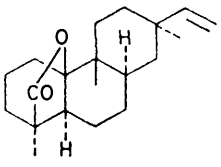
Studies on the Rearrangement of 8α,9α-Epoxy-12,12-ethylenedioxypodocarpan-16-ol Acetate by Boron Trifluoride–Ether. Formation of a Novel Product containing a C-seco, B-aromatic System

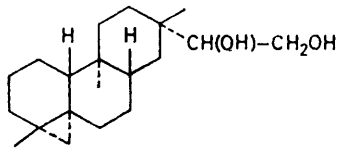
By **Tatsuhiko Nakano,* Alberto Haces,** and **Alfonso Martín,** Centro de Química, Instituto Venezolano de Investigaciones Científicas (I.V.I.C.), Apartado 1827, Caracas 1010–A, Venezuela
Anibal Rojas, Escuela de Química, Facultad de Ciencias, Universidad Central de Venezuela, Caracas, Venezuela

The rearrangement of 8α,9α-epoxy-12,12-ethylenedioxypodocarpan-16-ol acetate (3b) has been studied. Upon treatment with boron trifluoride–ether in a polar solvent (nitromethane), the epoxide (3b) yielded, besides compounds (8) and (7d), (9a) as the major product. In a non-polar solvent (benzene), however, compounds (18), (5c), and (5d) were obtained under the same conditions.

REARRANGEMENTS of the epoxides of pimarane derivatives have been exploited in biogenetically modelled synthesis [1a,b] of rosenonolactone (1). In connection



(1)



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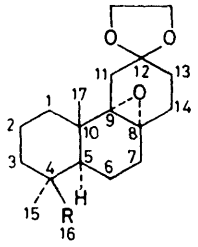
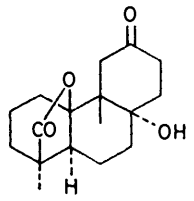
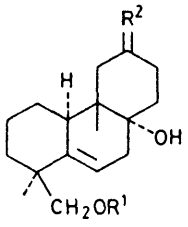


(3)



(4)

a; R = CO_2H
b; R = CH_2OAc



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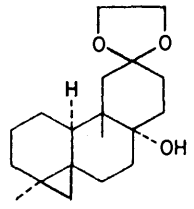


(6)

a; R^1 = Ac, R^2 = 
b; R^1 = Ts, R^2 = 
c; R^1 = Ac, R^2 = O
d; R^1 = Ac, R^2 = O, $\Delta^{5(10)}$

with the synthesis [2] of erythroxydiol X (2) which possesses a rosane-type structure containing a cyclopropane ring, we have also sought an intermediate which might be utilised for the construction of its fundamental skeleton. Mander and his co-workers [1b] prepared the α-epoxide (3a) of the $\Delta^{8(9)}$-ethylene acetal derived from 12-oxopodocarp-9(11)-en-16-oic acid, and by cleavage with boron trifluoride–ether obtained the hydroxylactone (4) for the construction of the rosenonolactone skeleton. We thought that if the acetate (3b) in place of the acid (3a) were used, then a product such as (5a) or (5d) might be formed upon rupture of the epoxide ring with boron trifluoride–ether. Once compound (5a) is formed, we might expect that its conversion into the 16-toluene-*p*-sulphonyl (5b) and subsequent reductive cyclisation [3] with lithium aluminium hydride would give a cyclopropane derivative such as (6).

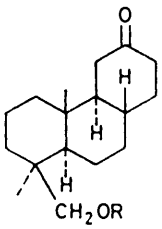
RESULTS AND DISCUSSION

The starting material for the synthesis of such an epoxide was the αβ-unsaturated ketone (7a) which was prepared *via* a known route [4] from methyl *O*-methylpodocarpate. The acetalisation of compound (7a) caused migration of the double bond to yield 12,12-ethylenedioxypodocarp-8-en-16-ol. Subsequent acetylation followed by epoxidation with *m*-chloroperbenzoic acid provided the desired α-epoxide (3b). We have studied the rearrangement † of this epoxide in both polar (nitromethane) and non-polar (benzene) solvents.†

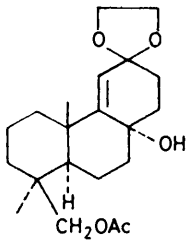
On treatment with boron trifluoride–ether (1 mol equiv.) in nitromethane, the epoxide (3b) yielded three products which could be separated by column chromatography over silica gel. The more polar product (5% yield) was a solid hydroxy-olefin, formulated as (8) on the basis of the following spectroscopic evidence. The mass spectrum gave a molecular ion at *m/e* 364. The i.r. spectrum showed the presence of an OH group (3 410 cm^{-1}), which was also confirmed by the ($M^+ - H_2O$) ion at *m/e* 346 in the mass spectrum. That the acetal group was intact was indicated by a four-proton singlet at δ 4.05 in its ^1H n.m.r. spectrum. An olefinic proton was found as a singlet at δ 5.52, while the remaining signals were very similar to those observed for the starting compound (3b).

† A brief account of this work has been presented in the Poster Sessions at the 12th International Symposium on the Chemistry of Natural Products, September 21—27, 1980, Tenerife, Canary Islands, Spain (Abstracts, p. 126).

The second product (6% yield) was the αβ-unsaturated ketone which was formulated as (7d). The mass spectrum gave a molecular ion at *m/e* 302. The presence of the heteroannular dienone chromophore was indicated



(7)

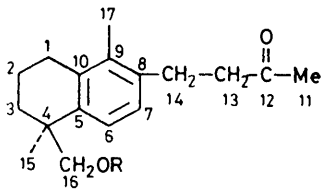


(8)

a; R = H, $\Delta^{9(11)}$
b; R = Ac, $\Delta^{9(11)}$
c; R = Ac
d; R = Ac, $\Delta^{7(8)}$ and $\Delta^{9(11)}$

by the u.v. [$\lambda_{max.}$ 234 nm (ε 8 500) and 288 nm (ε 19 000)] [5] and i.r. (1 670 cm^{-1}) spectra. The ^1H n.m.r. spectrum showed a one-proton singlet at δ 5.81 (11-H) and a one-proton multiplet at δ 6.01 (7-H).

The least polar product was obtained in 56% yield. It had the formula, $C_{19}H_{26}O_3$, and formed a crystalline 2,4-dinitrophenylhydrazone. In order to simplify the discussion on its structure, we at the outset formulate this compound as (9a); the relevant evidence is presented later. The i.r. spectrum showed two carbonyl bands at 1 740 (acetate CO) and 1 710 cm^{-1} (saturated CO). The ^1H n.m.r. spectrum exhibited, besides signals due to the CH_2OAc grouping [δ 4.13 (2 H, s) and 2.03 (3 H, s)], a six-proton singler at δ 2.15. We assumed that this signal was a result of the superimposition of two different three-proton singlets, *i.e.* a methyl ketone and a quaternary methyl. The alcohol (9b), derived from alkaline hydrolysis, showed practically the same spectrum, except that the CH_2OH group appeared at δ 3.65 as an AB quartet (*J* 11 Hz). Thus, upon addition of the lanthanide shift-reagent $Pr(fod)_3$ to (9b) the six-proton singlet at δ 2.16 was resolved into two three-proton singlets, both shifting to higher field. The spectra of both (9a) and (9b) also contained an AB quartet (*J* 8.4 Hz) at δ 7.05, probably due to aromatic protons. The



(9) a; R = Ac
b; R = H

aromatic nature of this compound was further supported by the u.v. spectrum [$\lambda_{max.}$ 265 nm (ε 751)].[6]

A detailed analysis of the ^{13}C n.m.r. spectrum of this compound made the assignment of its complete structure possible. The spectra of this compound and its alcohol (9b) are listed in the Table.

The presence of the aromatic ring B was inferred from the six signals at δ 124—140, which displayed chemical shifts and multiplicities resembling those of the hydrocarbon (10).[7] The quartet at δ 14.9 could be assigned to a methyl group bonded to an aromatic nucleus in a highly crowded environment such as the prehnitene structure (11).[8]

TABLE

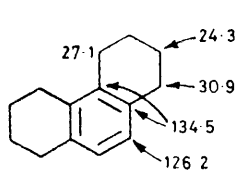
^{13}C N.m.r. spectral data [a]

	(7c) [b]	(9a) [b]	(9b)	(9a,b) + MeONa–CH_3OD	Δδ (Pr-shift) [c]
C-1	38.6	28.1 (t)	28.3	28.3	−1.7
C-2	18.3	19.1 (t)	19.4	19.3	−2.0
C-3	36.4	33.0 (t)	32.8	32.8	−3.4
C-4	37.2 [c]	37.4 (s)	39.4	39.4	−4.5
C-5	55.6	139.1 (s)	139.5	139.5	−4.9
C-6	21.5	124.6 (d)	124.2	124.2	−2.9
C-7	34.6 [d]	126.5 (d)	126.8	126.7	−1.6
C-8	35.6	134.2 (s)	134.6	134.5	−1.0
C-9	56.3	136.9 (s) [c]	137.3 [c]	137.2 [c]	−1.7
C-10	37.1 [c]	136.2 (s) [c]	136.8 [c]	136.7 [c]	−1.3
C-11	41.1	29.9 (q)	30.0		−1.3
C-12	212.9	208.2 (s)	208.1		−1.7
C-13	41.1	44.3 (t)	44.4		−1.1
C-14	34.2 [d]	27.9 (t)	27.9	27.7	−0.9
C-15	27.5	26.8 (q)	26.7	26.6	−3.9
C-16	67.0	71.8 (t)	71.9	71.8	−12.5
C-17	14.7	14.9 (q)	15.0	14.9	−0.9

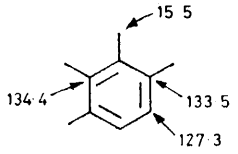
[a] In p.p.m. downfield from internal $SiMe_4$; multiplicities given are those in the off-resonance proton-decoupled spectra. [b] The acetyl group showed δ(C=O) 177.6 and δ(Me) 20.9 for (7c) and δ(C=O) 171.3 (s) and δ(Me) 20.9 (q) for (9a). [c,d] Signals in each vertical column may be reversed. [e] Δδ (p.p.m.) = [δ(9b) + Pr-shift] − δ(9b).

The deuterium-labelling experiments further supported the aromatization of ring B, migration of the methyl group from C-10 to C-9, and the rupture of ring C, as implied in structure (9a). After exhaustive deuteriation of this compound and its acetate (9b) with deuterio-

methanol and sodium methoxide, the spectrum did not exhibit the triplet at δ 44.3 [in (9a)] and 44.4 [in (9b)] and the quartet at δ 29.9 [in (9a)] and 30.0 [in (9b)].* Furthermore, the triplet at δ 27.9 underwent an upfield shift of 0.2 p.p.m. These observations were consistent



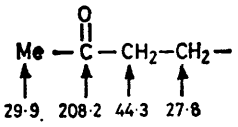
(10)



(11)

with the partial structure of the type (12), originating from the rupture of ring C.

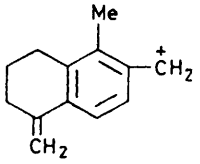
The assignments of the rest of the signals to the non-aromatic carbons of ring A were made by comparison with compound (7c) and other related podocarpane derivatives.[9] It should be noted that in the model



(12)

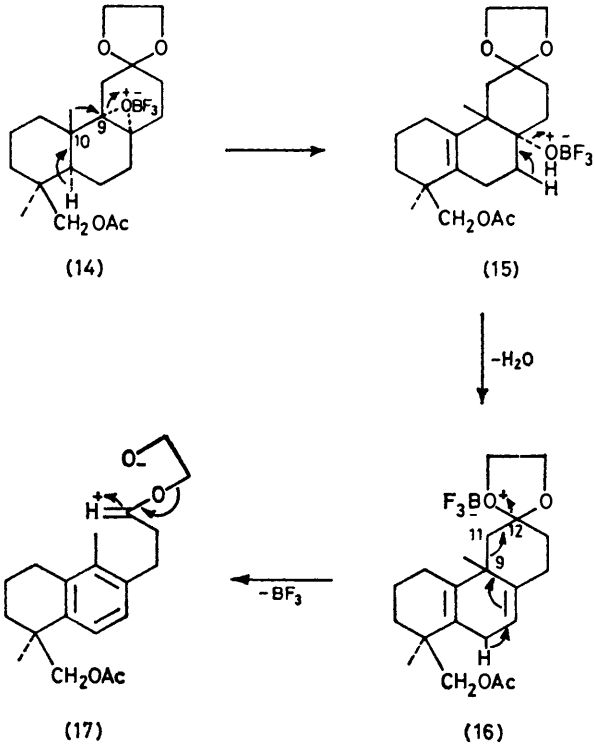
compound (7c) carbon-1 exhibits a shielding of *ca.* 11 p.p.m. and the value of its chemical shift is consistent with those for the α-methylene carbons of the hydroaromatic hydrocarbons such as (10). Furthermore, carbon-16 is deshielded by *ca.* 5 p.p.m. This change is compatible with the migration of the methyl from C-10 to C-9, which eliminates the 1,3-diaxial shielding interaction between C-16 and the methyl group. The upfield shifts caused by the shift-reagent $Pr(fod)_3$ on the alcohol (9b) also confirmed our assignments. Those carbons adjacent to the alcohol function experiences stronger effects as shown in the Table.

The mass spectrum of compound (9a) gave ions at *m/e* 44 (27%) ($C_2H_4O^+$), 171 (100), 229 (43) ($M^+ - CH_2OAc$), and 302 (1) (M^+). The base peak at *m/e* 171 is apparently responsible for the fragment (13).



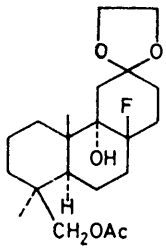
(13)

The formation of compound (9a) may be explained by postulating the following pathway (Scheme). Upon rupture of the epoxide ring, followed by migration of the methyl group from C-10 to C-9, compound (14) would give (15). Dehydration of the HO–BF_3 complex and subsequent addition of BF_3 to one of the acetal oxygens would lead to (16). The rupture of the C(12)–O bond, followed by that of the doubly allylic C(9)–C(11) bond, and aromatization of ring B would then occur in a concerted manner, as depicted by arrows, to form (17).



Compound (17), in the presence of a proton, would further decompose to (9a) by loss of MeCHO.

When the epoxide (3b) was treated with boron trifluoride–ether (1 mol equiv.) in benzene, four products were obtained after column chromatography over silica



(18)

gel. The least polar was the fluorohydrin (18) † (23% yield) which was obtained as a solid. The mass spectrum gave ions at *m/e* 364 (M^+ — HF) and *m/e* 384 (M^+). The presence of an OH group was indicated by a strong

* For the disappearance of the singlet at δ 208.2 [in (9a)] and 208.1 [in (9b)], due to the carbonyl carbon signal upon deuterium exchange at the neighbouring carbon atoms, see H. Eggert and C. Djerassi, *J. Org. Chem.*, 1973, **38**, 3788.

† Boron trifluoride–ether was purchased from Aldrich Chemical Co. Since it might contain fluoroboric acid in equilibrium with BF_3 + HF, which can act as a source of fluoride ions, it was repeatedly purified by distillation before use (see J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1966, **22**, 3195).

band at 3 500 cm^{-1} in the i.r. spectrum, and also by a one-proton singlet at δ 4.45 in the ^1H n.m.r. spectrum, which disappeared, on addition of D_2O. The second product (3% yield) was the αβ-unsaturated ketone (7d), which was obtained before. The third product (2% yield) was the rearranged hydroxy-ketone (5c), which was obtained as a solid. The mass spectrum gave a fragment at *m/e* 302 ($M^+ - H_2O$) as well as a molecular ion at *m/e* 320. The i.r. spectrum showed the presence of OH (3 430 cm^{-1}), a saturated six-membered CO (1 700 cm^{-1}), and acetate CO (1 735 cm^{-1}). A one-proton triplet was observed at δ 5.82 (6-H) in the ^1H n.m.r. spectrum. The fourth and most-polar product (4% yield), obtained as a solid, was an isomeric hydroxy-ketone which was formulated as (5d). The mass spectrum gave peaks at *m/e* 302 ($M^+ - H_2O$) and at *m/e* 320 (M^+). While the i.r. spectrum showed bands due to OH (3 550 cm^{-1}), a six-membered CO (1 690 cm^{-1}), and acetate CO (1 735 cm^{-1}), no olefinic proton was detected in the ^1H n.m.r. spectrum.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, i.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 spectrometer. U.v. spectra were measured on a Pye-Unicam SP 1800 instrument for ethanol solutions. ^1H and ^{13}C N.m.r. spectra were obtained for solutions in $CDCl_3$ on a Varian EM 3940 and a Bruker WP-80 spectrometer, respectively. Mass spectra were determined on a DuPont 21-492B (Data System 21-094B) at 70 eV using a direct-inlet system. For column chromatography silica gel 60 (Merck, 35—70 or 70—230 mesh) was used. Thin layer chromatograms were prepared on silica gel G or silica gel GF_{254} 60 (Merck) and the spots were observed by exposure to iodine vapour or u.v. light. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure below 60 °C. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

12,12-*Ethylenedioxypodocarp*-8-*en*-16-*ol Acetate*.—Ethane-1,2-diol (3.5 ml) and toluene-*p*-sulphonic acid (0.25 g) were added to a solution of 12-oxopodocarp-9(11)-en-16-ol [4] (9.5 g) in benzene (80 ml), and the mixture refluxed with a water separator. The reaction mixture was washed with water, dried, and evaporated. The crude product, obtained as an oil, was chromatographed in benzene over silica gel and elution with chloroform yielded the *acetal* (6.5 g), m.p. 86—88 °C (from ether–hexane); $\nu_{max.}$ 3 435 cm^{-1} (OH); δ 0.95 (3 H, s, Me), 0.99 (3 H, s, Me), 4.66 (2 H, AB q, *J* 11 Hz, CH_2OH), and 4.04 (4 H, s, OCH_2CH_2O); *m/e* 306 (M^+) (Found: C, 74.25; H, 9.65. $C_{19}H_{30}O_3$ requires C, 74.47; H, 9.87).

The above acetal (22 g) in pyridine (200 ml) was treated with acetic anhydride (100 ml) at room temperature overnight and then refluxed for 2 h. The *product* (20 g), isolated in the usual way, crystallised from ether–hexane, m.p. 81—82 °C; $\nu_{max.}$ 1 730 (acetate CO) and 1 300 cm^{-1} (C–O); δ 0.99 (6 H, s, 2 × Me), 2.06 (3 H, s, OCOMe), 4.00 (4 H, s, OCH_2CH_2O), and 4.11 (2 H, AB q, *J* 11 Hz, CH_2OAc); *m/e* 348 (M^+) (Found: C, 72.15; H, 9.0. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26).

8α,9α-*Epoxy*-12,12-*ethylenedioxypodocarpan*-16-*ol Acetate* (3b).—A solution of the above acetate (8 g) in chloroform (320 ml) was treated with *m*-chloroperbenzoic acid (8 g) and stirred at room temperature for 24 h. The solution was then washed with saturated aqueous sodium hydrogensulphite (120 ml), aqueous 2M sodium carbonate (150 ml), and dried. Removal of solvent yielded the *epoxide* (3b) (6 g), which upon crystallisation from ether–hexane had m.p. 85—87 °C; $\nu_{max.}$ 1 735 (acetate CO) and 1 240 cm^{-1} (C–O); δ 0.97 (3 H, s, Me), 1.06 (3 H, s, Me), 2.08 (2 H, s, OCOMe), 4.03 (4 H, s, OCH_2CH_2O), and 4.13 (2 H, AB q, *J* 11 Hz, CH_2OAc); *m/e* 364 (M^+) (Found: C, 69.0; H, 8.6. $C_{21}H_{32}O_5$ requires C, 69.20; H, 8.85).

Treatment of the Epoxide (3b) *with Boron Trifluoride–Ether in Nitromethane*.—The epoxide (3b) (0.2 g) was dissolved in nitromethane (4 ml), treated with freshly distilled boron trifluoride–ether (0.07 ml, 1 mol equiv.) and the solution was stirred at room temperature. After 20 min, all starting material had disappeared (t.l.c.), and the solution was treated with 5% aqueous sodium hydrogencarbonate (2 ml) and extracted with chloroform. The chloroform extract was dried and evaporated, and the crude product was chromatographed in benzene over silica gel. Elution with 1% ether in benzene yielded two fractions. The less polar fraction, after removal of solvent, gave as an oil *compound* (9a) (90 mg); δ 7.05 (2 H, AB q, *J* 8.4 Hz, 6-H and 7-H), 4.13 (2 H, s, CH_2OCOMe), 2.5—3.0 (6 H, m, 13-H, 14-H, and 1-H), 2.15 (6 H, s, 11-Me and 17-Me), 2.03 (3 H, s, OCOMe), 1.5—2.0 (4 H, m, 2-H and 3-H), and 1.3 (3 H, s, 15-Me). It formed a 2,4-*dinitrophenylhydrazone*, m.p. 162 °C (from chloroform–ethanol); *m/e* 482 (M^+) (Found: C, 62.0; H, 6.05; N, 11.45. $C_{25}H_{30}N_4O_6$ requires C, 62.23; H, 6.27; N, 11.61). On alkaline hydrolysis compound (9a) gave *compound* (9b); δ 7.05 (2 H, AB q, same as above), 3.65 (2 H, AB q, *J* 11 Hz, CH_2OH), 2.5—3.0 (6 H, m, same as above), 2.16 (6 H, same as above), 1.5—2.0 (5 H, m, 2-H, 3-H, and OH), and 1.25 (3 H, s, 15-Me).

The more polar fraction gave the αβ-*unsaturated ketone* (7d) (10 mg) as an oil; $\nu_{max.}$ (film) 1 736 (acetate CO), 1 670 (αβ-unsaturated CO), and 1 240 cm^{-1} (C–O); δ 1.00 (3 H, s, Me), 1.07 (3 H, s, Me), 2.08 (3 H, s, OCOMe), 4.19 (2 H, AB q, *J* 11 Hz, CH_2OAc), 5.81 (1 H, s, 11-H), and 6.01 (1 H, m, 7-H); *m/e* 302 (M^+) (Found: C, 75.25; H, 8.35. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67).

Elution with ether yielded the *hydroxy-olefin* (8) (10 mg) as an oil; $\nu_{max.}$ (film) 3 410 (OH), 1 735 (acetate CO), and 1 245 cm^{-1} (C–O); δ 1.03 (3 H, s, Me), 1.09 (3 H, s, Me), 2.11 (3 H, s, OCOMe), 4.05 (4 H, s, OCH_2CH_2O), 4.29 (2 H, AB q, *J* 11 Hz, CH_2OAc), and 5.52 (1 H, s, 11-H); *m/e* 364 (M^+) (Found: C, 68.95; h, 8.65. $C_{21}H_{32}O_5$ requires C, 69.20; H, 8.85).

Treatment of the Epoxide (3b) *with Boron Trifluoride–Ether in Benzene*.—The epoxide (3b) (0.4 g) in benzene (8 ml) was treated with freshly distilled boron trifluoride–ether (0.14 ml, 1 mol equiv.) and the solution was stirred at room temperature for 20 min. A solution of sodium hydrogencarbonate (0.25 g) in water (5 ml) was added and the mixture was extracted with chloroform. The chloroform extract was dried and evaporated, and the crude product (0.5 g) was chromatographed in benzene over silica gel. Elution with 1% ether in benzene yielded the *fluorohydrin* (18) (0.1 g), m.p. 72 °C; $\nu_{max.}$ 3 490 (OH), 1 735 (acetate CO), and 1 240 cm^{-1} (C–O); δ 1.06 (6 H, s, 2 × Me), 2.06 (3 H, s, OCOMe), 4.06 (4 H, s, OCH_2CH_2O), and

4.37 (2 H, AB q, J 11 Hz, CH_2OAc); m/e 384 (M^+) (Found: 65.25; H, 8.4; O, 20.65. $C_{21}H_{33}NO_5$ requires C, 65.59; H, 8.65; O, 20.80).

Elution with 2% ether in benzene gave the αβ-unsaturated ketone (7d) (10 mg).

Elution with 20% ether in benzene yielded the rearranged *hydroxy-ketone* (5c) (10 mg), m.p. 172—173 °C; $\nu_{max.}$ 3 430 (OH), 1 735 (acetate CO), 1 700 (six-membered CO), and 1 260 cm^{-1} (C–O); δ 1.03 (3 H, s, Me), 1.09 (3 H, s, Me) 2.08 (3 H, s, OCOMe), 4.02 (2 H, AB q, J 11 Hz, CH_2OAc), and 5.82 (1 H, t, 6-H); m/e 320 (M^+) (Found: C, 70.95; H, 8.65. $C_{19}H_{28}O_4$ requires C, 71.22; H, 8.81).

Further elution with 50% ether in benzene afforded the isomeric *hydroxy-ketone* (5d) (20 mg), m.p. 121—122 °C; $\nu_{max.}$ 3 550 (OH), 1 735 (acetate CO), 1 690 (six-membered CO), and 1 230 cm^{-1} (C–O); δ 0.98 (3 H, s, Me), 1.06 (3 H, s, Me), 2.02 (2 H, s, OCOMe), and 3.97 (2 H, AB q, J 11 Hz, CH_2OAc); m/e 320 (M^+) (Found: C, 71.0; H, 8.95. $C_{19}H_{28}O_4$ requires C, 71.22; H, 8.81).

We thank Mrs. M. C. de Hazos and Mr. J. Bermudez for determinations of the u.v., i.r., ^1H n.m.r., and mass spectra.

[0/1954 *Received*, 19*th December*, 1980]

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