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ALKALOIDS OF *ERYTHROXYLUM CUNEATUM*, *E. ECARINATUM* AND *E. AUSTRALE**

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Key Word Index—Erythroxylaceae; *Coelocarpus*; *Erythroxylum cuneatum*; *E. ecarinatum*; *E. australe*; tropane esters; 3α,6β-dibenzoyloxytropane; 3α-(4-hydroxyphenylacetoxy)tropane; 3-cinnamoyloxytropane-6,7-diol; methylecgonidine; nicotine; chemotaxonomy.

Abstract—From the leaves of *Erythroxylum cuneatum*, a new alkaloid (±)-3α,6β-dibenzoyloxytropane was isolated as principal alkaloid; four other benzoyl- and tigloyl-esters were obtained, together with nicotine. Three of these bases were also detected in the stem-bark. Tropacocaine was the principal alkaloid of *E. ecarinatum* leaves. *Erythroxylum australe* root-bark contained the new alkaloids 3α-(4-hydroxyphenylacetoxy)tropane and 3-cinnamoyloxytropane-6,7-diol, methylecgonidine as principal base, and other benzoyl- and cinnamoyl-esters.

INTRODUCTION

Section *Coelocarpus* O. E. Schulz [1] of the genus *Erythroxylum* contains some 16 species with a geographical distribution ranging from Australia through SE Asia and India to the eastern side of Africa. Few of the species have received a systematic phytochemical examination although a number have various, including medicinal, native uses [2]. Two such species are *E. cuneatum* (Wall.) Kurz and *E. ecarinatum* Burck. The former is a small tree, widely distributed in SE Asia, with reported uses as a fish poison on Luzon in the Philippines, and as a tonic on the Malay Peninsula [2]. Plowman and Rivier [3] detected neither cocaine nor cinnamoylcocaine in the leaves. *Erythroxylum ecarinatum* is known in Indonesia, New Guinea, the Solomon Islands and Queensland, Australia. The plant has local medicinal and other uses [2] and Australian material gave strongly positive field tests for alkaloids [4]. No detailed examination of the alkaloids of either of these species has been published. On the other hand *E. australe* F. Muell., a small tree of Queensland, has been more extensively studied. In 1889 Maiden [5] recorded that the plant contained no cocaine but that its red wood could be used in cabinet making and as a colourant for cotton and wool. Meteloidine (**3a**) is the principal alkaloid of the leaves [6] accompanied by smaller amounts of (±)-6β-hydroxy-3α-tigloyloxytropane (**2a**), 3α-hydroxy-6β-tigloyloxynortropane and a base tentatively identified as 7-hydroxy-6-(2-hydroxy-3-phenylpropionyloxy)-3α-tigloyloxynortropane [7]. The root contains 3α-benzoyloxytropane-6β,7β-diol (**3b**) [7] and the root-wood various stachene-related diterpenoids [8]. As a further contribution to our studies on the chemotaxonomy and pharmacologically active principles of the genus we now report our findings on the alkaloid composition of various morphological parts of these three species.

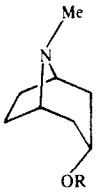
* Part 8 in the series 'Alkaloids of the Genus *Erythroxylum*'. For part 7 see ref. [9].

RESULTS AND DISCUSSION

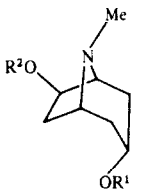
Five bases were characterized from the ether-soluble alkaloid fraction of *Erythroxylum cuneatum* leaves (Table 1). The principal alkaloid was the new natural base (±)-3α,6β-dibenzoyloxytropane (**2b**); its structure was elucidated by spectroscopy and by comparison with the base picrate prepared by partial synthesis. In contrast the corresponding ditigloyl ester found in most *Datura* species is optically active. 6β-Benzoyloxytropan-3α-ol (**2c**) has previously been reported as a constituent of *E. zambesiacum* root-bark [9], *E. glaucum*, *E. cumanense* [10] and *Knightia strobolina*, family Proteaceae [11]. Tropacocaine is a common constituent of the genus but 6β-tigloyloxytropan-3α-ol (**2d**), an alkaloid first isolated from *Datura cornigera* roots [12], has not previously been noted in *Erythroxylum* although its nor-derivative is a constituent of *E. australe* leaves [7]. Nicotine has previously been reported [13] in the young plants, and in roots and stems of mature plants, of *E. coca*; it also co-occurs with tropane alkaloids in section Salpiglossideae of the Solanaceae. The present report further demonstrates the apparent sporadic co-occurence in nature of these two ornithine-derived groups of alkaloids.

The two alkaloids obtained from *E. ecarinatum* leaves (Table 1), tropacocaine and 3α-benzoyloxynortropan-6β-ol, also co-occur in the leaves of *E. macrocarpum* and *E. sideroxyloides* (section Pachylobus) from Mauritius [14].

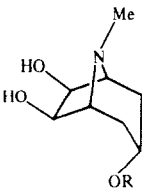
Methylecgonidine, the principal alkaloid of the root-bark of *E. australe* (Table 1), was originally isolated from the seeds of *E. coca* [15] and was later reported [16] from *E. dekindtii*. 3α-Benzoyloxytropane-6β,7β-diol (**3b**) originally recorded for this species by Griffin [7] has been confirmed for the current sample together with the detection, by mass spectroscopy, of its cinnamoyl analogue (**3c**), a base not previously known. The molecular ion ($C_{17}H_{21}NO_4$) and the ion at M−60 {M−[C(6)HOH −C(7)HOH]} clearly indicated a tropane-3,6,7-triol, esterified at C-3 by cinnamic acid (acylium ion at *m/z* 131). The structure of the second new alkaloid 3α-(4-hydroxyphenylacetoxy)tropane (**1a**) was determined by



1a R = 4-$HOC_6H_4CH_2CO$



2a R^1 = H(Me)C$\overset{*}{=}$C(Me)—CO, R^2 = H
2b R^1 = R^2 = PhCO
2c R^1 = H, R^2 = PhCO
2d R^1 = H, R^2 = H(Me)C$\overset{*}{=}$C(Me)—CO
2e R^1 = PhCH=CH—CO, R^2 = H



3a R = H(Me)C$\overset{*}{=}$C(Me)—CO
3b R = PhCO
3c R = PhCH=CH—CO

3c Stereochemistry unconfirmed

* *cis*

Table 1. Alkaloids of *Erythroxylum* sect. *Coelocarpus* O. E. Schulz

	Total alkaloid (% dry weight as tropacocaine)	Alkaloids characterized
Erythroxylum cuneatum		
Leaves	0.08	(±)-3α,6β-Dibenzoyloxytropane (**2b**) (new alkaloid); 6β-tigloyloxytropan-3α-ol (**2d**); tropacocaine; nicotine; uncharacterized base involving benzoyl moiety; 6β-benzoyloxytropan-3α-ol (**2c**)
Stem-bark	0.03	(±)-3α,6β-Dibenzoyloxytropane (**2b**); tropacocaine; nicotine
E. ecarinatum		
Leaves	0.11	Tropacocaine (principal alkaloid); 3α-benzoyloxynortropan-6β-ol
E. australe		
Root-bark	0.30	Methylecgonidine (principal alkaloid); 3α-(4-hydroxyphenylacetoxy)tropane (**1a**) (new alkaloid); 3-benzoyloxytropane-6,7-diol (**3b**); 3-cinnamoyloxytropane-6,7-diol (**3c**) (new alkaloid); 3α-cinnamoyloxytropan-6β-ol (**2e**); uncharacterized ester of tropine and acid ($C_9H_{10}O_3$)

spectroscopy. The molecular formula, $C_{16}H_{21}NO_3$, and the mass fragmentation pattern with ions at *m/z* 140 and 124 indicated a tropan-3-ol esterified with an acid $C_8H_8O_3$. The ^{1}H NMR spectrum showed a 3β-proton triplet at δ4.97; the singlet at δ3.51 and well-defined signals for a AA′XX′ aromatic proton system at δ 6.75 and 7.11, J = 8.5 Hz clearly established the ester as a 4-hydroxyphenylacetate. Supporting evidence for a hydroxyphenylacetate was provided by the ion at *m/z* 107 corresponding to $[HOC_6H_4CH_2CO-CO]^+$ [17]. This esterifying acid has not previously been observed in the genus but the corresponding 3-hydroxy-ester is a constituent of *E. hypericifolium* roots [17].

3α-Cinnamoyloxytropan-6β-ol (**2e**) was identified as a minor contaminant in the fraction containing the foregoing ester. By mass spectrometry the molecular formula was established as $C_{17}H_{21}NO_3$, and the ion at *m/z* 233, representing the loss of the CH_2–CHOH bridge, indicated a derivative of tropane-3,6-diol, with $C_9H_8O_2$ as the esterifying acid. The ^{1}H NMR signal at δ5.13 was a triplet, J = 5.1 Hz, consistent with a 3α-ester function; the 6β–OH stereochemistry followed from the coupling constants (J = 2.5, 7.4 Hz) for the 6α-^{1}H [17]. The acid residue gave signals for *trans*-alkene protons at δ6.42 and 7.66, J = 16 Hz, and for aromatic protons, in the ratio 2:3, at δ7.4 and 7.55. The (+)-3α,6β-stereoisomer occurs in *Knightia strobolina* (Proteaceae) [11] and as the major alkaloid in the leaves of *E. hypericifolium* [unpublished results]. Also isolated was an unidentified base, M_r 289, which was an ester of tropan-3-ol. As shown by TLC it was not a tropine ester of tropic acid, 2-hydroxy-3-phenylpropionic acid or 2-, 3- or 4-methoxyphenylacetic acids; the characteristics of the three latter compounds are recorded in the Experimental section. It is of interest that in 1949 Webb reported [4] *E. australe* to exhibit considerable variation in alkaloidal content according to the time and place of collection, a feature confirmed by a comparison of Griffin's study on the roots [7] with that of our own.

It has been suggested [9, 14] that the acids involved in the esterification of the tropanols might prove of intrageneric chemotaxonomic usefulness. In the three species of section Coelocarpus studied here benzoic acid appears to predominate and is probably of little chemotaxonomic significance. However the occurrence of tigloyl esters in two species is of interest as they have not so far been

reported in other sections. Further investigations are in progress.

EXPERIMENTAL

Plant material. Leaves and twigs of *E. cuneatum* (Wall.) Kurz collected from a single tree, Lower Bekerong Road, Changi Point, Singapore, Sept. 1980. Air-dried. Voucher: Evans s.n. lodged in City of Nottingham, Natural History Museum, Wollaton. *E. ecarinatum* leaves and twigs from tree, 20–30 m tall, Atherton Tablelands rain forest, 2 km from Yungaburra on road to Malanda, Queensland, Australia, Sept. 1981. Voucher: Plowman and Clarkson No. 10745, lodged in Field Museum of Natural History, Chicago, IL. *E. australe* F. Muell. roots collected Northern Queensland, Australia, 1967. Sample deposited at Pharmacy Department, University of Nottingham, U.K.

Extraction, fractionation and characterization of alkaloids. Ether-soluble alkaloids were extracted from plant material as previously described [10]. Total alkaloids were determined by titration and calculated as tropacocaine. The alkaloid mixtures were resolved by TLC (0.25 mm) and prep. TLC (0.5 mm) as follows: system A: silica gel with Me_2CO–H_2O–NH_4OH (sg 0.88) (80:15:2); system B: Al_2O_3 with Et_2O–EtOH (1:1); system C: Al_2O_3 with Et_2O; system D: silica gel with $CHCl_3$–Et_2NH (9:1). Instrumentation and chemical methods were as used previously [17].

E. cuneatum *leaves.* The leaves (360 g) gave 0.08% total ether-soluble alkaloids resolved into two main fractions by prep. TLC (system D). After further chromatography (system A) the first fraction afforded 6β-tigloyloxytropan-3α-ol (R_f values in three systems, mp, mmp of picrate, IR); EIMS *m/z*: 239.1551 (calc. for $C_{13}H_{21}NO_3$: M_r 239.1521) and 6β-benzoyloxytropan-3α-ol (R_f values, mp and mmp of picrate, IR); EIMS *m/z*: 261.1353 (calc. for $C_{15}H_{19}NO_3$: M_r 261.1365). The second main fraction gave four bases (a–d) by system A: (a) uncharacterized R_f 0.3 (system A); IR $\nu_{max}cm^{-1}$: 1715 (ester C=O); EIMS *m/z*: 122.0985 (calc. for $C_8H_{12}N$: 122.0970), 105.0338 (calc. for C_7H_5O: 105.0340); (b) tropacocaine (R_f values, mp, mmp of picrate, IR); EIMS *m/z*: 245.1423 $[M]^+$ (calc. for $C_{15}H_{19}NO_2$: M_r 245.1416); (c) nicotine [R_f (systems A, B and C) IR]; EIMS *m/z*: 162.1159 $[M]^+$ (calc. for $C_{10}H_{14}N_2$: M_r 162.1157); (d) characterized as (±)-3α,6β-dibenzoyloxytropane; R_f 0.94 (system A); picrate, mp 240° (plates from EtOH–H_2O), mmp with synthetic (±)-3α,6β-dibenzoyloxytropane picrate (mp 240°) 240° (Found: C, 56.2; H, 4.6; N, 9.4. $C_{22}H_{23}NO_4 \cdot C_6H_3N_3O_7$ requires C, 56.6; H, 4.4; N, 9.4%); IR (picrate) $\nu_{max}cm^{-1}$: 1725 (ester C=O); EIMS (probe) 70 eV, *m/z* (rel. int.): 365.1598 $[M]^+$ ($C_{22}H_{23}NO_4$ requires M_r 365.1627) (7), 229 [picric acid]$^+$ (18), 217.1100 (calc. for $C_{13}H_{15}NO_2$: 217.1103) (6), 138 (17), 122.0930 (calc. for $C_8H_{12}N$: 122.0969) (32), 122.0342 (calc. for $C_7H_6O_2$: 122.0368) (9), 105 (66), 94.0643 (calc. for C_6H_8N: 94.0656) (100). (±)-3α,6β-Dibenzoyloxytropane was prepared from (±)-3α,6β-dihydroxytropane and benzoyl chloride, picrate [plates from EtOH–H_2O (1:1)], mp 240° (found: C, 56.5; H, 4.7; N, 9.4%).

E. cuneatum *stem-bark.* Dried bark (27 g) afforded 0.03% ether-soluble alkaloids. Tropacocaine, nicotine and 3α,6β-dibenzoyloxytropane were identified by TLC (systems A, B and D).

E. ecarinatum *leaves.* Prep. TLC (system A) of the total ether-soluble alkaloids from 39 g of leaves gave two identifiable bases: (i) tropacocaine (TLC, mp, mmp of picrate, IR); EIMS *m/z*: 245.1412 $[M]^+$ (calc. for $C_{15}H_{19}NO_2$: M_r 245.1416]; (ii) 3α-benzoyloxynortropan-6β-ol [TLC, IR]; EIMS *m/z*: 247.1227 $[M]^+$ (calc. for $C_{14}H_{17}NO_3$: M_r 247.1208].

E. australe *root-bark.* The root-bark (280 g) gave 0.3% ether-soluble alkaloids separable into three groups (X, Y, Z) by prep. TLC (system B). Rechromatography of X (system A) gave a mixture which was recovered as picrate; it contained 3-benzoyloxytropane-6,7-diol and 3-cinnamoyloxytropane-6,7-diol (R_f 0.71; IR $\nu_{max}cm^{-1}$: 1710 (ester C=O), 3440 (OH)]; EIMS (probe) 70 eV, *m/z* (rel. int.): 303.1456 $[M_a]^+$ ($C_{17}H_{21}NO_4$ requires M_r 303.1471) (4), 277.1324 $[M_b]^+$ (calc. for $C_{15}H_{19}NO_4$: M_r 277.1314) (8), 243.1246 (calc. for $C_{15}H_{17}NO_2$: 243.1259 $[M_a - 60]$) (4), 229 (picric acid)$^+$ (50), 217.1104 (calc. for $C_{13}H_{15}NO_2$: 217.1103 $[M_b - 60]$) (10), 131.0502 (calc. for C_9H_7O: 131.0497) (5), 105.0295 (calc. for C_7H_5O: 105.0340) (15), 95.0714 (calc. for C_6H_9N: 95.0735) (100), 91 (11). Y gave by rechromatography (system D) two fractions. The first was a mixture of 3α-(4-hydroxyphenylacetoxy)tropane, IR $\nu_{max}cm^{-1}$: 1725 (ester C=O), 3420 (OH); EIMS (probe), 70 eV, *m/z* (rel. int): 275.1494 $[M]^+$ ($C_{16}H_{21}NO_3$ requires M_r 275.1521) (39), 140.1071 (calc. for $C_8H_{14}NO$: 140.1071) (28), 124.1123 (calc. for $C_8H_{14}N$: 124.1126) (100), 107.0433 (calc. for C_7H_7O: 107.0497) $[HOC_6H_4CH_2CO]^+$ (13); ^1H NMR (250 MHz, $CDCl_3$) base recovered from picrate: δ1.58, 1.65, 1.84, 2.2 (4 × *m*, H_2-2, H_2-4, H_2-6, H_2-7), 2.59 (3H, *s*, NMe), 3.1 (2H, *br s*, H-5, H-1), 3.51 (2H, *s*, $ArCH_2CO$), 4.97 (1H, *t*, $J = 5.2$ Hz, H-3β), 6.75 (2H, *d*, $J = 8.5$ Hz, ArH_2), 7.11 (2H, *d*, $J = 8.5$ Hz, ArH_2) and a small amount of 3α-cinnamoyloxytropan-6β-ol; EIMS (probe) 70 eV, *m/z*: 287.1514 $[M]^+$ ($C_{17}H_{21}NO_3$ requires M_r 287.1521), 243 $[M-(CH_2-CHOH)]^+$, 131 $[ArCH{=}CHCO]^+$; ^1H NMR (250 MHz, $CDCl_3$), base recovered from picrate: δ2.29 (3H, *s*, NMe), 2.35 (1H, *s*, exch. D_2O, OH-6), 3.40 (1H, *br s*, H-5), 4.64 (1H, *dd*, $J_{6\alpha,7\beta} = 2.5$ Hz, $J_{6\alpha,7\alpha} = 7.4$ Hz, H-6), 5.13 (1H, *t*, $J = 5.1$ Hz, H-3β), 6.42 and 7.66 (2 × H, 2 × *d*, $J = 16$ Hz, *trans* CH=CH), 7.4 (2H, *m*, *m*-ArH_2), 7.55 (3H, *m*, *o*- and *p*-ArH_3), signals for H_2-2, H_2-4, H-5 submerged under peaks for similar protons in the foregoing 4-hydroxyphenylacetate. The second fraction of Y gave IR $\nu_{max}cm^{-1}$: 1735 (ester C=O), 3460 (?OH); EIMS (probe) 70 eV, *m/z* (rel. int.): 289.1688 $[M]^+$ ($C_{17}H_{23}NO_3$ requires M_r 289.1678) (5), 140.1082 (calc. for $C_8H_{14}NO$: 140.1075) (13), 125 (9), 124.1122 (calc. for $C_8H_{14}N$: 124.1126) (100), 96 (17), 94 (19). This base was dissimilar (R_f values) to hyoscyamine and littorine and to the 2-, 3- and 4-methoxyphenylacetates of tropine. Fraction Z gave methylecgonidine (TLC, mp, mmp, IR); EIMS *m/z*: 181.1102 (calc. for $C_{10}H_{15}NO$: M_r 181.1103).

Preparation of 2-, 3- *and* 4-*methoxyphenylacetates of tropine.* By the method of Hassner and Alexanian [18] esters were prepared by direct esterification of tropine with the relevant acid. The basic products were purified by prep. TLC (system A) and picrates (from EtOH) prepared by standard methods.

3α-(2-*Methoxyphenylacetoxy*)*tropane picrate*, mp 210° (Found: C, 53.4; H, 4.9; N, 10.5. $C_{17}H_{23}NO_3 \cdot C_6H_3N_3O_7$ requires C, 53.3; H, 5.05; N, 10.8%). 3α-(3-Methoxyphenylacetoxy)tropane picrate, mp 152° (Found C, 53.5; H, 5.1; N, 10.9%). 3α-(4-Methoxyphenylacetoxy)tropane picrate, mp 173° (Found: C, 53.2; H, 5.0; N, 10.4%).

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