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THE STRUCTURE OF ROBUSTOL, A NOVEL PHENOL FROM GREVILLEA ROBUSTA A. CUNN.

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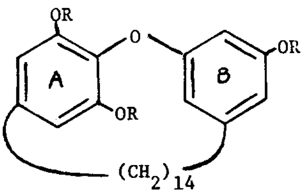
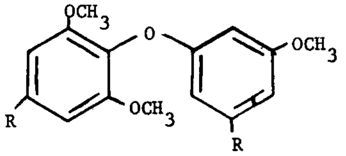
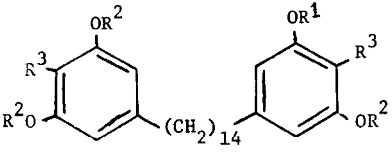
The alkali-soluble fraction of an ether extract of the leaves of Grevillea robusta A. Cunn. (family Proteaceae) has afforded 2,5-dihydroxycinnamic acid, methyl 4-hydroxycinnamate, and robustol which has now been assigned the novel macrocyclic structure Ia. Grevillol (5-n-tridecylresorcinol), the major phenolic constituent of the wood of this species (1), was not detected in the leaves.



Ia, R= H
Ib, R= CH_3CO
Ic, R= CH_3



IIIa, R= $COOCH_3$
IIIb, R= CH_2OH
IIIc, R= CHO
IIId, R= $CH{=}CH(CH_2)_2CH_2OCH_2C_6H_5$
IIIe, R= $(CH_2)_4CH_2OH$
IIIf, R= $(CH_2)_4CH_2Br$
IIIg, R= $(CH_2)_4CH_2OSO_2C_6H_4CH_3(p)$
IIIh, R= $(CH_2)_5C{=}CH$



IIa, R^1= H, R^2= CH_3, R^3= H
IIb, R^1= CH_3, R^2= CH_3, R^3=H
IIc, R^1= H, R^2= H, R^3= CH_3

Robustol (Ia), m.p. 143.5-144.5°, $[\alpha]_D = 0°$, analyses for $C_{26}H_{36}O_4$ and contains three phenolic groups for it forms a neutral triacetate (Ib) m.p. 90.5-92.5° and a

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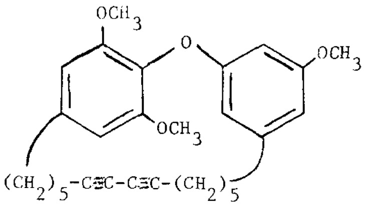
neutral trimethyl ether (Ic) m.p. 80-81°. The fourth oxygen atom in robustol was assigned to an ether linkage as tests for other functional groups were negative.

The n.m.r. spectra of Ic ($CDCl_3$) measured at 60 and 100 MHz showed a broad multiplet centred at ca. 8.75 τ which was assigned to a polymethylene chain, but no signal due to a terminal methyl group was observed. It was evident that five aromatic protons were present; two of these (ring A) gave rise to a sharp singlet at 3.53 τ, and signals for the other three (ring B) appeared as multiplets centred at 3.34, 3.62, and 4.17 τ. Double resonance experiments indicated that each of the three protons in ring B was meta-coupled to the other two. The unusually high field resonance at 4.17 τ for one of these protons is evidently due to shielding by ring A. The spectra also showed signals due to three methoxyl groups; two of these (ring A) appeared as a sharp singlet at 6.23 τ, and the other (ring B) gave rise to a signal at 6.20 τ. At 100 MHz the benzylic protons appeared as two apparent triplets centred at 7.37 τ (ring A) and 7.59 τ (ring B).

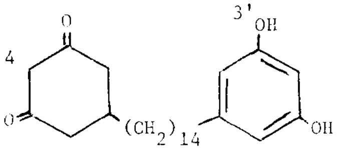
The mass spectrum of Ic revealed that the base peak is the molecular ion at m/e 454, which is consistent with the macrocyclic structure proposed for Ic. However, peaks at m/e 482 (1% of base peak, M+28), m/e 480 (0.5%, M+26) and m/e 452 (12%, M-2) were also present in the spectrum, and these have been assigned to impurities. It is suggested that the peak at m/e 482 is due to a homologue and the peaks at m/e 452 and m/e 480 arise from the presence of the corresponding mono-unsaturated substances, for after catalytic hydrogenation only the peak at m/e 482 (2% of base peak, M+28) remained. This treatment raised the m.p. of Ic to 81-82°, but produced no significant changes in the n.m.r. and i.r. spectra.

An attempt to cleave the diphenyl ether linkage by treatment of Ic with lithium in liquid ammonia was successful as it yielded a phenol (IIa) m.p. 54-55° which on methylation afforded IIb m.p. 63.5-64.5° which was identical (mixed m.p., n.m.r. and mass spectra) with a synthetic specimen (2).

The structure proposed for robustol trimethyl ether (Ic) has been confirmed by synthesis. 2,3',6-Trimethoxy-4,5'-dimethoxycarbonyldiphenyl ether (IIIa) m.p. 118.5-119.5° (lit.(3) m.p. 114.5-116°), prepared by an Ullmann reaction between methyl 3,5-dimethoxy-4-bromobenzoate and the potassium salt of methyl 3-hydroxy-5-methoxybenzoate, was reduced to the diol (IIIb) m.p. 152.5-153.5° by treatment with $LiAlH_4$. Oxidation of IIIb with CrO_3 in pyridine yielded the dialdehyde (IIIc) m.p. 139.5-140.5°. A Wittig reaction between one mole of IIIc and 2 moles of the ylid derived from triphenyl(4-benzyloxybutyl)phosphonium iodide (m.p. 171-173°) by treatment with 4 moles of C_6H_5Li gave the crude ether IIId. This product was not isolated; after chromatography on alumina and refluxing with concentrated hydrochloric acid to remove a trace of catalytic poison, it was subjected to hydrogenation and hydrogenolysis in the presence of a Pd/C catalyst when the diol (IIIe) m.p. 97.5-98° was obtained. Treatment of IIIe with PBr_3 gave the corresponding dibromide (IIIf) m.p. 86-87° in 25% yield. A higher overall yield (67%) of IIIf was obtained when the crude ditosylate (IIIg) of IIIe was refluxed with tetraethylammonium bromide in acetone. Treatment of the dibromide (IIIf) with sodium acetylide in liquid ammonia then afforded the oily diacetylene (IIIh).



IV



V

When IIIh was heated with cupric acetate in pyridine, using a high dilution technique, the cyclic diacetylene (IV) m.p. 139-140° was obtained in 55% yield. From the n.m.r. spectra (CCl_4) of IIIh and IV it was apparent immediately that formation of the macrocyclic ring had occurred under these conditions. The signals assigned to the aromatic protons and the methoxyl protons of IV closely resembled the corresponding signals in the spectrum of Ic, whereas the three non-equivalent aromatic protons of IIIh appear as a one proton multiplet centred at 3.79 τ and as a two proton multiplet centred at 3.93 τ. The two equivalent methoxyl groups in IV give rise to a singlet at 6.26 τ and the third methoxyl group appears at 6.24 τ. In the case of IIIh, the positions of these signals are reversed; the two equivalent methoxyls appear at 6.26 τ and the third methoxyl group gives rise to a signal at 6.30 τ.

Catalytic reduction of IV in the presence of Pd/C then afforded synthetic robustol trimethyl ether (Ic) m.p. 81-82°. The mixed m.p. with the substance prepared from natural robustol, and purified by hydrogenation, was undepressed. The n.m.r. and i.r. spectra of the two samples were identical and the mass spectra were also identical except for the presence of the small peak at m/e 482 (M+28) in the spectrum of the sample prepared from natural robustol.

Robustol (Ia) is clearly related to striatol (IIc), the biogenesis of which has been discussed by Rasmussen, Ridley, Ritchie, and Taylor (2). Model experiments are now in progress to test the possibility that robustol is formed by oxidative coupling between C_4 and O_3' of the dihydro-derivative (V) of bisdesmethylstriatol, followed by aromatization.

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