Phytochemistry, 1967, Vol. 6, pp. 1597 to 1599. Pergamon Press Ltd. Printed in England

SHORT COMMUNICATION

# A SYNTHESIS OF MANGIFERIN

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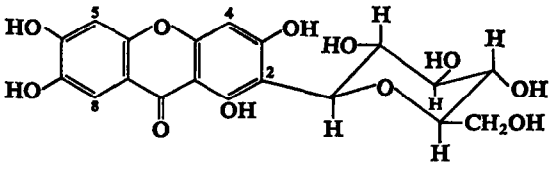
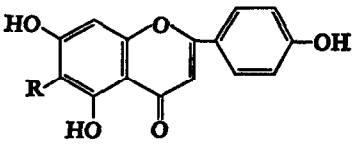
(*Received* 20 *April* 1967)

**Abstract**—A synthesis of mangiferin (I), 2-*C*-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-xanthone, is described.

A NUMBER of analytical, spectroscopic and degradative investigations[1–4] have established structure (I) for mangiferin, a metabolite of wide distribution[1] in the plant world. We now report a synthesis of this compound.



(I)



(II)

Chopin and his collaborators have recently developed a method[5–7] for the synthesis of 6-*C*-β-D-glucopyranosyl-5,7-dihydroxy-flavonoids. In this method, the appropriate 5,7-dihydroxy-flavonoid (e.g., II; R = H) is caused to react in anhydrous methanol with a large excess of α-acetobromoglucose in presence of sodium iodide and sodium methoxide. The mixture of products is submitted to acid hydrolysis (in order to destroy the *O*-glucosyl links) and the desired *C*-glucosyl compound (II; R = β-D-glucopyranosyl) is isolated by a long and complicated procedure involving solvent extractions and chromatographic techniques. The yields are poor (< 1 per cent) but the significance of the results overrules this objection. In

[1] P. E. NOTT and J. C. ROBERTS, *Phytochem.* **6**, 741 (1967).
[2] D. BILLET, J. MASSICOT, C. MERCIER, D. ANKER, A. MATSCHENKO, C. MENTZER, M. CHAIGNEAU, G. VALDENER and H. PACHECO, *Bull. Soc. Chim. France* 3006 (1965).
[3] L. J. HAYNES and D. R. TAYLOR, *J. Chem. Soc.* (*C*) 1685 (1966).
[4] V. K. BHATIA, J. D. RAMANATHAN and T. R. SESHADRI, *Tetrahedron* **23**, 1363 (1967).
[5] J. CHOPIN, M.-L. BOUILLANT and A. DURIX, *Compt. Rend.* **260**, 4850 (1965).
[6] J. CHOPIN and A. DURIX, *Compt. Rend.* **263**, 951 (1966).
[7] J. CHOPIN, A. DURIX and M.-L. BOUILLANT, *Tetrahedron Letters* 3657 (1966).

the flavonoid series, products resulting from Wessely–Moser rearrangements[8] are encountered.[7]

There is an obvious structural similarity between 5,7-dihydroxy-flavonoids and 1,3-dihydroxy-xanthones, and it seemed possible that reaction of 1,3,6,7-tetrahydroxy-xanthone with an excess of α-acetobromoglucose (using the Chopin procedure) might lead to mangiferin. In the event, a very small yield of a product was obtained which proved to be virtually identical with natural mangiferin (*ex* "Bitis" wood[1]). It should be noted that it is most improbable that our synthesis had proceeded by way of a Wessely–Moser rearrangement since xanthones do not easily undergo this type of isomerization.[9]

The structure (I) for mangiferin is thus confirmed.

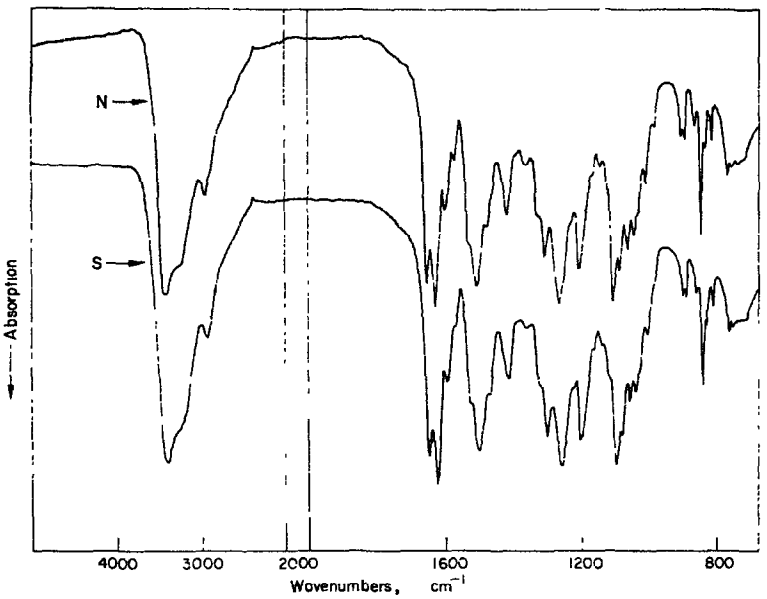



FIG. 1. I R. ABSORPTION SPECTRA (POTASSIUM BROMIDE DISCS) OF NATURAL MANGIFERIN (N) AND OF SYNTHETIC MANGIFFRIN (S).

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. U.V. spectra were recorded on a Unicam spectrophotometer (S.P. 700) and i.r. spectra were determined, on compounds in potassium bromide discs, with a Unicam spectrophotometer (S.P. 200).

*Mangiferin.* Powdered "Bitis" wood (*Madhuca utilis*) was extracted in the usual way.[1] The extract crystallized from 60% ethanol to give mangiferin as pale-yellow prisms, m.p. 266–269° (decomp.) (lit.,[10] 271°), $\lambda_{max}$ (80% ethanol) 205 (infl.), 240, 259, 273 (infl.), 318, and 370 nm (log ε 4·34, 4·43, 4·47, 4·05, 4·14, and 4·11), $\nu_{max}$ included strong bands at 3400 (OH), 1645 (C=O), and 1620 (aromatic C=C) cm.$^{-1}$ (see Fig. 1).

*1,3,6,7-Tetrahydroxy-xanthone.* This was prepared by Ueno's method,[11] or by treatment of natural mangiferin with HI and phenol.[12] The crude xanthone was conveniently purified *via* its acetate.

[8] F. WESSELY and G. H. MOSER, *Monatsh. Chem.* **56**, 97 (1930).
[9] E. M. PHILBIN, J. SWIRSKI and T. S. WHEELER, *J. Chem. Soc.* 4455 (1956).
[10] K. GORTER, *Bull. Jardin Botany Buitenz.* **4**, 260 (1922); *Chem. Abstr.* **17**, 1472 (1923).
[11] A. UENO, *J. Pharm. Soc. Japan* **82**, 1482 (1962); *Chem. Abstr.* **59**, 736 (1963).
[12] S. ISEDA, *Bull. Chem. Soc. Japan* **30**, 625, 629 (1957); *Chem. Abstr.* **52**, 6329 (1958).

*Synthesis of mangiferin.* The foregoing xanthone (1·82 g) was dissolved in anhydrous methanol (240 ml) containing sodium methoxide (from 1·20 g of sodium). NaI (145 mg) and α-acetobromoglucose (20 g) were added and the mixture was agitated at room temp. for 20 hr. The reaction mixture was evaporated *in vacuo* to about 50 ml and 2 N HCl (50 ml) was added. The solution, having been heated under reflux (steam-bath) for 5 hr, was cooled and extracted with ether. The residual aqueous layer was chromatographed on a column (4 × 4 cm) of polyamide (Woelm). Continued percolation with water gave a yellow eluate which was extracted twice with *n*-butanol. The combined butanol extracts were washed with water (until the washings were colourless) and the butanol was removed by evaporation *in vacuo*. The residue was dissolved in 60% aqueous ethanol (5 ml) and was chromatographed on a column (10 × 5 cm) of polyamide (Woelm) which had previously been washed with ethanol (99 per cent) for several hours. The chromatogram was developed with ethanol (99 per cent) and the eluate was collected in 10 ml fractions. Each fraction was investigated by thin-layer chromatography (on polyamide (Merck) plates, using ethanol (99 per cent) as solvent) with natural mangiferin as a "marker". All the ethanolic eluates containing mangiferin were combined and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in 60% aqueous ethanol (10 ml) and water (50 ml) was added. The solution was extracted with ether and the aqueous-ethanolic residue was evaporated *in vacuo*. The residue was crystallized from 60% aqueous ethanol to give synthetic mangiferin as a yellow-brown micro-crystalline solid (3·4 mg), m.p. (and mixed m.p. with a sample of natural mangiferin) 267–269° (decomp.), $\lambda_{max}$ (80% ethanol) 205 (infl.), 241, 259, 272 (infl.), 318, and 372 nm (log ε 4·35, 4·45, 4·45, 4·11, 4·09, and 4·15). The i.r. spectrum of the synthetic sample was virtually identical with that of natural mangiferin (see Fig. 1). Natural mangiferin and the synthetic material gave identical (green) ferric reactions in ethanol and, when adsorbed on a thin layer of polyamide (Merck), showed identical (apricot-coloured) fluorescences (in u.v. light). Natural and the synthetic mangiferin showed the following $R_f$ values: (i) on Whatman's 3MM paper (*n*-butanol, glacial acetic acid, water (2:1:2 by volume) as ascending solvent), 0·60 and 0·60; (ii) on polyamide (Merck) plates (ethanol (99 per cent), 0·30 and 0·30 (the $R_f$ values obtained under this set of conditions are markedly concentration-dependent); (iii) on silica ("Kieselgel H nach Stahl", Merck) plates (formic acid (98 per cent), 0·75 and 0·73 respectively.

*Acknowledgement*—We thank the S.R.C. for a maintenance grant (to P. E. N.).