Tetrahedron Vol. 46, No. 15, pp. 5199-5202, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

CROTOCORYLIFURAN AND CROTOHAUMANOXIDE, NEW DITERPENES FROM *Croton Haumanianus* J. Leonard.

Laurent Tchissambou[#], Angèle Chiaroni[##], Claude Riche[##] and Françoise Khuong-Huu[##*]

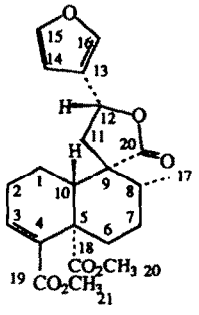
[#]CERVE, B.P.1249, Brazzaville, République Populaire du Congo.
[##*]CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France.

(*Received in France* 16 *May* 1990)

Abstract-The structures of two new diterpenes from *Croton Haumanianus* have been determined by spectroscopic data for crotocorylifuran, a clerodane-type diterpene and by spectroscopic data and X-ray crystallographic analysis for crotohaumanoxide, a crotofolane-type diterpene.

Croton haumanianus is a tropical shrub of which leaves and barks were used in folk medicine against blennoragy, gastric diseases and also as antihypertensive and antiepileptic drug.

From the petroleum ether extract, lupeol and two new diterpenes, crotocorylifuran **1** and crotohaumanoxide **2**, were obtained.



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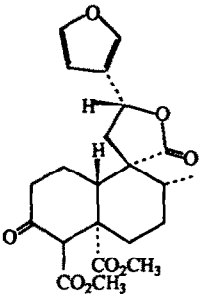

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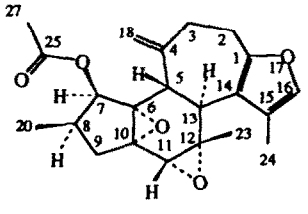

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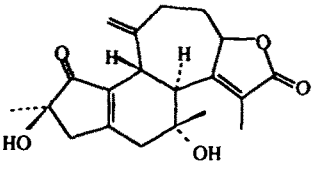

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Crotocorylifuran **1** has $C_{22}H_{26}O_7$ as molecular formula and its spectral properties indicated the presence of a secondary Me group (3H, *d*, J=7Hz, at δ 1ppm), two CO_2Me functions (2*s* of 3H each at δ 3.70 and 3.74 ppm), a γ-lactone ($\nu_{C=O}$ at 1760 cm^{-1}) bearing a substituent at its γ position (1H, *t*, J= 6Hz, at δ 5.36 ppm), a trisubstituted double bond conjugated to an ester function (1H, *m*, at δ 6.84 ppm, $\nu_{C=O}$ at 1720 cm^{-1}) and a monosubstituted furan ring (3*t* of 1H each at δ 6.38, 7.41 and 7.43 ppm, significant peaks at m/z 81 and 95 in the mass spectrum[1]). ^{13}C NMR spectrum supported these elements and indicated also the presence of 5 CH_2 and 2 sp^3 hybridized quaternary carbon atoms. A clerodane structure was supposed and examination of the litterature indicated that the product we isolated had identical data as the compound obtained by reduction and dehydration of corylifuran **3**, a clerodane diterpene from *Croton corylifolius* .[1] ^1H-^1H and ^1H-^{13}C correlations permitted the attribution of the main hydrogen and carbon signals in the ^1H and ^{13}C NMR spectra and confirmed the structure (see experimental section).

Crotohaumanoxide **2** has $C_{22}H_{26}O_5$ as molecular formula. Determination of its structure and relative configuration were effected through a single crystal X-ray analysis. Crystals of **2**, grown from methanol, belong to the monoclinic space group $P2_1$ with a = 8.083 (4), b = 7.951 (4), c = 15.105 (6) Å, β = 91.92(2)° and one molecule per asymmetric unit. 1979 unique reflexions were collected on a Philips PW1100 diffractometer using graphite monochromated Cu K_α (λ=1.5418 Å) and θ-2θ scan technique up to θ = 65°. 1754 reflexions with $I \geq 3\,\sigma(I)$ were considered as observed. The structure was solved by direct methods[2] and refined by full-matrix least-squares, minimizing the function $\Sigma\, w(Fo-Fc)^2$. The hydrogen atoms were located on successive difference maps and refined, with an isotropic temperature factor greater than 10% that one the bonded carbon atom. Convergence was reached at R=0.032 with a weighting scheme of $w= 1/\sigma^2(Fo) + 0.0013\, Fo^2$. Refinement was performed with Program SHELX76. [3] A perspective view of the molecule is shown in Fig. 1. [4]

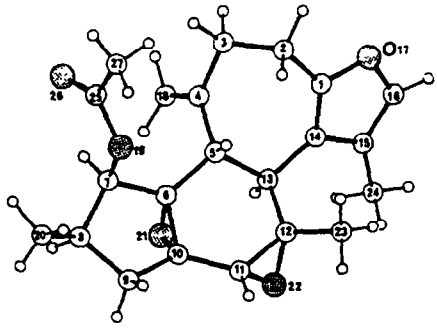

Fig. 1

The spectral data of **2** were fully interpretated with this structure. The acetate function was characterized by its IR absorption ($\nu_{C=O}$ at 1740 cm^{-1}), mass fragmentation pattern (peaks at M-42 and M-60), signals in ^1H NMR spectrum (CH_3 at δ 2.11 ppm, H-7 at δ 5.53 ppm) and ^{13}C NMR spectrum (C=O at δ 169.23 ppm). The two epoxide functions showed ^{13}C NMR peaks at δ 57.01, 60.45 and 68.63 ppm (3C) and 57.48 ppm (1CH), the chemical shift of H-11 was at δ 3.16 ppm.The furane ring was characterized by peaks at δ 117.22, 121.89, 150.15 (3C) and 136.69 ppm (CH) in the ^{13}C NMR spectrum and signals of H-16 and CH_3-24 at δ 7.03 ppm and 1.96 ppm respectively, in the ^1H NMR spectrum. The resonance of the exomethylene protons was at δ 4.91 and 5.03 ppm (2*d* of 1H each, J=2 Hz).

The assignments of main signals in the ^1H and ^{13}C NMR spectra were based on ^1H-^1H and ^1H-^{13}C correlations (see experimental section).

Crotohaumanoxide was a new crotofolane-type diterpene. [5] The first compound of this series was crotofoline **4**, isolated as corylifuran **3** from *Croton corylifolius* . [5]

Acknowledgement: We wish to thank C. Fontaine and C. Pasquier for recording ^1H-^1H and ^1H-^{13}C correlations.

Experimental

M.ps were determined in capillary tubes and are uncorrected. $[\alpha]_D$ were measured in $CHCl_3$ with 0.5% EtOH, at 20°C, on a PERKIN-ELMER 241 polarimeter. IR spectra were determined with a PERKIN-ELMER 257 spectrometer, UV spectra with a PERKIN-ELMER Lambda 205 spectrometer. NMR spectra were taken in $CDCl_3$, unless otherwise stated, with TMS as internal standard, chemical shifts δ were expressed in ppm, coupling constants in Hz, assignments were based on ^1H-^1H et ^1H-^{13}C correlations. They were recorded on BRUKER WP-200, BRUKER AC-200 or BRUKER WM-400 instruments. Mass spectra were run on AEI MS-50 or AEI MS-9 spectrographs.

Extraction.. Dried and finely ground trunk barks (80 g) were extracted with petroleum ether in a Soxhlet apparatus. After 11 hr., evaporation of the solution gave a residue (5.5 g, 6.4%) which was chromatographied on Silica gel column (Kieselgel 60H Merck, 120 g) with petroleum ether containing increasing percentage of CH_2Cl_2 and CH_2Cl_2 with increasing percentage of MeOH as eluents. Lupeol (1.6 g), identified by comparaison with an authentic sample, was first eluted, followed by crotocorylifuran **1** (0.97 g) and crotohaumanoxide **2** (0.105 g).

Crotocorylifuran **1**. M.p. 200° (cryst. MeOH), $[\alpha]_{D20°}$ =-164°($CHCl_3$ c=1); Analysis: $C_{22}H_{26}O_7$, found %: C 65.05, H 6.43, O 28.17, calc.%: C 65.66, H 6.51, O 27.83; IR: $\nu_{C=O}$ 1760 et 1725 cm^{-1} ;UV: λ_{max} 209 nm (ε 10500); MS EI: M^+ 402, m/z 384, 358, 342, 310, 95, 81; ^1H NMR 400 MHz: δ ppm 1.0 (3H, *d*, J=6, CH_3-17), 1.10(1H, *td*, J=12, J'=3, H-6b_a), 1.54 (2H, *m*, H-8 et H-7b_e),1.74 (1H, *dt*, J=12, J'=3, H-6a_e), 3.70 (3H, *s*, OCH_3), 3.74 (3H, *s*, OCH_3), 5.38 (1H, *t*, J=8, H-12), 6.38 (1H, *t*, J=1, H-14) 6.81, (1H, *m*, H-3), 7.42 (1H, *d*, J=1, H-15), 7.44 (1H, *d*, J=1, H-16); ^{13}C NMR: δ ppm 16,98 CH_3-17, 19.11 CH_2-1, 26.26 CH_2-11, 27.89 CH_2-7, 32.23 CH_2-6, 40.03 CH-8, 42.27 CH_2-2, 46.27 C-9, 51.30 OCH_3, 51.36 OCH_3, 51.51 CH-10, 51.70 C-5, 71.77 CH-12, 108.10 CH-14, 125.53 C-13, 136.38 C-4, 139.44 CH-16, 139.83 CH-3, 144.00 CH-15, 166.65 C=O-18, 172.83 C=O-19, 176.01 C=O-20.

Crotohaumanoxide **2**. M.p. 181° (cryst. MeOH), $[\alpha]_{D20°}$=-2° ($CHCl_3$ c=0.2); IR: 1740 cm^{-1} ($\nu_{C=O}$), 1250 cm^{-1}(C-O) ester ; Analysis: $C_{22}H_{26}O_5$, found%:C 71.27, H 7.23, calc.%: C 71.33, H 7.08; MS EI: M^+370, m/z 355, 328, 327, 310, 295, 267; ^1H NMR, 400 MHz: δ ppm, 0.91 (3H, *d*, J=7, CH_3-20), 1.10 (3H, *s*, CH_3-23), 1.65 (1H, *dd*, =14, J'=10, H-9a) 1.96 (3H, *d*, J =1, CH_3-24), 2.11 (3H, *s*, $COCH_3$), 2.23 (1H, *m*, H-8), 2.13

(1H, *m*, H-2a ou H-3a) 2.13 (1H, *dd*, J=14, J'=7, H-9b) 2.60 (1H, *m*, H-2b ou H-3b) 2.76 (1H, *m*, H-3a ou H-2a) 2.81 (1H, *dd*, J=12, J'=1, H-5), 2.98 (1H, *m*, H-3b ou 2b) 3.06 (1H, *d*, J=12, H-13), 3.16 (1H, *s*, H-11), 4.91 (1H, *m*, H-18a), 5.03 (1H, *d*, J=2, H-18b) 5.53 (1H, *d*, J= 5, H-7), 7.03 (1H,*t*, J=1, H-16). ^{13}C NMR: δ ppm, 8.43 CH_3-20, 12.46 CH_3-23, 19.83 CH_3-24, 20.46 $COCH_3$, 22.59 CH_2-2 (ou 3), 33.57 CH-8, 36.29 CH_2-3 (ou 2), 36.93 CH-13 et CH_2-9, 41.64 CH-5, 57.01 C-6[b], 57.48 CH-11, 60.45 C-10[b], 68.63 C-12[b], 75.02 CH-7, 113.61 CH_2-17, 117.22 C-14[c], 121.89 C-15[c], 136.69 CH-16, 145.33 C-4[d], 150.15 C-1[d], 169.23, C=O ([b,c,d] assignments may be reversed).

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