

THE SYNTHESIS OF AGGLOMERONE

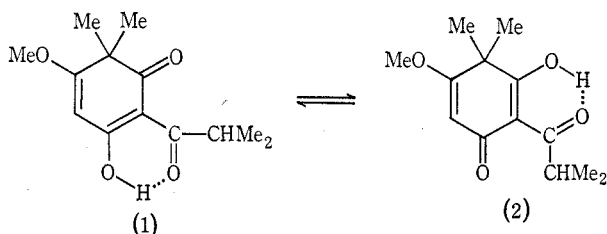
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Abstract

The naturally occurring β -triketone agglomerone has been synthesized by a method which confirms the pair of structures previously proposed for it.

Agglomerone was isolated¹ from the New South Wales eucalypts *E. agglomerata* and *E. mckieana*, and the pair of tautomeric structures (1) and (2) were assigned to it on the basis of degradative and spectroscopic evidence.¹ A later study² of its electronic spectrum indicated that (1) was the predominant tautomer, which from n.m.r. evidence¹ occurs to the extent of about 80% in the equilibrium mixture.



The starting material for the synthesis, phlorisobutyrophenone, was monomethylated in fair yield with diazomethane. The n.m.r. spectrum of the product indicated a symmetrical structure, and moreover, the magnitude of the bathochromic shift of the main u.v. band on addition of alkali³ showed that methylation had occurred on the *para* rather than on an *ortho* hydroxyl group, as expected from theoretical considerations and from analogy with other recorded examples.⁴

C-Methylation of the *O*-methylphlorisobutyrophenone by Riedl's method⁵ yielded as the main product a substance identical with natural agglomerone, for which the proposed structures are thus unequivocally confirmed. 2,6-Dihydroxy-4-methoxy-3-methylisobutyrophenone was obtained as a byproduct, together with a small quantity of another substance whose structure was not further investigated. The properties of the former compound agreed with those recorded for it by Riedl,⁶ who prepared it by another route.

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¹ Hellyer, R. O., *Aust. J. Chem.*, 1964, **17**, 1418.

² Elvidge, J. A., and Laws, D. R. J., *J. chem. Soc. (C)*, 1967, 1839.

³ Scott, A. I., "Interpretation of the Ultra-Violet Spectra of Natural Products," pp. 108-9 (Pergamon: Oxford 1964).

⁴ Sonn, A., and Bülow, W., *Ber. dt. chem. Ges.*, 1925, **58**, 1691; Widen, C. J., *Acta chem. fenn.*, 1968, **41**, 295.

⁵ Riedl, W., U.S. Pat. 2,898,374, 1959.

⁶ Riedl, W., *Chem. Ber.*, 1956, **89**, 2600; Riedl, W., and Mitteldorf, R., *Chem. Ber.*, 1956, **89**, 2589.

Experimental

Melting points are uncorrected. N.m.r. spectra were recorded on a Jeol JNM-4H-100 spectrometer in deuterochloroform with tetramethylsilane as internal standard. U.v. spectra were measured in methanol, and i.r. spectra in Nujol mulls with Perkin-Elmer spectrophotometers 124 and 221 respectively.

2,6-Dihydroxy-4-methoxyisobutyrophenone

Phlorisobutyrophenone (11 g), prepared in 34% yield by the Hoesch procedure,⁷ was dissolved in anhydrous ether (70 ml), and the solution, cooled to 0°, was treated with ethereal diazomethane solution (prepared from 8 g of nitrosomethylurea) which had been likewise cooled and dried (KOH). After 2 days, the mixture was again cooled to 0° and treated with a similar quantity of cold diazomethane solution. After nitrogen evolution had ceased, anhydrous sodium sulphate was added and the solution was stored at 0° for 3 days, then filtered and evaporated. The crude product was recrystallized from methanol and then from benzene to give 2,6-dihydroxy-4-methoxyisobutyrophenone (7 g), m.p. 153–155° (dec.) (Found: C, 63.1; H, 6.8; OMe, 13.9. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7; 1OMe, 14.8%). λ_{\max} : 228, 285.5, 324 nm (infl.) ($\log \epsilon_{\max}$ 3.4, 4.2, 3.4) [main E.T. peak calculated from Scott's rule:³ 285 nm]; λ_{\max} after addition of alkali: 224, 295, 375 nm ($\log \epsilon_{\max}$ 4.2, 4.2, 3.55) (main E.T. peak calculated from Scott's rule:³ 293 nm, for the 2,4-dihydroxy 6-methoxy isomer: 342 nm); ν_{\max} : 1634s, 1582s cm^{-1} . N.m.r.: δ 1.18 (d, 6H), 3.85 (s, 3H), 3.90 (m, 1H), 5.40 (s, 2H), 9.60 (b, 1H), 9.95 (b, 1H).

Agglomerone

2,6-Dihydroxy-4-methoxyisobutyrophenone (2 g) was dissolved in absolute methanol (15 ml) and cooled to 0°. A solution of sodium (0.66 g, 3 equiv.) in absolute methanol (6 ml) was added, followed by methyl iodide (3.55 ml, 6 equiv.). The reaction mixture was stored for 5 days at 0° in a dry atmosphere, then evaporated to dryness in vacuum. The residue was treated with ether (80 ml) and water (80 ml) and the mixture was acidified to Congo red with 10% sulphuric acid and well shaken. The ether layer was separated and extracted successively with (A) saturated aqueous sodium bicarbonate (8 × 10 ml), (B) 10% aqueous sodium carbonate (8 × 10 ml), (C) 5% aqueous sodium hydroxide (5 × 10 ml). Each extract was then acidified to Congo red with concentrated hydrochloric acid and extracted with ether, and the ether solutions were dried (Na_2SO_4) and evaporated.

Fraction (A) yielded 60 mg (3%) of white crystalline material, m.p. 101–103° (from 40–60° light petroleum), which was not further investigated.

Fraction (B) yielded 700 mg (31%) of white crystalline material, m.p. 72–75° (light petroleum), undepressed on admixture with a sample of naturally occurring agglomerone (Found: C, 65.0; H, 7.7. Calc. for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6%). The u.v., i.r., and n.m.r. spectra were identical with those of agglomerone.

Fraction (C) yielded 200 mg (9%) of pale yellow needles, m.p. 130–135° (light petroleum), sublimed at $110^\circ/2 \times 10^{-5}$ mm to give white crystals of 2,6-dihydroxy-4-methoxy-3-methylisobutyrophenone, m.p. 145–147° (lit.⁶ 141–142°) (Found: C, 64.3; H, 7.3. Calc. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2%). The u.v. spectra in neutral and in alkaline solution agreed closely with recorded data,⁶ and the wavelengths of the main absorption peaks in each case were in accord with those calculated from Scott's rule.³ ν_{\max} : 1636s, 1590s cm^{-1} . N.m.r.: δ 1.17 (d, 6H), 1.99 (s, 3H), 3.80 (s, 3H), 3.89 (m, 1H), 5.94 (s, 1H).

Acknowledgment

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⁷ Karrer, P., *Helv. chim. Acta*, 1919, 2, 466; Karrer, P., and Rosenfeld, S., *Helv. chim. Acta*, 1921, 4, 707.