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CONVERSION OF DEHYDROABIETIC ACID INTO A STEROID SKELETON: FORMATION OF THE A-RING1)

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Conversion of dehydroabietic acid (**1**) to a steroid skeleton was attempted, and the synthesis of 3-oxo compound (**22**) was successfully completed via the intermediates (**8** and **9**) by two methods.

Many investigators have attempted the conversion of abietic acid, the main component of pine rosin, to a steroid skeleton.3) We have also reported4) several attempts to convert dehydroabietic acid (**1**) to a steroid skeleton.

In the present series of work, conversion of **1** to a steroid skeleton, especially the formation of the A ring, was carried out by two methods, and 3-oxo compound (**22**) was successfully obtained via the intermediates (**8** and **9**).

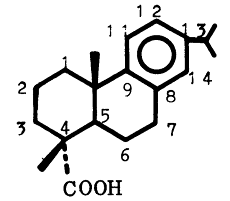
Method 1 The benzonilidene compound5)(**2**), derived from **1**, was dehydrogenated (chloranil, AcOH) to **3** in 70% yield; ir 1650, 1640; nmr 2.00 (bs, Wh/$_2$ = 4.5 Hz; 4-Me), 6.00 (b, Wh/$_2$ = 9 Hz; 3-H). The 3-4 double bond alone was epoxidized (m-ClC$_6$H$_4$CO$_3$H) to **4**, mp 110-111°, in 85% yield; ir 1660; nmr 1.30 (s; 10-Me), 1.56 (s; 4-Me), 3.06 (bs, Wh/$_2$ = 3.8 Hz; 3-H). Cleavage (HClO$_4$, Me$_2$CO) of this epoxide (**4**) gave $3\alpha,4\beta$-diol (**5**), mp 192-193.5°, in 65% yield; ir(KBr) 3375, 1652(sh), 1648; nmr(CD$_3$COCD$_3$) 1.58 (s; 4-Me), 1.70 (s; 10-Me), 3.76 (bs, Wh/$_2$ = 8 Hz; 3-H and 3- or 4-OH, which disappeared on D$_2$O treatment), 4.15 (s; 3- or 4-OH, which disappeared on D$_2$O treatment). In the nmr spectrum of **5**, the shift of 10-Me signal to a lower magnetic field by 0.40 ppm indicates that 4-OH and 10-Me are in 1,3-diaxial location and 4-OH takes a β-configuration.6) Catalytic reduction (Pt, AcOH) of **5** gave only the *cis* compound (**6**), mp 197-197.5°, in 50% yield; ir(CHCl$_3$)

3580, 3480, 1670; nmr 0.53 (s; 4-Me), 1.33 (s; 10-Me), 2.83 (bs, $W_{h/2}$ = 4.5 Hz; 3- and 4-OH, which disappeared on D_2O treatment), 3.55 (m; 3-H). Since the chemical shift of 4-Me (δ 0.53) appears in a higher magnetic field due to the anisotropic effect of the benzene ring, A/B ring junction must be *cis* (5β-H).

Reduction ($LiAlH_4$-$AlCl_3$) of 6 to 7 was accompanied by the formation of a by-product, detected by gas-liquid chromatography and nmr in ca. 9% yield, which was difficult to be separated.7) This diol (7) containing a small amount of the by-product was cleaved (HIO_4, dioxane), and the neutral product so obtained was oxidized ($KMnO_4$). Methylation (CH_2N_2) of the acid product gave the 5β-oxo ester (8), mp 82°, in 20% yield from 7; ir 1740, 1712; nmr 1.36 (s; 10-Me), 2.18 (s; COMe), 3.50 (s; COOMe). Hydrolysis (KOH-MeOH, room temp.) of 8 and methylation (CH_2N_2) of its acid product afforded the isomer (9) of 8 in 5-position in 57% yield; ir 1740, 1710; nmr 1.26 (s; 10-Me), 2.17 (s; COMe), 3.54 (s; COOMe). For a confirmation of the structure, 9 was also synthesized by another route using Huffman's method.8) Thus, dehydroabietic acid (1) was converted to 8 and 9, which are considered to be important intermediates in the synthesis of the 3-oxo compound (22).

Method 2 Conversion of 10, the compound having a double bond in the A ring,9) to 9 will now be described. Oxidation (SeO_2, dioxane, reflux) of 10 gave the 3-oxo compound (11), mp 162-165°, in 30% yield; ir 1755, 1695, 1665; nmr 6.19 (s; 6-H), 6.23 (d, *J* = 10 Hz; 2-H), 7.46 (d, *J* = 10 Hz; 1-H). Catalytic reduction (Pt, AcOH-H_2SO_4, 5 atm) of 11 afforded the *trans*-ester (12), mp 108-109.5°; ir 1745, 1712; nmr 1.31, 1.38 (each s; 4- and 10-Me), 3.69 (s; COOMe); and the *cis*-ester (13); ir 1735, 1712; nmr 1.23, 1.35 (each s; 4- and 10-Me), 3.10 (s; COOMe). The formation ratio of 12 and 13 was not constant. Decarboxylation (KOH-MeOH, room temp.) of 12 gave 14 in 60% yield3b,10); ir 1713; nmr 1.05 (d, *J* = 6 Hz; 4-Me). On the other hand, 13 failed to undergo any change on treatment under the same conditions. Oxidation (m-$ClC_6H_4CO_3H$-$CHCl_3$, room temp.) of 14 afforded the lactone (15) in 75% yield; ir 1740; nmr 1.35 (d, *J* = 6 Hz; 4-Me), 4.60 (t, *J* = 6 Hz; 4-H). Lactone (15) was cleaved (KOH-MeOH, room temp.) to the hydroxy-acid (16), mp 134-135.5°, in quantitative yield; ir 3600, 3500-2400, 1710; nmr($CDCl_3$) 1.28 (d, *J* = 4 Hz; 4-Me), 6.89 (bs, $W_{h/2}$ = 4 Hz; 4-OH, COOH, and one of aromatic protons; two of them disappeared on D_2O treatment); which was derived to its methyl ester (17), ir 3600, 3500, 1738; nmr 1.26, 1.30 (each s; 4- and 10-Me), 2.16 (bs, $W_{h/2}$ = 6 Hz, 4-OH, which disappeared on D_2O treatment), 3.55 (s; COOMe), 4.0 (b, Wh/2 = 22 Hz; 4-H). Jones' oxidation of 17 finally gave the 5α-keto ester (9) which was identical with 9 obtained by Method 1.

Bromination (Br_2-AcOH, room temp.) of the keto-esters (8 and 9) so obtained, followed by the Favorskii rearrangement (KOH-MeOH, reflux), gave two isomers (18 and 19). 18; ir 1740, 1637; nmr 3.48, 3.68 (each s; 2- and 4-COOMe),



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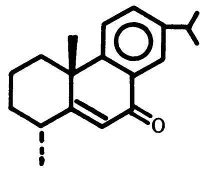

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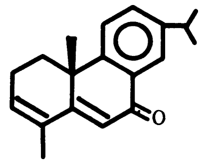

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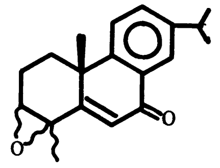

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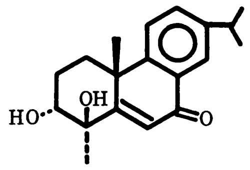

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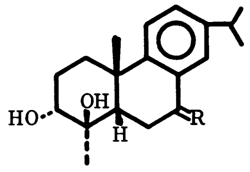
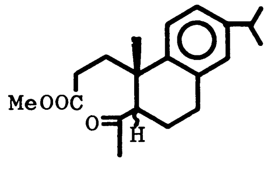
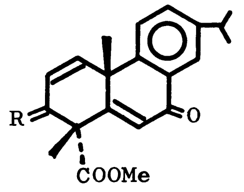


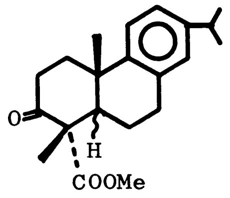
6: R=O
7: $R=H_2$



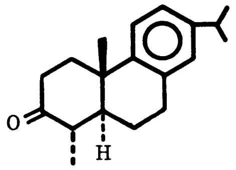
8: 5β-H
9: 5α-H



10: $R=H_2$
11: R=O



12: 5α-H
13: 5β-H



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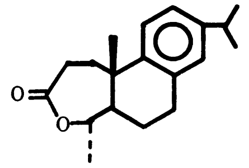

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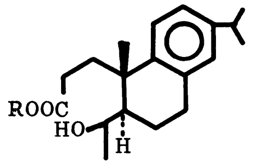
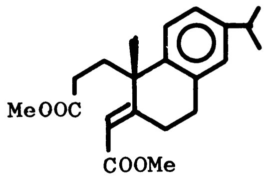


16: R=H
17: R=Me



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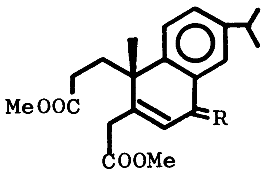
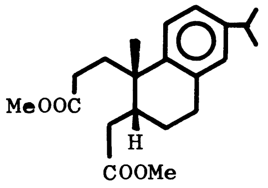


19: $R=H_2$
20: R=O



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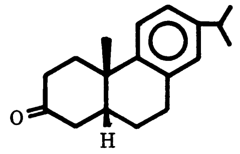

22

5.79 (bs, $W_{h/2}$ = 4 Hz; 4-H). 19; ir 1740. When left in the atmosphere, **19** rapidly underwent change to the α,β-unsaturated ketone (**20**), ir 1742, 1663. The mixture of **18** and **19** was catalytically reduced (Pt, AcOH) to 3:1 or 2:1 mixture of the 5β-H compound (**21**) and a compound considered to be 5α-H. Saturated diester (**21**) was obtained in 28% yield by column chromatographic separation; ir 1740; nmr 1.32 (s; 10-Me), 3.56, 3.66 (each s; 2- and 4-COOMe). The Dieckmann condensation (Ph_3CNa) of **21**, followed by hydrolysis (KOH-MeOH, reflux), finally gave the desired **22** in 15% yield; ir 1717; nmr 1.36 (s; 10-Me); CD (*c* 0.113, MeOH) $[\theta]^{16}$ (nm): 0 (310), -903 (300), -1129 (295), -903 (280), -3162 (265), 0 (245). From the result of CD data[11] of **22**, the A/B ring junction in **22** is *cis* (5β-H). Thus, the conversion of **1** to **22** having a steroid-type A ring was accomplished.

Notes and References

1) Compounds whose physical constants are given showed satisfactory analytical values (including mass spectral data). Ir (cm^{-1}) and nmr (δ vs. Me_4Si as internal reference, 60 MHz) spectra were measured in CCl_4 solution unless otherwise specified.

2) To whom inquiries regarding this communication should be addressed.

3) a) T. Wirthlin, H. Wehrli and O. Jeger; Helv. Chim. Acta, *57*, 351, 368 (1974), and references cited therein.

b) J. W. Huffman; J. Org. Chem., *35*, 478 (1970), and references cited therein.

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6) N. S. Bhacca and D. H. Williams; 'Applications of NMR Spectroscopy in Organic Chemistry', Holden-Day Inc., San Francisco, p.13 (1964).

7) Physical constants of this mixture are as follows: mp 123-124°; ir 3600, 3450; nmr 0.55 (s; 4-Me), 1.08 (s; 10-Me), 3.40 (b, $W_{h/2}$ = 14 Hz; 3-H), 3.56 (b, $W_{h/2}$ = 12 Hz; 3- and 4-OH, which disappeared on D_2O treatment).

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