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SYNTHESES OF (-)-OCCIDENTALOL AND ITS C-7 EPIMER

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For the structure of (+)-occidentalol, a sesquiterpene alcohol obtained from Thuja occidentalis L., the formula (A) has been postulated by Ziffer, et al. (1). However, the formula (A) has recently been revised to the formula (B) by Hortmann, et al. on the basis of the nmr spectrum as well as the ORD curve (2).

In this communication, we now wish to report the syntheses of the alcohol (I), an antipode to the one represented by (B), and of the C-7 epimer (II) of I, corresponding to (A), with the object of establishing the structure of natural (+)-occidentalol.

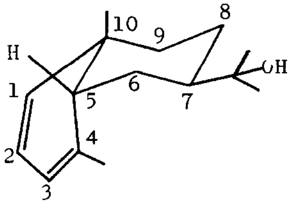
The olefinic ketone (III) prepared from α-santonin (3) was converted to an ester (IV), mp 71°; ir ($CHCl_3$), 1727, 1706 cm^{-1}, by oxidations with sodium metaperiodate-osmium tetroxide and subsequently with silver oxide and then by methylation with diazomethane. Bromination of IV with bromine in acetic acid in the presence of hydrobromic acid afforded two kinds of oily monobromides (Va and Vb). The splitting patterns of the nmr signals due to the bromomethine protons, δ 4.73 (1H, q, J=6, 12 Hz) and 4.72 (1H, q, J=6, 14 Hz) ppm for Va and Vb, respectively, indicate that both Va and Vb are α-bromoketones bearing the equatorial bromine atoms (4).

On dehydrobromination with lithium bromide and lithium carbonate in dimethylformamide at 140°C, Va gave an oily α,β-unsaturated ketone (VIa); ir (neat), 1732, 1680 cm^{-1}; nmr (CCl_4), 1.07 (3H, d, J=6.5 Hz), 1.27 (3H, s), 3.65 (3H, s), 5.77 (1H, d, J=10 Hz), 6.33 (1H, q, J=2, 10 Hz) ppm; CD (CH_3OH), $[\theta]_{225}$ -23,400, $[\theta]_{310}$ + 548. On the other hand, dehydrobromination of Vb gave the other oily α,β-unsaturated ketone (VIb); ir (neat), 1736, 1680 cm^{-1}; nmr (CCl_4), 1.10 (3H, d, J=6.5 Hz), 1.23 (3H, s), 3.60 (3H, s), 5.75 (1H, d, J=10 Hz), 6.47 (1H, d, J=10 Hz) ppm;

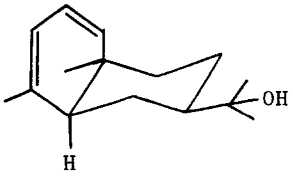
CD (CH_3OH), $[\theta]_{225}$ +33,900, $[\theta]_{320}$ -2,580. The non-steroid conformation for VIa is revealed from the nmr spectrum in which the long-range coupling between H-1 and H-5 ($J_{1,5}$ = 2 Hz) is observed (5), as well as the CD curve which shows the positive and negative Cotton effect associated with the n-π^* and π-π^* transition, respectively (6). On the other hand, the steroid conformation is assigned for VIb from the spectral observations; the nmr spectrum shows no long-range coupling between H-1 and H-5, and the CD curve shows the negative and positive Cotton effect associated with the n-π^* and π-π^* transition, respectively. The C-4 methyl groups in VIa and VIb are assumed to be in the α(equatorial)- and β(equatorial)-configurations, respectively, from the fact that the solvent effect on the C-4 methyl signals in their nmr spectra, δ 1.07 (CCl_4) and 1.12 (benzene) ppm for VIIIa and δ 1.10 (CCl_4) and 1.10 (benzene) ppm for VIIIb, is rather small (7) (8).

That VIa and VIb are the epimers at the C-4, but not at the C-7 is also supported by the chemical findings described below. Reduction of (VIa and VIb) with sodium borohydride gave oily mixtures of epimeric alcohols (VIIa) and of epimeric alcohols (VIIb), respectively. On being heated at 210°C in the presence of alumina containing 4% of pyridine (9), both mixtures of alcohols gave the same oily diene (VIII); ir (neat), 1730, 1645, 1193, 722 cm^{-1}; CD (MeOH), $[\theta]_{259}$ = -33,800; nmr (CCl_4, 100 MHz), 0.85 (3H, s. 10-CH_3) 1.81 (3H, broad s, 4-CH_3), 2.48 (1H, m, H-7), 3.63 (3H, s), 5.19 (1H, broad d, H-1), 5.53 (1H, m, H-3), 5.77 (1H, d, d, H-2) ppm. The diene (VIII) was conveniently prepared from IV by the same method described above, without the separation of the epimers in each steps, in 32.8% yield. The nonsteroid conformation bearing the β(axial)-methoxycarbonyl group at C-7 for VIII is revealed from the nmr spectrum which shows the long-range coupling between H-1 and H-5 (J=1.0 Hz), and a rather small magnitude of half-band width of H-7, $W_{\frac{1}{2}h}$ = 11 Hz. This is also supported from the observation on the CD curve which show the negative Cotton effect due to the skewing of the cisoid butadiene moiety in the sense of a left-hand helix (6).

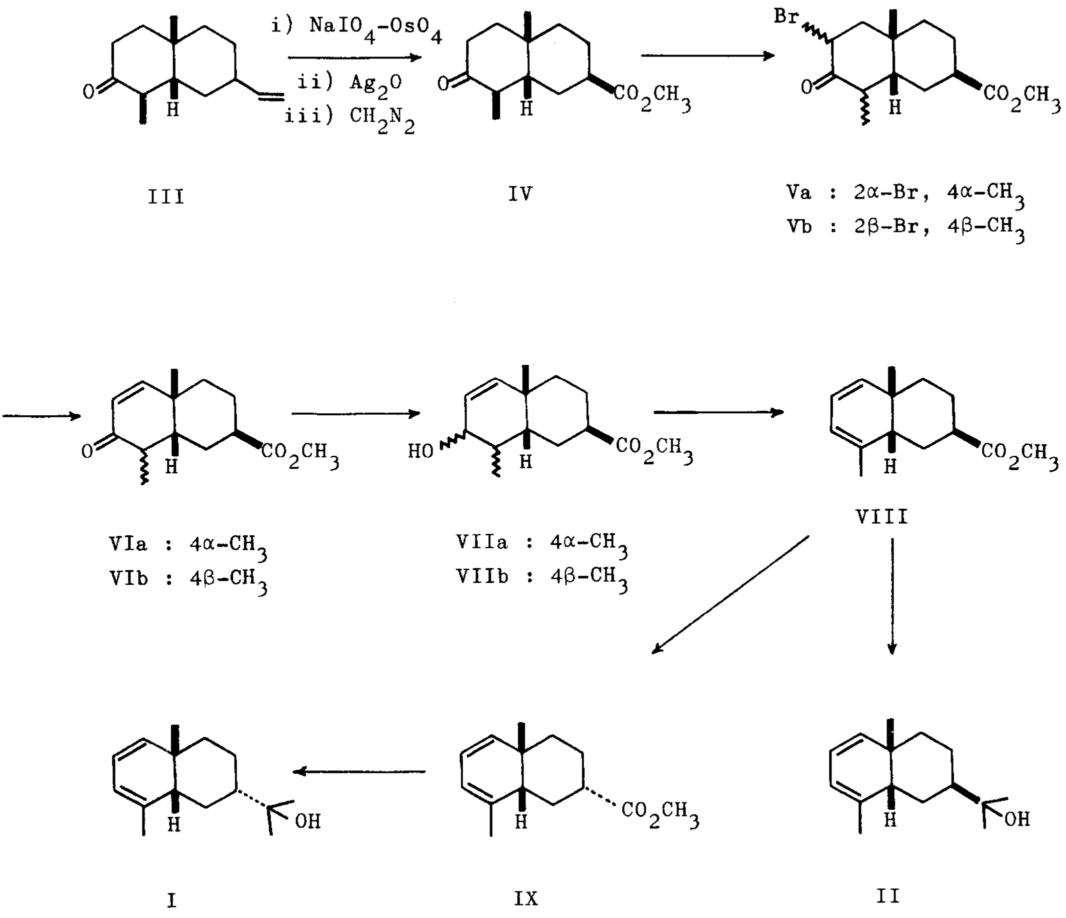
The treatment of VIII with methylmagnesium bromide gave an oily alcohol (II): ir (neat), 3350, 756, 732 cm^{-1}; nmr (CCl_4), 1.10 (3H, s), 1.13 (6H, s), 1.86 (3H, broad s), 5.8-5.2 (3H, m); CD (CH_3OH), positive Cotton effect, in 73.5% yield. The alcohol (II), structure of which is corresponding to (A), is different from


H
10
9
8
OH
1
5
6
7
2
4
3

(A)


OH
H

(B)


O
H
i) $NaIO_4$-OsO_4
ii) Ag_2O
iii) CH_2N_2
III
O
H
CO_2CH_3
IV
Br
O
H
CO_2CH_3
Va : 2α-Br, 4α-CH_3
Vb : 2β-Br, 4β-CH_3
O
H
CO_2CH_3
VIa : 4α-CH_3
VIb : 4β-CH_3
HO
H
CO_2CH_3
VIIa : 4α-CH_3
VIIb : 4β-CH_3
H
CO_2CH_3
VIII
H
OH
I
H
CO_2CH_3
IX
H
OH
II

natural (+)-occidentalol in the ir and nmr spectra.

The treatment of VIII with 1 N potassium t-butoxide in t-butanol under reflexing temperature for 2 hours gave a mixture of an acid and a t-butyl ester. Hydrolysis of the latter with aqueous alkali and subsquent methylation with diazomethane gave an 1:22-mixture of the methyl ester (VIII) and its C-7 epimer (IX), colorless oil; ir (neat), 1735, 1705 (sh), 728 cm^{-1}; nmr (CCl_4), 0.87 (3H, s), 1.80 (3H, broad s), 3.63 (3H, s), 5.33 (1H, broad d, J=10 Hz), 5.62 (1H, m), 5.88 (1H, d, d, J= 5.10 Hz); CD, $[\theta]_{262}$ = -49,200. The treatment of IX with methylamgnesium bromide gave the alcohol (I), which is identical with natural (+)-occidentalol in the ir and nmr spectra but shows the opposite signe in the CD curves. These results indicate that the structure of natural (+)-occidentalol must be represented by (B) and the alcohol (I) is its antipodal (-)-occidentalol (10).

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0) In a midcourse of this study, it has been informed by Hortmann that his group has synthesized (+)- and (-)-occidentalol and the alcohol (II) through the photo-chemical conversion of the trans-decalone derivative [A. G. Hortmann, J. E. Martinelli and Y. S. Wang, J. Org. Chem., 34, 732 (1969)]. Acknowledgements are made to Professor Alfred G. Hortmann for his kind offer of the unpublished data.