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Colouring Matters of Australian Plants. XVII* Synthesis of Lomandrone

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Abstract

The structure of lomandrone, one of the principal pigments of *Lomandra hastilis*, is confirmed as 3-ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone by a synthesis starting from gallic acid.

Lomandrone is one of many naphthoquinone pigments found in the roots of *Lomandra hastilis* R.Br. (Xanthorrhoeaceae).[1–3] Chemical properties, spectra and a synthesis of its methyl ether indicated the structure 3-ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone.[1,2] This compound had been reported earlier as a derivative obtained from a natural spinochrome but the published melting point was very much lower than that observed for lomandrone.[4] We have now completed an independent synthesis of this quinone, corresponding in all respects with natural lomandrone, by the following steps: gallic acid → methyl 3,4,5-trimethoxybenzoate → 3,4,5-trimethoxybenzyl alcohol → 3,4,5-trimethoxybenzyl chloride → 3,4,5-trimethoxybenzyl cyanide → methyl 3,4,5-trimethoxyphenylacetate → methyl 2-acetyl-3,4,5-trimethoxyphenylacetate → 2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone → 3-ethyl-2,5-dihydroxy-6,7-dimethoxy-1,4-naphthoquinone → 3-ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone.

Experimental

Methyl 3,4,5-Trimethoxybenzoate

A solution of gallic acid (17 g) in acetone was mixed with dimethyl sulphate (56 g) and anhydrous potassium carbonate (61 g) and the mixture was boiled and stirred under nitrogen for 6 h. The acetone was then distilled, the residue was mixed with ice-water and then extracted several times with ether. The extract was washed with 10% caustic soda and with water and, after drying ($MgSO_4$), the ether was evaporated. The recovered ester (yield 70%) crystallized from aqueous methanol in needles, m.p. 82·5–83° (lit.[5] 80–82°) (all melting points are corrected).

3,4,5-Trimethoxyphenylacetonitrile

The above ester was reduced with $LiAlH_4$ and the resulting alcohol was converted into the chloride essentially as described previously in the literature.[5,6]

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A solution of 3,4,5-trimethoxybenzyl chloride (6 g) in dimethyl sulphoxide (30 ml) was slowly added to a stirred slurry of dried sodium cyanide in dimethyl sulphoxide (15 ml) at 65–70°. After stirring at 70° for 2 h the mixture was cooled and poured into water (100 ml). The product was recovered by extraction several times with chloroform, washing the extract with water and removing the solvent. The resulting nitrile (yield 90%) after crystallizing from light petroleum (60–80°) had m.p. 77–78° (lit.[7] 78–80°).

3,4,5-Trimethoxyphenylacetic Acid

The above nitrile (5·3 g) was boiled with 10% NaOH (100 ml) until ammonia was no longer evolved (5–6 h). After cooling, the solution was neutralized (litmus) with HCl and the mixture was filtered. The filtrate was then acidified with more HCl (Congo red) and saturated with NaCl. The precipitated acid was collected and dried; yield 80%, m.p. 120–121° (lit.[7] 117·5–120·5°).

2-Hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone

The above acid (4·1 g) was esterified with diazomethane (4·6 g) in ether and the ester (3 g) was mixed with acetic anhydride (0·75 g) and polyphosphoric acid (19 g). The mixture was kept at 45° for 8 h with occasional shaking, left overnight at room temperature, and then kept at 45° for a further period of 6 h. It was then stirred into a large volume of ice-water and the product was extracted with chloroform. The extract was washed twice with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated to give crude methyl 2-acetyl-3,4,5-trimethoxyphenylacetate (3·5 g). This ester (1·5 g) was then cyclized and oxidized essentially as described previously.[8] The quinone (318 mg) separated from benzene in yellow crystals, m.p. 163–164° (lit.[8] 169–170°).

3-Ethyl-2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone

A solution of dipropionyl peroxide (49 mg) in ether was added to 2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone (80 mg) in glacial acetic acid (10 ml). The ether was removed under reduced pressure and the solution was then heated in a boiling water bath for 1 h. After adding water the product was extracted with chloroform, the extract was washed repeatedly with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by thin-layer chromatography on silica gel containing 2% oxalic acid using toluene–butyl acetate–acetic acid (80 : 20 : 1) as solvent. The major orange-yellow band was extracted with chloroform and the product was crystallized several times from benzene–light petroleum (60–80°). The *3-ethyl-2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone*, m.p. 169–170·5°, has λ_{max} 208, 268, 311, 353 nm; ν_{max} 3360, 2980, 2954, 2880, 2840, 1650, 1578, 1485, 1455, 1415, 1390, 1335 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) showed peaks at δ 1·11 (t, 3H), 2·58 (q, 2H), 3·92 (s, 3H), 3·96 (s, 3H), 3·98 (s, 3H), 7·48 (s, 1H), 7·05 (s, 1H removed by exchange with D_2O) (Found: C, 61·5; H, 5·5; *m/e* 292. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%; *m/e* 292).

3-Ethyl-5-hydroxy-2,6,7-trimethoxy-1,4-naphthoquinone (Lomandrone)

A solution of 3-ethyl-2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone (25 mg) in methanol (10 ml) and hydrobromic acid (48%, 10 ml) was boiled under reflux for 1 h and the reaction was followed by thin-layer chromatography. When the demethylated product was the major component the reaction mixture was poured into water and extracted with chloroform. The extract was washed, dried ($MgSO_4$) and evaporated to give a residue showing an n.m.r. spectrum with a peak at δ 12·65 consistent with a bonded hydroxy group in the 5-position. This material (25 mg) was then methylated with diazomethane in ether and the product was separated by thin-layer chromatography on silica gel containing 2% oxalic acid as described above. The major broad orange band was extracted and the compound was further purified by chromatography on a column of Sephadex in methanol–hydrochloric acid, sublimation under reduced pressure and crystallization from aqueous methanol to give orange-red needles, m.p. 116–117°, identical with natural lomandrone (m.m.p., R_F, n.m.r. and i.r.).

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