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CANTHIN-6-ONE ALKALOIDS FROM *EURYCOMA LONGIFOLIA*

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Key Word Index—*Eurycoma longifolia*; Simaroubaceae; bark; wood; canthin-6-one alkaloids.

Abstract—Five new canthin-6-one alkaloids, 9,10-dimethoxycanthin-6-one, 10-hydroxy-9-methoxycanthin-6-one, 11-hydroxy-10-methoxycanthin-6-one, 5,9-dimethoxycanthin-6-one and 9-methoxy-3-methylcanthin-5,6-dione were isolated from the bark and wood of *Eurycoma longifolia*, along with six known canthin-6-one alkaloids and two known β-carboline alkaloids. Their structures were determined from spectroscopic data and other chemical evidence.

INTRODUCTION

A number of canthin-6-one alkaloids have been isolated from natural sources and have been reviewed [1]. In our alkaloidal investigation of simaroubaceous plants, we investigated *Eurycoma longifolia*, a folk medicine commonly used in Indonesia. In some regions of Jawa, the plant is called 'Bidara pahit' and the roots are used for traditional treatment of dysentery and tertian malaria [2, 3]. With regard to chemical constituents, several alkaloids [4, 5] were isolated together with quassinoids [4–20], tirucalane-type triterpenes [18], squalene-type triterpene ethers [21], a biphenylneolignan and a biphenyl ether [22]. Recently, the cytotoxic activity of several quassinoids isolated from this plant was reported using cultured KB and P-388 cells [15]. This paper describes the isolation and structure determinations of five new canthin-6-one alkaloids, along with eight known alkaloids, from the bark and wood of *E. longifolia*.

RESULTS AND DISCUSSION

The bark of *E. longifolia* was extracted with chloroform and methanol. The chloroform fraction was repeatedly chromatographed to afford three new canthin-6-one alkaloids (**1**, **2**, **4**) and four known alkaloids (**6**–**9**). The methanol fraction was purified by successive silica gel column chromatography to give a known alkaloid (**10**). The wood of *E. longifolia* was extracted with chloroform. The chloroform fraction gave two new canthin-6-one alkaloids (**3**, **5**) and three known alkaloids (**11**–**13**).

Compound **1** was assigned the molecular formula $C_{16}H_{12}N_2O_3$ (HR mass spectrum). The UV spectrum was similar to those reported for canthin-6-one alkaloids [23]. The ^{1}H NMR showed two singlets (δ4.03, 4.08, OMe) and two pairs of doublets ascribed to *ortho*-couplings. The pairs of doublets (δ7.80/8.76, J = 4.9 Hz and δ6.93/7.97, J = 9.8 Hz) can be attributed to the pyridine and lactamic rings, respectively. Two methoxyl groups were located at C-9 and C-10, because in the ^{1}H NMR two signals of singlets (δ7.43 and 8.17) for H-11 and H-8 were observed and assignments were deduced by COLOC and NOE experiments. The NOESY experiment showed NOEs between the methoxyl protons (OMe-9) and H-8 and other methoxyl protons (OMe-10) and H-11. The structure of **1** was thus concluded to be 9,10-dimethoxycanthin-6-one.

Compound **2** was assigned the molecular formula $C_{15}H_{10}N_2O_3$ (HR mass spectrum). The IR spectrum indicated the presence of a hydroxyl group (ν_{max} 3404 cm^{-1}). The ^{1}H NMR showed the same general characteristics of **1**, except that only one methoxyl proton (δ4.11) was observed, so that **2** is thus a 9,10-disubstituted canthin-6-one alkaloid. The methoxyl group assignment was deduced by difference NOE experiments. Irradiation of the H-1 proton at δ7.86 induced NOEs at H-2 (9%) and H-11 (2%). Irradiation of the H-11 proton at δ7.60 induced 2% NOE at H-1. Irradiation of the methoxyl protons at δ4.11 induced 16% NOE at H-8. Treatment of **2** with diazomethane yielded 9,10-dimethoxycanthin-6-one (**1**). Thus, 10-hydroxy-9-methoxycanthine-6-one is proposed for **2**.

Compound **3** was assigned the molecular formula $C_{15}H_{10}N_2O_3$ (HR mass spectrum). The IR spectrum indicated the presence of a hydroxyl group (ν_{max} 3419 cm^{-1}) and the UV spectrum was similar to that of **2**. The ^{1}H NMR showed a singlet (δ4.02, OMe) and three pairs of doublets ascribable to *ortho*-couplings. The pairs of doublets (δ8.08/8.74, J = 4.8 Hz, δ6.92/8.05, J = 9.9 Hz and δ7.29/7.79, J = 8.0 Hz) can be attributed to the pyridine, lactamic and A-rings, respectively. These data show **3** to be a 8,9- or a 10,11-disubstituted canthin-6-one alkaloid. The hydroxyl group must be located at C-11

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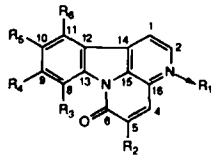

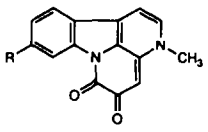

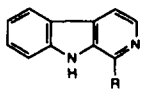

	R_1	R_2	R_3	R_4	R_5	R_6
1	–	H	H	OCH_3	OCH_3	H
2	–	H	H	OCH_3	OH	H
3	–	H	H	H	OCH_3	OH
4	–	OCH_3	H	OCH_3	H	H
6	–	H	H	H	H	H
7	O	H	H	H	H	H
8	–	H	H	OCH_3	H	H
11	–	H	H	H	H	OH
12	O	H	H	OCH_3	H	H

	R
5	OCH_3
13	H

	R
9	CH_2OCH_3
10	CH_2CH_2COOH

based on a comparison of the H-8 chemical shift with that of 11-hydroxycanthin-6-one (**11**). Methoxyl group assignment was deduced by difference NOE experiments. Irradiation of the methoxyl protons at δ4.02 induced 8% NOE at H-9. The structure of **3** was thus concluded to be 11-hydroxy-10-methoxycanthin-6-one.

Compound **4** was assigned the molecular formula $C_{16}H_{12}N_2O_3$ (HR mass spectrum). The UV spectrum was similar to that of **1**. The ^{1}H NMR showed two singlets (δ3.99, 4.05, OMe) and a pair of doublets (δ7.74/8.72, J = 5.1 Hz) can be attributed to H-1 and H-2. The ^{1}H NMR spectrum showed good agreement with that measured for 9-methoxycanthin-6-one (**8**), except that the signal for H-4 was singlet as in **8**. These data show the two methoxyl groups to be located at C-5 and C-9. The structure of **4** was thus concluded to be 5,9-dimethoxyxanthin-6-one.

Compound **5** was assigned the molecular formula $C_{16}H_{12}N_2O_3$ (HR mass spectrum). The UV spectrum was similar to that of **13** and showed a hypochromic shift on addition of acid, but was unchanged by base. The hypochromic shift of the absorption maxima in the presence of acid indicated **5** to have a canthin-5, 6-dione chromophore [24]. The ^{1}H NMR showed an ABX pattern of signals (δ8.02, *d*, J = 2.2 Hz, δ8.08, *d*, J = 8.4 Hz and δ7.13, *dd*, J = 8.4, 2.2 Hz) and a pair of *ortho*-coupled signals at δ7.35 and 7.95 (each, *d*, J = 6.6 Hz) assigned to H-1 and H-2, respectively, and two singlets (δ3.88, 3.89) attributable to methyl and methoxyl protons, and an olefin proton (H-4). Compound **5** was thus assigned as either 9-methoxy-3-methyl or 10-methoxy-3-methylcanthin-5,6-dione. A comparison of the ^{1}H NMR chemical shifts of **5** with those of **13** indicated a ^{1}H upfield shift for H-8 ($\Delta\delta$ = 0.45) in **5**. Thus, we propose 9-methoxy-3-methylcanthin-5,6-dione for **5**.

Compounds **6**–**13** were identified as canthin-6-one (**6**) [25], canthin-6-one-3*N*-oxide (**7**) [23], 9-methoxycanthin-6-one (**8**) [5, 6], 1-methoxymethyl-β-carboline (**9**) [26], β-carboline-1-propionic acid (**10**) [27], 11-hydroxycanthin-6-one (**11**) [28], 9-methoxycanthin-6-one-3*N*-oxide (**12**) [29] and 3-methyl-canthin-5,6-dione (picrasidine L) (**13**) [30] by direct comparison with TLC, mixed mp and spectral data from authentic samples.

EXPERIMENTAL

General. Mps: Uncorr. IR spectra were recorded as KBr pellets. UV spectra in MeOH. ^{1}H and ^{13}C NMR: 400 and 100 MHz, respectively. Chemical shifts are given as δ with TMS as int. standard. Silica gel (BW-820MH and Chromatorex NH type, Fuji Davison) and silica gel (CQ-3, 24 mm i.d. × 360 mm, Fuji Gel, detector 254 nm) was used for low-pressure LC. HPLC was performed using a silica gel column (Senshu Pak, SSC-silical gel 3251-N, 8 mm i.d. × 250 mm, detector 254 nm).

Extraction and isolation. Dried bark (2.5 kg) of *E. longifolia* Jack collected in Indonesia, in July 1986, was extracted with $CHCl_3$ (23 l) and MeOH (14 l). The $CHCl_3$ and MeOH extracts were concd under red. pres. to give residues, 25 g and 51 g, respectively. The $CHCl_3$-sol. fr. (25 g) was subjected to CC on silica gel (200 g). The alkaloid frs were subjected to repeated CC on silica gel and further purification by low-pressure LC to give 3 new canthin-6-one-alkaloids, **1** (28 mg), **2** (2 mg), **4** (0.4 mg) and 4 known alkaloids (**6**–**9**). The MeOH-sol. fr. (51 g) was subjected to CC on silica (1 kg) to afford a known alkaloid (**10**). Dried wood (10.5 kg) was extracted with $CHCl_3$ (42 l). The $CHCl_3$ extract was concd under red. pres. to give a residue (100 g). The $CHCl_3$-sol. frs. (100 g) was subjected to CC on silica gel (1 kg). The alkaloid frs were subjected to repeated CC on silica gel and then further purification by low-pressure LC and HPLC to give 2 new canthin-6-one alkaloids, **3** (1 mg), **5** (3 mg) and 3 known alkaloids (**11**–**13**).

9,10-*Dimethoxycanthin-6-one* (**1**). Yellow needles, mp 213–215°. IR ν_{max} cm^{-1}: 1655, 1630, 1480, 1435, 1410, 1355, 1330, 1280, 1230, 1210, 1180, 1155, 1115, 1050 and 1010. UV λ_{max} nm (log ε): 232 (3.87), 270 (sh) (4.05), 280 (4.17), 300 (3.61), 310 (3.56), 359 (3.79) and 375 (3.75). HRMS *m/z* 280.0850 $[M]^+$ (calcd for $C_{16}H_{12}N_2O_3$: 280.0845). EIMS *m/z* (rel. int.): 280 $[M]^+$ (100), 265 (55), 237 (41), 222 (10), 194 (15), 179 (15), 166 (7), 139 (5) and 83 (2). ^{1}H NMR: Table 1. ^{13}C NMR ($CDCl_3$): δ56.4 (10-OMe), 56.6 (9-OMe), 100.3 (C-8), 104.0 (C-11), 115.5 (C-1), 116.4 (C-12), 128.6 (C-5), 130.6 (C-14), 131.9 (C-15), 134.6 (C-13), 135.7 (C-16), 139.6 (C-4), 145.7 (C-2), 148.0 (C-10), 152.3 (C-9) and 159.6 (C-6).

Table 1. ^{1}H NMR spectral data for 1–5, 8, 11 and 13

H	1*	2*	3†	11†	4*	8*	5†	13†
1	7.80 *d* (4.9)	7.86 *d* (4.8)	8.08 *d* (5.5)	8.09 *d* (4.8)	7.74 *d* (5.1)	7.79 *d* (4.9)	7.35 *d* (6.6)	7.42 *d* (7.0)
2	8.76 *d* (5.4)	8.78 *d* (5.1)	8.74 *d* (4.8)	8.78 *d* (4.8)	8.72 *d* (5.1)	8.74 *d* (4.9)	7.95 *d* (6.6)	7.97 *d* (7.0)
4	7.97 *d* (9.8)	8.01 *d* (9.9)	8.05 *d* (9.9)	8.10 *d* (9.5)	7.21 *s*	7.98 *d* (9.9)	5.96 *s*	5.99 *s*
5	6.93 *d* (9.8)	6.97 *d* (9.9)	6.92 *d* (9.9)	6.96 *d* (9.9)	—	6.92 *d* (9.9)	—	—
8	8.17 *s*	8.24 *s*	7.79 *d* (8.0)	7.97 *d* (7.3)	8.27 *d* (2.2)	8.13 *d* (2.4)	8.02 *d* (2.2)	8.47 *d* (8.1)
9	—	—	7.29 *d* (8.0)	7.57 *t* (8.1)				7.68 *t* (7.3)
10	—	—	—	7.02 *d* (8.0)	7.10 *dd* (8.8, 2.2)	7.03 *dd* (8.6, 2.4)	7.13 *dd* (8.4, 2.2)	7.53 *t* (7.3)
11	7.43 *s*	7.60 *s*	—	—	7.96 *d* (8.8)	7.88 *d* (8.6)	8.08 *d* (8.4)	8.19 *d* (8.4)
OMe-5	—	—	—	—	4.05 *s*	—	—	—
OMe-9	4.08 *s*	4.11 *s*	—	—	3.99 *s*	3.97 *s*	3.89 s‡	—
OMe-10	4.03 *s*	—	3.91 *s*	—	—	—	—	—
N-Me	—	—	—	—	—	—	3.88 s‡	3.93 *s*

Coupling constants (*J* in Hz) are given in parentheses.
*In chloroform-*d*.
†In dimethylsulphoxide-d_6.
‡Assignments may be exchangeable.

10-*Hydroxy*-9-*methoxycanthin*-6-*one* (**2**). Yellow needles, mp 255–257°. IR ν_{max} cm^{-1}: 3404, 1667, 1633, 1486, 1461, 1445, 1428, 1350, 1301, 1268, 1232, 1203, 1156 and 1025. UV λ_{max} nm (log ε): 230 (sh) (3.02), 282 (3.17), 304 (sh) (2.63), 360 (2.75) and 375 (2.73). HRMS *m/z* 266.0663 [M]$^+$ (calcd for $C_{15}H_{10}N_2O_3$: 266.0689). EIMS *m/z* (rel. int.): 266 [M]$^+$ (66), 251 (41), 223 (30), 211 (5), 195 (10), 185 (14), 161 (5), 149 (13), 111 (17) and 43 (100). ^{1}H NMR: Table 1.

Methylation of **1**. A soln of **2** (1 mg) in Et_2O (0.5 ml) was treated with CH_2N_2 for 1 hr. The reaction mixt. was evapd to give yellow needles of **1** (1 mg). This compound was identified as 9,10-dimethoxycanthin-6-one by direct comparison with an authentic sample (TLC, IR, ^{1}H NMR and MS].

11-*Hydroxy*-10-*methoxycanthin*-6-*one* (**3**). Yellow needles, mp 235–237°. IR ν_{max} cm^{-1}: 3419, 1669, 1634, 1508, 1463, 1437, 1362, 1267, 1129 and 1049. UV λ_{max} nm (log ε): 218 (4.02), 245 (3.57), 265 (3.33), 320 (3.24) and 394 (3.24). HRMS *m/z* 266.0686 [M]$^+$ (calcd for $C_{15}H_{10}N_2O_3$: 266.0689). EIMS *m/z* (rel. int.): 266 [M]$^+$ (12), 251 (16), 223 (7), 203 (3), 185 (100), 167 (9), 158 (4), 149 (25), 139 (9), 125 (6), 112 (24), 97 (15), 83 (24), 71 (45), 57 (57) and 42 (34). ^{1}H NMR: Table 1.

5,9-*Dimethoxycanthin*-6-*one* (**4**). Needles, mp > 300°. IR ν_{max} cm^{-1}: 1679, 1634, 1458, 1440, 1426, 1379, 1289, 1266, 1241, 1147, 1129 and 1036. UV λ_{max} nm (log ε): 214 (sh) (3.80), 245 (3.40), 265 (sh) (3.29), 275 (3.41) and 330 (3.15). HRMS *m/z* 280.0853 [M]$^+$ (calcd for $C_{16}H_{12}N_2O_3$: 280.0845). EIMS *m/z* (rel. int.): 280 [M]$^+$ (100), 265 (5), 251 (64), 237 (26), 222 (12), 194 (22), 179 (8), 167 (24), 149 (87), 139 (16), 111 (17), 97 (26), 85 (33), 71 (51), 57 (77) and 43 (67). ^{1}H NMR: Table 1.

9-*Methoxy*-3-*methylcanthin*-5,6-*dione* (**5**). Yellow needles, mp > 300°. IR ν_{max} cm^{-1}: 1693, 1649, 1616, 1591, 1551, 1464, 1436, 1344, 1328, 1272, 1232, 1217, 1175, 1099, 1025, 927 and 840. UV $\lambda_{max}^{(MeOH)}$ nm (log ε): 230 (4.67), 258 (4.46), 278 (4.59), 345 (4.46) and 450 (4.41). UV $\lambda_{max}^{(MeOH)+HCl}$ nm (log ε): 220 (4.72), 258 (4.46), 280 (4.55), 355 (4.57) and 400 (sh) (4.25). HRMS *m/z* 280.0846 [M]$^+$ (calcd for $C_{16}H_{12}N_2O_3$: 280.0845). EIMS *m/z* (rel. int.): 280 [M]$^+$ (88), 252 (100), 223 (58), 209 (18), 193 (47), 181 (19), 168 (10), 140 (6), 126 (6), 96 (4), 75 (5), 63 (4), 51 (3) and 41 (4).^{1}H NMR: Table 1.

Canthin-6-*one* (**6**). Yellow needles, mp 155–156°. IR ν_{max} cm^{-1}: 1665, 1630, 1600, 1430, 1325, 1300 and 1135. EIMS *m/z* (rel. int.): 220 [M]$^+$ (100), 192 (51), 164 (7), 139 (6) and 96 (5).

Canthin-6-*one*-3N-*oxide* (**7**). Yellow needles, mp 244–245°. IR ν_{max} cm^{-1}: 3060, 1670, 1645, 1575, 1430, 1400, 1330, 1230 and 1135. EIMS *m/z* (rel. int.): 236 [M]$^+$ (100), 220 (27), 208 (10), 192 (28), 179 (12), 164 (11), 153 (12) and 139 (7).

9-*Methoxycanthin*-6-*one* (**8**). Yellow needles, mp 177–179°. IR ν_{max} cm^{-1}: 1665, 1630, 1610, 1490, 1450, 1420, 1330, 1270, 1220, 1150 and 1030. EIMS *m/z* (rel. int.): 250 [M]$^+$ (100), 235 (8), 221 (18), 207 (28), 192 (9), 179 (22), 164 (2) and 153 (8).

1-*Methoxymethyl*-β-*carboline* (**9**). Yellow needles, mp 123–125°. IR ν_{max} cm^{-1}: 3310, 1610, 1550, 1225, 1150 and 1070. EIMS *m/z* (rel. int.): 212 [M]$^+$ (21), 182 (100), 168

(4), 154 (13), 140 (8) and 127 (6).

Synthesis of **9**. A mixt. containing *dl*-tryptophan (2 g) and 1,1,2-trimethoxyethane (1.5 g) in H_2O (80 ml) and EtOH (1 ml) was heated at 60° for 20 hr. The soln was diluted to 500 ml with H_2O and boiled for a few min, and then 10% potassium dichromate soln (100 ml) and HOAc (20 ml) were added. Heating was continued for 3 min and the resulting brown suspension was cooled. After the addition of Na_2CO_3, extraction was conducted repeatedly with Et_2O. Evapn of the Et_2O left crude crystals (1.6 g). Recrystallization from Me_2CO gave needles of **9** (1 g).

β-Carboline-1-propionic acid (**10**). Yellow needles, mp 215–216°. IR ν_{max} cm^{-1}: 3420, 1680, 1620, 1550 and 1390. EIMS *m/z* (rel. int.): 240 $[M]^+$ (32), 222 (13), 195 (100), 181 (6), 168 (17), 154 (7), 140 (13), 115 (7), 96 (7), 63 (5) and 38 (3).

11-Hydroxycanthin-6-one (**11**). Yellow needles, mp > 300°. IR ν_{max} cm^{-1}: 3441, 1677, 1638, 1586, 1559, 1471, 1439, 1353, 1302, 1281, 1245, 1217, 1167, 1144, 1127 and 1062. EIMS *m/z* (rel. int.): 236 $[M]^+$ (100), 208 (57), 179 (18), 153 (9), 127 (8), 102 (5), 90 (11), 76 (9), 63 (11), 51 (6) and 38 (4).

9-Methoxycanthin-6-one-3N-oxide (**12**). Pale yellow neddles, mp 258–260°. IR ν_{max} cm^{-1}: 1683, 1650, 1610, 1498, 1452, 1439, 1403, 1325, 1282, 1214, 1145 and 1031. EIMS *m/z* (rel. int.): 266 $[M]^+$ (100), 250 (31), 235 (4), 222 (19), 207 (12), 195 (13), 179 (23), 167 (6), 153 (9), 140 (7) and 126 (5).

Synthesis of **12**. 9-Methoxycanthin-6-one (**8**, 5 mg) was dissolved in $CHCl_3$ (1 ml), with *m*-chloroperbenzoic acid (5 mg) in $CHCl_3$ (1 ml) added. After 24 hr at room temp., the reaction mixt. was washed with 5% $NaHCO_3$ soln (5 ml). The organic layer was sepd and evapd to give pale yellow needles of (**12**) (4 mg).

3-Methylcanthin-5,6-dione (*picrasidine L*, **13**). Orange-red needles, mp > 300°. IR ν_{max} cm^{-1}: 1689, 1508, 1542, 1508, 1486, 1447, 1409, 1337, 1310 and 1218. EIMS *m/z* (rel. int.): 250 $[M]^+$ (69), 222 (87), 193 (100), 179 (5), 168 (33), 152 (8) and 140 (4).

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