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LUPEOLACTONE, A NEW ß-LACTONE FROM *ANTIDESMA PENTANDRUM MERR.*

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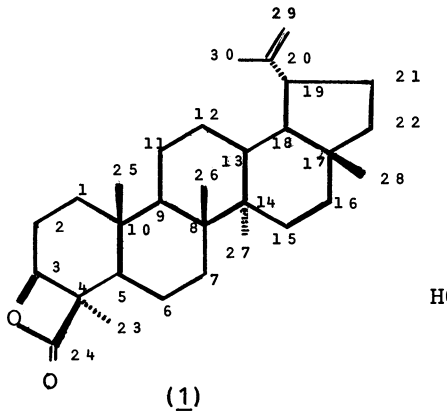
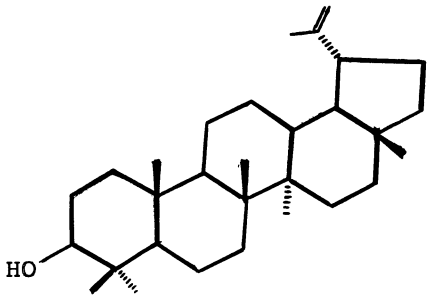
The structure of lupeolactone, a new triterpene ß-lactone from *Antidesma pentandrum Merr.*, has been dertermined from spectroscopic and X-ray crystallographic analyses.

During the course of a systematic pharmacological screening for naturally occuring hypolipidermic substances, we have isolated a new ß-lactone triterpene[1], lupeolactone (1), from *Antidesma pentandrum Merr.* (Euphorbiaceae) as an active substance. Here we wish to describe the isolation and structure elucidation of lupeolactone (1) on the basis of spectroscopic and X-ray crystallographic analyses.

The aerial part of *Antidesma pentandrum Merr.* was extracted with methanol. The ethyl acetate soluble part of the methanol extract was chromatographed on a Silica gel column using n-hexane-ethyl acetate as an eluant. The fraction containing lupeolactone (1) was further chromatographed on a Sephadex LH-20 column using methanol as an eluant, to give lupeolactone (1) (0.0005% yield) as colorless prisms; mp 186 - 191°C(dec.), $C_{30}H_{46}O_2$ (high resolution MS. Found 438.3501, Required 438.3498), positive in Liebermann-Burchard reaction.



(1)



(2)

The IR spectrum of 1 showed the presence of a ß-lactone moiety (1810 cm^{-1}) and a vinylidene group (1635 and 880 cm^{-1}). The presence of these groups were also supported by ^{13}C-NMR spectrum ($CDCl_3$, 25 MHz) of 1 as shown in Table; δ 175.5(s, >C=O), 77.3(d, >CHO-), 109.3(t, >C=$\underline{C}H_2$), 150.7(s, >$\underline{C}$=CH_2). The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) revealed the presence of five tertiary methyl groups {δ 0.78(3H, s), 0.92(3H, s), 0.97(3H, s), 1.08(3H, s) and 1.43(3H, s)} and an isopropenyl group {δ 1.68(3H, s), 4.58(1H, dd, J=2, 1 Hz) and 4.70 (1H, d, J=1 Hz)}.

These spectral data suggested that 1 is a lupane-series pentacyclic triterpene having a ß-lactone moiety. This was supported by comparison of the ^{13}C-MNR spectrum of 1 with that of lupeol (2)[2] (Table); The chemical shift of the signals of two compounds are very similar except for the signals due to the C-4, -23, -24 and -25 positions. The difference of the ^{13}C-NMR signals between 1 and 2 also suggested the position of the ß-lactone moiety as shown in the structure 1. The carbonyl carbon signal at δ 175.5 appears in the spectrum of 1 instead of disappearance of the signal at the position corresponding to the C-24 methyl resonance of 2, and the downfield shift of the C-3 carbon signal was observed from δ 38.9 in 2 to δ 55.4 in 1. From these spectroscopic evidence, the structure of lupeolactone was assigned as 1.

The absolute structure of 1 was decided by single-crystal analysis using direct method.

Table. ^{13}C-NMR Data of Lupeolactone (1) and (2)[3]

Number of Carbon	Substance		Number of Carbon	Substance	
	(1)	(2)		(1)	(2)
C-1	36.8	38.7	C-16	35.6	35.6
C-2	23.7	27.5	C-17	43.0	43.0
C-3	77.3	79.0	C-18	48.0	48.0
C-4	55.4	38.9	C-19	48.2	48.3
C-5	52.7	55.3	C-20	150.7	150.9
C-6	19.4	18.3	C-21	29.8	29.9
C-7	33.4	34.3	C-22	40.0	40.0
C-8	40.9	40.9	C-23	22.8	28.0
C-9	47.9	50.5	C-24	175.5	15.3
C-10	35.6	37.2	C-25	12.7	16.1
C-11	21.1	21.0	C-26	16.1	16.0
C-12	25.1	25.2	C-27	14.4	14.6
C-13	37.9	38.1	C-28	18.0	18.0
C-14	43.0	42.9	C-29	109.3	109.3
C-15	27.3	27.5	C-30	19.2	19.3

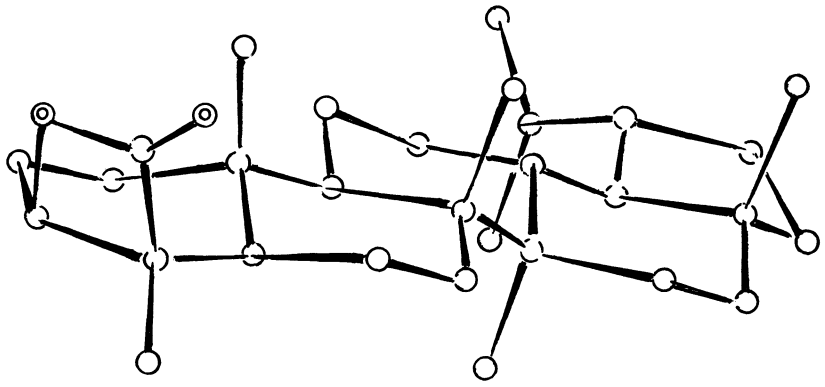


Fig. 1

Lupeolactone (1) crystallized in the monoclinic space group $P2_1$. The measured cell constants of a = 6.659(1), b = 27.397(5), c = 14.128(2) Å and ß = 86.11(2)° produced a calculated density of 1.128Mg m^{-3} for four molecules in the unit cell ; there are two independent molecules in an asymmetric unit. The reflection data were collected on a Rigaku automatic four circle diffractometer using the 2θ-ω scan technique up to 2θ value of 135° and CuKα radiation (λ = 1.5418 Å) with graphite monochrometer. The structure determination was done with an unique 4002 intensity greater than three times the estimated standard deviation. The structure was solved by the MULTAN 78 program[4] and refined by block-diagonal least-squares method with anisotropic temperature factors for non-hydrogen atoms and isotropic ones for hydrogen atoms except those attached to methyl groups to the final R factor of 0.084. The structure of the molecule is in Fig 1, which shows one of the two independent molecules in the unit cell. The conformation of two molecules are the same with each other.

Lupeolactone (1) shows, on oral administration, a significant lowering effect on serum cholesterol levels both in normal rats and in rats made hypercholesteremic beforehand by a high fat diet.

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References

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