Photochemical Approach to 4,5-Dioxoaporphine Alkaloids. The Total Synthesis of Pontevedrine

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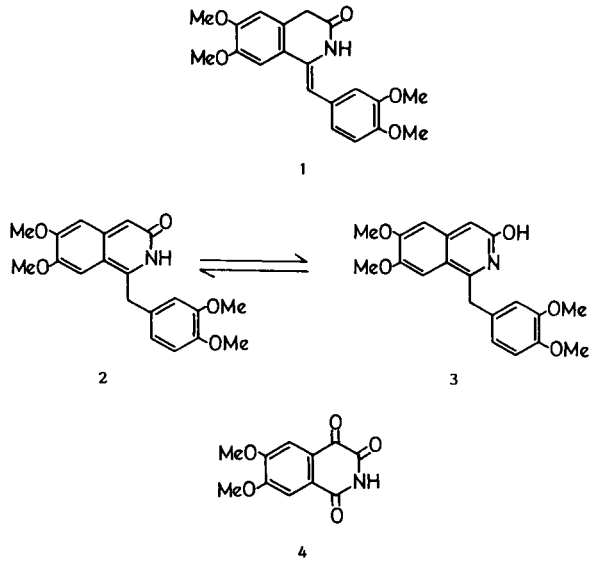
Received December 23, 1981

An easy and efficient total synthesis of pontevedrine **14b**, a 4,5-dioxoaporphine alkaloid, was achieved for the first time. It is based on the controlled photo-oxidation of the lactam **7c**, to give the benzylidene-dioxo compound **13b** and its subsequent photocyclizaton. A "one pot" transformation of the lactam **7c** into norpontevedrine **14a** was also achieved.

J. Heterocyclic Chem., **19**, 1319 (1982).

4,5-Dioxoaporphines constitute a small group of isoquinoline alkaloids found in minor amounts and most likely derived from aporphines by biological oxidation (1). They have been postulated as biogenetic precursors of aristolactams and aristolochic acids (1), the latter compounds of known antitumor activity (2). Only partial syntheses of 4,5-dioxoaporphines have been achieved, and these by two methods. Thus, cepharadione B and pontevedrine **14b** were prepared in low yields by photooxidation of the corresponding dehydroaporphines (3,4), and pontevedrine **14b** was obtained from 4-hydroxyglaucine (cataline) by oxidation with iodine or DDQ (dichlorodicyanoquinone) (1a). However, structural assignments for the carbonyl groups of 4,5-dioxoaporphines can not be unequivocally derived from the above synthetic studies. Consequently, there was a need for a general and practical route for the total synthesis of 4,5-dioxoaporphines and 4,5-dioxonoraporphines. We now report our results on this subject which led to the first total synthesis of pontevedrine **14b**, a 1,2,9,10-tetramethoxy-4,5-dioxoaporphine (5),

FIGURE 1

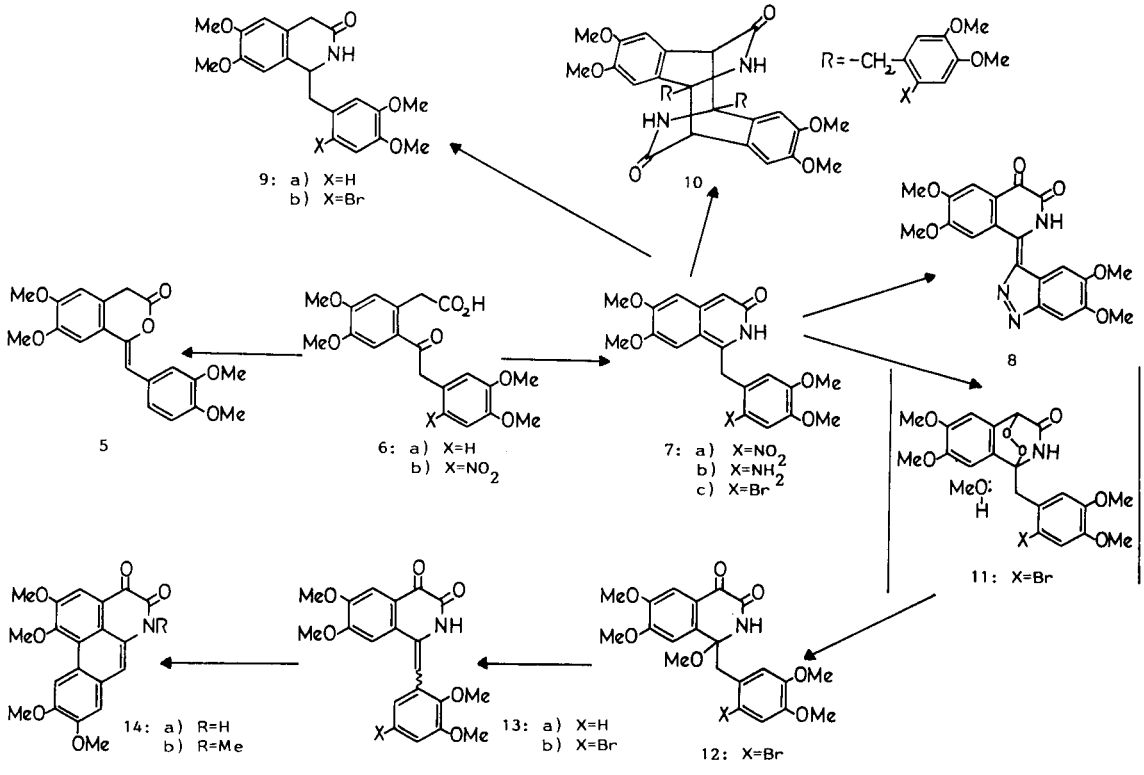


found in *Glaucium flavum Cr. var. Vestitum (Papaveraceae)* (1a,6).

The only attempt at total synthesis of a 4,5-dioxoaporphine has been reported by Elliot (7). It was based on the irradiation under oxidizing conditions of an isoquinolin-3-one first suggested to have the stilbene-like structure **1** (7) and later shown to exist in solution in a lactam-lactim tautomeric equilibrium (**2** ⇌ **3**) (7), which gave 6,7-dimethoxy-1,3,4-trioxoisoquinoline **4**. However, benzylidene isochromanones possess the required stilbene-like system for the expected electrocyclization. Therefore, the benzylidene isochromanone **5** was prepared from the corresponding ketoacid **6a** by dehydration (7). Nevertheless, when **5** was irradiated in acetonitrile no cyclized product was obtained. The $Z \rightleftharpoons E$ interconversion was the only process observed.

Consequently, the formation of the strategic biaryl bond of 4,5-dioxoaporphines was attempted through a Pschorr sequence. Hence, nitration of the ketoacid **6a** (8) with fuming nitric acid in glacial acetic acid gave the 6'-nitro compound **6b** in 75% yield, as shown by nmr spectroscopy which exhibited four aromatic protons as singlets at δ 6.71, 6.82, 7.38 and 7.73 ppm. Reaction of **6b** with ammonium acetate in acetic acid afforded in 80% yield the lactam **7a** as deduced from its spectroscopic data. The ir spectrum revealed the presence of a CO (1670 cm^{-1}) and a NO_2 group (1530 and 1340 cm^{-1}) and its nmr showed five aromatic protons as singlets at δ 6.64, 6.70, 6.77, 6.96 and 7.54 ppm. Catalytic hydrogenation of **7a** using Pd/C, followed by diazotization and subsequent decomposition of the resulting diazo compound, either in the presence or the absence of copper powder, led to the isolation of a solid product. This analyzed for $C_{20}H_{17}N_3O_6$ indicating that a nitrogen atom was added to the parent molecule and it showed four aromatic protons as singlets at δ 7.44, 8.01, 8.59 and 8.93 ppm. Hence, this compound was tentatively assigned the indazolic structure **8**, which is further supported by the fact that a similar reaction has been observed by Cava *et al.* in the diazotization of aminopapaverine (9). A second major product was isolated when the above diazotization was carried out in the absence of

FIGURE 11



copper powder. As this product was found to be unstable and its spectroscopic properties were also not the expected ones for the desired cyclized product, no further attempts were taken to identify it.

Since a halogen atom (preferably a bromine) at position 6′ increases the ability of benzylisoquinolines adequately protected on the nitrogen to photocyclize to the corresponding aporphine derivatives (10), the photocyclization of the 6′-bromobenzyl-isoquinolin-3-ones **9b** and **7c** was now attempted. Bromination of the isoquinolin-3-one **9a** (11) gave the corresponding 6′-bromo derivative **9b** as shown by nmr which exhibited four aromatic protons as singlets at δ 6.33, 6.55 (2H) and 6.98. However, irradation of **9b** in a methanolic alkali solution under an argon atmosphere with quartz filtered light was mainly accompanied by debromination, resulting in 70% yield of **9a** as the major product. On the other hand, irradiation of **7c** (11) in an ethanolic alkali solution, as above, afforded a white solid precipitate. It was supposed that this might have the dimeric structure **10**, as its physical properties were similar to those of the dimers which resulted in the solid-phase irradiation of isoquinolin-3-ones (12).

In order to overcome the above problems, the photocyclization of isoquinolinedione derivatives of type **13** was now investigated, as they possess the same functionalization in their isoquinoline nucleus as the 4,5-dioxoaporphines, as well as a stilbene-like system and the nitrogen atom protected as an amide. The synthesis of these benzylideneisoquinolinediones was carried out by the new method recently developed in our laboratory (5,13). When **13a** (14) was irradiated, *E,Z* isomerization appeared to be the only process observed. To increase its ability to photocyclize, the strategy of introducing a halogen atom at its position 6′ (14) was applied. Thus, the 6′-bromo derivative of **13a** was prepared by photocycloaddition of singlet oxygen to the 6′-bromobenzylisoquinolin-3-one **7c**, affording in high yield the desired product **12**, which seems to result from the opening of the corresponding endoperoxide intermediate **11** by the solvent (methanol) (13). The structure of **12** was supported by its ^{1}H-nmr which revealed the presence of a new methoxy group as a singlet at δ 3.17 and a methylene group at δ 3.42 ppm (dd, 2H) and confirmed by ^{13}C-nmr which showed besides an aliphatic methoxy group at δ 51.07(q), a methylene group at δ 49.71 (t) and a strongly deshielded quaternary carbon at δ 89.15 (s) ppm. It is worth noting that these photooxidations appear to be sensitized by the starting isoquinolin-3-ones. Presumably their excited state (T_1) is of a very low energy and therefore is efficient at transferring energy to the oxygen. In fact, when the reaction was carried out in the presence of an external sensitizer, an appreciable decrease of the isoquinolinedione **12** was observed.

As expected (13) the isoquinolinedione **12** readily eliminates methanol under acidic or basic conditions to give in 95% yield the 6'-bromobenzylideneisoquinolinedione **13b** as a mixture of the *E-Z* isomers (¼ ratio, approximately). By fractional crystallization from the reaction medium, the pure isomer *Z*-**13b** was obtained, as shown by nmr which exhibited one NH group at δ 8.44 (bs, 1H) and four aromatic and one olefinic protons as singlets at δ 6.71, 6.84, 7.12, 7.31 and 7.61 ppm. Subsequent irradiation of 6'-bromobenzylideneisoquinolinedione **13b** (*E,Z* mixture) in ethanolic alkali solution under argon atmosphere with Pyrex filtered light, afforded norpontevedrine **14a**, a 4,5-dioxonoraporphine, which represents the first synthetic example of this type of compounds. It was isolated in 43% yield from the reaction mixture by preparative tlc. Its structure was established from its spectroscopic data and further confirmed by its conversion into pontevedrine **14b**. Thus, treatment of norpontevedrine **14a** with sodium hydride, in dry DMF to prevent the decarbonylation of pontevedrine **14b** (1a), followed by the addition of methylfluorsulphonate gave in 76% pontevedrine **14b**, identified by direct comparison with authentic material. Under these conditions, the competitive *O*-methylation of norpontevedrine **14a** was practically avoided. This appears to be the major process observed when norpontevedrine **14a** was treated with diazomethane, as a faster moving spot (tlc) than pontevedrine **14b** resulted. This reaction product was not further investigated.

Finally, a "one pot" conversion of the isoquinolin-3-one **7c** into norpontevedrine **14a** was achieved by carrying out the irradation of **7c** in ethanolic alkali solution, under an oxygen atmosphere. Norpontevedrine **(14a)** was now isolated in 33% yield.

As a conclusion, it may be stated that this method of synthesising 4,5-dioxoaporphines seems to be of wide scope and therefore that different alkaloids of this type may be synthesised in a similar manner.

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were determined in potassium bromide on a Pye Unicam SP-1100 spectrophotometer. Ultraviolet spectra were recorded in ethanol solution on a Pye Unicam SP-1700 spectrophotometer. The ^{1}H and ^{13}C nuclear magnetic reesonance spectra were determined on a Varian CFT-20 spectrophotometer in deuteriochloroform solution (unless otherwise specified) containing tetramethylsilane as the internal standard. Photolyses were carried out using medium-pressure mercury arc lamps (Hanovia, 250 and 400 watts). Catalytic hydrogenations were achieved in a Parr hydrogenator. Thin layer chromatography (tlc) was taken using silica gel GF-254 (type 60) and chloroform-methanol or chloroform-ethanol mixtures as eluent; the tlc slides were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using silica gel Merck (type 60). The solvents were purified according to (15). Starting compounds **5, 6a, 9a** (7), **7c** and **13a** (13) were prepared by known methods.

2-[(3',4'-Dimethoxy-6'-nitrophenylacetyl)-4,5-dimethoxy]phenylacetic Acid **6b**.

To a cooled and stirred solution of the ketoacid **6a** (1 g, 2.67×10^{-3} mole) in glacial acetic acid (10 ml), maintained at about 10°, 1 ml of nitrating mixture (fuming nitric acid-glacial acetic acid, 3:2 by volume) was added dropwise during 5 minutes. The reaction mixture was poured into 100 ml of ice-water mixture and a precipitate separated out which was filtered off and washed free of acid. This solid was crystallized from methanol to give, in 75% yield, the nitroketoacid **6b** as white crystals (0.85 g), mp 211-213°; ir: ν max 3400-2600 and 1750 (COOH), 1680 (C=O), 1510 and 1330 (NO_2) cm^{-1}; uv: λ max (log ε) 230 (4.60), 275 (4.26) and 316 (4.12) nm; pmr δ 3.74 (s, 2H, -CH_2-COOH), 3.94 (s, 12H, 4 × *Me*O-), 4.60 (s, 2H, -CH_2-CO-), 6.71, 6.82, 7.38 and 7.73 (ss, each 1H, Ar-*H*) ppm; ms: m/e (%) 419 (4) (M^+), 223 (10), 195 (100), 164 (19).

Anal. Calcd. for $C_{20}H_{21}NO_9$: C, 57.27; H, 5.04; N, 3.34. Found: C, 57.17; H, 4.72; N, 3.48.

1-(3',4'-Dimethoxy-6'-nitrobenzyl)-6,7-dimethoxyisoquinolin-3-one **7a**.

A mixture of the nitroketoacid **6b** (1 g, 2.38×10^{-3} mole), ammonium acetate (10 g) and glacial acetic acid (20 ml) was slowly heated until complete dissolution and then refluxed gently for 30 minutes. The dark-brown solution, once cold, was poured into 100 ml of water and allowed to stand for several hours. The precipitate produced was collected by filtration, washed free of acid and crystallized from chloroform-methanol (1:1) to give the nitrolactam **7a** (0.76 g) as yellow crystals, 80% yield, mp 243-245°; ir: ν max 1670 (C=O), 1530 and 1340 (NO_2) cm^{-1}; uv λ max (log ε) 248 (4.74), 320 (3.97) and 350 (4.00) nm; pmr: δ 3.67, 3.84, 3.87 and 3.95 (ss, each 3H, 4 × *Me*O-), 4.85 (s, 2H, -CH_2-), 6.64, 6.70, 6.77,6.96 and 7.54 (ss, each 1H, Ar-*H*) ppm; ms: m/e (%) 400 (10) (M^+), 383 (7), 370 (7), 355 (57), 354 (100), 339 (41), 323 (20).

Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 59.99; H, 5.03; N, 6.99. Found: C, 59.70; H, 4.82; N, 6.97.

1-(3',4'-Dimethoxy-6'-aminobenzyl)-6,7-dimethoxyisoquinolin-3-one **7b**.

A suspension of the nitrolactam **7a** (0.5 g, 1.35×10^{-3} mole) and 10% Pd/C catalyst (0.3 g) in 96% ethanol (300 ml) was hydrogenated at an initial pressure of 1 atmosphere for 5 hours, until the disappearance of the starting material (tlc). Usual work-up gave a pure (tlc) and unstable solid residue of the amine **7b** (0.45 g), which was used without further purification.

Attempts at Pschorr Cyclization of the 6'-Aminobenzylisoquinoline-3-one **7b**.

A) A cooled and stirred solution of the recently obtained 6'-aminobenzylisoquinolin-3-one **7b** (0.4 g, 1.08×10^{-3} mole) in methanol (20 ml) and 10% sulphuric acid (20 ml), kept at 0-5°, was diazotizated with 1 *N* sodium nitrite (2 ml) and then refluxed for 30 minutes. After removal of the methanol under reduced pressure, the resulting mixture was poured into water (100 ml), basified with ammonia and extracted with dichloromethane. Usual work-up of the organic layer left a solid residue (0.35 g) which gave two major compounds (tlc), and it was submitted at column chromatography. Elution with 5% ethanol-dichloromethane left a solid residue which, after being washed several times with small volumes of ethanol, was cyrstallized from chloroform to give the indazole product **8** (80 mg) as a yellow-green powder, 20% yield, mp 286-288°; ir: ν max 1630 and 1610 (C=O) cm^{-1}; uv: λ max 220, 270, 286, 418 and 440 nm; pmr: δ 4.01 (s, 6H, 2 × *Me*O-), 4.08 (s, 6H, 2 × *Me*O-), 7.44, 8.01, 8.58 and 8.93 (ss, each 1H, Ar-*H*) ppm; ms: m/e (%) 395 (1) (M^+), 367 (100).

Anal. Calcd. for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.30; N, 10.63. Found: C, 60.90; H, 4.49; N, 10.78.

Further elution of the column with 10% methanol-dichloromethane gave the second major reaction product (0.175 g), which decomposed on standing.

B) A cooled and stirred solution of the aminobenzylisoquinolin-3-one **7b** (0.4 g, 1.08×10^{-3} mole) in methanol (20 ml) and 10% sulfuric acid (20 ml), kept at 0-5°, was diazotizated with 10% sodium nitrite (2 ml). After stirring for 20 minutes, copper powder (80 mg) was added and the

mixture was stirred for 20 minutes at room temperature, warmed to 40° for 1 hour, basified with ammonia and extracted with dichloromethane. Usual work-up of the organic extract left a solid residue which by column chromatography, as above, gave the compound **8** (0.15 g) in 35% yield.

1-(3',4'-Dimethoxy-6'-bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-3-one **9b**.

To a cooled and stirred solution of the tetrahydroisoquinolin-3-one **9a** (0.3 g, 0.84 × 10^{-3} mole) in 50% aqueous acetic acid (10 ml), kept around 10°, 1 ml of 10% solution of bromine in acetic acid was added dropwise during 30 minutes. The reaction was stirred for 30 minutes at room temperature, and a white precipitate separated out. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane. Usual work-up of this organic extract left a white solid residue (0.35 g) chromatographically pure (tlc). This was crystallized from acetone to give the bromolactam **9b** as white crystals, 98% yield, mp 200-201°; ir: ν max 3200 (-NH-) and 1660 (C=O) cm^{-1}; uv: λ max 230 and 285 nm; pmr: δ 3.00-3.30 (m, 4H, 2 × -C*H*$_2$-), 3.67 (s, 3H, *Me*O-), 3.84 (s, 9H, 3 × *Me*O-), 4.73 (m, 1H, -C*H*-), 6.33 (s, 1H, Ar-*H*), 6.55 (s, 2H, Ar-*H*) and 6.60-7.00 (m, 2H, Ar-*H* and -N*H*) ppm.

Anal. Calcd. for $C_{20}H_{22}BrNO_5$: C, 55.04; H, 5.08; N, 3.21; Br, 18.33. Found: C, 54.85; H, 5.17; N, 3.06; Br, 18.56.

Irradiation of the 6'-Bromobenzyl-1,2,3,4-tetrahydroisoquinolin-3-one **9b**.

A stirred solution of the bromolactam **9b** (0.15 g, 0.34 × 10^{-3} mole) in 0.5% methanolic sodium hydroxide (150 ml), in an argon atmosphere, was irradiated with quartz-filtered uv light (from a mercury-lamp, Hanovia 400 watts) for 30 minutes. The reaction mixture was then neutrallized with ammonium chloride and most of the methanol removed in a rotary evaporator. The resulting suspension was poured into water (100 ml) and extracted with dichloromethane. Usual work-up of the extract left a solid residue (0.12 g), which was submitted to preparative tlc (eluent: chloroform-ethanol 9.5:0.5) to give 86 mg of the lactam **9a**, identified by direct comparison.

Irradiation of the Bromobenzylisoquinolin-3-one **7c**.

A solution of the bromolactam **7c** (0.5 g, 1.5 × 10^{-3} mole) in 0.3% ethanolic sodium hydroxide (500 ml) was irradiated, in a Pyrex vessel, with uv light (from a mercury-lamp, Hanovia 400 watts) for 3 hours, until presence of starting material was not observed by tlc. The resulting yellow-brown solution was neutrallized (5% aqueous hydrochloric acid) and an abundant white precipitate separated out. This was filtered off and washed (1.-water, 2.-dichloromethane) to give a white solid residue (0.35 g), possibly the dimer **10**, as it was highly insoluble in usual organic solvents, aqueous sodium hydroxide and trifluoroacetic acid (12).

1-(3',4'-Dimethoxy-6'-bromobenzyl)-1,6,7-trimethoxyisoquinoline-3,4-dione **12**.

A stirred solution of the bromolactam **7c** (1 g, 2.3 × 10^{-3} mole) in 0.1% methanolic sodium hydroxide (1 ℓ), through which oxygen was bubbled for 20 minutes, was irradiated with Pyrex filtered uv light (from a mercury-lamp, Hanovia 250 watts) for about 3 hours, until total transformation of the starting material (tlc) was accomplished. The resulting solution was neutrallized (ammonium chloride) and most of the methanol removed in a rotary evaporator. The resulting suspension was poured into water (300 ml) and extracted with dichloromethane. Usual work-up of this extract left a white solid residue. It was crystallized from methanol to give compound **12** (1 g), as colourless prismatic crystals, 95% yield, mp 196-197°; ir: ν max 1690 (C=O) cm^{-1}; uv: λ max (log ε) 213 (4.29), 245 (4.02), 292 (3.69) and 340 (3.54) nm; pmr: δ 3.17 (s, 3H, *Me*O-C$_1$), 3.42 (dd, J = 9 Hz, 2H, -C*H*$_2$-), 3.59, 3.79, 3.94 and 3.97 (ss, each 3H, 4 × *Me*O-Ar), 6.26, 6.87, 6.91 and 7.45 (ss, each 1H, Ar-*H*), 6.68 (bs, 1H, -N*H*-) ppm; cmr: δ 49.71 (-C*H*$_2$-), 51.07 (*Me*O-C$_1$), 56.13, 56.44 and 56.63 (4 × *Me*O-Ar), 89.15 (*C*$_1$), 108.00, 108.49, 115.12 and 115.69 (=*C*H-), 116.89 (=*C*-Br), 125.28 and 135.65 (=*C*-), 148.14, 149.31, 150.58 and 155.56 (=*C*-OMe), 158.12 (-*C*O-NH) and 175.97 (-*C*O-Ar) ppm; ms: m/e (%) 481, 479 (28) (M^+), 250 (100), 222 (75), 190 (75).

Anal. Calcd. for $C_{21}H_{22}BrNO_7$: C, 52.50; H, 4.61; N, 2.91; Br, 16.65. Found: C, 52.24; H, 4.76; N, 2.81; Br, 16.40.

1-(*E,Z*)-(3',4'-Dimethoxy-6'-bromobenzylidene)-6,7-dimethoxyisoquinoline-3,4-dione **13b**.

To a solution of the isoquinoline-3,4-dione **12** (0.3 g, 0.62 × 10^{-3} mole) in dioxane (15 ml), 10% hydrochloric acid (10 ml) was added. This mixture was maintained at around 60° for 30 minutes and then allowed to stand for several hours. Yellow-orange needle-shaped crystals which separated out were collected by filtration and were washed free of acid, to give *Z*-**13b** (0.15 g) chromatographically pure.

The mother liquor from the filtration was poured into water (100 ml) and extracted with dichloromethane. Usual work-up of this extract left a solid residue (0.125 g), which showed two visible spots by tlc. This was crystallized from ethanol to give a *Z-E* mixture of **13b** as yellow-orange crystals (total yield, 98%), mp 252-254°.

Anal. Calcd. for $C_{20}H_{16}BrNO_4$: C, 53.57; H, 4.04; N, 3.12; Br, 17.80. Found: C, 53.44; H, 4.04; N, 2.91; Br, 18.01.

Spectroscopic data of *Z*-**13b** was: ir: ν max 1680 (C=O) cm^{-1}; uv: λ max (log ε) 244 (4.27), 296 (4.26) and 402 (4.08) nm; pmr: δ 3.87, 3.90, 3.96 and 4.06 (ss, each 3H, 4 × *Me*O-), 6.71, 6.84, 7.12, 7.31 and 7.61 (ss, each 1H, Ar-*H* and C=C-*H*), 8.44 (bs, 1H, -N*H*-) ppm; ms: m/e (%) 449, 447 (100) (M^+), 368 (78), 340 (39), 309 (56).

1,2,9,10-Tetramethoxy-6a,7-didehydro-4,5-dioxonoraporphine (Norpontevedrine) **14a**.

A) From the 6'-Bromobenzylideneisoquinoline-3,4-dione **13b**.

A stirred suspension of the isoquinoline-3,4-dione **13b** (0.1 g, 0.22 × 10^{-3} mole) (*E,Z* mixture) in 0.1 *M* ethanolic sodium hydroxide (150 ml), in an argon atmosphere, was irradiated with Pyrex filtered uv light (from a mercury-lamp, Hanovia 250 watts) for 6 hours, until total transformation of the starting material occurred. The resulting red solution was neutrallized (ammonium chloride) and most of the ethanol was removed in a rotary evaporator. The remaining solution was diluted with water (100 ml), acidified and extracted with dichloromethane. Usual work-up of this extract left a solid residue (75 mg). This was submitted to preparative tlc (eluent: chloroform-methanol 9:1) to give 35 mg of **14a** (the slowest moving spot), which crystallized from ethanol-diethyl ether (5:4) as red crystals, 43% yield, mp 284-286°; ir: ν max 1700 (C=O) cm^{-1}; uv: λ max (log ε) 238 (4.60), 313 (3.99), 325 (4.24) and 478 (3.95) nm; pmr (DMSO-d_6): δ 3.93 (s, 6H, 2 × *Me*O-), 4.06 (s, 6H, 2 × *Me*O-), 7.37, 7.43, 8.08 and 8.92 (ss, each 1H, Ar-*H*) ppm; ms: m/e (%) 367 (100) (M^+).

B) From the 6'-Bromobenzylisoquinolin-3-one **7c**.

A stirred solution of the bromolactam **7c** (0.15 g, 0.34 × 10^{-3} mole) in 0.1 *M* ethanolic sodium hydroxide (150 ml), was irradated with Pyrex filtered uv light (from a mercury-lamp, Hanovia 250 watts) for 4 hours, until total transformation of the starting material (tlc). Work-up of the reaction mixture, as above, gave a solid residue (0.135 g), which was submitted to preparative tlc (eluent: chloroform-methanol 9.5:0.5) to give 40 mg of norpontevedrine **14a** (the slowest moving spot), yield 33%.

1,2,9,10-Tetramethoxy-6a,7-didehydro-4,5-dioxoaporphine (Pontevedrine) **14b**.

To a stirred solution of norpontevedrine **14a** (0.1 g, 0.27 × 10^{-3} mole) in dried DMF, in an argon atmosphere, 15 mg of sodium hydride (80%) were added. To the resulting red mixture an excess of methyl fluorosulphonate was added, and the reaction stirred at room temperature for about 1 hour, until total transformation of the starting material (tlc). The excess sodium hydride and methyl fluorosulphonate were destroyed by adding methanol to the reaction mixture. Then, this was poured into water (100 ml), acidified (5% aqueous hydrochloric acid) and extracted with dichloromethane. Usual work-up of the extract left a solid residue, which was purified by preparative tlc (eluent: chloroform-ethanol 9.7:0.3) and then by crystallization (ethanol) to give pontevedrine **14b** (79 mg,76% yield), identical in all respects with authentic specimen from

natural sources (mp, tlc, ir and pmr).

Pontevedrine from Natural Sources.

This compound had mp 269-271°; ir: ν max 1660 (C=O), 1615 and 1590 (C=C and C=N$^+$ groups); uv: λ max (log ϵ) 245 (4.59), 312 (4.28), 325 (4.39) and 470 (4.01) nm; pmr δ 3.79 (s, 3H, N-*Me*), 4.07 (s, 12H, 4 × *Me*O-Ar), 7.17, 7.34, 8.12 and 9.02 (ss, each 1H, Ar-*H*) ppm.

Synthetic Pontevedrine **14b**.

This compound had mp 269-271°; ir: ν max 1660, 1615 and 1590 cm^{-1}; uv: λ max 245, 312, 325 and 470 nm; pmr: δ 3.79 (s, 3H), 4.07 (s, 12H), 7.17, 7.34, 8.12 and 9.02 (ss, each 1H) ppm.

Acknowledgements.

To the Comisión Asesora de Investigación Científica y Técnica (Spain) for its financial support, to Dr. A. García Martínez (Departamento de Química Orgánica, Facultad de Ciencias de la Universidad Complutense, Madrid) for recording the mass spectra and to Dr. Vega (Instituto de Química Médica, C.S.I.C., Madrid) for providing the microanalyses.

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