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NEW DITERPENE, 13-OXYINGENOL, DERIVATIVE ISOLATED FROM EUPHORBIA KANSUI LIOU.

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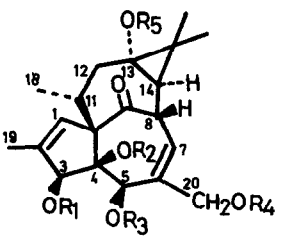
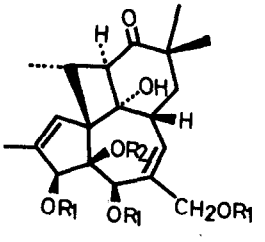
"Kansui (E. kansui Liou.)[1]" has been known of the toxicity for a long time. As the active components did not make clear, we started to study this active constituent. Several active compounds are obtained and now we wish to report the structure of new diterpene, 13-oxyingenol derivative, the unique cyclobutanol formation by intra-molecular aldol condensation, and the mild decomposition by 1,3-fragmentation reaction.

Ethanol extracts of dried roots of the title plants (commercially avaiable as chinese drag) were treated by an ordinary method. High pressure liquid chromatography and another works afforded an oily product (1): $C_{38}H_{60}O_8$ [IR ($CHCl_3$) 3500, 1725, 1620 cm^{-1}; Mass 644 (m^+); NMR Fig. 1].





(1) R_1= R_2= R_3= H, R_4= $CO(CH_2)_4CH_3$, R_5= dodecanoyl

(2) R_1= R_2= R_3= R_4= H, R_5= dodecanoyl

(8) R_1= R_2= R_3= R_4= CH_3, R_5= dodecanoyl

(9) R_1= R_2= R_3= R_4= CH_3, R_5= H

(13) R_1, R_2= CO, R_3, R_4= CO, R_5= dodecanoyl

(3) R_1= R_2= H

(4) R_1= $COCH_3$, R_2= H

(12) R_1= R_2= CH_3

This compound (1) gave 13-oxyingenol dodecanoate (2) with sodium methoxide in methanol followed by the treatment with IRC-50, whose nmr spectrum was similar to that of ingenol[2]. But the acyloxy group to attach at the tertiary carbon atom of ingenol was suggested from the molecular formula and the abscence of new low-field signal in the nmr spectrum. Moreover, the attached position is at C-13 because of the following facts. The signal of doublet assigned to secondary methyl group was observed in the nmr spectrum of compound (2). Though the proton at C-14 is not assigned in the nmr spectrum at Fig. 1, the coupling of the proton at C-8 to that at C-7 and C-14 showed the presence of the proton without the acyloxy group at C-14. To obtain a parent alcohol, the next reaction were tried.

13-Oxyingenol dodecanoate (2) was stable for alkali, so we attempted a reductive cleavage of the ester with lithium aluminum hydride for 10 minutes at 0° in ether. No parent alcohol, 13-oxyingenol, were obtained. But we caught the novel structural compound (3), $C_{20}H_{28}O_6$: IR (KBr) 3550, 1700, 1660, 1635 cm^{-1}; Mass 364 (m^+); NMR Fig. 2. In this compound a cyclopropanol was disappeared because of the stability for bases, acids, and electrophilic reagents (e.g. lead tetraacetate and bromine)[3]. The occurrence of intra-molecular aldol condensation was considered. We tried the following reactions to obtain the evidence.

After acetylation of compound (3), a triacetate (4) was converted to an alcohol (5) [NMR (δ in $CDCl_3$) 2.18 (1H, d of d, J= 7, 11 Hz, H-12), 2.65 (1H, d of q, J= 7, 7 Hz, H-11), 3.65 (1H, d, J= 11Hz, H-13)]. Alcohol (5) was treated with methanesulfonyl chloride in pyridine to give a compound (6). The 1,3-fragmentation[4] containing the cleavage of four-membered ring was achieved with DBU in benzene at 50° for 3 hours, afforded the compound (7). The presence of cyclopropanol in the parent alcohol was approved by the next evidence.

The methylation of compound (2) with silver oxide and methyl iodide in DMF gave a tetramethyl ether (8), which was converted to a cyclopropanol (9) with lithium aluminum hydride in ether at 0° for 15 minutes: (9); IR (KBr) 3450, 1730, 1665, 1630 cm^{-1}; Mass 420 (m^+); NMR (δ in $CDCl_3$) 1.81 (1H, d of d, J= 7, 16 Hz, H-12α), 2.52 (1H, d of d, J= 3, 16 Hz, H-12β), 2.80 (1H, d of d of q, J= 7, 3, 7 Hz, H-11). The unstability caused by the cyclopropanol moiety was disappeared by the treatment with lead tetraacetate in benzene at 5°.
In the reaction product (10), the presence of the isopropenyl group and new ketone were observed by the nmr spectrum [δ 1.66 (3H, d, J=1 Hz), 4.91 (1H, d of q, J= 1,2 Hz), 5.09 (1H, d of q, J= 1, 2 Hz)] and the formation of product (11) by reduction with sodium borohydride. The reason why the tetramethyl ether (8) produce no cyclobutanol compound with lithium aluminum hydride

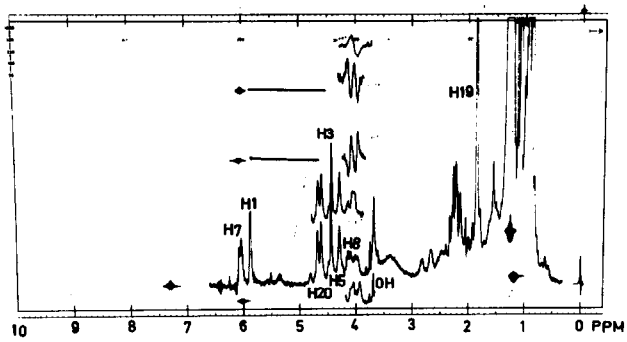


Fig. 1 100 MHz normal and INDOR spectra of compound (1) in $CDCl_3$.

Irradiate	Observe
H-18	H-11 (d, J= 10 Hz)
βH-14	αH-14 (d, J= 14 Hz)
	H-8 (br. d)
H-19	H-1 (s)
αH-14	βH-14 (d, J= 2.5 Hz)
	H-8 (br. s)
H-8	αH-14 (d, J= 14 Hz)
	βH-14 (d, J= 14 Hz)
	H-7 (s)

* H-13 (d, J= 10 Hz)

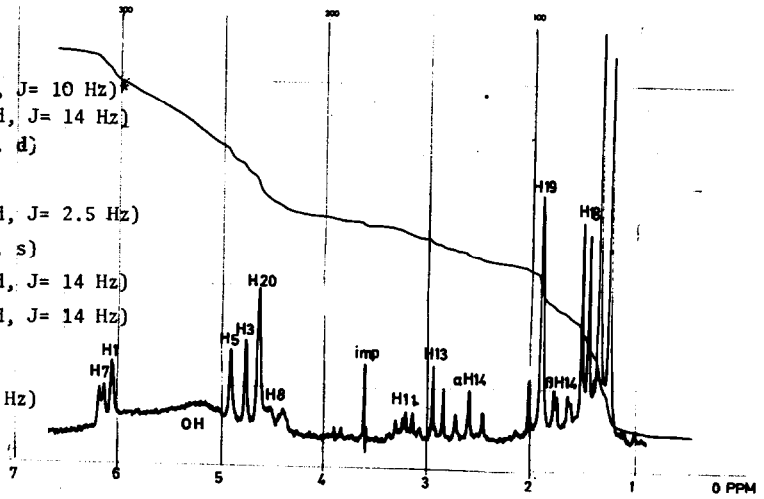
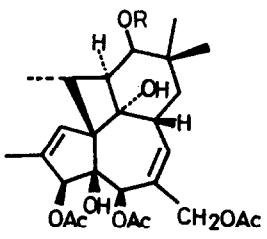
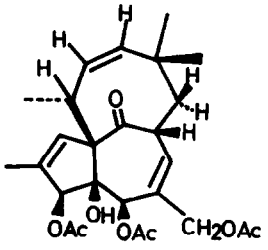


Fig. 2 The 100 MHz spectrum of compound (3) in C_5D_5N.

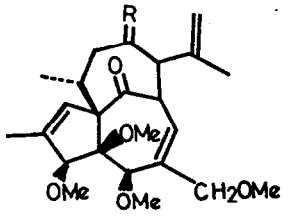


(5) R= H

(6) R= SO_2CH_3



(7)



(10) R= O

(11) R= 

may be the steric effect by the methoxy group at C-4[5]. Actually, the treatment of the cyclopropanol (9) with the more suitable base (potassium t-butoxide) for aldol condensation afforded compound (12).

We considered the stereochemistry of 13-oxyingenol derivatives as the picture from the following results. As the compound (2) gave dicarbonate (13) with N,N'-carbonyldiimidazole and the nmr spectrum was similar to of the ingenol dicarbonate, oxygen groups at C-3, C-4, and C-5 have the same configuration as ingenol. The relationship between the oxygen groups at C-3 and C-4 is cis. Moreover, we concluded that the oxygen group at C-5 is β equatorial configuration from easy formation of six-membered carbonate ring and from the consideration that, if it was reverse configuration against the picture, the chemical shifts of protons at C-3 and C-5 in the nmr spectra should change obviously[6]. The coupling constant between H-8 and H-14 in the nmr spectrum of compound (1) shows the diaxial relationship of H-8 and H-14. In the nmr spectra of compound (9), the coupling constant between H-11 and H-12 proposes that a secondary methyl group at C-11 is equatorial. With the aid of Dreiding models configurations of those proton (H-8, H-14, and H-11) are β, α, and β, respectively. And absolute configuration of the compound (2) was determined by the mesurement of CD spectrum [290 nm ($\Delta\varepsilon$= -1.5)] and the comparison with that of ingenol.

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5) The cis-juncture of four-membered system to six-membered ring was suggested by the result that the stable product in the equilibium in the basic circumstance is dominant. and the formation of the compound (3) may proceed via the enol intermediate. Especially, the CD spectrum of compound (3) was resonable for our assignment. The detailed arguement about CD spectra of related compounds is described in the following paper.

6) We can expect so because the proton at C-3 suffer the effect from oxygen group at C-5 and the proton at C-5 is effected by ketone on the opposite site.