

Alkaloids of the Genus *Erythroxylum*. Part 1. *E. monogynum* Roxb. Roots

By Joseph T. H. Agar and William C. Evans,* Department of Pharmacy, The University, Nottingham NG7 2RD

Three new bases from the root-bark of *Erythroxylum monogynum* have been identified on the basis of chemical and spectroscopic evidence; they are 1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxybenzoate, 1 α H,5 α H-tropane-3 α ,6 β -diol 3-(3,4,5-trimethoxycinnamate) 6-benzoate, and 1 α H,5 α H-tropane-3 α ,6 β ,7 β -triol 3-(3,4,5-trimethoxybenzoate). 1 α H,5 α H-Tropan-3 α -yl 3,4,5-trimethoxycinnamate was also isolated. Alkaloids were not detected in the root-wood.

FROM the leaves of the Indian tree *Erythroxylum monogynum* Roxb. (Erythroxylaceae), (–)-ecgonine and

¹ R. N. Chopra and N. N. Ghosh, *Arch. Pharm.*, 1938, **276**, 340.

² J. C. Fairlie, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. (C)*, 1969, 2115, and references cited therein.

cinnamylcocaine have been isolated;¹ the stem-wood is a source of terpenoids.² We have noted³ the presence, in the root-bark, of a number of new alkaloids including

³ J. T. H. Agar, W. C. Evans, and P. G. Tregust, *J. Pharm. Pharmacol.*, 1974, **26**, Suppl., 111P.

1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxybenzoate; the known bases 1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxycinnamate, tropine, and ψ -tropine were also recorded. We present here the evidence for the structures of the new alkaloids.

Partition, and preparative t.l.c. of the root-bark extract afforded seven principal basic fractions representing 0.85% of the dried material. A fraction having R_F 0.48 (system C; see Experimental section) gave a crystalline hydrobromide, $C_{18}H_{25}NO_5 \cdot HBr$, and a picrate. Alkaline hydrolysis of the base gave tropine (1) and 3,4,5-trimethoxybenzoic acid; this observation, supplemented by n.m.r. and mass spectroscopic measurements, and by partial synthesis, established the new base as 1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxybenzoate. The 3 β -isomer possessed properties (R_F values, m.p., and n.m.r. data) dissimilar to those of the natural product and its presence in the root-bark was not detected.

A base of R_F 0.35 (system C), isolated as the picrate, was identified as 1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxycinnamate (3), which has been reported as a constituent of *Erythroxylum ellipticum* leaves.⁴ It was compared with the analogous 3 β -compound which appeared to be absent from the bark.

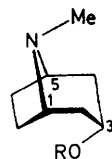
The non-crystalline base, $C_{27}H_{31}NO_7$, of highest R_F (0.90; system C) possessed a substituted hydroxytropane nucleus (mass spectrum), two dissimilar carbonyl groups, and substituted aromatic systems (i.r.). Hydrolysis gave benzoic acid, 3,4,5-trimethoxycinnamic acid and tropane-3 α ,6 β -diol (4). These units were clearly accommodated in the mass spectrum and an ion of m/e 333, consistent with structure (11) (cf. ref. 5) established the presence of the trimethoxycinnamoyl group at C-3; no peak at m/e 217 was observed thus eliminating benzoyl-substitution at this position. On this evidence, the alkaloid can be identified as 1 α H,5 α H-tropane-3 α ,6 β -diol 3-(3,4,5-trimethoxycinnamate) 6-benzoate (5). The determination of its optical rotation was precluded by the small amount of sample available. The structure was confirmed by partial synthesis of the (\pm)-isomer from (\pm)-6 β -hydroxytropan-3-one (7). Conversion of this ketone into the benzoyl derivative (8) followed by stereospecific reduction with Raney nickel (W-7) and hydrogen yielded tropane-3 α ,6 β -diol 6-benzoate (6). The 3 α -orientation of the hydroxy-group was confirmed by n.m.r. spectroscopy (triplet, $W_{\frac{1}{2}}$ 13 Hz, at δ 4.16; cf. quintet, $W_{\frac{1}{2}}$ ca. 28 Hz for 3 β -derivatives). Esterification with trimethoxycinnamoyl chloride yielded the diester, (\pm)-(5), which possessed the same i.r. and mass spectroscopic properties and R_F values as the natural base; the product gave a picrate, $C_{27}H_{31}NO_7 \cdot C_6H_3N_3O_7$, with m.p. 5 °C greater than that of the picrate of the natural compound.

A fourth crystalline base of R_F 0.17 (system C) had

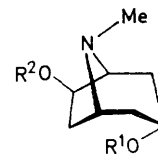
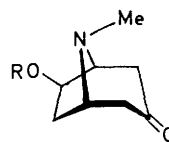
⁴ S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 421.

⁵ E. C. Blossy, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, 1964, **20**, 585.

ester (ν_{\max} 1700 cm^{-1}) and free hydroxy-group (ν_{\max} 3400 cm^{-1}) i.r. absorption. Mass spectrometry of the picrate gave, for the base, the molecular formula $C_{18}H_{25}NO_7$; other ions indicated the presence of trimethoxybenzoic acid and tropane-3 α ,6 β ,7 β -triol (9) units. Hydrolysis afforded the relevant acid and the triol. An

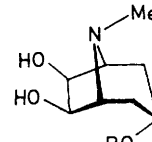


(1) R = H

(2) R = (MeO)₃C₆H₂·CO (Tmb)(3) R = (MeO)₃C₆H₂·CH:CH·CO (Tmc)(4) R¹ = R² = H(5) R¹ = Tmc, R² = Bz(6) R¹ = H, R² = Bz

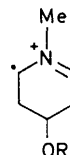
(7) R = H

(8) R = Bz



(9) R = H

(10) R = Tmb

(11) m/e 333, R = Tmc(12) m/e 307, R = Tmb

ion at m/e 307 in the mass spectrum was consistent with the fragment (12), which would arise from an esterifying substituent of teloidine at C-3. The α -orientation of the trimethoxybenzoyl moiety was indicated by the bandwidth ($W_{\frac{1}{2}}$ 14 Hz) of the H-3 n.m.r. signal at δ 5.23; integration showed the presence of two hydroxy-groups. From the above it follows that this new alkaloid is 1 α H,5 α H-tropane-3 α ,6 β ,7 β -triol 3-(3,4,5-trimethoxybenzoate) (10).

A number of other bases were detected in other fractions of the chromatographed plant extract, but their small quantity and their isolation as mixtures, have so far precluded their precise identification. Extracts of the root-wood, after fractionation by t.l.c., did not give positive results in tests for alkaloids.

The considerable range of tropane ester alkaloids present in the root-bark of *E. monogynum* is noteworthy; to date, only in *Datura* and *Anthocercis*,⁶ of the Solanaceae, has the co-occurrence of tropine, dihydroxytropane, and teloidine esters also been recorded. *Erythroxylum*, in common with these genera, possesses free ψ -tropine and tropine in the roots but only the latter also occurs as a variety of esters. Outside *Datura*, *Erythroxylum*

⁶ W. C. Evans, A. Ghani, and V. A. Woolley, *Phytochemistry*, 1972, **11**, 2527; W. C. Evans and P. G. Treagust, *ibid.*, 1973, **12**, 2505.

appears to be the first genus from which a bisacyloxytropine involving two different acids has been isolated; a full survey of alkaloids within the genus (*ca.* 200 spp.) may well offer considerable chemotaxonomic interest.

EXPERIMENTAL

I.r. spectra (KBr discs) were recorded with a Unicam SP 200 instrument; n.m.r. spectra were obtained for solutions in CDCl_3 with a Perkin-Elmer R 10 spectrometer (tetramethylsilane as internal standard); mass spectra were determined with A.E.I. MS902 and MS9 instruments. G.l.c. was performed with a Pye 104 series chromatograph (OV-101 on a solid, silanised support). For t.l.c. and p.l.c. alumina (Merck G) plates with (A) ether; (B) ether-ethanol (1:1); or (C) chloroform-ethanol (98:2), and (D) silica plates with acetone-ammonia (s.g. 0.88) (4:1) were used. Separated alkaloids were detected with u.v. light and iodoplatinate reagent. The conditions for the hydrolysis of esters were as recorded previously.⁷

Plant Material.—Dried root-bark and herbarium specimens were obtained from the region of Madras and Coimbatore, India.

Extraction of Alkaloids.—In typical experiments powdered root-bark (100 g) was mixed with calcium hydroxide (20 g) and water (40 ml), set aside overnight, and exhaustively extracted with ether (4 l). The concentrated extract (25 ml) was passed through kieselguhr (15 g) supporting 1N-sulphuric acid (7.5 ml). After extraneous material had been washed from the column with ether, the bases were collected in ammoniacal chloroform. Evaporation afforded a crude alkaloid mixture which, in ether (2 ml), was submitted to partition chromatography at pH 8.0 and partially fractionated by successive elution with light petroleum (b.p. 40–60°), ether, and chloroform. Pure alkaloids were obtained by the use of a second partition column and by p.l.c. (system C).

1 α H,5 α H-Tropan-3 α -yl 3,4,5-Trimethoxybenzoate (2).—A base isolated by p.l.c. and having R_F 0.48 (system C) afforded a *hydrobromide*, fine needles from ethanol, m.p. 212° (decomp.) (Found: C, 51.7; H, 6.3; N, 3.4. $\text{C}_{18}\text{H}_{25}\text{NO}_5\cdot\text{HBr}$ requires C, 51.9; H, 6.3; N, 3.4%), and a *picrate*, prisms from aqueous ethanol, m.p. 201° (Found: C, 50.7; H, 5.1; N, 9.8. $\text{C}_{18}\text{H}_{25}\text{NO}_5\cdot\text{C}_6\text{H}_3\text{N}_3\text{O}_7$ requires C, 51.1; H, 5.0; N, 9.9%), ν_{max} 1700 cm^{-1} (ester C=O), *m/e* 42, 82, 83, 94, 96, and 124 (100%) (characteristic of tropine esters),⁵ 212 (14%, trimethoxybenzoic acid), 195 (15%, acyl unit), and 335 (39%, M^+). The base recovered from the picrate showed δ 1.64br, 1.79br, and 2.00 (8 H, s, s, and m, respectively, 2-, 4-, 6-, and 7- H_2), 2.21 (3 H, s, NMe), 3.06br (2 H, m, 1- and 5-H), 3.99 (9 H, s, 3 \times OMe), 5.12 (1 H, t, $W_{\frac{1}{2}}$ 11 Hz, 3 β -H), and 7.17 (2 H, s, ArH). Alkaline hydrolysis of the base (0.02 g) gave 3,4,5-trimethoxybenzoic acid (0.01 g), m.p. and mixed m.p. 170°, identical (i.r., mass, and n.m.r. spectra) with authentic material (Found: C, 56.5; H, 6.0. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_5$: C, 56.6; H, 5.7%), and tropine, identical (R_F in system D, and R_F and i.r. spectrum of tigloyl ester) with authentic material.

Tropine (0.1 g) and 3,4,5-trimethoxybenzoyl chloride (0.27 g) were intimately mixed and maintained at 100 °C for 6 h. The resulting solid mixture was dispersed in ammonia solution (30 ml; 5N) and liberated basic material was collected in chloroform (3 \times 30 ml). Evaporation and p.l.c. gave a product which, on treatment of the sulphate with sodium picrate solution, furnished 1 α H,5 α H-tropan-3 α -yl 3,4,5-trimethoxybenzoate *picrate* (0.082 g), m.p. 201° (Found:

C, 50.9; H, 5.3; N, 9.3%), identical with the natural derivative (m.p., mixed m.p., and i.r., n.m.r., and mass spectra).

The 3 β -Isomer of the Base (2).—Esterification of ψ -tropine with 3,4,5-trimethoxybenzoyl chloride as above, followed by picrate formation, gave 1 α H,5 α H-tropan-3 β -yl 3,4,5-trimethoxybenzoate *picrate*, prisms from aqueous ethanol, m.p. 226° (Found: C, 51.4; H, 5.2; N, 9.8%). The base, needles, m.p. 98°, had R_F 0.75 (system C), δ 5.16 (1 H, m, $W_{\frac{1}{2}}$ 21 Hz, 3 α -H).

1 α H,5 α H-Tropan-3 α -yl 3,4,5-Trimethoxycinnamate (3).—This base, R_F 0.35 (system C), was isolated by p.l.c. of components of ethereal eluates from partition columns, and was identified by i.r., n.m.r., and mass spectroscopy (Found: M^+ , 361.1899. Calc. for $\text{C}_{20}\text{H}_{27}\text{NO}_5$: M , 361.1899). The alkaloid formed a *picrate*, prisms from aqueous ethanol, m.p. 210° (Found: C, 52.5; H, 5.0; N, 9.1. $\text{C}_{20}\text{H}_{27}\text{NO}_5\cdot\text{C}_6\text{H}_3\text{N}_3\text{O}_7$ requires C, 52.9; H, 5.1; N, 9.5%). The product resulting from esterification of the tropine and 3,4,5-trimethoxycinnamoyl chloride [as for the trimethoxybenzoate (2)] gave a picrate (0.090 g), m.p. 210°, identical with that derived from the natural product (Found: C, 53.0; H, 5.0; N, 9.5%).

The 3 β -Isomer of the Base (3).—Esterification of ψ -tropine with 3,4,5-trimethoxycinnamoyl chloride, as above, gave a base, R_F 0.73 (system C), which furnished with sodium picrate solution 1 α H,5 α H-tropan-3 β -yl 3,4,5-trimethoxybenzoate *picrate*, small prisms from aqueous ethanol, m.p. 253° (decomp.) (Found: C, 51.8; H, 5.8; N, 8.9%).

1 α H,5 α H-Tropane-3 α ,6 β -diol 3-(3,4,5-Trimethoxycinnamate) 6-Benzoate (5).—P.l.c. of the combined light petroleum eluates from partition columns gave basic material (5) (R_F 0.9 in system C) which on salt formation yielded a *hydrobromide*, prisms from hot water, m.p. 195–200° (Found: M^+ , for basic unit, 481.2091. $\text{C}_{27}\text{H}_{31}\text{NO}_7$ requires M , 481.2101), ν_{max} 1701 (doublet, 2 \times ester C=O) and 1624 cm^{-1} (CH=CH), and an *aureichloride*, plates from dilute hydrochloric acid, m.p. 148° (Found: M^+ , for basic unit, 481.2105), *m/e* (characteristic signals from spectra of aureichloride and hydrobromide) 105 ($\text{C}_6\text{H}_5\cdot\text{CO}$) 122.0365 (Calc. for PhCO_2H : 122.0368), 221.0811 [Calc. for $(\text{MeO})_3\cdot\text{C}_6\text{H}_2\cdot\text{CH}\cdot\text{CH}\cdot\text{CO}$ 221.0813], 238 [$(\text{MeO})_3\cdot\text{C}_6\text{H}_2\cdot\text{CH}\cdot\text{CH}\cdot\text{CO}_2\text{H}$], and 333.1564 [$\text{C}_{18}\text{H}_{23}\text{NO}_5$, formula (11), requires 333.1576]. The picrate, prisms from aqueous ethanol, had m.p. 224°. The products of alkaline hydrolysis of the new base were examined by g.l.c. The components of the mixed acid fraction, in ether, after conversion into their methyl esters with diazomethane, had the same retention times as methyl benzoate and methyl 3,4,5-trimethoxycinnamate; the basic unit, recovered from aqueous solution, gave peak enhancement when mixed with, and had the same retention time as (\pm)-1 α H,5 α H-tropane-3 α ,6 β -diol.

(\pm)-1 α H,5 α H-tropane-3 α ,6 β -diol 6-benzoate (6) (0.25 g), mixed with an excess of 3,4,5-trimethoxycinnamoyl chloride (0.7 g) and maintained at 100 °C for 2 h under a dry air stream, gave, after p.l.c. (system A), a base (5) characterised as the *picrate*, prisms from aqueous ethanol, m.p. 228° (Found: C, 55.6; H, 5.1; N, 7.3. $\text{C}_{27}\text{H}_{31}\text{NO}_7\cdot\text{C}_6\text{H}_3\text{N}_3\text{O}_7$ requires C, 55.8; H, 4.8; N, 7.9%). The i.r. and mass spectroscopic data of this compound were the same as for the natural product derivatives; mixed m.p. 225°.

1 α H,5 α H-Tropane-3 α ,6 β -diol 6-Benzoate (6).—(\pm)-6 β -Hydroxytropan-3-one (7) (2.0 g) was treated (140 °C; 1 h) with benzoyl chloride (1.6 g), the mixture in chloroform was

⁷ W. C. Evans and V. A. Major, *J. Chem. Soc. (C)*, 1966, 1621.

washed with sodium carbonate solution (2N; 3 × 30 ml), and basic material was isolated by standard procedures. P.l.c. (system C) and recovery of the alkaloid, R_F 0.90 (system B), gave 3-oxotropan-6 β -yl benzoate (8), isolated as the *picrate* (1.2 g), prisms from aqueous ethanol, m.p. 172° (Found: C, 51.6; H, 4.3; N, 11.2. $C_{15}H_{17}NO_3 \cdot C_6H_5N_3O_7$, requires C, 51.6; H, 4.1; N, 11.5%), ν_{max} 1710 cm^{-1} (doublet, 2 × C=O), m/e 84, 112, 138, 154, and 259 (M^+). The ketone (8) (0.5 g) on reduction with hydrogen and Raney nickel (W-7) at room temperature and atmospheric pressure for 18 h gave a base (6) isolated as (\pm)-1 α H,5 α H-tropane-3 α ,6 β -diol 6-benzoate *picrate* (0.27 g), prisms from aqueous ethanol, m.p. 203° (Found: C, 51.1; H, 4.5; N, 11.7. $C_{15}H_{19}NO_3 \cdot C_6H_5N_3O_7$, requires C, 51.4; H, 4.5; N, 11.5%), ν_{max} 1695 (C=O) and 3410 cm^{-1} (OH), δ 1.7–2.5 (6 H, m, 2-, 4-, and 7-H₂), 2.58 (1 H, s, 3-OH, lost on deuteration), 2.71 (3 H, s, NCH₃), 3.49 (2 H, m, 1- and 5-H), 4.16 (1 H, t, $W_{\frac{1}{2}}$ 14 Hz, 3-H), 5.94 (1 H, q, 6-H), 7.51 (3 H, m, aromatic *m*- and *p*-H), and 8.05 (2 H, m, aromatic *o*-H), m/e 96, 113, 156, and 261 (M^+).

1 α H,5 α H-Tropane-3 α ,6 β ,7 β -triol 3-(3,4,5-Trimethoxybenzoate) (10).—The first fractions of the chloroform eluate of a partition column, pH 6.8, used for the resolution of a crude alkaloid fraction afforded a crystalline solid, m.p. 112°; the solid (10) was characterised as the *picrate*, prisms from

aqueous ethanol, m.p. 188° (Found: M^+ , 367.1621. $C_{18}H_{25}NO_7$, requires M , 367.1631), ν_{max} 1700 (ester C=O) and 3380 cm^{-1} (OH). The base (10), recovered from the *picrate*, showed δ 2.56 (3 H, s, NCH₃), 3.12br (2 H, s, 1- and 5-H), 3.92 (9 H, s, OCH₃), 4.56 (2 H, s, 6- and 7-OH), 5.23 (1 H, m, $W_{\frac{1}{2}}$ 14 Hz, 3-H), and 6.73 (2 H, s, aromatic *o*-H), m/e 172 (teloidine unit, $C_8H_{14}NO_3$), 195 [(MeO)₃C₆H₂CO], 212.0684 (calc. for $C_{10}H_{12}O_5$: 212.0685), and 307 [(MeO)₃C₆H₂CO·O·C₆H₁₀N]. Hydrolysis of the base (24 mg) with aqueous barium hydroxide gave 3,4,5-trimethoxybenzoic acid (9 mg), m.p. and mixed m.p. 171°, M^+ 212, identical (i.r. spectrum) with the authentic compound, together with tropane-3 α ,6 β ,7 β -triol (9), identical (R_F values of free base and its triacetate) with an authentic specimen.

Root-wood.—The powdered root-wood (1 g), treated with calcium hydroxide (0.2 g) and water (0.4 ml), was exhausted with ether and submitted to standard procedures for the isolation of alkaloids. Thin-layer chromatograms (system C) of the extract were sprayed with iodine and iodoplatinate reagents.

We are indebted to Dr. C. L. Madan, Jammu Tawi, and the Tropical Products Institute, London, for the supply of plant material.

[6/121 Received, 19th January, 1976]