ANTITUMOR DITERPENOIDS FROM RABDOSIA TRICHOCARPA: TRICHORABDAL E, F, AND H AND G ACETATE

Manabu Node, Midori Sai, Eiichi Fujita, and Kaoru Fuji*
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

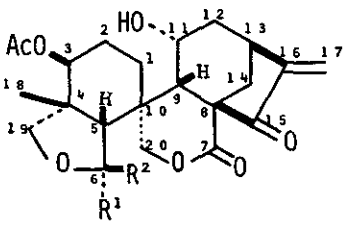
Abstract ——— The structure determination and conformation of antitumor diterpenoids, trichorabdal E, F, and H, are described.

In the course of our investigation of antitumor diterpenoids in *Rabdosia trichocarpa* (Maxim.) Hara,[1] we have isolated two new diterpenoids, trichorabdal E (T-E, 1) and H (T-H, 2) and other two trichorabdals (F and G) as acetates 3 and 4, respectively. These natural products and their derivatives showed potent *in vivo* antitumor activity against Ehrlich ascites carcinoma.[2] Here, we describe structure elucidation of these diterpenoids.

T-E (1), $C_{22}H_{28}O_8$, mp 291°C (decomp.); $[\alpha]_D$ (EtOH) -98.4°; νmax (KBr) 3450, 1740, 1720, 1695, 1640 cm^{-1}; λmax (EtOH) 229 nm (ε 7700), on acetylation with Ac_2O-pyridine afforded an acetate 5, mp 229 - 231°C, which was identical with the product derived from trichorabdal D (6)[1b] on the treatment with acetic acid. Mild acid hydrolysis of 5 gave T-E (1) back, confirming the structure of T-E (1). The ^1H NMR spectrum[3] of T-E (1) showed a complex pattern due to an equilibrium between 1a and 1b in the solution.[4]

The seven oxygen atoms in T-H (2), $C_{22}H_{28}O_7$, mp 217 - 219°C, $[\alpha]_D$ +19.4° (MeOH), can be assigned to a secondary hydroxyl group [νmax (KBr) 3420; ^1H NMR ($CDCl_3$) δ 4.39 (m, 1H)], an α-methylene-cyclopentanone moiety [λmax (MeOH) 229 nm (ε 8850); νmax 1700, 1635 cm^{-1}; δ 5.52 (s, 1H), 6.04 (s, 1 H], a δ-lactone (νmax 1740 cm^{-1}), an aldehyde group [νmax 2850, 2740 cm^{-1}; δ 9.78 (d, 1H, J = 5 Hz)], and an acetoxyl group [δ 2.00 (s, 3H)]. The structure of T-H (2) including the position and stereochemistry of the substituents was determined by its conversion to nodosin (7)[5] on the treatment with hydrochloric acid-acetic acid.

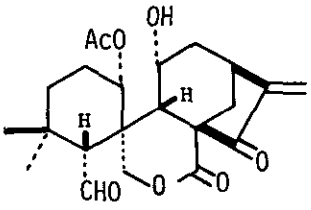
T-F and T-G were characterized as acetates 3, $C_{22}H_{28}O_7$, mp 221 - 223°C; $[\alpha]_D$ - 78.0° (EtOH); νmax ($CHCl_3$) 3600, 3400, 1755, 1735, 1715, 1640 cm^{-1}; λmax (EtOH) 228 nm (ε 9400); ^1H NMR (C_5D_5N) δ 1.01 (s, 3H, $-CH_3$), 2.20 (s, 3H, $-OCOCH_3$), 2.64 (d, 1H, J = 5.5 Hz, 5-H), 3.12 (dd, 1H, J = 8, 4 Hz, 13-H), 3.49, 3.85 (ABq, each 1H, J = 8 Hz, 19-H_2), 3.63 (d, 1H, J = 11.5 Hz, 14α-H), 4.08 (dd, 1H, J = 12, 1.5 Hz, 20-H), 4.48 (m, 1H, 11-H), 5.32 (d, 1H, J = 12 Hz, 20-H), 5.46, 6.13 (br s each



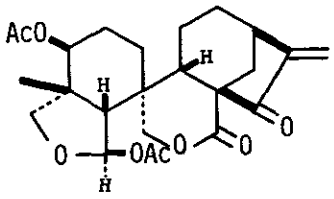
1a ; R^1= H, R^2= OH

1b ; R^1= OH, R^2= H

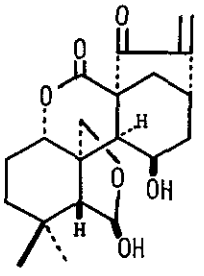
5 ; R^1= H, R^2= OAc



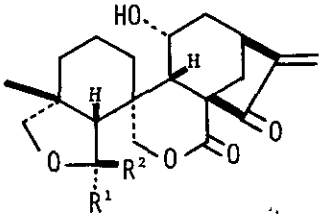
2



4



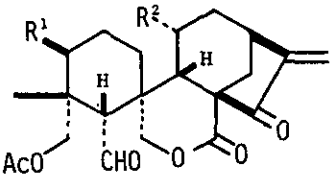
7



3 ; R^1= H, R^2= OAc

9a ; R^1= H, R^2= OH

9b ; R^1= OH, R^2= H



6 ; R^1= R^2= OH

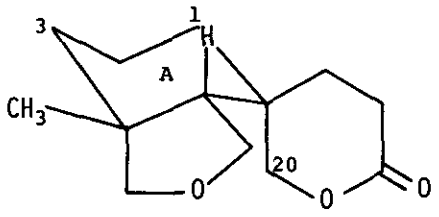
8 ; R^1= H, R^2= OH

10 ; R^1= OH, R^2= H

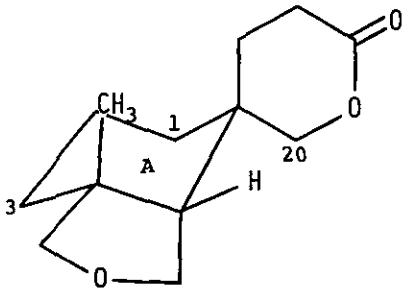
1H, 17-H_2), 6.85 (d, 1H, J = 5.5 Hz, 6-H) and 4, $C_{24}H_{30}O_8$, mp 214 - 215°C; $[\alpha]_D$ -65.2° (EtOH); νmax ($CHCl_3$) 1755, 1730, 1720, 1640 cm^{-1}; λmax (EtOH) 230 nm (ε 7700); ^{1}H NMR (C_5D_5N) δ 1.17 (s, 3H, $-CH_3$), 2.03 (s, 3H, $-OCOCH_3$), 2.18 (s, 3H, $-OCOCH_3$), 2.40 (d, 1H, J = 12 Hz, 14-H), 2.62 (br d, 1H, J = 5.5 Hz, 5-H), 2.92 (dd, 1H, J = 9, 4 Hz, 13-H), 3.69, 3.78 (ABq, each 1H, J = 8 Hz, 19-H_2), 3.90 (dd, 1H, J = 12, 2 Hz, 20-H), 4.24 (d, 1H, J = 12 Hz, 20-H), 5.13 (dd, 1H, J = 12, 4 Hz, 3-H), 5.42, 6.09 (s, each 1H, 17-H_2), 6.80 (d, 1H, J = 5.5 Hz, 6-H). The known diterpene, trichorabdal B (8)[1a] was treated with aqueous hydrochloric acid in tetrahydrofuran followed by acetylation to afford an acetate which was identical with T-F acetate (3). Thus, the structure 3 for T-F acetate was confirmed. T-F acetate (3) was reverted to T-F (9)[6] on acidic hydrolysis, which indicated that no skeletal rearrangement took place during acetylation and hydrolysis. T-F (9) exists as a mixture of 9a and 9b as in the case of T-E (1), when it is dissolved in the solvent. Though the structure of T-G acetate (4) was confirmed by the conversion from trichorabdal C (10)[1b] on treatment with acetic acid, the structure of T-G itself remains to be clarified. It has been reported that the ring A of trichorabdal C (10) exists in the chair form A with the axially oriented C(20) as in the case of normal kaurene-type diterpenoids.[1b] On the other hand,

the ring A of T-B (8)[1a] and T-D (6)[1b] takes another chair form B in which the C(20) is equatorial. Thus, a comment on the conformation should be necessary to describe the complete structure of trichorabdals.

It follows from the coupling pattern (δ 5.16 ppm, dd, J = 11, 4 Hz for 5 and δ 5.13 ppm, dd, J = 12, 4 Hz for 4) of the ^{1}H NMR signal of 3-H that the proton at C(3) is axially oriented in T-E acetate (5) and T-G acetate (4). This indicates that ring A of 4 and 5 exists as a chair form B. An X-ray crystallographic determination[8] showed that ring A in T-F acetate (3) took the same conformation as 4 and 5. T-H (2) has the ring A of normal chair form A, because 1-H appeared as a broad triplet with J = 8 Hz at δ 5.70 ppm, suggesting the axial nature of this proton.



A



B

ACKNOWLEDGEMENT

Partial support for this work by Suzuken Memorial Foundation is gratefully acknowledged.

REFERENCES AND NOTES

1. a) E. Fujita, K. Fuji, M. Sai, M. Node, W. H. Watson, and V. Zabel, *J. Chem. Soc. Chem. Commun.*, 1981, 899. b) M. Node, M. Sai, K. Fuji, E. Fujita, T. Shingu, W. H. Watson, and D. Grossie, *Chem. Lett.*, 1982, 2023. c) K. Fuji and M. Node, *Rev. Latinoamer. Quim.*, 1983, 14, 55.
2. To be published elsewhere.
3. Taken at 400 MHz.
4. The ratio can be calculated from the integration of methyl signals (δ 1.06 and 0.99 ppm, 2 : 1 in $CDCl_3$, δ 1.02 and 0.93 ppm, 5 : 2 in DMSO-d_6/$CDCl_3$).
5. E. Fujita, T. Fujita, and M. Shibuya, *Chem. Pharm. Bull.*, 1968, 16, 509.
6. The structure 9a was assigned to shikodonin isolated from *Rabdosia shikokianus*.[7] However, in our experience 9a cannot exist in the single form in pyridine-d_6 or $CDCl_3$, but gives an

equilibrium mixture of 9a and 9b whose ratio depends upon the solvent. Moreover, the pertinent ^{1}H NMR data for shikodonin reported in the literature corresponded to neither 9a nor 9b in the equilibrium mixture. It, therefore, seems to us that the structure of shikodonin should be reinvestigated.

7. I. Kubo, M. J. Pettei, K. Hirotsu, H. Tsuji, and T. Kubota, *J. Am. Chem. Soc.*, 1978, 100, 628.

8. R. P. Kashyap, W. H. Watson, D. A. Grossie, M. Node, M. Sai, E. Fujita, and K. Fuji, to be published.

Received, 11th April, 1984