The Structure of Crotonitenone, a Novel Casbane Diterpene from *Croton nitens* Sw. (Euphorbiaceae)
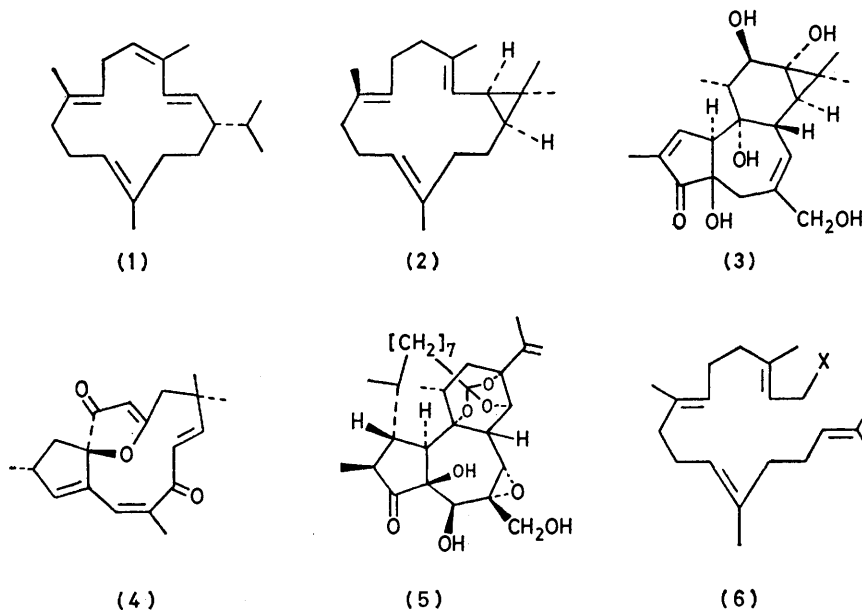
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A novel casbane diterpene, crotonitenone {(*E*)-(1*R**,5*S**,7*R**,11*S**,14*S**)-5-hydroxy-3,7,11,15,15-pentamethyl-bicyclo[12.1.0]pentadec-2-ene-4,8-dione} (7), $C_{20}H_{32}O_3$, has been isolated from *Croton nitens* (Euphorbiaceae) and its structure and relative stereochemistry have been established by chemical, spectral, and X-ray crystallographic means. Crystals of (7) are monoclinic, space group $P2_1$, with $a = 12.446(1)$, $b = 13.285(1)$, $c = 5.872(1)$ Å, $\beta = 97.02(1)°$, and $Z = 2$. The structure was refined by least squares to R 0.040 and R' 0.038.

THE macrocyclic diterpenes cembrene (1)[1] and casbene (2)[2] are 14-membered ring compounds that are regarded as the progenitors of a wide variety of natural products, many of which display pronounced biological activity. Prominent among these compounds are the diterpenes that are formally derived from casbene by transannular cyclisation and shown to be responsible for

the co-carcinogenic, antileukemic, and irritant properties associated with certain members of the Euphorbiaceae and the Thymelaeaceae.[3] Examples are the esters of phorbol (3) (cocarcinogens),[4] jatrophone (4) (antileukemic),[5] and the *Pimelea* factors, *e.g.*, (5) (irritants).[6] Cembrene and casene are most probably derived by head-to-tail cyclisation of a geranyl-geranyl precursor (6).

Although cembrenoids are abundant,[7] it is surprising that no other natural product possessing the casbene skeleton has been isolated. Casbene itself is rare. Its only source to date has been cell-free extracts of castor bean (*Ricinus communis*, Euphorbiaceae) seedlings. The

original isolation by Robinson and West[2] yielded only 3.2 mg of casbene from 10 000 seedlings, a yield that was subsequently increased when the seedlings were exposed to certain fungi.[8] Because of the small quantity of casbene that was isolated originally, the stereochemistry was not defined with complete assurance. However, a recent synthesis[9] provides evidence for the stereochem-


(1)

(2)

(3)

(4)

(5)

(6)

istry indicated in (2). In the present paper we report the isolation and structural characterization of crotonitenone (7), which appears to be the first naturally occurring oxygenated derivative of casbene to be isolated. Crotonitenone was obtained from the dried leaves and twigs of *Croton nitens* (Euphorbiaceae)[10] during an investigation aimed at finding precursors of the crotofolanes, *e.g.*, (10).[11]

Crotonitenone (7) has the molecular formula $C_{20}H_{32}O_3$ (from elemental and mass spectral analyses). Its infrared spectrum disclosed the presence of hydroxy ($\nu_{max.}$ 3 430 cm⁻¹), saturated carbonyl (1 710 cm⁻¹), and $\alpha\beta$-unsaturated carbonyl (1 650 and 1 620 cm⁻¹) groups.

The presence of a one-proton doublet of doublets at δ 4.54 (*J* 7 and 1 Hz) in the ¹H n.m.r. spectrum suggested

that the alcohol group in crotonitenone was secondary. This was confirmed by conversion of (7) into the acetate (8), in which the absorption at δ 4.54 was shifted to δ 5.26, and by Jones oxidation, which gave the triketone (9). The ^{1}H n.m.r. spectrum of (7) also showed absorption due to the presence of two secondary methyl groups [two 3 H doublets at δ 0.92 and 1.15 ($J = 7$ Hz)], geminal methyl groups on the cyclopropane ring (3 H singlets at δ 0.94 and 1.17), a vinylic methyl group [3 H doublet at δ 1.91 (J 2 Hz)], and an olefinic proton whose chemical shift [doublet at δ 6.11 ($J = 10$ Hz)] indicated that it was

(7) R = OH
(8) R = OAc
(9) R = =O

(10)
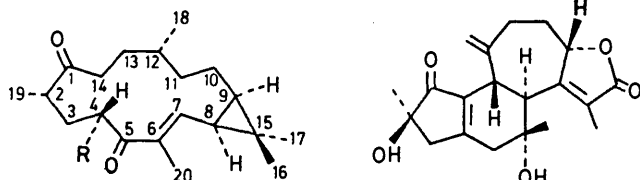
β to a carbonyl group. The appearance of this β-proton, together with a u.v. maximum of 267 (ε 16 000) nm in crotonitenone, suggested the presence of the cyclopropyl enone moiety common to many of the lathyranes.[12]

The presence of the above structural features was substantiated by examination of the ^{13}C n.m.r. (CDCl₃, p.p.m.) spectrum of (7). Thus, there were absorptions due to five methyl carbons (quartets at δ 12.3, 16.25, 17.83, 20.83, and 29.23), five methylene carbons (triplets at δ 23.25, 26.51, 30.18, 33.50, and 42.39), and five methine carbons (doublets at δ 27.60, 31.55, 34.00, 45.16, and 69.77); the absorption at δ 69.77 was due to the secondary carbon bearing the hydroxy-group, i.e., C-4. A singlet at δ 27.10 is ascribed to a fully substituted sp³ carbon (C-15), while absorptions due to two olefinic carbons appeared as a singlet at δ 134.85 (C-6) and as a doublet at δ 142.76 (C-7). Absorptions due to the carbonyl carbons were observed at δ 201.74 (C-5) and 213.63 (C-1).

The relationship between the αβ-unsaturated ketone and the hydroxy-group in (7) was established by Jones oxidation, which gave the triketone (9) as pale yellow crystals having $\lambda_{max.}$ 292 and 227 nm (ε 18 285 and 7 950, respectively); (9) was readily reduced with zinc–acetic acid to give crotonitenone (7).

The structure and relative stereochemistry of crotonitenone (7) were eventually established by a single-crystal X-ray analysis using direct methods. Details of the X-ray analysis are given in the Experimental section and listings of final atom parameters, bond lengths, bond angles, and torsion angles are given in Tables 1—4. An ORTEP perspective drawing of (7) as determined from the X-ray crystallographic analysis is displayed in the Figure. As can be seen from the Figure, the cyclopropane ring in (7) is cis and the double bond is E. These stereochemical features are also present in casbene.

TABLE 1

Final atomic parameters for compound (7) with standard deviations in parentheses

Atom	x	y	z	B
O(1)	0.077 6(3)	0.5011	0.400 4(5)	
O(2)	0.342 8(3)	0.460 8(4)	0.193 2(5)	
O(3)	0.503 5(3)	0.349 6(4)	0.358 1(5)	
C(1)	0.133 7(4)	0.530 8(5)	0.569 0(8)	
C(2)	0.244 1(4)	0.575 8(4)	0.552 2(7)	
C(3)	0.332 6(3)	0.495 3(4)	0.594 7(7)	
C(4)	0.331 7(3)	0.415 0(4)	0.408 2(7)	
C(5)	0.427 2(3)	0.343 4(5)	0.469 3(7)	
C(6)	0.429 2(4)	0.273 3(4)	0.664 8(7)	
C(7)	0.338 4(4)	0.245 9(5)	0.744 1(7)	
C(8)	0.332 3(4)	0.180 6(5)	0.945 9(7)	
C(9)	0.224 2(4)	0.152 9(5)	1.023 1(7)	
C(10)	0.120 6(4)	0.191 2(5)	0.892 7(8)	
C(11)	0.094 1(4)	0.299 1(5)	0.952 7(8)	
C(12)	0.007 0(3)	0.348 2(5)	0.782 0(7)	
C(13)	−0.004 1(4)	0.460 2(5)	0.822 2(7)	
C(14)	0.095 9(3)	0.524 0(5)	0.806 1(7)	
C(15)	0.291 1(4)	0.072 7(5)	0.932 5(8)	
C(16)	0.255 7(4)	0.024 3(5)	0.702 6(9)	
C(17)	0.351 7(4)	0.001 2(5)	1.104 1(9)	
C(18)	−0.100 4(4)	0.297 7(5)	0.792 4(10)	
C(19)	0.269 9(4)	0.665 2(5)	0.715 2(8)	
C(20)	0.538 4(4)	0.234 5(5)	0.761 9(8)	
HO(2)	0.409	0.439	0.168	7.0
H(2)	0.245	0.603	0.388	5.0
H(3)A	0.324	0.463	0.751	6.0
H(3)B	0.407	0.530	0.617	6.0
H(4)	0.258	0.377	0.396	6.0
H(7)	0.268	0.277	0.666	6.0
H(8)	0.392	0.193	1.073	6.0
H(9)	0.223	0.154	1.202	6.0
H(10)A	0.128	0.190	0.722	6.0
H(10)B	0.057	0.148	0.918	6.0
H(11)A	0.068	0.301	1.109	6.0
H(11)B	0.162	0.342	0.960	6.0
H(12)	0.030	0.337	0.626	6.0
H(13)A	−0.063	0.490	0.704	6.0
H(13B)	−0.029	0.474	0.979	6.0
H(14)A	0.085	0.596	0.862	6.0
H(14B)	0.158	0.495	0.917	6.0
H(16A)	0.318	−0.003	0.629	9.0
H(16)B	0.217	0.076	0.591	9.0
H(16)C	0.203	−0.032	0.718	9.0
H(17)A	0.372	0.035	1.253	8.0
H(17)B	0.414	−0.029	1.044	8.0
H(17C)	0.298	−0.056	1.132	8.0
H(18)A	−0.126	0.304	0.952	10.0
H(18)B	−0.104	0.226	0.749	10.0
H(18)C	−0.161	0.335	0.684	10.0
H(19)A	0.268	0.647	0.878	9.0
H(19)B	0.223	0.726	0.676	9.0
H(19)C	0.349	0.691	0.705	9.0
H(20)A	0.574	0.280	0.892	8.0
H(20)B	0.590	0.232	0.643	8.0
H(20)C	0.534	0.165	0.831	8.0

TABLE 2

Bond lengths (Å) for compound (7) with standard deviations in parentheses

O(1)–C(1)	1.206(5)	C(7)–C(8)	1.479(7)
O(2)–C(4)	1.423(6)	C(8)–C(9)	1.517(7)
O(3)–C(5)	1.219(6)	C(8)–C(15)	1.521(9)
C(1)–C(2)	1.512(7)	C(9)–C(10)	1.506(7)
C(1)–C(14)	1.526(6)	C(9)–C(15)	1.490(8)
C(2)–C(3)	1.535(7)	C(10)–C(11)	1.522(9)
C(2)–C(19)	1.534(8)	C(11)–C(12)	1.530(6)
C(3)–C(4)	1.528(7)	C(12)–C(13)	1.515(9)
C(4)–C(5)	1.531(7)	C(12)–C(18)	1.503(7)
C(5)–C(6)	1.476(7)	C(13)–C(14)	1.518(7)
C(6)–C(7)	1.324(7)	C(15)–C(16)	1.511(7)
C(6)–C(20)	1.500(7)	C(15)–C(17)	1.516(8)

TABLE 3

Bond angles (°) for compound (7) with standard deviations in parentheses

O(1)–C(1)–C(2)	121.0(4)	C(7)–C(8)–C(15)	124.2(4)
O(1)–C(1)–C(14)	121.1(4)	C(9)–C(8)–C(15)	58.7(4)
C(2)–C(1)–C(14)	117.9(4)	C(8)–C(9)–C(10)	120.2(4)
C(1)–C(2)–C(3)	110.7(5)	C(8)–C(9)–C(15)	60.8(4)
C(1)–C(2)–C(19)	112.9(4)	C(10)–C(9)–C(15)	122.8(4)
C(3)–C(2)–C(19)	110.2(4)	C(9)–C(10)–C(11)	113.4(4)
C(2)–C(3)–C(4)	115.3(3)	C(10)–C(11)–C(12)	114.0(4)
O(2)–C(4)–C(3)	110.2(5)	C(11)–C(12)–C(13)	112.8(4)
O(2)–C(4)–C(5)	108.4(4)	C(11)–C(12)–C(18)	110.2(5)
C(3)–C(4)–C(5)	109.2(4)	C(13)–C(12)–C(18)	109.5(4)
O(3)–C(5)–C(4)	117.7(5)	C(12)–C(13)–C(14)	116.6(4)
O(3)–C(5)–C(6)	121.3(5)	C(1)–C(14)–C(13)	115.9(4)
C(4)–C(5)–C(6)	120.9(4)	C(8)–C(15)–C(9)	60.5(4)
C(5)–C(6)–C(7)	120.9(4)	C(8)–C(15)–C(16)	120.4(4)
C(5)–C(6)–C(20)	116.1(4)	C(8)–C(15)–C(17)	114.7(4)
C(7)–C(6)–C(20)	123.0(5)	C(9)–C(15)–C(16)	120.5(4)
C(6)–C(7)–C(8)	124.9(4)	C(9)–C(15)–C(17)	117.7(4)
C(7)–C(8)–C(9)	121.1(4)	C(16)–C(15)–C(17)	113.2(5)

TABLE 4

Torsion angles (°) for compound (7) with standard deviations in parentheses

C(1)–C(2)–C(3)–C(4)	68.6(5)
C(2)–C(3)–C(4)–C(5)	177.5(4)
C(3)–C(4)–C(5)–C(6)	69.5(6)
C(4)–C(5)–C(6)–C(7)	22.4(8)
C(5)–C(6)–C(7)–C(8)	−176.7(4)
C(6)–C(7)–C(8)–C(9)	−179.7(5)
C(7)–C(8)–C(9)–C(10)	0.6(8)
C(8)–C(9)–C(10)–C(11)	−80.3(6)
C(9)–C(10)–C(11)–C(12)	165.1(4)
C(10)–C(11)–C(12)–C(13)	−170.1(4)
C(11)–C(12)–C(13)–C(14)	59.7(5)
C(12)–C(13)–C(14)–C(1)	66.3(6)
C(13)–C(14)–C(1)–C(2)	−168.3(5)
C(14)–C(1)–C(2)–C(3)	85.9(6)

The absolute stereochemistry of crotonitenone was not determined, but is under investigation.

The co-occurrence of crotonitenone, phorbol, the crotofolanes,[11] and related compounds [3,13] in the genus *Croton* provides further circumstantial evidence for the
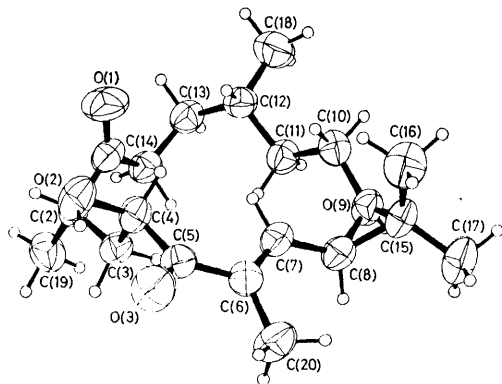
An ORTEP perspective drawing of crotonitenone (7)

pivotal role of casbene (or a closely related substance) in the biogenesis of many of the diterpenes occurring in the Euphorbiaceae and the Thymelaeaceae.

EXPERIMENTAL

M.p.s were determined in capillaries. I.r. and n.m.r. spectra were determined in chloroform and deuteriochloro-

form, respectively. The ^{1}H n.m.r. and ^{13}C n.m.r. spectra were determined at 100 and 25.4 M Hz respectively. Chemical shifts are expressed in p.p.m. downfield from tetramethylsilane with coupling constants (J) in Hz. Mass spectra were recorded at 70 eV. Thin layer chromatography (t.l.c.) was carried out on silica gel (Pf 254, Merck) plates and spots were visible under short-wavelength ultraviolet light.

Isolation of Crotonitenone (7).—Dried milled leaves and twigs of *Croton nitens* Sw. (' Cascarilla Bark '; *C. nitens* is the Jamaican variety of *C. eluteria* L.) [10] (150 g) were percolated with benzene (2 l) until no more material was extracted. Evaporation gave a dark green gum (8 g, 5%), which was subjected to column chromatography (silica gel) with benzene–ethyl acetate (6 : 1 v/v) as eluant. Elution with *ca.* 500 ml of the eluant gave an oil (2.3 g); further elution with 600 ml of the eluant gave a fraction (2.4 g), which was shown (t.l.c.) to contain two substances. Crotonitenone had the higher R_F of the two and was isolated by preparative t.l.c. (silica gel; 5 : 1 (v/v) light petroleum–acetone). Crystallization from methanol yielded (7) (630 mg) as *needles*, m.p. 128—129 °C; $[\alpha]_D^{25}$ +176° (*c*, 1 in CHCl$_3$); $\lambda_{max.}$ 267 nm (ε 16 000); $\nu_{max.}$ 3 430, 1 710, 1 650, and 1 620 cm^{-1}; Raman (neat) 1 650, 1 620, and 1 045 cm^{-1}; δ_H 0.92 (3 H, d, J 7 Hz, CH_3-18), 0.94 (3 H, s, CH$_3$-17), 1.15 (3 H, d, J 7 Hz, CH$_3$-19), 1.17 (3 H, s, CH$_3$-16), 1.91 (3 H, d, J 2 Hz, CH$_3$-20), 3.57br (1 H, s, exchangeable with D$_2$O), 4.54 (1 H, dd, J 7 and 1 Hz CH-4), and 6.11 (1 H, d, J 10 Hz, CH-7); δ_C 12.23 (q, CH$_3$-17), 16.25 (q, CH$_3$-16), 17.83 (q, CH$_3$), 20.83 (q, CH$_3$), 23.25 (t, CH$_2$), 26.51 (t, CH$_2$), 27.10 (s, C-15), 27.60 (d, CH-12), 29.23 (q, CH$_3$-20), 30.18 (t, CH$_2$), 31.55 (d, CH-9), 33.50 (t, CH$_2$), 34.00 (d, CH-8), 42.39 (t, CH$_2$), 45.16 (d, CH-2), 69.77 (d, CH-4), 134.85 (s, C-6), 142.76 (d, CH-7), 201.74 (s, C-5), and 213.63 (s, C-1); *m/e* 320.2352 (M^+, 10%), 302 (10), 278 (43), 259 (8), 207 (8), 194 (11), 163 (21), 134 (71), 109 (100), and 95 (75) (Found: C, 74.9; H, 10.1. C$_{20}$H$_{32}$O$_3$ requires C, 74.96; H, 10.06%).

Crotonitenone Acetate (8).—Crotonitenone (120 mg) was acetylated with an excess of acetic anhydride in pyridine at room temperature for 4 days. Reaction of the excess of acetic anhydride with methanol followed by extraction with ethyl acetate gave the crude acetate (8) as a gum (112 mg); $\lambda_{max.}$ (MeOH) 278 nm (ε 13 032); δ_H 0.91 (3 H, d, J 7 Hz, CH$_3$-18), 1.05 (3 H, s, CH$_3$-17), 1.14 (3 H, d, J 7 Hz, CH$_3$-19), 1.16 (3 H, s, CH$_3$-16), 1.83 (3 H, d, J 2 Hz, CH$_3$-20), 2.07 (3 H, s, OCOCH$_3$), 5.26br (1 H, t, J 6 Hz, CH-4), and 6.43 (1 H, d, J 10 Hz, CH-7); *m/e* 362.2474 (M^+, 6%), 319.1895 (100, M^+ − C$_3$H$_7$), 302.2214 (16, M^+ − CH$_3$CO$_2$H), and 259 (6, M^+ − C$_3$H$_7$ − CH$_3$CO$_2$H).

Oxidation of Crotonitenone (7) *with Jones Reagent.*—To a stirred, cold (*ca.* 5 °C) solution of (7) (140 mg) in acetone (5 ml) was added Jones reagent until an orange colour persisted. After 15 min, the reaction was extracted with ethyl acetate, washed, and dried (MgSO$_4$). Evaporation gave the *triketone* (9), (125 mg), which crystallized from acetone as pale yellow needles, m.p. 127—131 °C; $\lambda_{max.}$ (MeOH) 227 (ε 7 950) and 292 nm (ε 18 285); $\nu_{max.}$ 1 690 cm^{-1}; δ_H 0.88 (3 H, d, J 7 Hz, CH$_3$-18), 1.05 (3 H, s, CH$_3$-17), 1.16 (3 H, d, J 7 Hz, CH$_3$-19), 1.18 (3 H, s, CH$_3$-16), 1.92 (3 H, d, J 2 Hz, CH$_3$-20), and 6.54 (1 H, d, J 11 Hz, CH-7); *m/e* 318 (M^+, 26%) 315 (4), 275 (12), and 247 (100) (Found: C, 75.4; H, 9.5. C$_{20}$H$_{30}$O$_3$ requires C, 75.43; H, 9.50%).

Zn–Acetic Acid Reduction of Triketone (9).—Zinc dust (60 mg) was added to a stirred solution of (9) (40 mg) in acetic

acid (2 ml). The mixture was stirred at room temperature for 12 h, diluted with ethyl acetate, and filtered. The filtrate was washed with dilute sodium hydrogencarbonate, water, and dried (MgSO₄). Evaporation gave a solid, which was crystallized from acetone to give crotonitenone (20 mg), identical with an authentic sample (m.p., t.l.c., and u.v., i.r., and n.m.r. spectra).

X-*Ray Crystallographic Analysis of Crotonitenone* (7).— $C_{20}H_{32}O_3$, $M = 320.47$. Monoclinic, space group $P2_1$, $a = 12.446(1)$, $b = 13.285(1)$, $c = 5.872(1)$ Å, $\beta = 97.02(1)°$, $Z = 2$; $D_c = 1.104$ g cm⁻³, μ (Cu-K_α) = 5.8 cm⁻¹. The intensity data, uncorrected for absorption, were measured on a fully-automated Hilger-Watts diffractometer (Ni filtered Cu-K_α radiation, θ—2θ scans, pulse height discrimination) using a crystal of approximately $0.05 \times 0.10 \times 0.50$ mm grown from methanol. Of the 1 374 independent reflections for $\theta < 57°$, 1 092 were considered to be observed [$I > 2.5\sigma$ (I)]. The structure and relative stereochemistry of (7) were solved by a multiple solution procedure[14] and refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters and isotropic temperature factors were used for non-hydrogen and hydrogen atoms, respectively. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices were $R = 0.040$ and $R' = 0.038$ for the 1 092 observed reflections. The final difference map had no peaks greater than ± 0.1 eÅ⁻³. Listings of final atom parameters, bond lengths, bond angles, and torsion angles are given in Tables 1—4. Observed and calculated structure factors and atom thermal parameters are given in Supplementary Publication No. SUP 23105 (8 pp.).*

* For details see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 1*, 1980, Index issue.

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