Structure of Isodomedin, a Novel *ent*-Kaurenoid Diterpene

By ISAO KUBO,* IWAO MIURA, and KOJI NAKANISHI
(*Department of Chemistry, Columbia University, New York* 10027)
TADAO KAMIKAWA and TAKAHIKO ISOBE
(*Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka* 558, *Japan*)
and TAKASHI KUBOTA
(*School of Medicine, Kinki University, Sayama-cho, Osaka* 589, *Japan*)

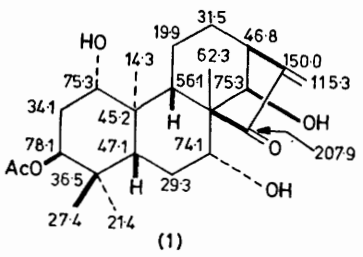
Summary Chemical investigation of bitter principles from *Isodon skikokianus* var *intermedius* has led to the isolation and characterization of a new *ent*-kaurenoid, isodomedin, which exhibits antibacterial and cytotoxic activities as well as antifeedant activity against the African army worm.

IN the continuing search for biologically active diterpenoids of the *Isodon* species,[1] we have examined *I. shikokianus* var *intermedius*, from which a new antibacterial and cytotoxic principle,† isodomedin, m.p. 217—218 °C, has been isolated in 0·0004% yield from dry leaves. Isodomedin exhibited antifeedant activity against the larvae of the African army worm, *Spodoptera exempta*.

We now propose the *ent*-kaurenoid structure (**1**) for this bitter principle. Isodomedin, which is closely related to kamebanin (**2**)[2] isolated from *I. kameba*, gives the following data: $C_{22}H_{32}O_6$ (high resolution m.s. and elemental analysis), $[\alpha]_D - 59°$ (*c* 1·0, EtOH); λ_{max} (EtOH) 233·5 nm (ϵ 8020); ν_{max} (Nujol) 3570 and 3420 (OH), 1710 and 1270 (OAc), and 1700 and 1650 cm^{-1} (5-membered ring ketone conjugated with exocyclic methylene). The ^{13}C n.m.r. data of isodomedin (Figure 1) showed the presence of 3 × Me, 1 × Ac, 4 × CH_2, 7 × CH groups, and three tetrasubstituted carbon atoms together with two olefinic and two carbonyl carbon atoms.[3]‡

† The cytotoxicity (KB) effect (LD_{50}) was 4·0 μg ml^{-1}. The detailed study will be published elsewhere.

‡ The results are based on a combination of proton-noise decoupling, off-resonance decoupling, and Fourier transform off-resonance decoupling techniques, (P. Zanno, I. Miura, K. Nakanishi, and D. Elder, *J. Amer. Chem. Soc.*, 1975, **97**, 1975).



(1)

FIGURE 1. Isodomedin; ^{13}C n.m.r. data (δ/p.p.m.) for C_5D_5N solution.

The pertinent ^1H n.m.r. data are shown in Figure 2; the gross structure of rings A–B–C was established by observation of a nuclear Overhauser effect (n.O.e.) on 10-Me upon irradiation of the 14α-H signal. Dihydroisodomedin (**3**), obtained from catalytic hydrogenation of (**1**), has a negative c.d. (MeOH) $\Delta\epsilon_{300}$ −0·86 and hence the D-ring is β-oriented.[4] High resolution electron impact mass spectrometry of isodomedin showed peaks at *m/e* 194 and 176 which were formed by cleavage of the B-ring.[5] Comparison of the ^{13}C and ^1H n.m.r. spectra of isodomedin with those of kamebanin indicated that the only difference between these two compounds was an additional acetoxy group in the A-ring of isodomedin. The dd splitting pattern of the C*H*–OH signal (δ 3·86) showed that a methylene group was adjacent to this proton and thus that the hydroxy group should be attached either to C-1 or C-3. The *J* values of this dd signal (10 and 6 Hz) showed the hydroxy group to be equatorial. To determine the position of the acetoxy group, n.O.e. studies were performed on (**5**). Observation of a 10% n.O.e. on 18-Me upon irradiation of the original –C*H*–OAc signal (which is easily distinguished from other protons on the carbon atoms bearing an acetoxy group by their coupling constants) revealed that the acetoxy group in (**1**) is at the 3 position. It is clear that this group is β-oriented from the values of $J_{2\alpha,3\alpha} = J_{2\beta,3\alpha} = 3$ Hz.

The 1,15-dione (**4**) was derived by oxidation of (**3**) with Jones' reagent. The 7- and 14-hydroxy groups were not oxidized under these conditions because of intermolecular H-bonding. In the ^{13}C n.m.r. spectrum of (**4**), the doublet resonance of C-1 was replaced by a singlet and the C-2 and C-10 signals had undergone the expected downfield shifts of the adjacent C-1 ketone group. The negative c.d. (MeOH) $\Delta\epsilon_{300}$ −1·80 of (**4**) was almost identical with that of the 1,15-dione (**6**) which had been obtained from (**2**) in a similar manner. This supports the assignment of the hydroxy group at the 1 position.

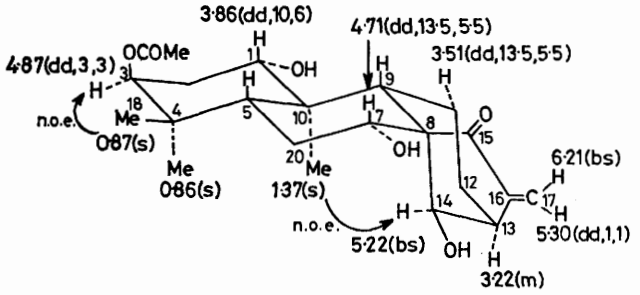
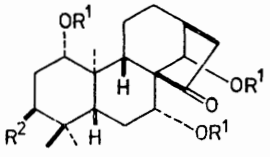
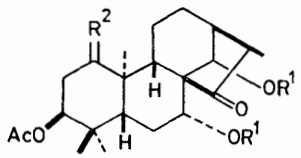


FIGURE 2. ^1H n.m.r. data for (**1**); C_5D_5N solution; δ values; multiplicity and *J* values (in Hz) in parentheses.

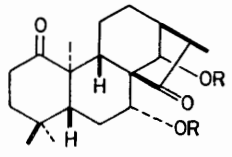
The structure was confirmed by correlation with kamebanin (**2**). The hydroxy group of (**4**) was protected with phenylboric acid, followed by treatment with 1N-K_2CO_3 in 50% aq. MeOH to give an enone (**7**). This was then hydrogenated to yield a deacetyldione (**8**), which was identical in all respects with the compound derived from (**2**) in a similar manner.



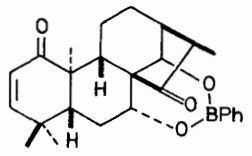
(2) $R^1 = R^2 = H$
(5) $R^1 = Ac, R^2 = OAc$



(3) $R^1 = H, R^2 = \overset{OH}{H}$
(4) $R^1 = H, R^2 = O$



(6) R = H
(8) RR => BPh



(7)

This work was partly supported by the N.I.H.

(*Received*, 19*th May* 1977; *Com.* 486.)

[1] E. Fujita, Y. Nagao, and M. Node, *Heterocycles*, 1976, **5**, 793 and references cited therein.
[2] I. Kubo, I. Miura, T. Kamikawa, T. Isobe and T. Kubota, submitted for publication.
[3] I. Miura and I. Kubo, submitted for publication.
[4] L. H. Briggs, R. C. Cambie, and P. S. Ruttedge, *J. Chem. Soc.*, 1963, 5374; W. Herz and R. P. Sharma, *J. Org. Chem.*, 1976, **41**, 1021.
[5] I. Kubo, T. Kamikawa, T. Isobe, and T. Kubota, *Bull. Chem. Soc. Japan*, 1974, **47**, 1277.