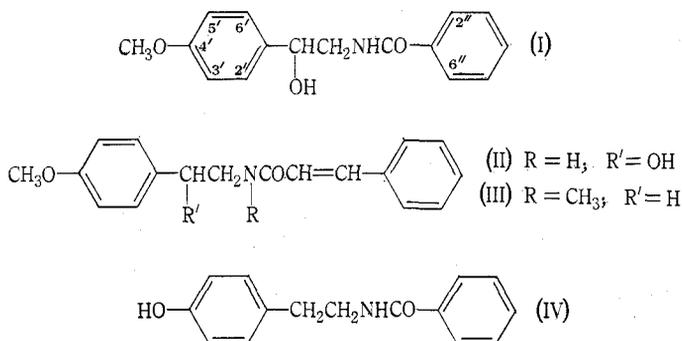


(±)-*N*-BENZOYL[2-HYDROXY-2-(4'-METHOXYPHENYL)]ETHYLAMINE  
FROM *CLAUSENA BREVISTYLA* OLIVER (FAMILY RUTACEAE)\*

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Extracts of leaves and branchlets of *Clausena brevistyla* Oliver, a shrub of the family Rutaceae, did not yield significant amounts of basic alkaloids, but a neutral amide,  $C_{16}H_{17}NO_3$ , has been isolated and shown to be (±)-*N*-benzoyl[2-hydroxy-2-(4'-methoxyphenyl)]ethylamine (I). Amides of this type have been found previously in other rutaceous species, and there is a close relationship between the amide (I) from *C. brevistyla* and the amides aegelin (II) from *Aegle marmelos*,<sup>1</sup> herclavin (III) from *Zanthoxylum clava-herculis*,<sup>2</sup> and *N*-benzoyltyramine (IV) from *Casimiroa edulis*.<sup>3</sup>



The amide (I) has a strong band at  $1650 \text{ cm}^{-1}$  in its infrared spectrum in chloroform solution. The n.m.r. spectrum (60 Mc/s;  $\text{CDCl}_3$  solution) shows a three-proton singlet at  $\delta 3.77$  due to the methoxyl group, and the assignment of the methoxyl group to the C4' position, as indicated in (I), follows from the splitting pattern of the signals from the aryl protons. The signals from the protons at C2'' and C6'' appear furthest downfield (452–470 c/s), and as they show both a large and a small coupling to *ortho* and *meta* protons respectively, the methoxyl group must be attached to the other phenyl ring. As a well-defined  $A_2B_2$  pattern can be discerned ( $\delta_A 6.85$ ,  $\delta_B 7.23$ ,  $J_{AB} 8.5 \text{ c/s}$ ) the methoxyl group can be assigned to the C4'

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<sup>1</sup> Chakravarti, R. N., and Dasgupta, B., *J. chem. Soc.*, 1958, 1580.

<sup>2</sup> La Forge, F. B., and Barthel, W. F., *J. org. Chem.*, 1944, 9, 250.

<sup>3</sup> Kincl, F. A., Romo, J., Rosenkranz, G., and Sondheimer, F., *J. chem. Soc.*, 1956, 4163.

position. The benzylic proton resonates at 280–300 c/s as the X quartet of an ABX system ( $\delta$  4.83;  $J_{AX}$  4 c/s;  $J_{BX}$  8 c/s) and the methylene group as a multiplet (c. 205–225 c/s) which is partly obscured by signals from protons (NH, OH) which were found to be exchanged with deuterium oxide. The four-line n.m.r. signal from the benzylic CH proton is attributed to non-equivalence of the vicinal  $-\text{CH}_2-$  protons which are adjacent to an asymmetric centre. Comparison with the n.m.r. spectrum of the *O*-acetyl derivative shows a normal "acylation shift" for the benzylic proton of approximately 1.1 p.p.m.,<sup>4</sup> which in the spectrum of the acetyl compound gives rise to a multiplet between 352 and 364 c/s.

The mass spectrum of (I) shows a peak of highest mass number at  $m/e$  253, which is 18 mass units less than the molecular weight. Failure to observe a molecular ion peak is presumably explained by the ready loss of water from (I). Other major peaks in the mass spectrum are fully consistent with the structure of (I).

A study of the products formed from (I) by hydrolysis in hydrochloric acid confirmed the conclusions based on spectroscopic data. In accordance with the observations<sup>1</sup> of Chakravarti and Dasgupta on the degradation of aegelin, acid hydrolysis led to the elimination of ammonia, and benzoic acid and a neutral compound were produced. Although it was reported to be obtained from aegelin, no anisaldehyde could be detected in the hydrolysis of (I), but the neutral product from the reaction afforded anisic acid on vigorous oxidation with potassium permanganate.

### Experimental

Leaves of *C. brevistyla* were collected near Cairns in northern Queensland. Milled leaves (500 g) were extracted continuously with hot methanol, and the methanol extract evaporated under vacuum until a dark residue (45–50 g) remained. The residue was extracted with warm 1% hydrochloric acid ( $3 \times 200$  ml) and the combined extracts were basified ( $\text{NH}_3$ ). Extraction with chloroform then gave 1.53 g of a "basic" fraction which was partly crystalline. Chromatography on alumina afforded crystalline fractions, amounting to 0.71 g, eluted by benzene and benzene/chloroform mixtures. Later fractions eluted by methanol were gummy and did not dissolve in aqueous hydrochloric acid. The crystalline fractions were combined, and crystallization from benzene gave amide (I) as colourless prisms, m.p. 150–152°. Recrystallization from methanol finally gave (I) as colourless prisms, m.p. 153–153.5°,  $[\alpha]_D \pm 0^\circ$  (c, 0.83 in  $\text{CHCl}_3$ ),  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 3650, 3500, 1650, 1610, 1590  $\text{cm}^{-1}$  (Found: C, 71.0; H, 6.4; N, 5.3;  $\text{OCH}_3$ , 11.3.  $\text{C}_{16}\text{H}_{17}\text{NO}_3$  requires C, 70.9; H, 6.3; N, 5.2;  $\text{OCH}_3$ , 11.4%). The amide (I) showed no basic properties: in hydrochloric acid solution, it did not give a precipitate with Mayer's reagent, it did not form a picrate, and a solution in chloroform containing methyl yellow indicator was turned red by addition of only a drop of a 0.01N solution of *p*-toluenesulphonic acid in chloroform.

The mass spectrum of (I) shows major peaks at  $m/e$  ( $M^+ - 18$ , 70% of base peak), 148 (17), 135 (10), 134 (12), 118 (20), 117 (base peak, 100%), 105 (47), and 77 (35).

The *O*-acetyl derivative of (I), prepared by reaction with acetic anhydride/pyridine mixture at room temperature, was obtained as a colourless gum. It was characterized by its i.r. spectrum (ester band at 1725  $\text{cm}^{-1}$  and amide band at 1650  $\text{cm}^{-1}$ ) in  $\text{CHCl}_3$  solution, and by the n.m.r. spectrum (60 Mc/s,  $\text{CDCl}_3$ ) which showed a three-proton singlet at  $\delta$  3.78 ( $\text{OCH}_3$ ), a three-proton singlet at  $\delta$  2.06 ( $\text{O}-\text{CO}-\text{CH}_3$ ), a one-proton multiplet ( $J$  6.0 c/s) at  $\delta$  5.93 (benzylic CH), and a multiplet extending from 405 to 470 c/s (nine aryl protons). The signal from the  $-\text{CH}_2-$  group is partly obscured by the  $\text{OCH}_3$  signal.

<sup>4</sup> Jackman, L. M., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," p. 55. (Pergamon Press: London 1959.)

When (I) (50 mg) was heated in a solution of glacial acetic acid (2 ml) and concentrated hydrochloric acid (1 ml) for 3 hr, the solution became dark in colour and an insoluble gum separated from the solution. The solution was diluted with water and extracted repeatedly with chloroform. Evaporation of the aqueous solution left a crystalline residue of ammonium chloride. The chloroform solution was extracted with aqueous sodium bicarbonate solution, and from the bicarbonate solution benzoic acid (20 mg), m.p. 120°, was recovered by acidification and extraction with ether. The neutral products remaining in the chloroform solution did not contain an appreciable amount of aromatic aldehyde (n.m.r. spectrum). After removal of solvent, the remaining gum was dissolved in dry acetone and oxidized by addition of powdered potassium permanganate at reflux temperature. A crude acid (10 mg) was isolated from the reaction mixture, and after purification by sublimation in vacuum was identified as anisic acid, m.p. 183–184°.