Tetrahedron Letters No. 1, pp. 9-14, 1962. Pergamon Press Ltd. Printed in Great Britain.

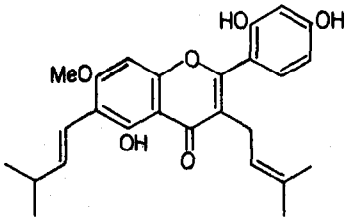
FLAVONOID PIGMENTS OF THE HEARTWOOD OF ARTOCARPUS INTEGRIFOLIA

K.G. Dave, S.A. Telang and K. Venkataraman

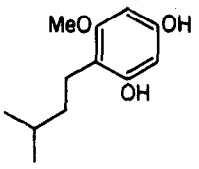
National Chemical Laboratory, Poona

(Received 6 December 1961)

MORIN (3, 5, 7, 2', 4'-pentahydroxyflavone) and the colourless cyanomaclurin, to which Appel and Robinson[1] assigned the structure of a cyclic hemiketal of 5, 7, 2', 4'-tetrahydroxy-3-ketoflavan, were isolated by Perkin and Cope[2,3] from the heartwood of Artocarpus integrifolia. We have recently shown that this wood contains two new flavones, artocarpin (I) and artocarpetin (5, 2', 4'-trihydroxy-7-methoxyflavone), and a new flavanone, artocarpanone (5, 2', 4'-trihydroxy-7-methoxyflavanone).[4,5,6] We have now isolated another new flavone, isomeric with artocarpin and named isoartocarpin, from the heartwood of a log of Artocarpus integrifolia obtained from Kerala



I



II

[1] H. Appel and R. Robinson, J. Chem. Soc. 752 (1935).

[2] A.G. Perkin and F. Cope, J. Chem. Soc. 67, 937 (1895).

[3] A.G. Perkin, J. Chem. Soc. 87, 715 (1905).

[4] K.G. Dave and K. Venkataraman, J. Sci. Ind. Res. 15B, 183 (1956).

[5] K.G. Dave, S.A. Telang and K. Venkataraman, J. Sci. Ind. Res. 19B, 470 (1960).

[6] K.G. Dave, R. Mani and K. Venkataraman, J. Sci. Ind. Res. 20B, 112 (1961).

State. Hexane extraction yielded artocarpin and isoartocarpin, which were separated by taking advantage of the sparing solubility of the latter in methanol; benzene extraction yielded artocarpanone in addition.

Colour reactions and ultra-violet spectra of isoartocarpin, which will be discussed in detail elsewhere in comparison with those of artocarpin and artocarpetin, indicated that isoartocarpin is a flavone probably similar to the latter two pigments in the orientation of hydroxyl and methoxyl groups. Isoartocarpin contains one methoxyl group like artocarpin, but it differs from artocarpin in containing only two phenolic hydroxyl groups, yielding a diacetate and a ditosylate. One of the hydroxyl groups was methylated by diazomethane in ether, and both the hydroxyl groups were methylated by dimethyl sulphate and potassium carbonate in acetone. By catalytic hydrogenation in cellosolve in presence of palladium on carbon, isoartocarpin absorbed one mole of hydrogen in about 30 minutes and a second mole in about 20 hours. Both dihydro- and tetrahydro-isoartocarpin are crystalline. Alkaline hydrolysis of isoartocarpin dimethyl ether with boiling 10 per cent ethanolic potassium hydroxide for 14 hours yielded 2-hydroxy-4-methoxybenzoic acid as the bicarbonate soluble part. The formation of 2-hydroxy-4-methoxybenzoic acid from isoartocarpin dimethyl ether, which contains no phenolic hydroxyl group, showed that the 2'-position in isoartocarpin is occupied by a readily hydrolysable alkoxy group.

Alkali fusion of tetrahydroisoartocarpin gave β-resorcylic acid and a phenol, $C_{12}H_{18}O_3$, m.p. 88°, which contained one methoxyl group and one C-alkyl group, and was identified as 2-isoamylphloroglucinol 1-methyl ether (II) by direct comparison with the synthetic substance;[7] the m.p.s and mixed m.p. of the bisphenylazo derivatives obtained by coupling with diazotized aniline were also identical. Tetrahydroartocarpin gave the same

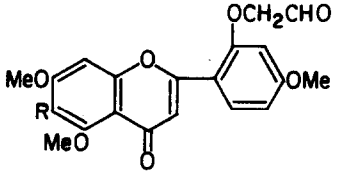
---

[7] M. Vandewalle and M. Verzele, Bull. Soc. Chem. Belg. 68, 711 (1959).

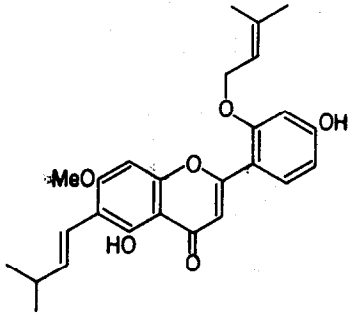
phenol (II) by alkali fusion.

The structure of the side-chains in isoartocarpin has been established by ozonolysis of isoartocarpin dimethyl ether and dihydroisoartocarpin dimethyl ether. Isoartocarpin dimethyl ether was ozonized in ethyl acetate at -50°, and the ozonide decomposed by hydrogenation in presence of palladized carbon. The volatile products were removed by distillation of ethyl acetate, and converted to the dinitrophenylhydrazones, identified by paper chromatography and by fractional crystallization as the dinitrophenylhydrazones of acetone and isobutyraldehyde. The nonvolatile product corresponded in its elementary analysis to the dialdehyde (III; R = CHO), but with one molecule of water of crystallization. The ozonolysis of dihydroisoartocarpin dimethyl ether exclusively yielded acetone as the volatile product. The nonvolatile component was a monoaldehyde, the elementary analysis of which corresponded to (III; R = C_5H_{11}), but with one molecule of water of crystallization as in the case of the dialdehyde (III; R = CHO). Phenoxyacetaldehyde[8] crystallizes with one molecule of water of crystallization.

On the basis of the experimental evidence it is clear that isoartocarpin has the structure (IV). The presence of the 3,3-dimethylallyl ether



III

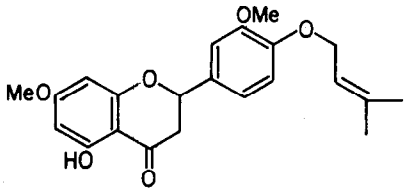


IV

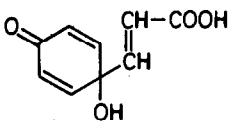
[8] M. Rotbart, Ann. Chim. 1, 479 (1934).

group was confirmed by the ready hydrolysis of dihydroisoartocarpin, on warming with glacial acetic acid containing a trace of hydrochloric acid, to a compound, the elementary analysis of which corresponded to the loss of a C_5H_8 residue.

Artocarpin is unique among flavones because of the attachment of an isoprenoid side-chain in the 3-position, and the biogenetic aspects have been discussed earlier.[6] Isoartocarpin is also unique as the only natural flavone so far isolated which contains a prenyl (3,3-dimethylallyl) ether group. There are several examples of the occurrence of isoprene residues attached to oxygen in natural coumarins, but among the flavonoids the only example preceding isoartocarpin is the flavanone (V) isolated by Geissman[9] from the bark of Melicope sarcococca.



V



VI

The isoprenoid side-chain in the A-ring of artocarpin and isoartocarpin has analogies in several other flavonoids and the rotenoids, and the biological introduction of a C-pentenyl group in the A-ring by the attack of isopentenylpyrophosphate or "active isoprene"[10] on the phloroglucinol nucleus or a poly-β-ketonic precursor[11] is easy to picture.[6] The second isoprene unit must then attack the 2'-hydroxyl group in the B-ring at some stage to produce isoartocarpin, instead of the β-carbon atom of the C_6-C-C-C skeleton which was postulated to explain the formation of artocarpin.[6]

[9] T.A. Geissman, Aust. J. Chem. 11, 376 (1958).
[10] J.W. Cornforth and G. Popjak, Tetrahedron Letters No. 19, 29 (1959).
[11] A.J. Birch, Fortschr. Chem. Org. Naturstoffe 14, 186 (1957).

The only natural flavones with a resorcinol pattern in the B-ring (morin, artocarpetin, artocarpin and isoartocarpin) and the only flavanone (artocarpanone) occur together in the heartwood of Artocarpus integrifolia, and two of them (artocarpin and isoartocarpin) have also been isolated from Artocarpus hirsutus. Ferreirin and homoferreirin are two isoflavones of this type. Among the numerous plant flavonoids, very few contain a hydroxyl or methoxyl group in the o-position of the B-ring.[12,13] Although it is not unlikely that flavonoids with a hydroxyl or methoxyl group in the o-position of the B-ring may be isolated in the future from other plants, the infrequency of their occurrence in comparison with flavonoids carrying hydroxyl and methoxyl groups in the 3-, 3,4- and 3,4,5-positions of the B-ring must have a biogenetic reason.

In the shikimic acid pathway for aromatic biosynthesis, cinnamic acids are probable intermediates for both coumarins and the B-ring of flavonoids.[14] Cinnamic acids may be transformed to coumarins by specific hydroxylation ortho to the acrylic acid chain (followed by lactonization)[15,16] or by intramolecular oxidation leading directly to coumarins.[17] The conversion of p-hydroxycinnamic acid to 7-hydroxycoumarin (umbelliferone, occurring in many plants) may proceed alternatively through the cyclohexadienone intermediate (VI).[14b] If an o-coumaric acid is an intermediate in the formation of a 2'-hydroxyflavonoid, the acid will have to be produced by the opening of the coumarin ring and perhaps also stabilized by temporary protection of

---

12 K. Venkataraman, Fortschr. Chem. Org. Naturstoffe 17, 1 (1959).

13 F. Sondheimer and A. Meisels, Tetrahedron 9, 139 (1960).

14 For reviews and references see (a) A.C. Neish, Ann. Rev. Plant Physiol. 11, 5 (1960); (b) H. Grisebach and W.D. Ollis, Experientia 11, 4 (1961).

15 F. Weygand and H. Wendt, Z. Naturf. 14b, 421 (1959).

16 T. Kosuge and E.E. Conn, J. Biol. Chem. 234, 2133 (1959).

17 K. Chambers, G.W. Kenner, M.J. Temple Robinson and B.R. Webster, Proc. Chem. Soc. 291 (1960).

the o-hydroxyl group. The special mechanism required for this purpose is apparently possessed by A. integrifolia.