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LEVATIN, AN 18-NORCLERODANE DITERPENE FROM *CROTON LEVATII*

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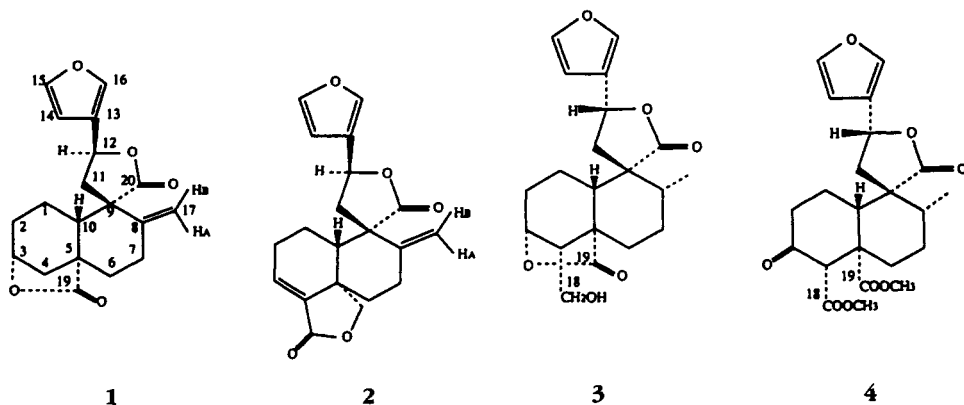
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ABSTRACT.—A new *ent*-norclerodane diterpenoid named levatin [1] was isolated from the stem bark of *Croton levatii*. Its structure was elucidated by means of 2D nmr experiments as *ent*-15,16-epoxy-18-norcleroda-8(17),13(16),14-triene-19,3:20,12*S*-diolide.

Trunk bark of *Croton levatii* Guill. (Euphorbiaceae) is reported to be used as perfume and as an aphrodisiac for dancers (1) on the island Ifate (Vanuatu). In our continuing search for mono- and sesquiterpenoids in the less polar chromatographic fractions of this plant we isolated from the CH₂Cl₂ extract a new diterpenoid named levatin [1].

RESULTS AND DISCUSSION

The CH₂Cl₂ extract was fractionated as described in the Experimental section, and levatin was recrystallized as plates from MeCN. Ms showed the molecular peak at *m/z* 328 consistent with the molecular formula C₁₉H₂₀O₅, indicating that levatin was a norditerpene. The ir spectrum showed γ -lactone (1767, 1751 cm⁻¹), a furan ring (1500, 873 cm⁻¹), and double bond (1635 cm⁻¹) functionalities. The ¹³C and the ¹H-¹³C COSY (Figure 1) spectra revealed the presence of seven methylene groups, six methine groups, and six quaternary carbon atoms. Thus levatin was pentacyclic. Spectral data are reported in Table 1, and the ¹H-¹H COSY/NOESY spectra are presented in Figure 2. These data, when compared with those of closely related diterpenoids, suggested that levatin had an *ent*-clerodane skeleton (2) but with no methyl group at C-4, C-5, C-8, or C-9. The signal of H-12 of levatin appeared at 5.44 ppm as in other neo-clerodane (20 \rightarrow 12)-olides (3). The methyl group at C-8 was substituted by an exocyclic methylene as reported in swassin [2] isolated from *Croton joufra* (4). Levatin was a 19 or 18 norditerpene, and one carbonyl group (at C-4 or C-5) was present in its structure as a lactone moiety. Nmr data showed that C-6 and C-7 were methylenic. Thus, ring A possessed three methylene groups and a methine group. In addition C-5 is a quaternary car-



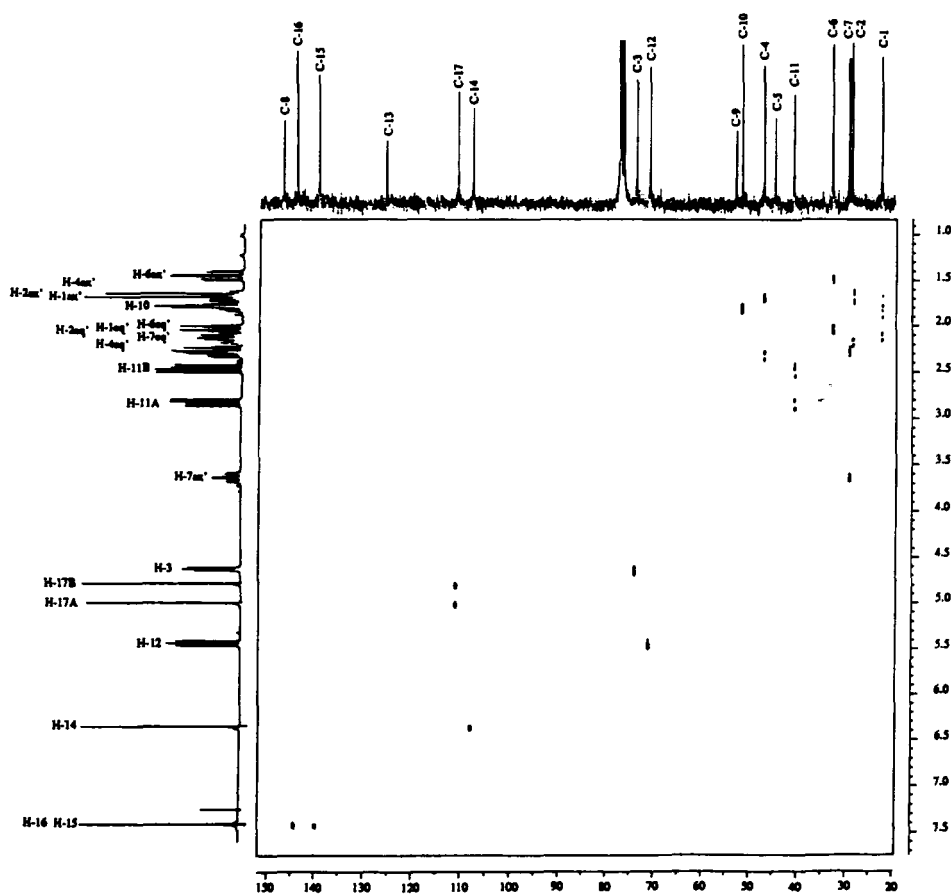


FIGURE 1. ^1H - ^{13}C COSY of levatin [1].

bon atom; consequently, the bridgehead of a second γ -lactone ring was proposed to be at C-3. The remaining methylene groups were placed at C-1, C-2, and C-4, so that levatin is considered to be an 18-norclerodane diterpene 19,3:20,12 diolide. Levatin is the first diolide of this type found as a natural product. A very closely related compound **3** was obtained by reduction of corylifuran [4] with NaBH_4 (5). The structure of levatin [1] was supported with a Dreiding model and further examination of the nmr data for coupling constants and connectivities in the ^1H - ^1H COSY and NOESY spectra (Figure 2). Downfield chemical shifts were observed for C-4 and $\text{H}_{\text{ax}}-7$ due to the anisotropy effects of double bonds $\text{O}=\text{C}-19$ and $\text{C}-8=\text{C}-17$, respectively. Nmr data showed that H-10 has a β configuration and $\text{O}=\text{C}-19$ an α configuration, indicating a trans decalin moiety (6). Cross peaks between $\text{H}_{\text{eq}}-2$ and $\text{H}_{\text{eq}}-4$ due to a 4J coupling via W interaction were observed, confirming the chair conformation of ring A. The connectivities for the methylene protons at C-1 and C-2 and at C-6 and C-7 were observed on the ^1H - ^1H COSY spectrum. The axial proton at C-7 is in turn coupled to the methylene protons at C-17, and the connectivities $\text{H}_{\text{eq}}-2 \rightarrow \text{H}_{\text{eq}}-3 \rightarrow \text{H}_{\text{eq}}-4$ showed that the bridgehead proton was $\text{H}_{\text{eq}}-3$. Cross peaks were also observed between H_B-17 and H_A-11 , and between H-12 and the methylene protons at C-11. The ^1H - ^1H NOESY spectrum displayed in Figure 2 showed cross peaks between $\text{H}_{\text{eq}}-3$ and $\text{H}_{\text{eq}}-4$, $\text{H}_{\text{eq}}-7$ and H_A-17 , and H_B-17 and H_A-11 . Furthermore, cross peaks between the furanic protons at C-14 and at C-15 with H_A-17 and H_B-17 showed that the furanic ring and the C-17 methylenic protons are on the same side of the plane defined by the $\text{C}-20 \rightarrow \text{C}-12$ lactone

TABLE 1. ^1H - (300 MHz, CDCl_3) and ^{13}C - (75.45 MHz, CDCl_3) nmr Data of Levatin [1].

Position	^1H δ (ppm) mult J (Hz)	conformation	^{13}C δ (ppm)	$\Delta\delta$ with $\text{Eu}(\text{fod})_3^a$
1	$^1\text{B} = 1.73 \text{ m}, J = 11.8$ and $^3J_{1-10} = 3$ $^1\text{A} = 2.12 \text{ m}, J = 11.8$	ax eq	CH_2 22.48	+ 0.54
2	$^2\text{B} = 1.71 \text{ m}, J = 10.5$ $^2\text{A} = 2.17 \text{ m}, J = 10.5, J_{2-3} = 4.2$ and $^4J_{2-4\text{eq}} = 2.14$	ax eqW	CH_2 28.62	+ 0.28
3	$4.64 \text{ dd } ^3J_{3-4\text{eq}} = 6^3J_{\text{eq}-3} = 4.2$ and $^3J_{3-4\text{ax}} = 4$	eq	CH 74.00	+ 0.61
4	$^4\text{B} = 1.67 \text{ m}, J = 11.7$ and $J_{3-4} = 4$ $^4\text{A} = 2.31 \text{ ddd}, J = 11.7, J_{3-4} = 6$ and $^4J_{2\text{eq}-4} = 2.2$	ax eqW	CH_2 46.93	+ 0.45
5			Cq 44.60	+ 0.79
6	$^6\text{B} = 1.45 \text{ td}, J = 13.5, ^3J_{6-7\text{ax}} = 13.5$ and $^3J_{6-7\text{eq}} = 3.8$ $^6\text{A} = 2.03 \text{ dt}, J = 13.5, ^3J_{6-7\text{eq}} = 3.8$ and $^3J_{6-7\text{ax}} = 3.8$	ax eq	CH_2 32.50	+ 0.70
7	$^7\text{B} = 2.26 \text{ dt}, J = 13.7, ^3J_{6\text{ax}-7} = 3.8$ and $^3J_{6\text{eq}-7} = 3.8$ $^7\text{A} = 3.65, J = 13.7, ^3J_{6\text{ax}-7} = 13.5, ^3J_{6\text{eq}-7} =$ 3.8 and $J_{7-17} = 1.6, 0.8$	eq ax	CH_2 29.23	+ 0.75
8			Cq 146.93	+ 0.58
9			Cq 52.76	+ 0.58
10	$1.79 \text{ m}, ^3J_{1\text{ax}-10} = 3$	ax	CH 51.53	+ 0.59
11	$^{11}\text{B} = 2.47 \text{ dd}, J = 14.3$ and $^3J_{11-12} = 8.6$ $^{11}\text{A} = 2.48 \text{ dd}, J = 14.3$ and $^3J_{11-12} = 7.1$		CH_2 40.62	+ 0.31
12	$5.44 \text{ dd}, J_{11-12} = 8.6$ and 7.1		CH 71.11	+ 0.50
13			Cq 125.66	+ 0.13
14	$6.35 \text{ t}, J_{14-15} = J_{14-16} = 1.6$		CH 107.97	+ 0.10
15	$7.41 \text{ d}, J_{14-15} = 1.6$		CH 139.65	+ 0.09
16	$7.41 \text{ d}, J_{14-16} = 1.6$		CH 144.17	+ 0.12
17	$^{17}\text{B} = 4.80 \text{ bs}, J_{7\text{ax}-17} = 0.8$ $^{17}\text{A} = 5.01 \text{ d}, J_{7\text{ax}-17} = 1.6$		CH_2 111.00	+ 0.43
19			Cq 173.88 ^b	+ 1.01
20			Cq 176.75 ^b	+ 1.71

^aLevatin-Eu(fod)₃ (2:1).^bAssignments may be reversed.

ring. Thus the configuration at C-12 was *S* (7, 8). The configuration at the C-10 was also confirmed by the cross peaks between H-10 β and H_{ax}-4 and the conformation of the B ring by cross peaks between H_{eq}-7 and H_A-17. The decalin moiety presented a trans A/B ring junction with a chair conformation for ring A and a half-boat conformation for ring B as observed with a Dreiding molecular model. All the nmr data were fully in agreement with the relative configuration and conformation as shown in Figure 3.

EXPERIMENTAL

PLANT MATERIAL.—Stem bark of *C. levatii* was collected and identified in 1985 by Dr. P. Cabalion in Vanuatu near Port-Vila (ORSTOM centre). A voucher specimen is deposited in the herbarium of the Faculty of Pharmacy, University of Toulouse, France.

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were recorded on a Perkin-Elmer 983 spectrophotometer. The mass spectrum was obtained with a Nermag 10 10A spectrometer at 70 eV. ^1H - and ^{13}C -nmr spectra were recorded in CDCl_3 at 300.13 and 75.43 MHz, respectively, on a Bruker AM 300 WB with TMS as internal reference; lanthanide shift effects have been exploited in ^{13}C nmr [levatin-Eu(fod)₃ ratio 2:1]. Kieselgel (0.006–0.035 mm; SDS) was used for cc and Kieselgel 60 PF (7749 Merck) for centrifugal preparative tlc. Chromatograms from analytical tlc (Kieselgel 60 F254 Merck) were visualized by spraying plates with Ehrlich's reagent and anisaldehyde- H_2SO_4 .

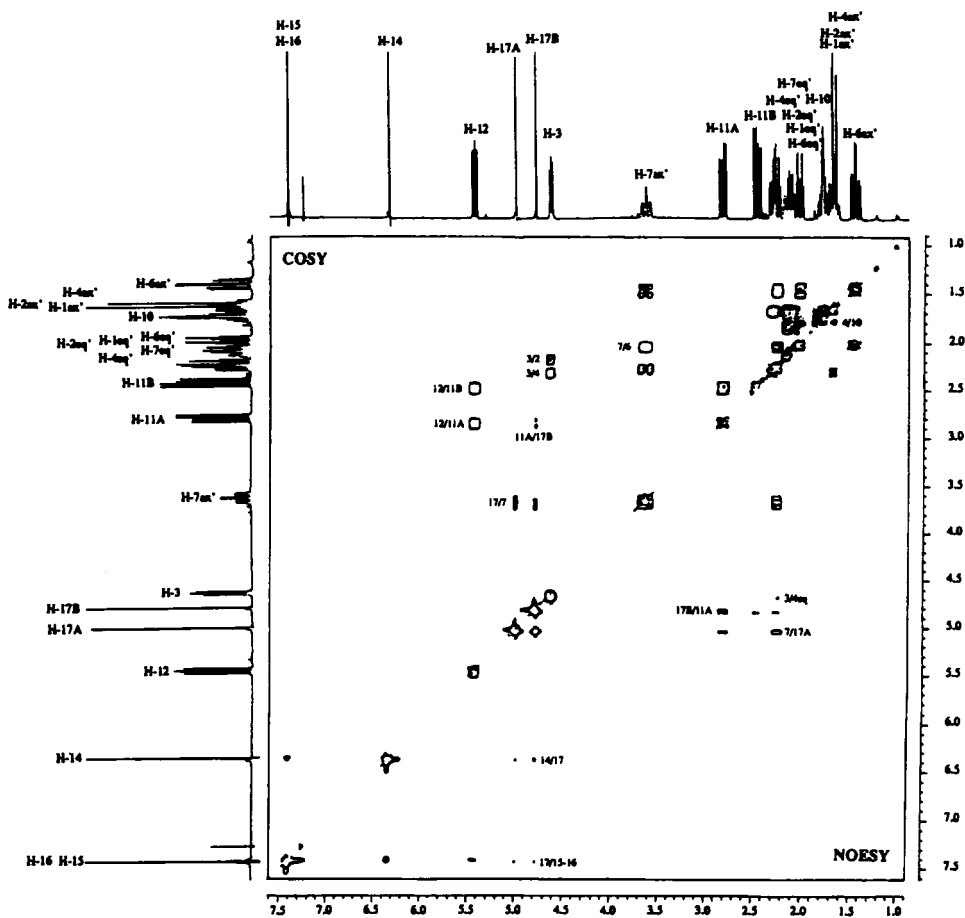


FIGURE 2. ^1H - ^1H COSY/NOESY of levatin [1].

ISOLATION OF LEVATIN.—Air-dried, ground trunk bark (2 kg) was extracted by percolation with hexane to remove mono- and sesquiterpenoids, and the residue was extracted with CH_2Cl_2 . After evaporation, the CH_2Cl_2 solution gave 120 g of extract. An aliquot of this (30 g) was fractionated by medium pressure cc [Büchi pump 681 at 30 bars with CH_2Cl_2 -MeOH (99:1 to 97:3)]. Levatin showed a positive test with Ehrlich's reagent, and fractions were collected on the basis of analytical tlc. Further purification by centrifugal preparative tlc [CH_2Cl_2 -MeOH (19:1)] afforded levatin (464 mg).

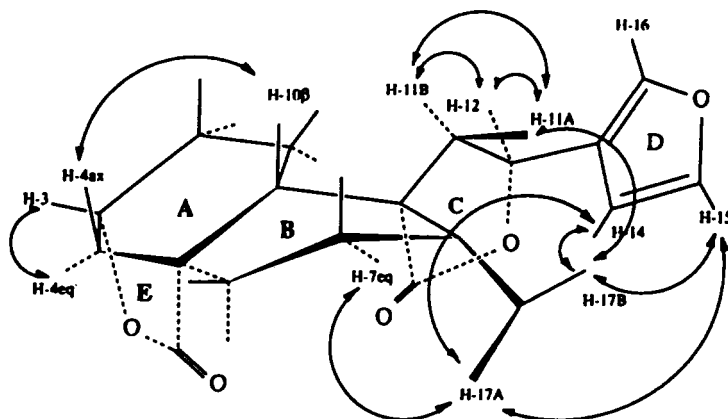


FIGURE 3. Summary of the results of ^1H NOESY spectrum of levatin [1].

LEVATIN [1].—Plates were recrystallized from MeCN. *Anal.* calcd for $C_{19}H_{20}O_5$, C 69.51, H 6.09, O 24.39; found C 69.29, H 6.19, O 24.45. Mp 197°; $[\alpha]^{25}_D +62^\circ$ ($CHCl_3$, $c \approx 0.5$); ir ν max (KBr) cm^{-1} 3491, 3147, 2930, 1767, 1751, 1635, 1500, 1449, 1332, 1304, 1159, 1150, 1084, 873; ms m/z (rel. int.) $[M]^+$ 328 (5), 210 (55), 282 (50), 237 (36), 219 (22), 197 (38), 129 (30), 91 (100); 1H and ^{13}C nmr see Table 1.

ACKNOWLEDGMENTS

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