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XANTHONES FROM ROOTS OF THREE *CALOPHYLLUM* SPECIES

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Key Word Index—*Calophyllum thwaitesii*, *C. calaba*; *C. bracteatum*; Guttiferae; root bark; calothwaitesixanthone; 6-deoxy-γ-mangostin; thwaitesixanthone.

Abstract—The root bark of *Calophyllum thwaitesii* has been shown to contain two new xanthones: 6,8-dihydroxy-2,2-dimethyl-7(3-methylbut-2-enyl)-2H,5H-pyrano-(3,2-a)xanthen-5-one (calothwaitesixanthone) and 1,3,7-trihydroxy-2,8-di(3-methylbut-2-enyl)xanthone (6-deoxy-γ-mangostin). Thwaitesixanthone has also been isolated from the root bark extracts of *C. thwaitesii*. The root bark extracts of *C. calaba* var. *calaba* and *C. bracteatum* contained calabaxanthone and calocalabaxanthone. Trapezifolixanthone has also been isolated from *C. calaba* var. *calaba*.

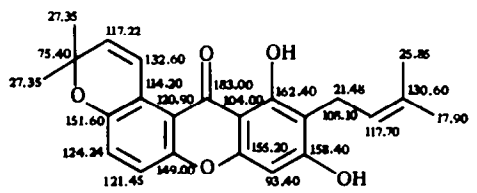
INTRODUCTION

The investigation of the bark and timber extracts of *Calophyllum bracteatum* Thw., *C. calaba* var. *calaba* L. and *C. thwaitesii* Planch and Triana were previously reported. The timber was shown to contain mainly oxygenated xanthones [1], whereas the bark had prenylated xanthones [1] and acids [2]. We now report the characterization of two more new xanthones named calothwaitesixanthone (**1**) and 6-deoxy-γ-mangostin (**2**) from the root outer bark of *C. thwaitesii*. The root outer bark extracts of *C. calaba* var. *calaba* and *C. bracteatum* contained the hitherto reported but rare xanthones.

RESULTS AND DISCUSSION

Calothwaitesixanthone (**1**) is a new xanthone (M_r 378.1472: $C_{23}H_{22}O_5$) and was isolated from the root outer bark of *C. thwaitesii*. The UV and IR spectra showed the natural product to be a xanthone. The UV spectrum of the hydrogenated xanthone was very similar to that of tetrahydrocalabaxanthone and tetrahydrothwaitesixanthone indicating the presence of a 1,3,7-trioxygenated xanthone moiety [1]. The ^{1}H NMR spectrum (300 MHz) of the xanthone, named calothwaitesixanthone, showed the presence of a chelated hydroxyl (δ13.58). This and the signal at δ6.20 (1H) were exchangeable with D_2O confirming the presence of two free hydroxyl groups in **1**. The singlet at δ1.46 (6H, 2 × Me), doublets at δ8.01 (1H, J = 10.20 Hz) and δ5.81 (1H, J = 10.20 Hz) suggested the presence of one 2,2-dimethyl-2H-pyrano ring. The singlets at δ1.77 (3H, Me) and 1.84 (3H, Me), and triplets at δ5.30 (1H) and 3.45 (2H) indicated the presence of a 3-methylbut-2-enyl (isoprenyl) side chain. Calothwaitesixanthone also had three aromatic protons and these protons appeared as two singlets at δ7.15 (1H), 7.16 (1H) and 6.34 (1H). The upfield aromatic proton should be in an electron rich environment such as the phloroglucinol ring of the xanthone. Calothwaitesixanthone on oxidation with 2,2-dichloro-5,6-dicyanobenzoquinone (DDQ) [3] gave another xanthone which was identical with thwaitesixanthone (**2**) isolated in this study from the root outer bark of *C. thwaitesii*. Thwaitesixanthone (**2**) was previously reported from *C. thwaitesii* by Sultanbawa [4]. From these observations calothwaitesixanthone has been identified as 6,8-dihydroxy-2,2-dimethyl-7(3-methylbut-2-enyl)-2H,5H-pyrano-(3,2-a)xanthen-5-one (**1**). The ^{13}C NMR data further confirmed structure **1**. The complete ^{13}C NMR chemical shifts of **1** (in $CDCl_3$) are given in the formula. This is the first report of **1** whose co-occurrence with **2** in *C. thwaitesii* strongly suggests that **1** is a putative isoprenyl precursor of **2**.

6-Deoxy-γ-mangostin (**3**) is another new compound (M_r 380.1625: $C_{23}H_{24}O_5$). Here again from the UV and IR data, the natural product was inferred to be a hydroxyxanthone. Its UV spectrum was similar to that of tetrahydrocalabaxanthone, tetrahydrothwaitesixanthone [1] and dihydrocalothwaitesixanthone. Thus **3** is also a 1,3,7-trioxygenated xanthone. Acetylation gave a triacetate and out of the three free hydroxyl groups in **3**, one was shown to be a chelated hydroxyl group (δ13.61). 6-Deoxy-γ-mangostin has three aromatic protons at δ7.18 (2H, *s*) and δ6.40 (1H, *s*). As in the case of **1**, the upfield



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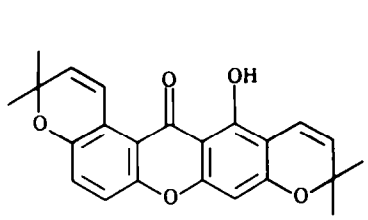
*To whom correspondence should be addressed.



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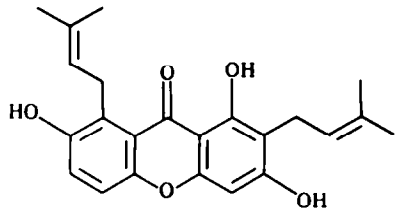

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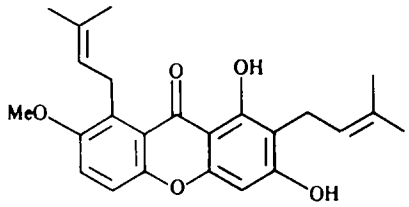

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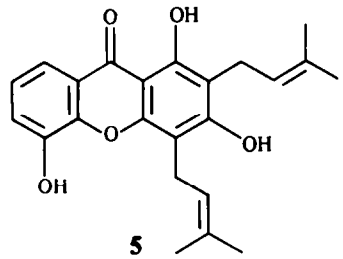

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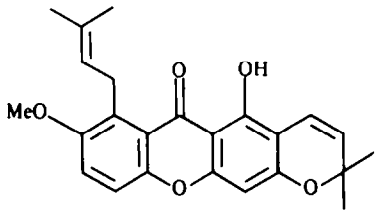

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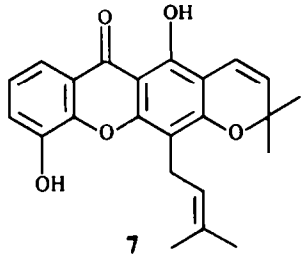

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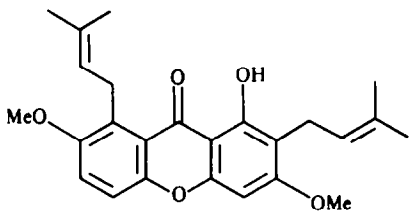

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aromatic proton should be in the phloroglucinol ring of the xanthone. The presence of signals at δ1.90 (3H, *s*), 1.87 (3H, *s*) and 1.77 (6H, *s*) due to four methyl groups of the type Me–C=, doublets at δ4.27 (2H) and 3.47 (2H), and the two proton multiplet at δ5.30 confirmed the presence of two 3-methylbut-2-enyl (isoprenyl) side chains. The presence of low field benzylic protons (δ4.27) shows that one of the isoprenyl side chains is attached to C-1 or C-8 of the xanthone moiety. The close similarity of the aromatic proton chemical shifts of **3** and **1** showed that the former had an aromatic substitution pattern similar to that of the latter. 6-Deoxy-γ-mangostin was rapidly converted to **2** by oxidation with DDQ. Besides, methylation of **3** with diazomethane gave a product (**8**) which was identical with the diazomethane methylation product of calocalabaxanthone (**4**). It is well known that diazomethane does not normally methylate chelated hydroxyl groups. Thus 6-deoxy-γ-mangostin isolated from *C. thwaitesii* has been assigned the structure 1,3,7-trihydroxy-2,8-di(3-methylbut-2-enyl)xanthone (**3**). The trioxygenated diprenylated xanthones are rare in nature. Apart from **3** and **4** [5], the only known example is 8-deoxygartenin (**5**) [1]. It is biogenetically significant that **3** co-occurs with **1** and **2** in the root outer bark of *C. thwaitesii*. Thwaitesixanthone (**2**) is probably the end product of the biosynthetic conversion **3** → **1** → **2**.

The hot petrol extracts of the root outer bark of *C. calaba* var. *calaba* gave three xanthones which have been identified as calabaxanthone (**6**) [5], calocalabaxanthone (**4**) and another rare xanthone trapezifolixanthone (**7**). DDQ oxidation of **4** gave **6**. The hexane extracts of the root outer bark of *C. bracteatum*

gave two xanthones which were identified as **6** and **4**. This is the second report of the isolation of **4**. It is interesting to note that the xanthones **1–4** and **6** all have the same oxygenation patterns and the C_5 chains are either free or ring closed at identical positions in the aromatic rings. Therefore, it is probable that the trioxygenated diprenylated xanthone **3** is the precursor of the xanthones **1**, **2**, **4** and **6**. The absence of a methylating enzyme system in *C. thwaitesii* has enabled the biosynthesis of **1** and **2** from **3**. The presence of a methylating enzyme system in *C. calaba* var. *calaba* and *C. bracteatum* has probably made it impossible for the biosynthesis of **1** and **2** in these two *Calophyllum* species. Thus the existence of two chemotypes of *Calophyllum* species has now been recognized. This point will be amplified in a subsequent publication.

EXPERIMENTAL

Plant parts were collected in different parts of Sri Lanka. High and low resolution NMR data were obtained using a 300 or 60 MHz instruments, respectively. Mps are uncorr.

C. thwaitesii. Hot hexane extraction of the root outer bark yielded 3 g of extract. Isolations of compounds were carried out using a pre-packed column C 440-37 Li chroprep Si 60 (63–125 μm) for LC. Elution with $CHCl_3$ gave **2** (0.4 g), mp 221–224°, lit. [4] 221–224°. Continued elution with $CHCl_3$ gave **1** (0.1 g), mp 169–172°; UV λ_{max}^{MeOH} nm (log ε): 238 (4.52), 246 (4.53), 286 (4.70), 319 (4.41) and 391 (3.88); IR ν_{max}^{KBr} cm^{-1}: 3395, 2920, 1642, 1610, 1575, 1470, 1360, 1310, 1275, 1175, 1120, 1080, 1060, 900 and 818; ^1H NMR ($CDCl_3$, 300 MHz): δ13.58 (1H, *s*, OH), 8.01 (1H, *d*, J = 10 Hz), 7.15 and 7.16 (2H, *s*), 6.20 (1H, *s*, OH), 6.34 (1H, *s*), 5.81 (1H, *d*, J = 10 Hz), 5.30 (1H, *t*, J = 7 and 16 Hz), 3.45 (2H, *t*), 1.84 (3H, *s*), 1.77 (3H, *s*) and 1.46 (6H, *s*); MS *m/z* 378.1472, $C_{23}H_{22}O_5$ requires 378.1467. 378 $[M]^+$ (62%), 363 (100), 355 (18), 323 (11), 321 (11), 307 (77), 295 (8), 279 (39), 265 (8), 253 (8) and 237 (5).

Cyclization of calothwaitesixanthone (**1**). Compound **1** (5 mg), DDQ (5 mg) and dry C_6H_6 (5 ml) were heated under reflux for 2 hr. The reaction mixture was solvent evapd and subjected to prep. TLC ($CHCl_3$) to give **2** (2 mg), mp 220–222°, lit. [4] 221–224°. Identical to authentic sample (mmp, IR, ^1H NMR and co-TLC).

Further elution of the column with $CHCl_3$ gave **3** (0.09 g), mp 171–174°; UV λ_{max}^{MeOH} nm (log ε): 240 (4.60), 264 (4.59), 314 (4.35) and 267 (3.80); IR ν_{max}^{KBr} cm^{-1}: 3390, 2920, 1645, 1610, 1575, 1470, 1455, 1320, 1170, 1150, 1130, 1085 and 820; ^1H NMR ($CDCl_3$, 60 MHz): δ13.61 (1H, *s*, OH), 7.18 (2H, *s*), 6.40 (1H, *s*), 5.30 (1H, *m*), 4.27 (2H, *d*, J = 7 Hz), 3.47 (2H, *d*, J = 7 Hz), 1.90 (3H, *s*), 1.87 (3H, *s*), 1.77 (6H, *s*). MS *m/z* 380.1625, $C_{23}H_{24}O_5$ requires 380.1624. 380 $[M]^+$ (100%), 337 (54), 324 (77), 309 (93), 281 (80), 269 (19), 225 (6), 155 (6), 115 (8), 55 (14), 41 (30).

Methylation of **3**. Compound **3** (18 mg) in Et_2O (1 ml) was treated with excess CH_2N_2. The product was purified by prep. TLC (CH_2Cl_2) to give a diMe derivative, mp 171.2°. This was identical with 2,8-di-(3 methylbut-2-enyl)-3,7-dimethoxyl-1-hydroxyxanthone (**8**) prepared by the CH_2N_2 methylation of **4**; MS *m/z* (rel. int.): 408 $[M]^+$ (91%), 365 (71), 352 (100), 337 (73), 321 (24), 309 (52), 297 (16), 283 (11). The monoMe derivative, mp 165° in the above reaction was identical with **4** (mmp, co-TLC, IR, UV, ^1H HMR).

Cyclization of 6-deoxy-γ-mangostin (**3**). Compound **3** (5 mg), DDQ (5 mg) and dry C_6H_6 (10 ml) were heated under reflux for 45 min. The crude product was separated by silica gel CC ($CHCl_3$) to give 2 mg of a xanthone which was identified as **2** (co-TLC, mmp and MS).

Acetylation of 6-deoxy-γ-mangostin (**3**). Compound **3** (15 mg), Ac_2O (1 ml) and pyridine (1 ml) were heated under reflux for 16 hr. Excess reagents were removed by evapn with C_6H_6. The crude product was separated by prep. TLC ($CHCl_3$) to give the triacetate (10 mg), mp 176–180°; ^1H NMR ($CDCl_3$, 300 MHz): δ7.26 (2H, *s*), 6.47 (1H, *s*), 5.28 (1H, *m*), 3.90 (2H, *m*), 3.40 (1H, *m*), 2.46 (3H, *s*), 2.34 (6H, *s*), 1.81 (3H, *s*), 1.75 (3H, *s*) and 1.67 (6H, *s*); MS *m/z* (rel. int.): 506 $[M]^+$ (21%), 446 (10), 379 (5), 305 (5), 149 (5), 111 (2), 85 (3), 71 (3), 57 (11) and 43 (100).

Isolation of calabaxanthone (**6**) *and calocalabaxanthone* (**4**). These two xanthones were isolated from the hot petrol extracts of the root outer barks of *C. calaba* var *calaba* and *C. bracteatum* by CC on a pre-packed column C (440-37) Lichroprep Si 60 (63–125 μm). Elution with $CHCl_3$ gave **6**, mp 171–172°, lit. [5] 171–172° which was identical with an authentic sample (mmp, co-TLC, IR, UV, ^1H NMR). Continued elution with $CHCl_3$ gave **4**, mp 171–175°, lit. [5] 164–166°; UV λ_{max}^{MeOH} nm (log ε): 240 (4.78), 262 (4.74), 314 (4.56) and 365 (3.97); IR ν_{max}^{KBr} cm^{-1}: 3430, 2900, 1640, 1603, 1570, 1470, 1310, 1265, 1178, 1090, 1075 and 810; ^1H NMR ($CDCl_3$ 60 MHz): δ13.80 (1H, *s*, OH), 7.25 (2H, *s*), 6.33 (1H, *s*), 5.33 (2H, *m*), 4.21 (2H, *d*, J = 6 Hz), 3.91 (3H, *s*), 3.50 (2H, *d*, J = 7 Hz), 1.89 (6H, *s*), 1.82 (3H, *s*) and 1.70 (3H, *s*).

Methylation of calocalabaxanthone (**4**). Compound **4** (22 mg) was treated with excess CH_2N_2. Usual work up gave a crude product which was separated by prep. TLC ($CHCl_3$) to give the diMe derivative **8**, mp 170–172°; UV λ_{max}^{MeOH} nm (log ε): 242 (4.38), 264 (4.37), 309 (4.11), 365 (3.54); IR ν_{max}^{KBr} cm^{-1}: 2900, 1640, 1590, 1565, 1490, 1445, 1370, 1300, 1210, 1185, 1100, 1030, 840 and 750; ^1H NMR ($CDCl_3$, 300 MHz): δ13.40 (1H, *s*, OH), 7.25 (2H, *s*), 6.33 (1H, *s*), 5.23 (2H, *t*), 4.17 (2H, *d*, J = 6 Hz), 3.90 (3H, *s*), 3.87 (3H, *s*), 3.36 (2H, *d*, J = 7 Hz), 1.85 (3H, *s*), 1.85 (3H, *s*) and 1.69 (6H, *s*); MS *m/z* (rel. int.): 408 $[M]^+$ (100%), 365 (70), 352 (100), 337 (70), 321 (20), 309 (42), 297 (16), 283 (10), 265 (8).

Cyclization of calocalabaxanthone (**4**). Compound **4** (20 mg) was treated with DDQ (20 mg) in dry C_6H_6 (20 ml) and the mixture heated under reflux for 30 min. The crude product was purified by prep. TLC ($CHCl_3$) to give **6**, mp 171–172°, lit. [5] 171–172°, identical to an authentic sample (mmp, co-TLC).

Isolation of trapezifolixanthone (**7**). The compound was isolated from the root outer bark extracts of *C. calaba* var. *calaba*. The hot petrol extracts when chromatographed on a pre-packed column C (440-37) Lichroprep Si 60 (63–125 μm) gave the xanthones **6**, **4** and **7**, respectively, when eluted with $CHCl_3$. Compound **7**, mp 178–180°, lit. [6] 171–172°, identical to an authentic sample (mmp, co-TLC, IR, UV, ^1H NMR and MS).

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