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ISOLATION AND STRUCTURES OF IRRITANT SUBSTANCES OBTAINED FROM EUPHORBIA SPECIES (EUPHORBIACEAE)

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Previously, we and another groups reported new compounds from Euphorbia species.[1-7] Now we wish to describe the isolation and structural elucidation of irritant substances, milliamine C (1) obtained from E. millii Ch.des Moulins, and ingenol 2,4,6,8,10-tetradecapentaen -oate (2) from E. jolkini Boiss.

[Milliamine C]

Crude milliamine C obtained from fractions containing milliamines A and B[6] was purified with column chromatography (silicic acid) and preparative thin layer chromatography. Physical and spectral properties of milliamine C are as follows: $C_{43}H_{47}N_3O_9$ (amorphous powder); $[\alpha]_D^{22}$ = +11° (c, 1 in $CHCl_3$): IR ($CHCl_3$) 2800-3600, 1715, 1695, 1680, 1630, 1610 cm^{-1}; UV (MeOH) 228 (42000), 260 (19000), 315 nm (ε, 14000); NMR (60 MHz, δ, $CDCl_3$) 1.02 (3H, d, J= 6.0 Hz, 18-CH_3), 1.03 (6H, s, 16,17-CH_3), 1.80 (3H, d, J= 1.0 Hz, 19-CH_3), 2.80 [6H, s, -$N(CH_3)_2$], 3.65 (1H, s, exchangeable with D_2O), 3.8-4.5 (4H and 2H exchangeable with D_2O, m), 5.75 (1H, s, 3-H), 6.0-6.2 (2H, m, 1,7-H), 7.0-7.8 (8H, m), 7.9-8.3 (2H,m), 8.8 (1H, m), 9.5, 11.5, 13.2 (1H each, br.s, exchangeable with D_2O).

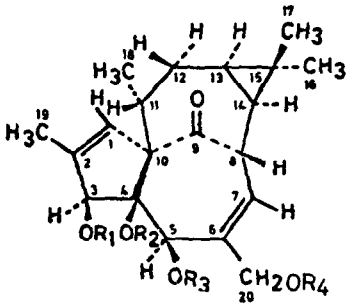
Methanolysis (MeONa-MeOH, room temperature) of milliamine C (1) afforded a compound (3) [m.p. 160-161°][6] and ingenol (4) which was identified by conversion to ingenol triacetate (5) [m.p. 197-198°][6]. The position of the ester linkage was concluded to be at C-3 from the signal of C-3 proton at δ 5.75 in the nmr spectrum of milliamine C. The assignment of signal (δ 5.75) of C-3 proton in the nmr spectrum was made not only from the nuclear magnetic double resonance experiment[6] but from the next results. Treatment of ingenol with N,N'-carbonyldiimidazole in THF gave a monocarbonate (6) [IR ($CHCl_3$) 3450, 1745, 1725 cm^{-1}] and this six-membered carbonate compound was further converted to a dicarbonate (7) [m.p. 204-206°; IR ($CHCl_3$) 1830, 1780,1740 cm^{-1}] by the same procedure with the longer reaction period. The signal assigned to C-3 proton

moved to low field (δ 5.32) only in the nmr spectrum of the dicarbonate (7) which possesses a five-membered carbonate ring. Furthermore cleavage of the bond between C-3 and C-4 was performed by oxidation of 6 with sodium periodate (overnight at 40° in acetone-H_2O), giving a compound (8): $C_{21}H_{24}O_6$ (a glassy compound); IR ($CHCl_3$) 3400, 1820 (five-membered carbonate) 1725 cm^{-1}; NMR ($CDCl_3$, δ) 0.97 (3H, s), 1.08 (3H, s), 1.10 (3H, d, J= 6.0 Hz) 1.91 (3H, d, J= 1.0 Hz), 3.10 (1H, m, 8-H), 4.28, 4.50 (2H, AB q, J= 12 Hz, 20-H), 5.50 (1H, q, J= 1.0 Hz, 1-H), 5.78 (1H, m, 3-H), 6.40 (1H, d of m, J= 4.5 Hz, 7-H)[In the nmr spectrum of urethane (9) of this compound (8) signal of two protons at C-20 appeared at δ 4.80 as a siglet]. It was considered that this compound was formed by aldol condensation of the keto-aldehyde intermediate and subsequent migration of the carbonate group.

[Ingenol 2,4,6,8,10-tetradecapentaenoate]

Fresh roots of E. jolkini were crushed in methanol, and yellow methanolic solution was filtrated and evaporated under a reduced pressure. Residual extracts were washed several times with benzene. The combined benzene solution was dried with Na_2SO_4 and concentrated to give a brown residue, which was chromatographed with florisil. Purification of irritant ester (2) was carried out by preparative thin layer chromatography and high speed liquid chromatography[8]. The physical and spectral properties of this compound were: $C_{34}H_{44}O_6$ (amorphous powder); $[\alpha]_D^{20}$ = +23° (c, 0.6 in $CHCl_3$); UV (MeOH) 222 (19000), 365 nm (ε, 42600); IR ($CHCl_3$) 3500, 1720, 1615, 1580 cm^{-1}; NMR (60 MHz, δ, $CDCl_3$) 1.82 (3H, d, J= 1.0 Hz, 19-CH_3), 3.55 (1H, s, exchangeable with D_2O), 4.15 (2H, s, 20-H), 3.8-4.0 (2H and 2H exchangeable with D_2O, m), 5.60 (1H, s, 3-H), 5.7-6.8 (12H, m).

Methanolysis (MeONa-MeOH) of 2 gave methyl 2,4,6,8,10-tetradecapentaenoate (10) [m.p. 155-158°; UV (MeOH) 365 nm (ε, 58000); NMR ($CDCl_3$, δ) 0.92 (3H, t, J= 6.0 Hz), 1.2-1.5 (2H, m), 1.9-2.3 (2H, m), 3.72 (3H, s), 5.7-6.6 (10H, m)] and ingenol (4), which was identified by being converted to ingenol triacetate (5). Catalytic hydrogenation of the ester (10) gave methyl tetradecanoate, which was identified with authentic sample. Stereochemistry regarding the double bonds of the ester (10) remained unsettled. The position of the ester linkage in compound (2) was shown to be at C-3 because of an appearance of the signal of C-3 proton at δ 5.60 in nmr spectrum, which was previously characterized.



(1) R_1= X, R_2= R_3= R_4= H

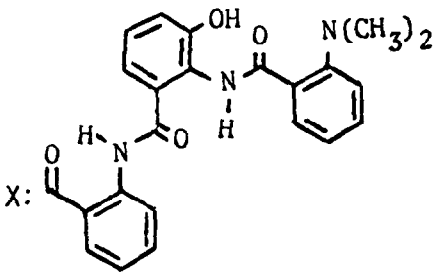
(2) R_1= Y, R_2= R_3= R_4= H

(4) R_1= R_2= R_3= R_4= H

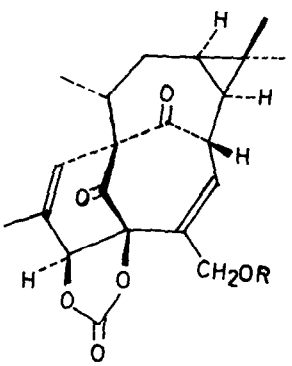
(5) R_1= R_3= R_4= CH_3CO, R_2= H

(6) R_1= R_2= H, R_3, R_4= >CO

(7) R_1, R_2= >CO, R_3, R_4= >CO



Y : $CO(CH=CH)_5CH_2CH_2CH_3$



(8) R= H

(9) R= - $CONHC_6H_5$

(3) X-OMe

(10) Y-OMe

E. Hecker and W. Adolf reported the compound L_3 obtained from E. lathyris; this compound possesses the same components as our compound (2), and no information as to the location of the ester linkage was described[9]. Furthermore, the presence of the compound esterified at C-20 position of ingenol with 2,4,6,8,10-tetradecapentaenoic acid was detected by the high speed liquid chromatogram and by the nmr spectrum (δ 4.58, 4.90, 2H, AB q, J= 13 Hz), but detailed chemical studies could not be performed owing to the quite limited amount of the sample.

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