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THREE NEW ANTI-TUMOR DITERPENOIDS, TRICHORABDALS A, C, AND D

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Structures of trichorabdals A, C, and D, isolated from *Rabdosia trichocarpa* have been determined by means of chemical, spectroscopic, and X-ray crystallographic methods. The compounds possess potent anti-tumor activity.

In a previous communication we have reported the isolation of trichorabdals A, B, C, and D (T-A, -B, -C, and -D), from *Rabdosia trichocarpa* and the structure determination of T-B.[1] Here we describe the structure elucidation of T-A, -C, and -D, which show potent *in vivo* antitumor activity[2] against Ehrlich ascites carcinoma inoculated into mice.

A close inspection of Tables I and II reveals that T-A (**1**), -C (**3**) and -D (**4**) possess the same basic skeleton as T-B (**2**). T-A (**1**) shows two singlet methyls at 0.97 and 1.00 while the AB type signal of 19-H_2 is abscent. These data easily lead to structure **1** for T-A. More direct evidence for the structure **1** was obtained by identifying its acetate **5** with the product derived from the periodate oxidation of longikaurin E[3] (**6**).

Molecular composition and ^{1}H NMR data indicate that T-C (**3**) is an isomer of (**2**) with respect to the position of a hydroxyl group. T-D (**4**) has two hydroxyl groups in the molecule. Comparison of ^{1}H NMR data of T-D (**4**) with that of T-B (**2**) indicates that one of them is located on C-11 with α-configuration. Especially,

Table I. Physical Data of Trichorabdals

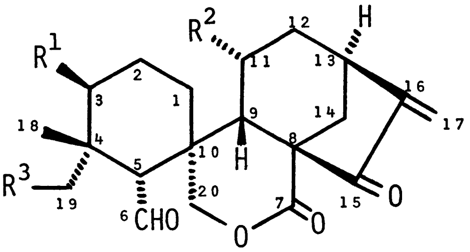
trichorabdals	mp, °c	$[\alpha]_D^a$	λ_{max}, nm $(\varepsilon)^a$	ν_{max}, cm^{-1}
A (1), $C_{20}H_{26}O_5$	198-201	-63.9°	232 (8500)	3600, 2820, 1740, 1640^b 3450, 2750, 1710
C (3), $C_{22}H_{28}O_7$	143.5-145	+31.5°	235 (9000)	3450, 2750, 1745, 1640, 1230^c 1715
D (4), $C_{22}H_{28}O_8$	213-215	-89.2°	230 (10200)	3550, 2840, 1745, 1640, 1240^b 3470, 2750, 1730, 1710

a) In ethanol. b) KBr C) In $CHCl_3$

Table II. Pertinent ^1H NMR Data of Trichorabdal A, B, C, and D

	chemical shift^a										
compound	$-CH_3$	-OAc	$=CH_2$	3-H	5-H	CHO	11-H	13-H	14α-H	$19-H_2$	$20H_2$
T-A (1) (d_5-py), 40°	0.97 1.00		5.37 5.99	b	2.88 (d)^c	10.03 (d)^c	4.60	3.12	3.45		4.71 5.10
T-B (2) (d_5-py) 60°	1.19	2.00	5.46 6.05	b	3.11 (d)^d	10.19 (d)^d	4.50	3.11	3.50	4.03 4.16	4.50 5.15
T-C (3) ($CDCl_3$), rt	1.21	2.04	5.50 6.01	3.65	2.86 (d)^c	9.82 (d)^c	b	3.10	b	4.58 4.69	4.07 4.20
T-D (4) (d_5-py), 60°	1.40	2.02	5.48 6.06	4.20	3.48 (d)^d	10.22 (d)^d	4.58	3.14	3.50	4.27 4.52	4.30 5.16

a) Reported in δ using TMS as internal reference. b) Unable to be extracted due to overlapping. C) J = 3 Hz. d) J = 4 Hz.



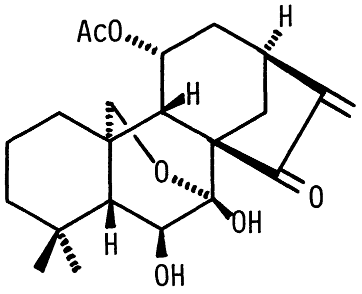
1 : $R^1 = R^3 = H$, $R^2 = OH$

2 : $R^1 = H$, $R^2 = OH$, $R^3 = OAc$

3 : $R^1 = OH$, $R^2 = H$, $R^3 = OAc$

4 : $R^1 = R^2 = OH$, $R^3 = OAc$

5 : $R^1 = R^3 = H$, $R^2 = OAc$



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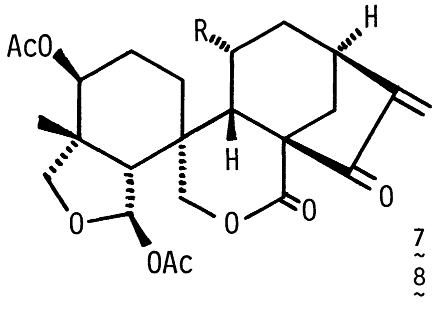
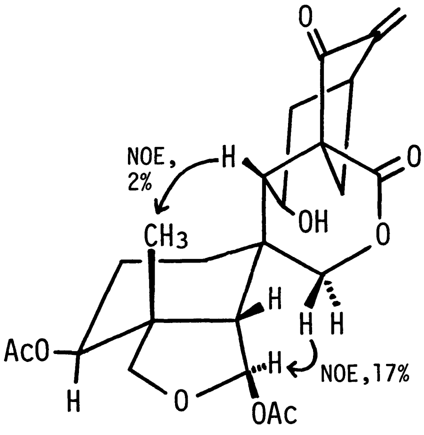


7 : R = H

8 : R = OH

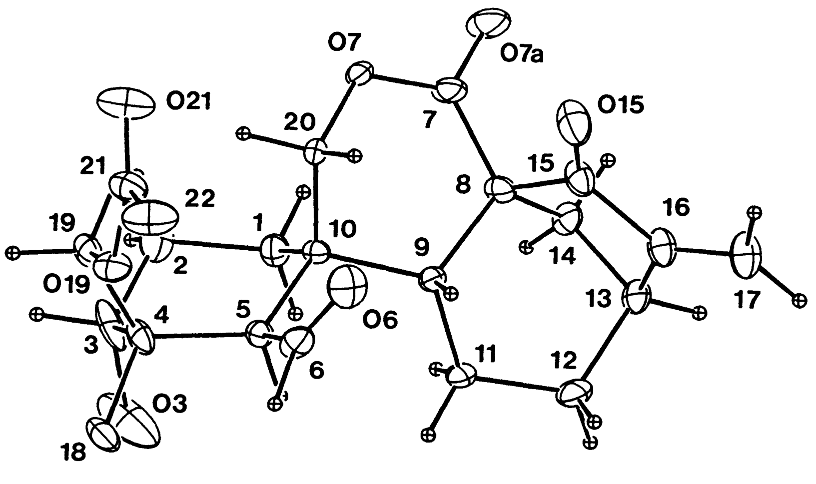
significant is the downfield shift of 14α-H (δ 3.50, d, J=12 Hz) which is clear evidence for the existence of a 11α-hydroxyl moiety. On treatment with acetic acid at 90°C under nitrogen T-C (3) and T-D (4) afforded acetates 7 and 8 respectively. They may be formed through an acyl migration from the oxygen atom at C-19 to the hydroxyl group at C-3 followed by hemiacetal formation and substitution with acetoxyl group on C-6. Detailed nuclear Overhauser experiments confirm the stereochemistry of 8 as shown in Figure 1, where ring A has a chair conformation with C-9 axial and C-20 equatorial. ^{1}H NMR signal of H-3 at δ 5.16 (dd, J=11, 4 Hz) in 8 and at δ 5.08 (dd, J=11, 4 Hz) in 7 indicates the β-equatorial orientation of the acetoxyl groups on C-3 in both compounds. Thus, the structures of T-C and T-D are unequivocally assigned as 3 and 4 respectively.

Figure 1. NOE measurements on 8.



A comment on the conformation of ring A in trichorabdals seems necessary. Though axial orientation of the proton on C-3 in T-D (4) is suggested from the coupling pattern of ^{1}H NMR signal at δ 4.20 (t, J=8, shifted to δ 5.26, t, J=8 Hz on acetylation), in T-C (3) the proton on C-3 appeared as a triplet with a small coupling constant (J=3 Hz) at δ 3.65 indicating equatorial nature of the proton

Figure 2. Ortep drawing of the relative configuration of T-C (3).



in question. Thus, conformational change of the A ring in T-C (3) must occur during the transformation to 8, which suggests that the A ring in T-C (3) has a different conformation from that in trichorabdals B and D[4]. This was confirmed unambiguously by an X-ray structural analysis (See Fig. 2).

Compound 3 crystallizes in space group $p2_12_12_1$ with cell dimensions a = 11.382 (3), b = 16.46(1) and c = 10.612(7) Å. The structure was solved by direct methods and refined to a final R value of 0.062 using 1284 unique reflections[5].

The circular dichroism curve ($[\theta]_{310}$ -2850) of 16,17-dihydro derivative of 7 established the absolute configuration of T-C to be that shown in 3. The absolute stereochemistry of T-A and -D was assumed to be that of an *ent*-kaurane in analogy with T-B and -C.

Recently, two diterpenoids which possess spirosecokaurane skeleton were isolated from Rabdosia species.[6]

References

1) E. Fujita, K. Fuji, M. Sai, M. Node, W. H. Watson, and V. Zabel, J. Chem. Soc. Chem. Commun., 1981, 899.

2) For example, T-C showed T/C % walue of 256 at the 20 mg/kg level. Detailed discussion will be published elsewhere.

3) T. Fujita, Y. Takeda, and T. Shingu, Heterocycles, 16, 227 (1981).

4) It is inappropriate to discuss the conformation of ring A in T-A, because T-A has no hydroxy group on ring A. However, we suspect that ring A in T-A exists in the same chair conformation as T-B and -D, since the α-hydroxy group at C-11 seems to have a crucial effect on the conformation of ring A of tricholabdals.

5) Tables of positional coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

6) (a) I. Kubo, M. J. Pettei, K. Hirotsu, H. Tsuji, and T. Kubota, J. Am. Chem. Soc., 100, 628 (1978). (b) I. Kubo, T. Kamikawa, T. Isobe, and T. Kubota, J. Chem. Soc. Chem. Commun., 1980, 1206.

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