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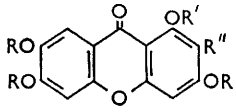
C-Glycosyl Compounds. Part V *. Mangiferin; the Nuclear Magnetic Resonance Spectra of Xanthones [1]

By L. J. Haynes and D. R. Taylor

Nuclear magnetic resonance studies and chemical degradations confirm that mangiferin is the *C*-glycosyl derivative 2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone.

MANGIFERIN, a crystalline compound first isolated from the bark of the mango tree (*Mangifera indica* L., Anacardiaceae),[2] has been assigned the *C*-glucosyl structure (I; R = R′ = H, R″ = D-glucopyranosyl) by Ramathan and Seshadri [3] and we have reported support-



(I)

ing evidence from n.m.r. spectroscopy and chemical degradation.[1,2] We now present a full report of our work: most of the analysis of the n.m.r. spectra agrees with that reported by Roberts [4] and Billet *et al.*[5] and will not be discussed further here. Our assignment of the glucosyl residue to C-2 of the tetrahydroxyxanthone nucleus followed from a comparison of the n.m.r. spectrum of mangiferin hepta-acetate with that of 3,6,7-triacetoxy-1-hydroxyxanthone and the observation that the sugar had replaced the *meta*-coupled proton at highest field. A study of the n.m.r. spectra of 7-acetoxy-5-hydroxyflavones and isoflavones [6] shows that the H-6 resonance is always at higher field than the H-8 resonance and it is reasonable to assume that the *meta*-coupled proton at the higher field in the triacetoxyhydroxyxanthone is that at C-2. There is also good agreement between the chemical shifts due to H-2 and H-4 of the triacetoxyhydroxyxanthone and those due to the corresponding protons in 7-acetoxy-5-hydroxyisoflavones.[6]

Confirmatory chemical evidence for the structure (I; R = R′ = H, R″ = β-D-glucopyranosyl) was obtained as follows. Mangiferin 3,6,7-trimethyl ether (I; R = Me, R′ = H, R″ = D-glucosyl) was converted into the trimethyl ether tetra-acetate (I; R = Me, R′ = H, R″ = 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)

* Part IV, L. J. Haynes, J. I. Henderson, and Jean M. Tyler, *J. Chem. Soc.*, 1960, 4879.

[1] An account of this work was presented at the Symposium on Recent Advances in Plant Phenolics held at Delhi, India, in October 1964; see L. J. Haynes and D. R. Taylor, *Proc. Nat. Acad. Sci. India*, Section A, 1966, **32**, in the press.

[2] For reviews of earlier work see L. J. Haynes, *Adv. Carbohydrate Chem.*, 1963, **18**, 227; 1965, **20**, 357.

[3] (*a*) J. D. Ramanathan and T. R. Seshadri, *Current Sci.*, 1960, **29**, 131. See also (*b*) B. J. Hawthorne, N. F. Janes, F. E. King, and J. W. W. Morgan in "Recent Progress in the Chemistry of Natural and Synthetic Colouring Matters and Related Fields," eds., T. S. Gore, B. S. Joshi, S. V. Sunthankar, and B. D. Tilak, Academic Press, New York and London, 1962, p. 331, and J. D. Ramanathan, *Bull. Nat. Inst. Sci. India*, 1963, No. 23, 26.

[4] Reported by Dr. J. C. Roberts at the Symposium on Plant Pigments held in Aberdeen in September 1965.

[5] D. Billet, J. Massicot, C. Mercier, D. Anker, A. Matschenko, C. Mentzer, M. Chaigneau, G. Valdener, and H. Pacheco, *Bull. Soc. chim. France*, 1965, 3006.

[6] J. Massicot and J. P. Marthe, *Bull. Soc. chim. France*, 1962, 1962; J. Massicot, J. P. Marthe, and S. Heitz, *ibid.*, 1963, 2712.

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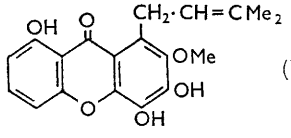
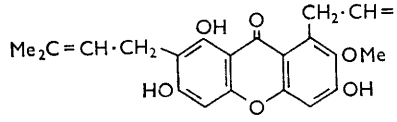
with acetic anhydride, and thence into the tetramethyl ether tetra-acetate with methyl iodide and silver oxide: hydrolysis with ammonia then gave the 1,3,6,7-tetramethyl ether (I; R = R′ = Me, R″ = D-glucopyranosyl). Oxidation of this compound with sodium metaperiodate gave no tractable product, but oxidation with potassium permanganate in acetone gave an acid which was characterised as its methyl ester, $C_{19}H_{18}O_8$, m. p. 208—210°. This was identical with an authentic sample of 1,3,6,7-tetramethoxy-2-methoxycarbonylxanthone derived from methylation and oxidation of 2-allyl-1-hydroxy-3,6,7-trimethoxyxanthone obtained by the Claisen rearrangement of 1-allyloxy-3,6,7-trimethoxyxanthone.



(II)



(III)

The chemical shifts shown in the Table are in accord with those previously reported for similarly constituted protons in other xanthones [7] and in flavones.[6,8,9]

It should be noted that the low-field shift of the signals from the side-chain methylene groups in celebixanthone (II) and mangostin (III) is due to the deshielding due to the carbonyl group [10,11] and not to electronic effects.[12]

It has been suggested that C-5 [6,8] and C-8 [6] acetoxyl groups in flavones give signals at low field. The C-1 acetate in derivatives of 1-acetoxy-3,6,7-trihydroxyxanthone is also deshielded. However, in several acetylated flavonoid, flavanoid, and isoflavonoid *C*-glycosyl compounds it is impossible to distinguish between acetoxyl groups at C-5 and those at other positions.[9] One of the phenolic acetates in mangiferin hepta-acetate (free C-1 phenol) is also deshielded. Hence care must be exercised in assigning slightly deshielded phenolic acetate resonances to a C-1 acetate in xanthones or a C-5 acetate in flavones.

Nuclear magnetic resonance spectral data *

Compound	H-2	H-4	H-5	H-8	OCH_3	ArOAc	ROAc	—OH
Mangiferin † (in dimethylformamide)		6·45	6·94	7·53				
Mangiferin hepta-acetate [3b]		6·76	7·40	8·03		2·33 (2), 2·43	1·78, 2·01, 2·06 (2)	13·19
Mangiferin trimethyl ether tetra-acetate		6·35	6·81	7·48	3·97 (2), 4·00		1·77, 2·03, 2·08 (2)	13·55
Mangiferin trimethyl ether penta-acetate [3b]		6·75	6·75	7·46	3·93, 3·98 (2)	2·54	1·79, 2·02, 2·07 (2)	
Mangiferin tetramethyl ether tetra-acetate		6·67	6·82	7·64	3·97 (2), 4·00 (2)		1·75, 2·02, 2·05, 2·07	
2-Allyl-1-hydroxy-3,6,7-trimethoxyxanthone		6·29	6·74	7·46	3·88, 3·95, 3·98			13·01
1-Acetoxy-2-allyl-3,6,7-trimethoxyxanthone		6·63	6·72	7·51	3·88, 3·95 (2)	2·49		
2-Allyl-1,3,6,7-tetramethoxyxanthone		6·56	6·73	7·62	3·89, 3·95, 3·97 (2)			
3,6,7-Triacetoxy-1-hydroxyxanthone	6·58 (dm)	6·74 (dm)	7·39	8·03		2·32 (3)		12·53
1,3,6,7-Tetra-acetoxyxanthone [13]	6·83 (dm)	7·20 (dm)	7·35	7·99		2·29 (3), 2·44		
1-Hydroxy-3,6,7-trimethoxyxanthone [13]	6·32	6·32	6·79	7·50	3·86, 3·98 (2)			12·91
1-Acetoxy-3,6,7-trimethoxyxanthone [13]	6·52 (dm)	6·62 (dm)	6·70	7·48	3·84, 3·94 (2)	2·48		
1,3,6,7-Tetramethoxyxanthone [3b]	6·29 (dm)	6·36 (dm)	6·70	7·61	3·87, 3·97 (3)			

* Chemical shifts are in p.p.m. on the δ scale; da = doublet (J = 9·5 c./sec.); dm = doublet (J = 2·4 c./sec.). Numbers in parenthesis refer to the number of methyl groups. † Benzylic proton 4·94 (da).

EXPERIMENTAL

N.m.r. spectra were run on a Varian A60 spectrometer in deuterochloroform (unless otherwise specified). Chemical shifts are given in p.p.m. from tetramethylsilane as internal reference. Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. Thin-layer chromatograms were run on silica gel and the spots viewed under ultraviolet light and then made visible with iodine vapour. Light petroleum refers to the fraction of b. p. 60—80°.

[7] E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron*, 1965, **21**, 2653.
[8] C. A. Henrick and P. R. Jeffries, *Austral. J. Chem.*, 1964, **17**, 934.
[9] W. E. Hillis and D. H. S. Horn, *Austral. J. Chem.*, 1965, **18**, 531.
[10] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959.
[11] N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalogue," vol. 2, No. 650, Varian Associates, Palo Alto, California, 1963.
[12] G. H. Stout, V. F. Stout, and M. J. Welch, *Tetrahedron*, 1963, **19**, 667.
[13] S. Iseda, *Bull. Chem. Soc. Japan*, 1957, **30**, 625.

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Mangiferin.—Dried and milled mango bark (380 g.) was extracted in a Soxhlet apparatus with light petroleum for two days and then with methanol for two days. The volume of methanol was reduced and the solid (12 g.) collected. Recrystallisation from methanol gave mangiferin, m. p. 269° (decomp.) and $[\alpha]_D^{18}$ + 33·6° (pyridine) [lit.,[3b] m. p. 268°, $[\alpha]_D$ + 36° (pyridine)]. It was identical by mixed m. p. and comparison of ultraviolet and infrared spectra with a sample kindly supplied by Dr. J. W. W. Morgan. Hepta-acetate, m. p. 227—231° (lit.,[3b] 229—230°).

1,3,6,7-*Tetrahydroxyxanthone*.[3b]—A mixture of mangiferin (4 g.), phenol (24 g.) and hydriodic acid (40 ml., d = 1·94) was heated under reflux for 6 hr. When cool the mixture was poured into aqueous sodium hydrogen sulphite solution (300 ml., 20%). The solid was separated in a centrifuge, the black tar which floated being discarded. The solid was repeatedly washed with water, sodium hydrogen carbonate, and again with water by suspension in the aqueous medium and collecting by centrifuging. Drying over sodium hydroxide in a desiccator gave the product (2·36 g.) shown by t.l.c. to be one major compound contaminated with a small amount of phenol.

3,6,7-*Triacetoxy*-1-*hydroxyxanthone*.—The tetrahydroxyxanthone (above) was acetylated by heating under reflux with acetic anhydride (cf. Ref. 3*b*). The product was sublimed and then crystallised from acetone–ethanol as pale yellow needles, m. p. 184—187° (Found: C, 58·2; H, 3·6; OAc, 32·4. $C_{19}H_{14}O_9 \cdot 1/3\ H_2O$ requires C, 58·2; H, 3·8; $(OAc)_3$, 32·9%).

Mangiferin Trimethyl Ether Tetra-acetate.—Mangiferin trimethyl ether [3b] (260 mg.) was heated under reflux in acetic anhydride (7 ml.) for 1 hr. and then poured into water. The solid was crystallised from acetone–methanol, m. p. 163—167° (Found: C, 56·6; H, 4·7; OMe, 14·3; OAc, 28·4. $C_{30}H_{32}O_{15}$ requires C, 57·0; H, 5·1; $(OMe)_3$, 14·7; $(OAc)_4$, 27·2%).

Mangiferin Tetramethyl Ether Tetra-acetate.—Mangiferin trimethyl ether tetra acetate (280 mg.) was heated under reflux in A.R. acetone with excess of methyl iodide and silver oxide for 8 hr. The tetramethyl ether (188 mg.) crystallised from methanol, m. p. 182—185°. Recrystallisation from methanol gave needles, m. p. 188·5—191° (Found: C, 57·4; H, 5·3; OMe, 17·2; OAc, 27·4. $C_{31}H_{34}O_{15}$ requires C, 57·6; H, 5·3; $(OMe)_4$, 19·2; $(OAc)_4$, 26·6%).

Potassium Permanganate Oxidation of β-D-*Glucopyranosylbenzene*.—β-D-Glucopyranosylbenzene (200 mg.) and potassium permanganate (800 mg.) were heated under reflux in acetone for 2 hr. The acetone was evaporated and the residue suspended in water. Sulphur dioxide was passed through the mixture until a clear solution was obtained. Extraction with chloroform gave benzoic acid (25 mg.).

1,3,6,7-*Tetramethoxy*-2-*methoxycarbonylxanthone*.— (from mangiferin) Mangiferin tetramethyl ether tetra-acetate (700 mg.) in methanol (60 ml.) and concentrated aqueous ammonia (10 ml.) was set aside at room temperature for two days. The solvent was evaporated, the residue suspended in acetone, and potassium permanganate (1·4 g.) added. The mixture was heated under reflux for 6 hr. The acid product (106 mg.) was methylated with diazomethane in ether, filtered in chloroform through a short alumina column (grade 3) until all the blue fluorescent band (ultraviolet illumination) was eluted (90 mg.). Crystallisation (twice) from methanol gave the methyl ester, m. p. 208—210° identical (mixed m. p. and infrared spectrum) with authentic 1,3,6,7-tetramethoxy-2-methoxycarbonylxanthone described below.

1-*Allyloxy*-3,6,7-*trimethoxyxanthone*.— 1-Hydroxy-3,6,7-trimethoxyxanthone [13] (570 mg.) was heated under reflux with an excess of freshly distilled allyl bromide and anhydrous potassium carbonate in dry acetone until the reaction was complete (t.l.c. control). Crystallisation of the product from ethyl acetate–light petroleum gave the *allyl ether* (521 mg.), m. p. 147—150°. On recrystallisation from ethyl acetate–hexane it had m. p. 151·5—153·5° (Found: C, 67·1; H, 5·3. $C_{19}H_{18}O_6$ requires C, 6·7; H, 5·3%).

Claisen Rearrangement of the Allyl Ether.—The allyl ether (680 mg.) in dimethylaniline (6 ml.) was heated under reflux for 1 hr. Dilute hydrochloric acid was added in excess and the solid (650 mg.) collected. Crystallisation from acetone gave 2-*allyl*-1-*hydroxy*-3,6,7-*trimethoxyxanthone* (507 mg.), m. p. 184—187° (Found: C, 66·6; H, 4·8. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

2-*Allyl*-1,3,6,7-*tetramethoxyxanthone*.—2-Allyl-1-hydroxy-3,6,7-trimethoxyxanthone (92 mg.) was heated under reflux with excess of methyl iodide and anhydrous potassium carbonate in dry acetone until methylation was complete (6 hr.; t.l.c. control). Filtration, evaporation, and crystallisation of the residue from methanol gave colourless crystals of 2-*allyl*-1,3,6,7-*tetramethoxyxanthone* (65 mg.), m. p. 148—149° (Found: C, 67·0; H, 5·6. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%).

1,3,6,7-*Tetramethoxy*-2-*methoxycarbonylxanthone* (authentic).—Potassium permanganate (1·6 g.) was added over 12 hr. to 2-allyl-1,3,6,7-tetramethoxyxanthone (90 mg.) in refluxing acetone (50 ml.). The acid product (42 mg.) was methylated with diazomethane, chromatographed on alumina (grade 3) and crystallised (twice) from methanol, m. p. 208—210° (Found: C, 60·6; H, 5·1; OMe, 39·4. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8; $(OMe)_5$, 41·5%).

1-*Acetoxy*-2-*allyl*-3,6,7-*trimethoxyxanthone*.—2-Allyl-1-hydroxy-3,6,7-trimethoxyxanthone (100 mg.) was heated under reflux in acetic anhydride (3 ml.) and pyridine (3 ml.) for 2 hr. The *product* crystallised from acetone–methanol as needles (75 mg.), m. p. 186—188° (Found: C, 65·9; H, 5·3. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2%).

Compounds cited in the Table other than those described above were prepared by literature methods.

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T.P.I. Natural Products Research Unit,
Chemistry Department,
University of the West Indies, Kingston 7,
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