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FOUR ANALOGUES OF ARTOCARPIN AND CYCLOARTOCARPIN FROM MORUS ALBA*

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The heartwood of Morus alba contains morin, maclurin and 2,4,6,4'-tetrahydroxybenzophenone.[1] From the stem and root bark we have now isolated betulinic acid and four new flavone derivatives, mulberrin (I), mulberrochromene (II), cyclomulberrin (III) and cyclomulberrochromene (IV), which have the indicated structures. Like artocarpin and cycloartocarpin occurring in Artocarpus heterophyllus (another member of the family Moraceae), they are derived from 5,7,2',4'-tetrahydroxyflavone and two isoprene units and can be readily fitted into the biosynthetic scheme suggested for the Artocarpus flavonoids.[2]

The stem or root bark powder was extracted successively with hexane and benzene. The residue from the benzene extract was dissolved in the minimum amount of methanol and allowed to stand, when betulinic acid separated. After removal of this acid, the filtrate was evaporated, taken up in benzene and submitted to column chromatography on silica gel, monitoring the separation on TLC plates. Elution with benzene gave (III) and (IV) in yields of 0.02 and 0.01%, and further elution with benzene containing 1%

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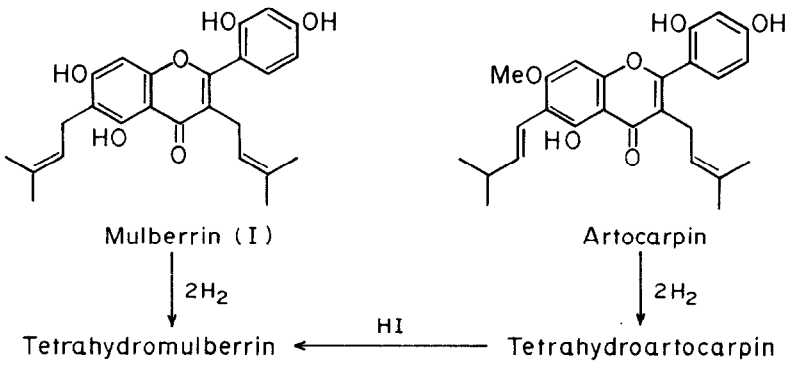
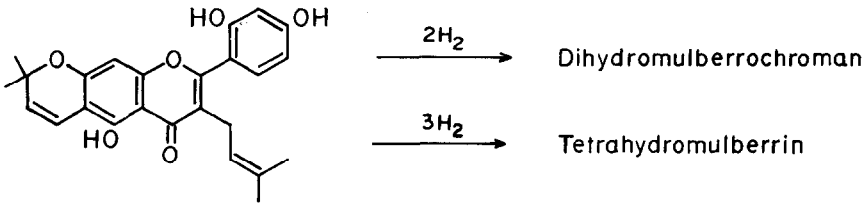
acetone gave (I) and (II) (0.15 and 0.2% respectively). All the pigments gave a wine-red colour in the Shinoda test and a green ferric colour.

Mulberrin, m.p. 153-156°, $C_{25}H_{26}O_6$ (M 422), has λ_{max}^{EtOH} 258 and 310-315 mμ (ε 26200 and 18000), shifting to 270 and 370 mμ on the addition of alkali. The NMR spectrum (chemical shifts on the τ scale) in DMSO-d_6 showed signals characteristic of two γ,γ-dimethylallyl groups: signals at 8.42 and 8.57 (combined intensity of 12 protons); a broad signal at 4.85 (intensity of 2 protons) due to vinylic protons split by adjacent methylene groups, associated with a pair of doublets (J = 7 c/s) at 6.67 and 6.90 (allylic methylenes attached to a γ-pyrone and to a benzene ring); a doublet (J = 9.5 c/s) at 2.87 (6'-H) and a sharp singlet at 3.67 (8-H). The absence of a singlet at about 3 in the NMR spectra of all the four flavones showed that this position carries a substituent. The data support structure (I), confirmed by the identity of tetrahydromulberrin, m.p. 232°, with the demethylation product of tetrahydroartocarpin.



Mulberrochromene, m.p. 232-235°, $C_{25}H_{24}O_6$ (M 420), has λ_{max}^{EtOH} 266 mμ (ε 33000) with shoulders at 300 and 340 mμ (ε 7900 and 5900), shifting to 266 and 365 mμ on the addition of alkali. In the NMR spectrum (DMSO-d_6) two vinyl doublets (J = 10 c/s) at 3.37 and 4.45 in conjunction with a singlet at 8.58 for two methyl groups suggested a 2,2-dimethylchromene. A sharp singlet at -3.50, which readily collapsed on the addition of D_2O, showed a chelated hydroxyl group. A broad vinyl signal at 4.87 and signals due to two olefinic

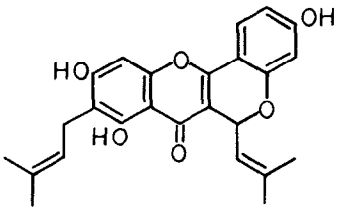
methyl groups at 8.42 and 8.58, in conjunction with a doublet (J = 7 c/s) at 6.90 for a methylene group suggested a γ,γ-dimethylallyl group. The attachment of this group to the 3-position of a flavone was shown by the 6'-proton appearing as a doublet (J = 9.5 c/s) at 2.87, 0.62 upfield from the corresponding proton of cycloartocarpin, and by the hypsochromic shift of the long wavelength band in the UV spectrum as a result of the B-ring being twisted out of conjugation with the chromone system.[3] A singlet single-proton signal at 3.80 (8-H) and signals at 3.45 (doublet of 3'-H and part of the quartet of 5'-H) and at 3.62 (remainder of quartet of 5'-H) suggested an orientation of substituents in the B-ring similar to artocarpin and its analogues. Hydrogenation of mulberrochromene (PtO, 40 psi, 12 hr) gave the tetrahydro-derivative (dihydromulberrochroman), m.p. 243-244°, accompanied by a small amount of tetrahydromulberrin (formed by hydrogenolysis of the chromene ring), confirming structure (II) for mulberrochromene.



Mulberrochromene (II)

Cyclomulberrin, m.p. 231-232°, $C_{25}H_{24}O_6$ (M 420), has λ_{max}^{EtOH} 214, 274 and 370 mμ (ε 39600, 21000 and 16000). The NMR spectrum in acetone-d_6 disclosed the presence of a γγ-dimethylallyl substituent attached to an aromatic ring: methyls at 8.15 and 8.33; broad doublet (J = 7 c/s) at 6.45 due to methylene, both allylic and benzylic; and a broad signal at 4.65 for a vinyl proton. A sharp singlet at -2.80 indicated a chelated hydroxyl. Two non-equivalent olefinic methyls at 8.05 (doublet, J = 1.3 c/s) and 8.33 (merged with the signal for a methyl of the dimethylallyl group) in conjunction with a broad doublet (J = 10 c/s) at 4.55 due to a vinyl proton and a doublet (J = 9.5 c/s) at 3.78 due to an allylic proton adjacent to a γ-pyrone ring and to ether-oxygen, suggested that the 2'-hydroxyl of the B-ring has oxidatively cyclised with the allylic methylene

of a prenyl chain in the 3-position of a flavone, as in cycloartocarpin. This was substantiated by the chemical shift of the 6'-proton of the B-ring (2.32), which has come to a more normal value than in mulberrin and mulberrochromene, and by the bathochromic shift of the long wavelength band in the UV spectrum.[3] Positive chemical proof for the formulation of cyclomulberrin as (III) was provided by its hydrogenation to tetrahydrocyclomulberrin, m.p. 241°, accompanied by tetrahydromulberrin as a result of the hydrogenolytic cleavage of an allylic C-O bond. Cycloartocarpin similarly yields the tetrahydro derivative, m.p. 234-235°, together with a small amount of tetrahydroartocarpin, m.p. 162° (wrongly cited earlier as 116°).[4]



$2H_2$ → Tetrahydrocyclomulberrin

$3H_2$ → Tetrahydromulberrin

Cyclomulberrin (III)

Cyclomulberrochromene, m.p. 233-234°, $C_{25}H_{22}O_6$ (M 418), has λ_{max}^{EtOH} at 219, 254, 274 and 370 mμ (ε 26000, 16000, 16500 and 11000). The NMR spectrum in acetone-d_6 revealed the 2,2-dimethylchromene ring system (AE); the aromatic region is shown in Fig. 1. A sharp singlet at -2.95 showed a chelated hydroxyl. The presence of ring D, as in cycloartocarpin and cyclomulberrin, was shown by two non-equivalent olefinic methyls at 8.03 (J=1.3 c/s) and 8.30 (J=1.0 c/s), a broad vinyl doublet (J = 10 c/s) at 4.55, and a doublet (J = 9.5 c/s) at 3.78. Chemical proof for structure (IV) assigned to cyclomulberrochromene was obtained, when tetrahydrocyclomulberrin and traces of tetrahydromulberrin and dihydromulberrochromene were isolated in addition to the major product, tetrahydrocyclomulberrochromene (dihydrocyclomulberrochroman), m.p. 261-262°, by catalytic hydrogenation.

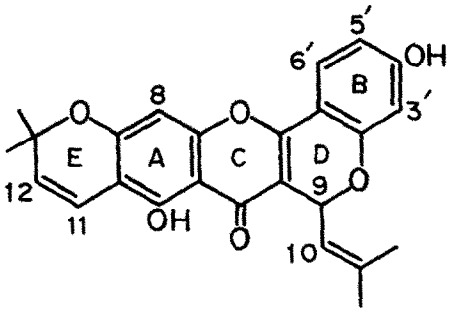
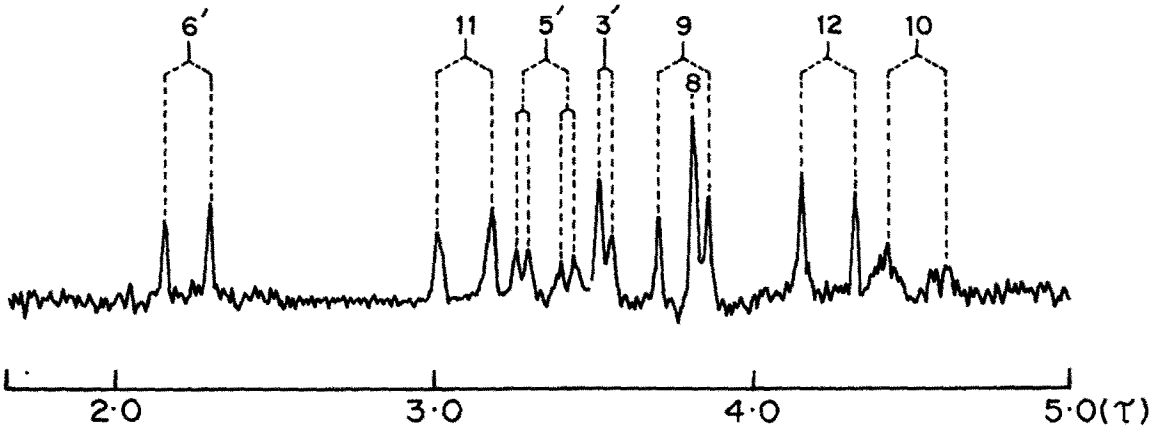


Fig. 1

Cyclomulberrochromene

(IV)



All the compounds gave satisfactory elemental analysis. All the molecular weights were determined from the mass spectra.

Acknowledgement

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References

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3. P.M. Nair, A.V. Rama Rao and K. Venkataraman, Tetrahedron Letters, No. 2, 125 (1966); Festschrift Kurt Mothes, p. 317, Fischer Verlag, Jena, 1965.

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