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KANSUININE B, A NOVEL MULTI-OXYGENATED DITERPENE FROM EUPHORBIA KANSUI LIOU.

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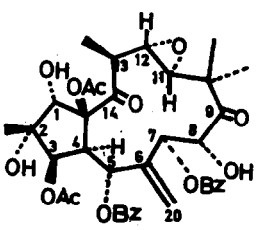
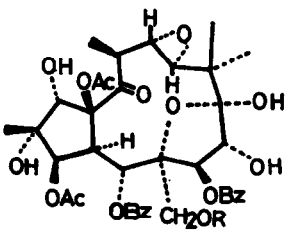
In the course of a continuing search for toxic natural products, we obtained two novel compounds, named kansuinine A and B. We report herein the isolation and structural elucidation of kansuinine B (1), structurally related with kansuinine A[1]. These diterpenoids are the first members of the rare jatrophone class[2] which have been shown to possess analgesic and anti-writhing activities.

Fractionation of an ethanol extract, guided by toxicity, was made by column chromatography (on silicic acid), preparative thin layer chromatography, and high speed liquid chromatography (with MicroPak NH_2 column)[3]. The result of the structural study of the toxic compound was published in 1974[4]. Kansuinine B was obtained by further purification by recycle operation in high speed liquid chromatography as a crystalline compound [$C_{38}H_{42}O_{14}$; m.p. 160-162°; $[\alpha]_D^{23}$ +37 (c, 0.27 MeOH); IR(KBr) 3500, 1720 (broad absorption), 1640, 1609, 1590 cm^{-1}; NMR Fig.1; Mass m/e 722.2489 (m^+ calcd. 722.2494)].

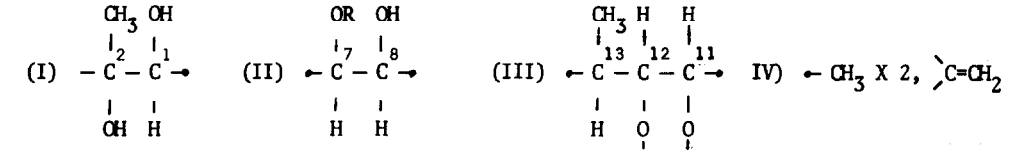


(1) kansuinine B



(2) R= H
(3) R= p-bromobenzoate

Kansuinine B has two acetate groups and two benzoate groups as shown in the nmr spectrum. Consequently, the parent alcohol is $C_{20}H_{30}O_{10}$, a highly oxygenated diterpene. We obtained information about functional groups of kansuinine B by following reactions. Kansuinine B (1) afforded a diol (2) with osmium tetroxide in pyridine followed by treatment with sodium bisulfite, and purification by preparative thin layer chromatography. In the nmr spectrum of compound (2) the signal attributed to two protons of a hydroxy methylene group appeared at δ 4.18 as a broad singlet. And the p-bromobenzoate (3), m.p. 216-218°, was obtained from (2) by the action of p-bromobenzoyl chloride in pyridine, which was esterified at the hydroxy group at C-20 judging from the chemical shift of two protons (δ 5.02). Furthermore, the oxidation of kansuinine B by periodic acid afforded a keto-aldehyde (4) [m.p. 240-242°; Mass 720 (m^+); NMR (δ, $CDCl_3$) 1.89 (3H, s, C-CO-$\underline{CH_3}$), 4.68 (1H, br.s, H-8), 9.56 (1H, s, -$\underline{CHO}$)], which was converted to a monoacetate (5) with acetic anhydride in pyridine. From the nmr spectra of these compounds (1), (2), (3), (4), and (5), the presence of the six groups shown below for kansuinine B were revealed.



The structure of compound (3) was unambiguously established by X-ray analysis[5] as shown in Fig.2 and Fig.3. The space group is $P\bar{1}$ and the lattice constants are a=10.57 A, b=11.97 A, c=9.96 A, α=103.3°, β=104.1°, and γ=82.2°. The final R index for 3527 reflections is 0.07.

The oxorane ring in compound (3) was present in compound (2) because the signal of the proton attached at C-8 appeared at δ 4.0-4.1 as a broad singlet, in the nmr spectra of compounds (2) and (3), respectively. Kansuinine B lacks this oxorane ring, but instead possesses an α-ketol group, since the signal of the proton at C-8 in the nmr spectrum of kansuinine B was observed at lower field (δ 4.68) than the corresponding one in compounds (2) and (3). That the intramolecular hemiketal formation occurred during the preparation of (2) and (3) was made clear. But the epimerization of the α-ketol group $\underline{via}$ the ene-diol form was not observed under these conditions in kansuinine B.

From the above results the structure of kansuinine B was established as shown in $\underline{1}$. Intramolecular formation of the oxorane ring was also observed in the acidic media. Keto aldehyde (4) afforded compound (6) [m.p. 260-261°; Mass 720 (m^+); NMR(δ, $CDCl_3$) 1.86

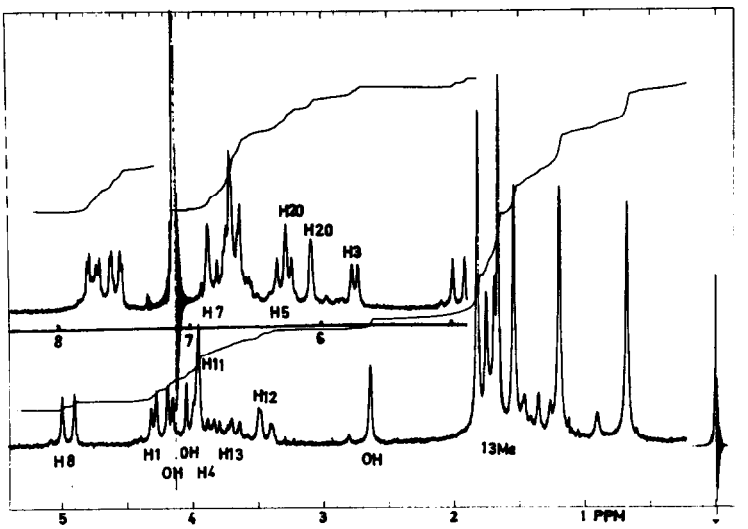


Fig. 1 The nmr spectrum (100 MHz, C_6D_6) of kansuinine B

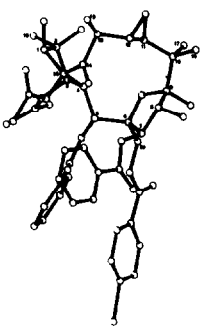


Fig. 2

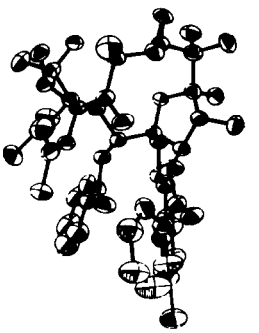
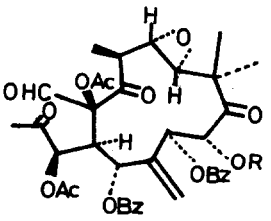
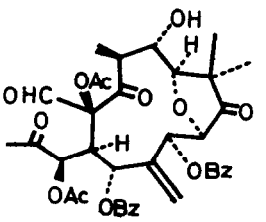


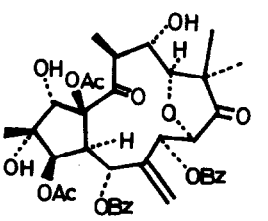
Fig. 3



(4) R= H
(5) R= Ac



(6)



(7)

(3H, s, C-CO-$\underline{CH}_3$), 3.55 (1H, d of q, J= 7, 10 Hz, H-13), 3.69 (1H, d, J= 10 Hz, H-11), 4.50 (1H, t, J= 10 Hz, H-12), 4.73 (1H, br.s, H-8), 9.69 (1H, s, -$\underline{CH}$O)] with HCl gas in MeOH. The structure was suggested by the nmr spectrum of compound (6). The signal of two protons on the carbon atoms bearing oxygen atom constituting oxirane ring disappeared, and new signals of protons at C-11 and C-12 appeared at δ 3.69 and δ 4.50, respectively. Also, treatment of kansuinine B (1) with HCl gas in MeOH gave compound (7) [m.p. 235-236°; IR($CHCl_3$) 3500, 1765, 1725, 1640, 1600, 1585 cm^{-1}; Mass 722 (m^+); NMR(δ, $CDCl_3$) 1.86 (3H, br.s[6], $OCO\underline{CH}_3$), 3.46 (1H, d of q, J= 6, 10 Hz, H-13), 3.57 (1H, d, J= 9 Hz, H-11)]. Furthermore, compound (7) was converted to compound (6) with periodic acid in acetone-water. The relationship between conformations and reactions of kansuinine B is under investigation.

REFERENCES

1) D. Uemura, Y. Hirata, Y.P. Chen, and H.Y. Hsu, Tetrahedron Letters, this issue.

2) S.M. Kupchan, C.W. Singel, M.J. Matz, J.A. Saenz Renauld, R.C. Haltiwanger, and R.F. Bryan J. Amer. Chem. Soc., 92, 4476 (1970).

3) We thank Dr. R.L. Stevenson (Varian Aerograph, Walnut Creek, California) for helpful discussions.

4) D. Uemura, Y. Hirata, Y.P. Chen, and H.Y. Hsu, Tetrahedron Letters, 2527, 2528 (1974).

5) We prepared several derivatives for X-ray analysis, but only this compound was suitable for the purpose.

6) This signal may be attributed to the acetoxyl group at C-15.