Tetrahedron Letters No.20, pp. 1267-1274, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF ROBUSTIC ACID

A.P.Johnson and A.Pelter
Department of Chemistry, The University, Manchester
M.Barber
A.E.I.Ltd., Trafford Park, Manchester

(Received 30 March 1964)

Robustic acid, a compound isolated from the roots of Derris robusta was first investigated by Harper[1] and then by Seshadri.[2,3] The formula $C_{20}H_{22}O_6$ was assigned to it, and it was shown to contain two methoxyl groups and one hydroxyl group. It was stated to be stable to aqueous and alcoholic base and to yield p-hydroxybenzoic acid on oxidation with alkaline hydrogen peroxide.

The molecular weight of robustic acid, m.p. 208-210°, readily obtainable from an Indian variety of D.robusta, was precisely determined as being 380.1259. This confirms the formula $C_{22}H_{20}O_6$ (380.1258). Analysis for C-Me showed 0.80 C-Me groups. The oxidation with alkaline hydrogen peroxide was repeated but did not give p-hydroxybenzoic acid, instead p-methoxybenzoic acid was obtained.

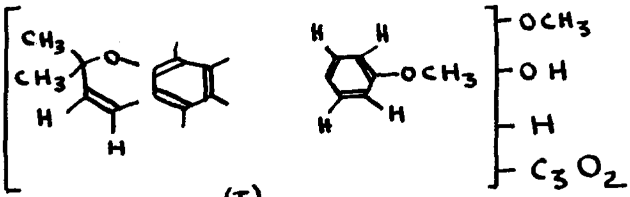
---

[1] S.Harper, J.Chem.Soc., 181 (1942).

[2] N.V.Subba Rao and T.R.Seshadri, Proc.Ind.Acad.Sci.,A, 24, 465 (1946).

[3] V.V.S.Murti, N.V.Subba Rao and T.R.Seshadri, Proc.Ind.Acad.Sci.,A, 26, 41 (1948).

All twenty hydrogen atoms were defined in the N.M.R. spectrum. Two methoxyl groups showed at τ 6.18 (3H) and τ 6.04 (3H) and one hydroxyl group was identified at τ - 0.05. A 2,2-dimethylchromene ring system was characterised by a singlet at τ 8.52 (6H) and two doublets, one centred at τ 4.23 (1H) the other at τ 3.48 (1H) J = 10.1 c/s. There were five aromatic hydrogens, four in two doublets centred at τ 3.05 (2H) and τ 2.51 (2H), the other hydrogen atom producing a singlet at τ 3.37. The partial formula (I) may be written, suggesting that the molecule is basically a C_{15} compound plus one C_5 unit and two methoxyl carbons.



(I)

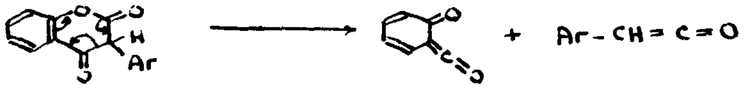
The ultraviolet spectum showed $\lambda_{max.}$ 233 mμ (4.265) 255 mμ (4.29), 264 mμ (i) (4.30), 342.5 mμ (4.27), which on treatment with sodium acetate moved to $\lambda_{max.}$ 250 mμ (4.38), 279 mμ (4.26) and 334 mμ (4.12). With aluminium chloride there was little change in the long wave-band absorption, showing that the hydroxyl is not chelated with a carbonyl group.

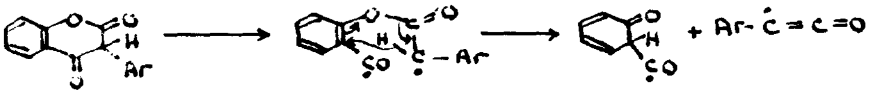
The infrared spectrum (nujol) showed a carbonyl-stretching frequency at 1708 cm.$^{-1}$, well above that for the known types of flavonoid. In the spectrum of the sodium salt this band had vanished, a new band at 1535 cm.$^{-1}$ appearing. The grouping HO–(C=C)–CO– was therefore present.

A 4-hydroxy-3-phenylcoumarin was identified in two ways.

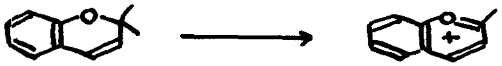
(i) Prolonged hydrolysis of robustic acid with 10% aqueous sodium hydroxide in a slow stream of nitrogen yielded acetone (identified as the 2,4-dinitrophenylhydrazone), O-methylphloroglucinol, separated by thin layer chromatography and identified by comparison with an authentic sample, and p-methoxyphenylacetic acid, identified by comparison of m.p. infrared and ultraviolet spectra with a synthetic sample. This last product places robustic acid in the isoflavonoid series, whilst the production of acetone confirms the presence of a 2,2-dimethylchromene ring. The phloroglucinol derivative defines the oxygenation pattern of one benzene ring.

(ii) A study of the mass spectra of 4-hydroxy-3-phenylcoumarins has been made and the following modes of breakdown of these compounds have been defined and confirmed by deuteration experiments.

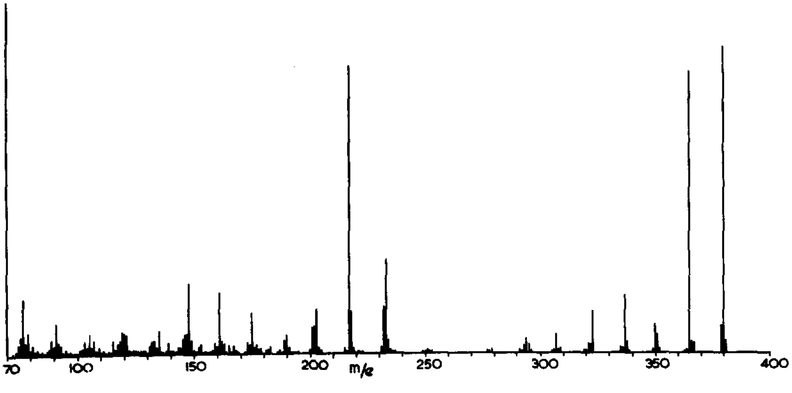




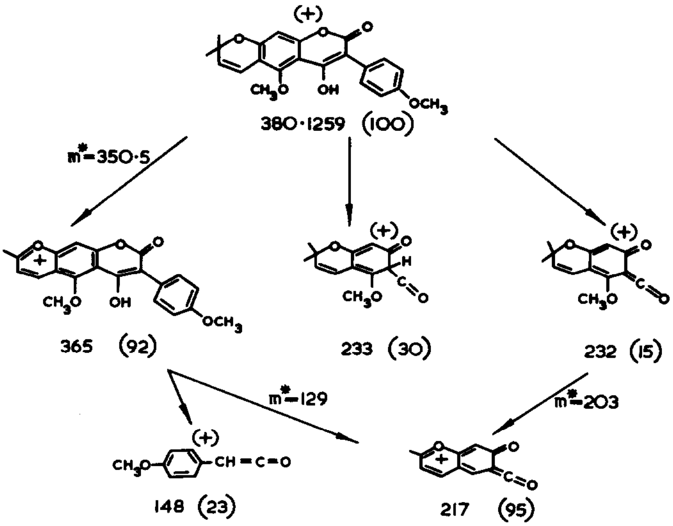
Either fragment is capable of carrying the charge. On this basic pattern is superimposed, in the case of the 2,2-dimethylchromenes, the loss of allylic methyl as a highly favoured process.



The mass spectrum of robustic acid is shown below:

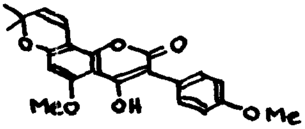


This spectrum leads to the annexed scheme to account for part of the breakdown pattern in the mass spectrometer.

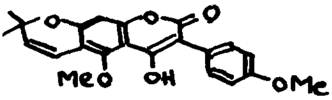


Dihydrorobustic acid m.p. 198-200° was produced by catalytic hydrogenation. In the N.M.R. spectrum two triplets at τ 8.17 (2H) and τ 7.20 (2H), J = 6.5 c/s, together with a singlet at τ 8.60 (6H) define the 2,2-dimethylchroman ring. The positions of the bands due to the methoxyl groups had not changed.

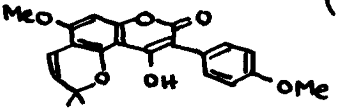
From these facts only three formulae for robustic acid are possible.



(II)



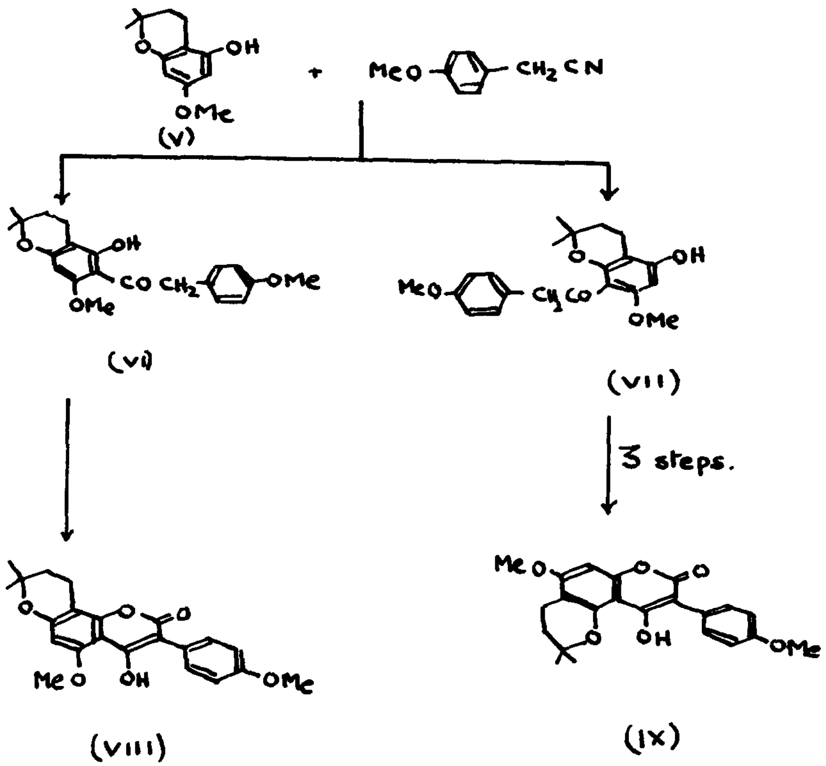
(III)



(IV)

The methoxyl groups of robustic acid show at τ 6.04 and τ 6.18 in the N.M.R. spectrum. That at τ 6.18 is assigned to the 4'-methoxyl group by analogy with model compounds bearing a methoxyl group in this position only, and therefore the methoxyl at τ 6.04 must be on ring A. Methyl robustic acid shows methoxyl groups at τ 6.18, 6.20 and 6.47. That at τ 6.47 is assigned to the 4-methoxyl group and so on methylation the methoxyl group on ring A has shifted its position upfield by at least τ 0.14. In this series this shift is characteristic of a 5-methoxyl group and is due to the structure being fixed on methylation. Formula (IV) does not therefore represent robustic acid.

That robustic acid must be represented by (III) was proven by synthesis of the two dihydro-derivatives corresponding to (II) and (IV). The following route was used:



The chroman (V) on reaction with p-methoxybenzyl/cyanide under Hoesch conditions, gave an equimolar mixture of (VI) m.p. 120-121°, and (VII) m.p. 149-151°, readily separable and identified by their carbonyl stretching frequencies in the infrared spectrum. With methyl chloroformate, compound (VI) gave rise to the 4-hydroxycoumarin (VIII) m.p. 258-262°, in high yield. The N.M.R. spectrum of this compound differed from that of dihydrorobustic acid only in that the singlet aromatic proton on ring A showed at τ 3.71 instead of τ 3.37. The mixed melting point of (VIII) with dihydrorobustic acid was from 185-215°, and the infrared spectra were similar but quite distinct, leaving no doubt that dihydrorobustic acid is not represented by formula (VIII).

Methylation of (VII) proceeded smoothly to give the dimethyldeoxybenzoin m.p. 103-105°. Preferential demethylation with boiling dilute hydrochloric acid for 1 hour, followed by cyclisation with methyl chloroformate give (IX) m.p. 247-251°. The N.M.R. spectrum confirmed the formula (IX), the methoxyl groups showing at τ 6.21 and τ 6.17, and the singlet aromatic proton at τ 3.57. The mixed melting point with dihydrorobustic acid was 182-193°, and with (VIII) was 220-255°. Again the infrared confirmed the non-identity of (IX) with dihydrorobustic acid. In this way both angular formulae (VIII) and (IX) for dihydrorobustic acid are excluded, and therefore the linear formula must be correct for this compound. This leads directly to the exclusion of formulae (II) and (IV) for robustic acid itself, which must therefore be represented by formula (III).

Robustic acid is the first naturally occurring 4-hydroxy-3-phenylcoumarin to be completely characterised. These compounds may be written as being in tautomeric equilibrium with 2-hydroxyisoflavones, their position as isoflavonoids thus being defined. Robustic acid is closely related to scandenin, another of this class under examination. It is likely that lonchocarpic acid, as postulated earlier[3] is also a member of the same group as robustic acid and scandenin.

We are indebted to the Department of Scientific and Industrial Research for a Scholarship (to A.P.J.). Professor W.D.Ollis kindly informed us that he has also examined D.robusta and had, on other grounds, assigned formula III to robustic acid.