results in a wide variety of oxidized, methylated and heterocyclic ring fused analogs.[1] Among the more common of these are the 7-hydroxy- and methylaporphines, and the fully aromatic 7-oxoaporphines.[2,3+]

We have recently described the synthesis of 7-hydroxy- and 7-methoxyaporphines by photocyclization of a functionalized benzylideneisoquinoline.[4] A common intermediate in these syntheses was a 7-oxygenated dehydronoraporphine, which could be isolated as its ether, but not as the free phenol. Subsequently, we have found that these 7-hydroxydehydronoraporphines can be readily oxidized to oxoaporphines or phenanthrenediones. Previously, oxoaporphines have been prepared by oxidation of aporphines,[5,6] noraporphines,[6,7] dehydroaporphines,[8,9] dehydronoraporphines,[10] and 7-hydroxyaporphines.[11] Since oxidation of 7-hydroxyaporphines could result in the 7-keto compound, which would enolize to the 7-hydroxydehydroaporphine, the intermediacy of the 7-hydroxydehydronoraporphine may represent a latter stage in the metabolic conversion of some aporphines into oxoaporphines. Oxidation of aporphines to phenanthrenediones is limited to a single synthetic transformation,[12] but the occurence of N-formyldehydronoraporphines indicates that formation of these types of diones could occur in nature.[13]

The oxidation of N-carbethoxy-7-hydroxydehydronoraporphines to phenanthrenediones is illustrated in Scheme 1. The previously described acetoxybenzylideneisoquinoline (1) is oxidatively

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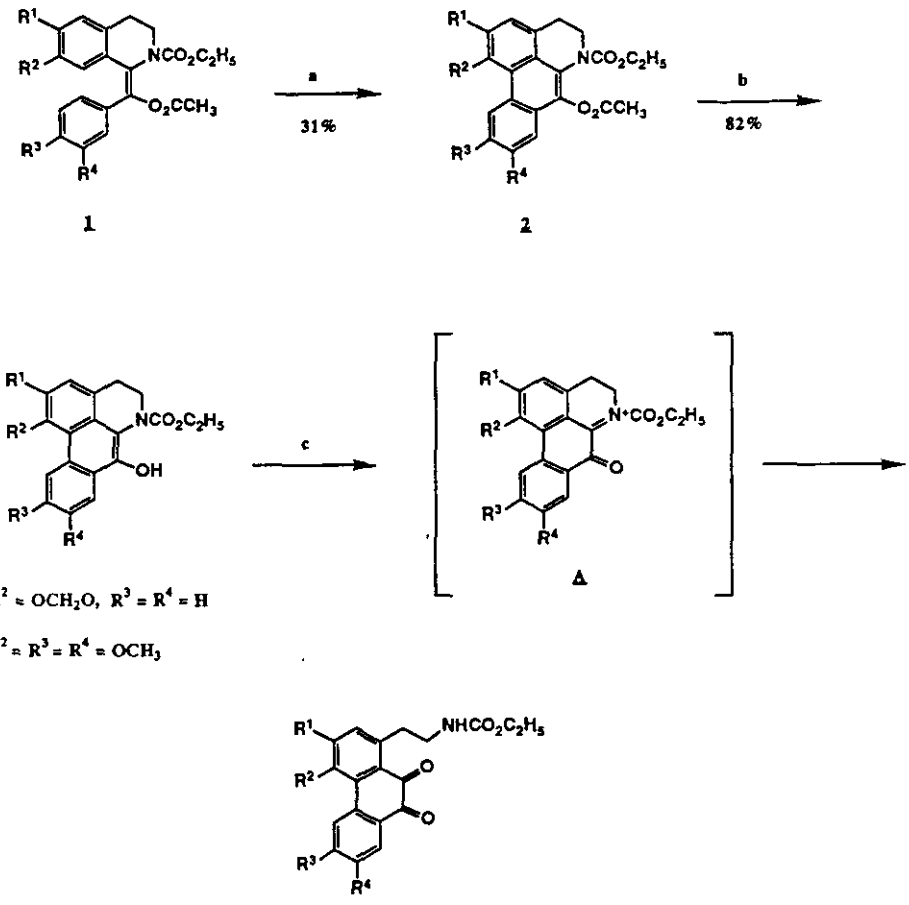
+Note: The compounds are described and numbered as aporphine alkaloids, except in the Experimental Section where Chemical Abstracts names and numbering are used.

Scheme 1



1

2

3 $R^1 = R^2 = OCH_2O$, $R^3 = R^4 = H$

5 $R^1 = R^2 = R^3 = R^4 = OCH_3$

Δ

4 $R^1 = R^2 = OCH_2O$, $R^3 = R^4 = H$ (98%)

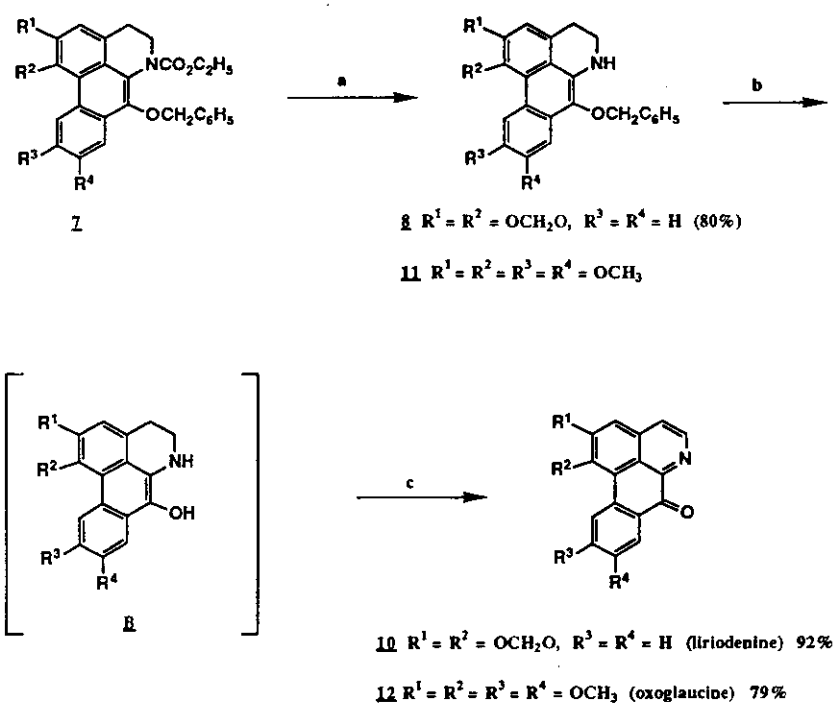
6 $R^1 = R^2 = R^3 = R^4 = OCH_3$ (75%)

Reagents : a) $h\nu/I_2$, b) $NaOCH_3$ / CH_3OH , c) Cu(I) / O_2

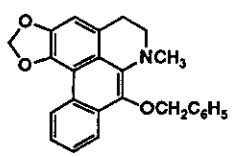
photocyclized to the 7-acetoxydehydronoraporphine (2).[4,14] After hydrolysis of the acetate, the resulting 7-hydroxydehydronoraporphine is oxidized with copper(I) and air to the phenanthrenedione (4). Similarly, the known tetramethoxy compound (5)[4] is also smoothly converted into dione (6). The spectral data (nmr and ir and particularly the mass spectrum of 6 which possesses a strong parent peak and a consistent fragmentation pattern) support the assigned structures. The uv spectrum of 6 is similar to a known, similarly substituted, phenanthrenedione.[12] Mechanistically, the oxidation of compounds (3) and (5) proceeds through the intermediate ethoxycarbonyliminium quinone (A), which is trapped by water and ring opens to the observed products.

In contrast, when the 7-hydroxydehydronoraporphine itself is oxidized, the reaction takes a different course as shown in Scheme 2. We had previously demonstrated that 7-hydroxydehydronoraporphines are unstable and rapidly degraded in the presence of air.[4] Consequently, they have to be generated <u>in situ</u>. The phenolic hydroxyl group in compound (3) is protected as its benzyl ether (7). Hydride reduction gave the protected nor-compound (8) as the major product (80%), together with its <u>N</u>-methyl derivative (9) (15%). In a one pot reaction, the 7-hydroxydehydronoraporphine is generated and oxidized to the oxoaporphine. Reductive cleavage of the benzyl group in 8 with Pd-C and hydrogen yields a solution of the hydroxydehydro-

Scheme 2



Reagents : a) $Na(CH_3OCH_2CH_2O)_2AlH_2$; b) Pd-C or Pt, H_2 ; c) Pd-C or Pt, O_2



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compound (B). After thorough removal of the hydrogen with nitrogen, air was introduced and the oxoaporphine (10), liriodenine, was formed in excellent yield, with spectral properties in agreement with the published values.[15,16] Similarly, cleavage of the benzyl ether in the tetramethoxy derivative (11)[4] with platinum and hydrogen, followed by oxidation

with air over platinum yielded the known oxoaporphine (12), oxoglaucine. The presence of the catalyst appears necessary, since, in its absence, only degradation occurs and no oxoaporphine was detectable.

In summary, oxidation of 7-hydroxydehydronoraporphines leads to the naturally occurring oxoaporphines in good yields. However, when the amino group is acylated, an oxidative ring opening occurs forming phenanthrenediones also in good yield.

EXPERIMENTAL

General Methods

Melting points were obtained on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Ir spectra were recorded as KBr pellets, and uv-visible spectra were run in methanol unless otherwise indicated. An IBM AF-270 or a Varian Associates FT-80 NMR spectrometer was used and the spectra were run in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra were determined on an AEI-MS-30. Microanalyses were determined by the BOC Group Technical Center microanalytical service under the direction of Allan Ellgren.

Ethyl 8-Acetoxy-5,6-dihydro-7H-benzo[g]-1,3-benzodioxolo-[6,5,4-de]quinoline-7-carboxylate (2).

Ethyl 7,8-dihydro-5-(phenyl-α-acetoxymethylene)-1,3-dioxolo-[4,5-g]isoquinoline-6(5H)-carboxylate (1),[4] 1.0 g (2.53 mmol), was dissolved in benzene (190 ml) containing iodine (129 mg) and irradiated under argon (Pyrex filter) using a 450 watt lamp for 4.5 h. The irradiation solution was washed with 2% aqueous sodium bisulfite. After drying over sodium sulfate, the solvent was removed and the residual oil was crystallized from methanol to yield the 7-acetoxydehydroaporphine derivative (2), (310 mg, 31%), mp 208-211°C, ir 1775, 1710 cm^{-1}; uv 376.5 (ε 2900), 367 (min, 1750), 357 (3430), 352 (min, 3700), 326 (9100), 297 (min, 4900), 287 (14900), 281 (min, 10800), 277 (sh, 12100), 251.5 (50600), 245 (sh, 41500), 226 (min, 15700) nm; nmr ($CDCl_3$) δ 9.02 (m, 1H), 7.86(m, 1H), 7.58 (m, 2H), 7.02 (s, 1H), 6.22 (s, 2H), 4.21 (q, J=7 Hz, 2H), 4.05 (br s, 2H), 3.13 (t, J=6 Hz, 2H), 2.40 (s, 3H), 1.26 (t, J=7 Hz, 3H) Anal. Calcd for $C_{22}H_{19}NO_6$: C,67.17; H,4.87; N,3.56 Found C,67.11; H,4.71; N,3.45.

Ethyl 5,6-Dihydro-8-hydroxy-7H-benzo[g]-1,3-benzodioxolo[6,5,4-de]-quinoline-7-carboxylate (3).

A suspension of the acetoxy derivative (2), 1.93 g (4.9 mmol), was dissolved in tetrahydrofuran (75 ml) with heating. The

solution was allowed to partially cool and then was diluted with methanol (50 ml) and placed under argon. When the magnetically stirred solution was at room temperature, sodium methoxide (2.0 g) was added. The solution immediately turned green and then orange-red. After 15 min, the excess base was quenched with citric acid (4 g). After stirring for 18 h, the suspension was diluted with water and the organic solvents were evaporated. The aqueous suspension was extracted with methylene chloride (4x50 ml). After drying over sodium sulfate, the solvent was evaporated and the residue was flash-chromatographed using ethyl acetate : methylene chloride (1:99) to yield the phenol (3) (1.42 g, 82%), mp 165-166.5°, ir 3440, 1655, 1630, 1610, 1600 cm^{-1}; uv 386 (ε 3300), 375 (min, 3000), 366 (3300), 355 (min, 2700), 330 (9000), 321 (9200), 297 (min, 4700), 287 (12300), 281.5 (min, 9500), 251.5 (45000), 246 (42000), 231 (min, 24600), 228 (25000) nm; nmr ($CDCl_3$) δ 9.00 (m, 1H),1 8.47 (m, 1H), 7.59 (m, 2H), 6.97 (s, 1H), 5.19 (s, 2H), 4.37 (q, J=7 Hz, 2H), 4.00(t, J=6 Hz, 2H), 3.27(t, J=6 Hz, 2H), 1.38 (t, J=7 Hz, 3H). Anal. Calcd for $C_{20}H_{17}NO_5$: C,68.37; H,4.88; N,3.99 Found: C,68.13; H,4.83; N,4.00.

Ethyl [2-(9,10-Dihydro-6,7-dioxophenanthro[3,4-d]-1,3-dioxol-5-yl)-ethyl]carbamate(4).

A solution of the ethyl isoquinoline-6-carboxylate (3), (71 mg, 0.21 mmol) in 4.4 ml of 10% aqueous dimethylformamide was

stirred magnetically, open to the atmosphere, in the presence of imidazole (80 mg) and bis(trimethylphosphine)copper (I) iodide (approx. 100 mg), for 2 days. After dilution with water, the solution was extracted with four portions of methylene chloride. After drying over sodium sulfate, the solvent was removed and residue was flash-chromatographed using a 2-12% methanol gradient in methylene chloride to yield the orange phenanthrenedione (4) (74 mg, 98%), mp 164-165.5°C (methanol-water), ir 3370, 1710, 1685, 1665 cm^{-1}; uv 420 (ε 4600), 321 (3500), 305 (min, 3000), 260 (sh, 25500), 255 (27800), 232 (min, 16700) nm; nmr ($CDCl_3$) δ 8.48 (d, J=7 Hz,1H), 8.13 (dd, J=7,2 Hz,1H), 7.68 (dd, J=7,2 Hz, 1H), 7.42 (dd, J=7,2 Hz, 1H) 6.77 (s, 1H), 6.22 (s, 2H), 4.08 (q, J=7 Hz, 2H), 3.42 (t, J=6 Hz, 2H), 3.19 (m, 2H), 1.22 (t, J=7 Hz, 3H). Anal. Calcd for $C_{20}H_{17}NO_6$: C,65.39; H,4.66; N,3.81 Found: C,65.25; H,4.60; N,3.83.

Phenanthrenedione, ethyl [2-(9,10-dihydro-3,4,6,7-tetramethoxy-9, 10-dioxo-1-phenanthrenyl)ethyl]carbamate (6), from the glaucine analog (5).

A solution of 137 mg (0.32 mmol) of ethyl 4,5-dihydro-7-hydroxy-1,2,9,10-tetramethoxy-6H-dibenzo[de,g]quinoline-6-carboxylate (5) in 22 ml of 10% aqueous dimethylformamide was heated to 100°C in the presence of 50 mg of bis(trimethylphosphine)copper (I) iodide for 4 h and then stirred at room temperature for an additional 48 h. The mixture was diluted with water and

extracted with chloroform. After drying over sodium sulfate, the solvent was removed and the residue was flash-chromatographed on silica gel with methanol: methylene chloride (3:97) to yield 110 mg (75%) of phenanthrenedione (6), mp 136.5-137°C (decompt.) (methanol-water), ir 3320, 1715(sh), 1695, 1665, 1655(sh) cm^{-1}; uv 353 (ε 9000), 318(min, 5750), 282 (37750), 273 (sh, 31000), 250 (min, 15750), 232 (21000) nm; nmr ($CDCl_3$) δ 8.45 (s, 1H), 7.51 (s, 1H), 6.73 (s, 1H), 4.10 (q, J=7 Hz, 2H), 3.99 (s, 6H), 3.97 (s, 3H), 3.76 (s, 3H), 3.43 (t, J=6 Hz, 2H), 3.17 (t, J=6 Hz, 2H), 1.23 (t, J=7 Hz, 3H); ms m/z 443 (30%, parent), 427 (30%), 415 (6%), 414 (9%), 397 (14%), 354 (76%), 342 (51%), 341 (100%). Anal. Calcd for $C_{23}H_{25}NO_8$ 0.5 H_2O: C,61.04; H,5.79; N,3.12. Found: C,60.99; H,5.88; N,2.90.

Ethyl 5,6-Dihydro-8-(phenylmethoxy)-5H-benzo[g]-1,3-benzodioxolo-[6,5,4-de]quinoline-7-carboxylate (7).

The phenol (3), 782 mg (2.23 mmol), was dissolved in acetone (40 ml) containing 765 mg of benzyl bromide (4.46 mmol) and 620 mg of potassium carbonate (4.46 mmol), and refluxed, under argon, for 18 h. The solvent was evaporated, and the organic residue was dissolved in methylene chloride and flash-chromatographed with ethyl acetate: methylene chloride (4:96) to yield the benzyl derivative (7) (943 mg, 96%), mp 152-153°C (methanol), ir 1700 cm^{-1}; uv 381 (ε 3800), 370 (min, 2400), 361 (3400), 331 (8700), 321 (8100), 298 (min, 3800), 288 (13200), 282 (min, 9600), 278 (1100), 252.5 (47200), 246 (sh, 38900), 225 (min,

18500) nm; nmr ($CDCl_3$) δ 9.02 (m, 1H), 8.23 (m, 1H), 7.58 (m, 2H), 7.36 (m, 5H), 6.98 (s, 1H), 6.21 (s, 2H), 4.00 (s, 2H), 3.17 (q, J=7 Hz, 2H), 3.80 (br s, 2H), 3.12 (t, J=6 Hz, 2H), 1.18 (t, J=7 Hz, 3H). Anal. Calcd for $C_{27}H_{23}NO_5$ 0.5 H_2O: C,71.98; H,5.37; N,3.11. Found: C,71.77; H,5.13; N,3.00.

6,7-Dihydro-8-(phenylmethoxy)-5H-benzo[g]-1,3-benzodioxolo-[6,5,4-de]quinoline (8), and its 7-methyl derivative (9).

A solution of the urethane (7), 1.15g (2.55 mmol) in toluene (150 ml) was dried under argon by refluxing using a Dean-Stark apparatus. The solution was subsequently cooled to -20°C (CCl_4/dry ice) and 8 ml of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene added. The reaction mixture was warmed to room temperature over 2-3 h, when tlc (benzene/silica) indicated the reduction was complete. Excess hydride was quenched with saturated Rochelle salt. The toluene solution was separated, dried over sodium sulfate, and evaporated. The residue was flash chromatographed using benzene to give the 7-methyl derivative (9) (150 mg, 15%), mp 108-109°C (ethanol), uv 388 (ε 4300), 338 (11600), 327 (9800), 298 (min, 2600), 280 (sh, 11200), 262 (39700), 257 (min, 37900), 254 (38800), 238 (min, 21600) nm; nmr ($CDCl_3$) δ 8.98 (m, 1H), 8.15 (m, 1H), 7.45 (m, 7H), 6.97 (s, 1H), 6.18 (s, 2H), 5.09 (s, 2H), 3.38 (distorted t, 2H), 3.12 (s, 3H), 3.09 (distorted t, 2H). Anal. Calcd for $C_{25}H_{21}NO_3$: C,78.31; H,5.52; N,3.65. Found: C,78.03; H,5.57; N,3.90.

Continued elution with benzene furnished the nor-compound (8), (750 mg, 80%), mp 109.5-111.5°C, uv 387 (ε 4300), 365 (min, 2700), 335 (13400), 292 (min, 3900), 259 (46800), 254 (47000), 231 (min, 19100) nm; nmr ($CDCl_3$) δ 8.95 (d, J=7 Hz, 1H), 7.95 (d, J=7 Hz, 1H), 7.25-7.60 (m, 7H), 6.95 (s, 1H), 6.19 (s, 2H), 5.00 (s, 2H), 3.25 (m, 4H). EIms m/z 278 (m-91, 27%), 275 (77%), 91 ($C_6H_5CH_2$,100). CIms m/z 369. Anal. Calcd for $C_{24}H_{19}NO_3$: C,78.03; H,5.18; N,3.79. Found: C,77.73; H,5.22; N,3.85.

Liriodenine (10)

The protected 7-hydroxydehydronoraporphine (8), 700mg (1.90 mmol) was dissolved in 30 ml of acetic acid containing 350 mg of 5% Pd/C. The mixture was hydrogenated and oxidized in a manner similar to oxoglaucine (12). After filtration and solvent evaporation, the residue was flash chromatographed using methanol-chloroform (3:97) to yield liriodenine (10), (483mg, 92%), whose melting point and spectral properties are in agreement with the published values.[15,16]

Oxoglaucine (12)

A solution of 4,5-dihydro-1,2,9,10-tetramethoxy-7-(phenylmethoxy)-6H-dibenzo[de,g]quinoline (11), 64 mg (0.14 mmol) in 30 ml of acetic acid was hydrogenated over prereduced platinum

oxide (32 mg) at room temperature and pressure until two equivalents of hydrogen were consumed. The residual hydrogen was flushed out with nitrogen and then air was introduced. The colorless solution then turned to a deep burgundy. The solution was stirred open to the air for 18 h, when the catalyst was filtered and the solvent evaporated. The residue was flash chromatographed using methanol : chloroform (4:96) to yield 7-oxoglaucine (**12**) (40 mg, 79%), whose melting point and spectral properties are in agreement with the published values.[15,17]

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