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CHEMICAL CONSTITUENTS OF *GARCINIA MANGOSTANA*

WILAWAN MAHABUSARAKAM, PICHAET WIRIYACHITRA,*

Department of Chemistry, Prince of Songkla University, Hat Yai 90112, Thailand

and WALTER C. TAYLOR

Department of Organic Chemistry, University of Sydney, New South Wales 2006, Australia

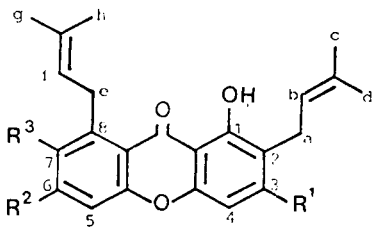
Garcinia mangostana L. (Guttiferae), the Mangosteen tree, has received rather extensive investigation from various research groups. These investigations have resulted in the isolation of anthocyanin glycosides (1), a benzophenone, maclurin (2), and several xanthone derivatives (3-9), such as mangostin [**1**] (8). The usage of the fruit hull (pericarp) in Thai folk medicine (10) for healing skin infection and wounds and for the relief of diarrhea has led us to reexamine the plant with a view to identifying the biologically active compounds.

Extraction of the pericarp with C_6H_6 followed by extensive quick column chromatography of the extract has resulted in the isolation of eight xanthone derivatives. Four of the xanthones have previously been isolated: mangostin [**1**] (8), gartanin [**2**] (6), γ-mangostin [**3**] (7), and β-mangostin [**4**] (9). The other four are synthetically-known compounds but are new natural products: 1-isomangostin [**5**] (11), 3-isomangostin [**6**] (11), 3-isomangostin hydrate [**7**] (11), and 1-isomangostin hydrate [**8**] (11).

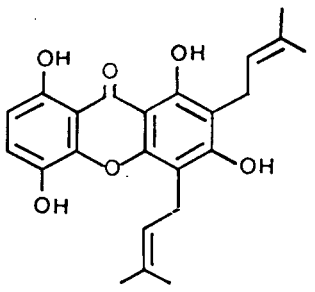
Five compounds were isolated from the arils: the known compounds, mangostin [**1**] (8), calabaxanthone [**11**] (12), 2-(γ,γ-dimethylallyl)-1,7-dihydroxy-3-methoxyxanthone [**12**] (14) and the new substances, demethylcalabaxanthone [**9**] and 2,8-bis-(γ,γ-dimethylallyl)-1,3,7-trihydroxyxanthone [**10**].

Elucidation of the structures of compounds **5-12** was based largely on comparison of ^{1}H-nmr spectral data with those of mangostin and some of its simple derivatives. NOe enhancements were useful for making some assignments. Use was also made of the well-known deshielding effect of the C9 carbonyl group on protons or CH_2 groups at C8, and the fact that, generally, H4 resonates at noticeably higher field than H5. Thus, for example, in mangostin [**1**] the methylene group of the prenyl chain at C8 (CH_2e) resonated at δ 4.11 (cf. δ CH_2a 3.45) and showed a nOe enhancement of 3% on irradiation of the methoxyl group [other enhancements were of Hf (2.3%) and of OH (1.5%)]. With **4** irradiation of the methoxyl group δ 3.81 gave enhancements to the signals of CH_2e (2%), Hf (1.8%), and OH (1%); irradiation of the methoxyl group δ 3.90 gave strong enhancement (21%) of the signal of H4 (δ 6.35) and only weak enhancement of the signal from CH_2a (0.8%) (the bias in the last case was typical for the structural situation; in fact, enhancement of the neighboring CH_2 group was usually not detected at all in many compounds). In a similar fashion it was possible to assign the nmr spectra of compounds **2-13**. Assignments are shown in Table 1.

Compound **9** had the molecular formula $C_{23}H_{22}O_5$. In the ^{1}H-nmr spectrum H5 and H6 formed an AB pattern (δ 7.21, 7.22); H4 appeared as a fine doublet (δ 6.26) with long-range coupling (J=0.7 Hz) to Ha. The two olefinic protons in the chromene ring formed an AB quartet (δ 6.73 and 5.57), Ha and Hb, respectively, and the two methyl groups appeared together as a singlet (δ1.47); the methylene protons in the prenyl side chain appeared as a doublet (δ 4.29), the olefinic proton as a triplet (δ 5.27), and the two methyl groups as



1 $R^1=R^2=OH$, $R^3=OMe$
3 $R^1=R^2=R^3=OH$
4 $R^1=R^3=OMe$, $R^2=OH$
10 $R^1=R^3=OH$, $R^2=H$
13 $R^1=R^3=OMe$, $R^2=H$



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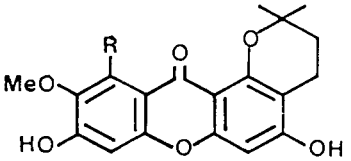
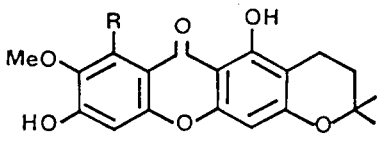
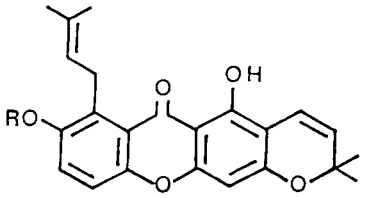


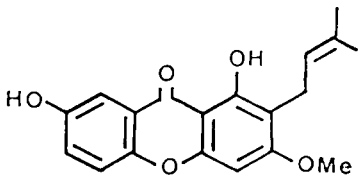
5 R=
8 R=



6 R=
7 R=



9 R=H
11 R=Me



12

two singlets (δ 1.88 and 1.77); the C1-OH and C7-OH groups resonated at δ 13.55 and 5.37, respectively. Methylation of the compound gave calabaxanthone [**11**] (12), which was identified by its ^{1}H-nmr spectrum.

Xanthone **10** had the molecular formula $C_{23}H_{24}O_5$. The ^{1}H-nmr spectrum (Table 1) indicated the structure of **10** [in C_6D_6 H5, H6 resonated at δ 6.74 and 7.00, respectively, (AB quartet, J=8 Hz)]. In the ^{1}H-nmr spectrum ($CDCl_3$-C_6D_6, 1:1) of the dimethyl ether derivative **13**, C7-OMe (δ 3.74) gave a 12% nOe enhancement to H6 (δ 7.10, d, J=8 Hz); C3-OMe (δ 3.76) gave a 10% nOe enhancement to H4 (δ 6.33). H5 resonated at δ 7.18 (d, J=8 Hz).

It is interesting that the previously reported (3) garcinones A, B, and C were not isolated in the present work. Some variability in the range of constituents must be possible.

The biological activities of these compounds will be reported elsewhere.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Low and high resolution mass spectra were obtained on a AEI MS 902 instrument at 70 ev. ^{1}H-nmr spectra were recorded in $CDCl_3$ (TMS as internal reference) at 400 MHz with Bruker WM-400 instrument. NOe enhancements were measured in the difference mode by the method previ-

TABLE 1. ^{1}H-nmr Assignments of Mangostin and other Xanthones[a]

Compound	Position										
	1	3	4	5	6	7	a	b	e	f	c+d+g+h
1	13.80 (s) (OH)	6.16 (s) (OH)	6.28 (s)	6.82 (s)	6.31 (s) (OH)	3.81 (s) (OCH_3)	3.45 (d) J=7 Hz	5.28 (t) J=7 Hz	4.11 (d) J=7 Hz	5.28 (bt) J=7 Hz	1.70 (s), 1.78 (s), 1.82 (s), 1.85 (s)
3[b]	13.93 (s) (OH)	6.37 (s) (OH)	6.37 (s)	6.81 (s)	3.31 (s) (OH)	2.91 (b) (OH)	3.35 (d) J=7 Hz	5.30 (t) J=7 Hz	4.19 (d) J=7 Hz	5.30 (bt) J=7 Hz	1.64 (s), 1.64 (s), 1.78 (s), 1.84 (s)
4	13.41 (s) (OH)	3.90 (s) (OCH_3)	6.35 (s)	6.82 (s)	6.33 (s) (OH)	3.81 (s) (OCH_3)	3.35 (d) J=7 Hz	5.24 (t) J=7 Hz	4.09 (d) J=7 Hz	5.28 (bt) J=7 Hz	1.68 (s), 1.69 (s), 1.79 (s), 1.83 (s)
5	—	1.68 (b) (OH)	6.34 (s)	6.67 (s)	1.68 (b) (OH)	3.78 (s) (OCH_3)	2.65 (t) J=7 Hz	1.82 (t) J=7 Hz	4.08 (d) J=7 Hz	5.34 (bt) J=7 Hz	1.40 (s), 1.40 (s), 1.61 (s), 1.76 (s)
6	13.71 (s) (OH)	—	6.24 (s)	6.83 (s)	6.35 (b) (OH)	3.80 (s) (OCH_3)	2.72 (t) J=7 Hz	1.83 (t) J=7 Hz	4.11 (d) J=7 Hz	5.28 (bt) J=7 Hz	1.37 (s), 1.37 (s), 1.69 (s), 1.83 (s)
7	13.60 (s) (OH)	—	6.24 (s)	6.83 (s)	6.36 (b) (OH)	3.85 (s) (OCH_3)	2.71 (t) J=7 Hz	1.82 (t) J=7 Hz	3.44 (m)	1.79 (m)	1.36 (s), 1.36 (s), 1.32 (s), 1.32 (s)
8[c]	—	5.33 (s) (OH)	6.34 (s)	6.70 (s)	5.33 (s) (OH)	3.81 (s) (OCH_3)	2.64 (t) J=7 Hz	1.79 (t) J=7 Hz	3.36 (m)	1.79 (m)	1.39 (s), 1.39 (s), 1.26 (s), 1.26 (s)
9	13.55 (s) (OH)	—	6.26 (d) J=0.7 Hz	7.21 (d) or 7.22 (d) J=8 Hz	7.22 (d) or 7.21 (d) J=8 Hz	5.37 (b) (OH)	6.73 (dd) J=10, 0.7 Hz	5.57 (d) J=10 Hz	4.29 (d) J=7 Hz	5.27 (bt) J=7 Hz	1.47 (s), 1.47 (s), 1.77 (s), 1.88 (s)
10	13.63 (s) (OH)	6.37 (b) (OH)	6.30 (s)	7.19 (s)	7.19 (s)	5.45 (b) (OH)	3.45 (d) J=7 Hz	5.26 (bt) J=7 Hz	4.27 (d) J=7 Hz	5.30 (bt) J=7 Hz	1.78 (s), 1.78 (s), 1.84 (s), 1.89 (s)
11	13.67 (s) (OH)	—	6.24 (d) J=0.7 Hz	7.26 (s)	7.26 (s)	3.87 (s) (OCH_3)	6.74 (dd) J=10, 0.7 Hz	5.57 (d) J=10 Hz	4.16 (d) J=7 Hz	5.27 (bt) J=7 Hz	1.46 (s), 1.46 (s), 1.68 (s), 1.84 (s)
12[c,d]	13.03 (s) (OH)	3.92 (s) (OCH_3)	6.41 (s)	7.29 (d) J=8 Hz	7.26 (dd) J=8,2 Hz	9.25 (s) (OH)	3.36 (d) J=7 Hz	5.23 (bt) J=7 Hz	—	—	1.68 (s), 1.79 (s) — —
13	13.39 (s) (OH)	3.91 (s) (OCH_3)	6.34 (s)	7.26 (s)	7.26 (s)	3.87 (s) (OCH_3)	3.36 (d) J=7 Hz	5.23 (bt) J=7 Hz	4.17 (d) J=7 Hz	5.25 (bt) J=7 Hz	1.68 (s), 1.68 (s), 1.80 (s), 185 (s)

[a]TMS as internal reference; $CDCl_3$ as solvent unless stated otherwise, s=singlet; d=doublet; t=triplet; b=broad peak; m=second order multiplet.
[b]In CD_3COCD_3.
[c]In $CDCl_3+CD_3SOCD_3$.
[d]The spectrum of compound **12** has the additional signal of H8 at δ 7.64 (d), J=2 Hz.

ously described (13). The ir spectra were measured on a Beckman Acculab 3 Infrared Spectrometer in KBr pellets or in Nujol mulls. The uv spectra were run on a Beckman UV/VIS Spectrometer 26. Melting points were recorded on a Buchi Tottoli melting point apparatus. Analytical tlc, preparative tlc, and quick column chromatography were performed on Si gel (Merck GF_{254}). For quick column chromatography mixtures were dissolved in the minimum amount of solvent and then adsorbed on Si gel prior to elution with solvents. Known compounds were identified by comparison of mp and spectral data with those previously reported.

PLANT MATERIAL.—Fruits of *G. mangostana* were collected in the Nakhon Si Thammarat Province, Thailand. A herbarium specimen has been deposited in the herbarium, Department of Biology, Prince of Songkla University, Thailand.

EXTRACTION OF PERICARPS OF *G. MANGOSTANA*.—The powdered, dry pericarp of *G. mangostana* (1 kg) was immersed in C_6H_6 (5 liters) for 3 days. The extraction was repeated three times, and the combined solution was concentrated to 700 ml; a yellow precipitate which formed on cooling the solution was collected (30 g). The precipitate was separated on a quick column eluting with hexane, hexane/C_6H_6, C_6H_6, CH_2Cl_2, EtOAc, Me_2CO, and then with MeOH. The eluents containing similar components were combined into seven fractions. Fractions 1,3,5 each contained one major component while fractions 2,4,6, and 7 contained mixtures of several compounds. Fraction 1 yielded gartanin [**2**] (1.4 g), yellow needles from hexane/C_6H_6, mp 170-172° [lit. (6) mp 167°]. Fraction 3 consisted of mangostin [**1**] (11.3 g), mp 180-182° [lit. (8) mp 182-183°]. Fraction 5 gave γ-mangostin [**3**] (1.2 g), mp 207-211° [lit. (7) mp 207°].

The mother liquors from fractions 1 and 3 were combined with fraction 2, and the material was subjected to another quick column separation. Three major fractions (tlc) were obtained: A,B, and C. Fraction B was mainly mangostin; fraction C gave β-mangostin [**4**] (0.03 g), mp 176-180° [lit. (9) mp 175-176°]. Fraction A yielded on fractional crystallization from C_6H_6, firstly γ-mangostin (0.2 g) and then 3-isomangostin [**6**] (0.15 g) mp 155-160° [lit. (11) mp 154-155°]. From the mother liquors β-mangostin (0.03 g) was obtained.

ISOLATION OF 1-ISOMANGOSTIN [**5**], 3-ISOMANGOSTIN HYDRATE [**7**], AND 1-ISOMANGOSTIN HYDRATE [**8**].—Fraction 4 and 6 from the initial quick column were combined with the mother liquor of fraction 5, and the material was separated on a quick column, eluting with C_6H_6, CH_2Cl_2, CH_2Cl_2/EtOAc, then MeOH. The fractions containing similar components were combined into four fractions, D,E,F, and G. Fractions D and E contained mangostin [**1**] and γ-mangostin [**3**], respectively, as the major components. Fraction F yielded 1-isomangostin [**5**] (0.06 g), mp 245-249° [lit. (11) mp 241-243°]. Crystallization of Fraction G from CH_2Cl_2 gave, as a first crop, 3-isomangostin hydrate [**7**] (0.015 g), mp 180-182° [lit. (11) mp 182-183°] and, as a second crop, 1-isomangostin hydrate [**8**] (0.03 g), mp 255-257° [lit. (11) mp 261-263°].

EXTRACTION OF ARILS OF *G. MANGOSTANA*.—Fresh arils obtained from seeds of *G. mangostana* (2.7 kg) were macerated in Me_2CO. The Me_2CO extract gave on evaporation a syrup which was fractionated between a minimum amount of H_2O (150 ml) and a large quantity of EtOAc until no significant quantity of substance was obtained from the EtOAc layer. The combined EtOAc solution was evaporated to afford a syrup (6.2 g) which was separated on a quick column eluting with hexane, hexane/C_6H_6, C_6H_6, C_6H_6/CH_2Cl_2, CH_2Cl_2, then EtOAc. The fractions containing similar components were combined into seven fractions: I,J,K,L,M,N, and O. Fraction J consisted of a mixture. Each of the other fractions contained a major component. Fraction I yielded calabaxanthone [**11**] (0.014 g), mp 170-172° [lit. (12) mp 172°]. Fraction O was largely mangostin [**1**] (0.1 g), and Fraction N consisted of 2-(γ,γ-dimethylallyl)-1,7-dihydroxy-3-methoxyxanthone [**12**] (0.1 g), identical with that obtained previously (4).

ISOLATION OF DEMETHYLCALABAXANTHONE [**9**].—Crystallization of Fraction K from CH_2Cl_2 gave yellow needles (0.06 g) of demethylcalabaxanthone [**9**], mp 184-190°. Elemental analysis found: C, 72.5; H, 5.9. $C_{23}H_{22}O_5$ requires C, 73.0; H, 5.9%; uv λ max (EtOH) (nm, log ε) 225 (4.28), 235 (4.26), 286 (4.74), 386 (4.21); ir (KBr) (cm^{-1}) 3450, 1640, 1610; ms *m/z* (rel. int. %) $M^{+\cdot}$ 378 (15), 363 (46), 335 (13). Methylation of **9** (Me_2SO_4/NaOH, room temperature) gave calabaxanthone [**11**], identical with the sample previously isolated.

ISOLATION OF 2,8-BIS(γ,γ-DIMETHYLALLYL)-1,3,7-TRIHYDROXYXANTHONE [**10**].—Fraction M was purified on ptlc, eluting with CH_2Cl_2. The substance from the major band was crystallized from C_6H_6 to give yellow prisms (0.04 g) of 2,8-bis(γ,γ-dimethylallyl)-1,3,7-trihydroxyxanthone [**10**], mp 168-170° (Found: $M^{+\cdot}$ 380.1651. $C_{23}H_{24}O_5$ requires 380.1623); uv λ max (EtOH) (nm, log ε) 241(4.52), 266(4.49), 315(4.25), 379(3.72); ir (KBr) (cm^{-1}) 3390, 1635; ms *m/z* (rel. int. %) $M^{+\cdot}$ 380(100) 337(51), 324(71), 309(82). Methylation of **10** gave the dimethyl ether **13**, mp 181-183° (Found: $M^{+\cdot}$ 408.1970. $C_{25}H_{28}O_5$ requires

408.1936); ms *m/z* (rel. int. %) $M^{+\cdot}$ 408(100), 365(68), 352(88), 337(68), 321(19), 309(37).

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