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OXIDATION OF UNACTIVATED CARBON ATOMS OF CEDROL AND CEDROL ACETATE WITH m-CHLOROPERBENZOIC ACID.

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Abstract: Cedrol and cedrol acetate were reacted with m-CPBA to give the corresponding 2α-ol, 2β-ol, 4β-ol, 5β-ol and 7β-ol.

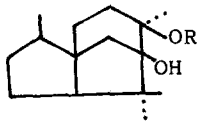
Currently in our laboratories much effort was made to introduce hydroxyl group and carbonyl group into cedranoid compounds, which were isolated from the wood of Juniperus squamata Lamb.[1-3]. There are numerous methods reported by oxidation reaction of natural products, microbial oxidation[4], oxidation using mammals[5], dry ozonization[6], and remote oxidation[7]. None of these, however, is convenient as a synthetic method and ozonization also can be dangerous[6]. m-Chloroperbenzoic acid(m-CPBA) has been used as an oxidizing agent to introduce a hydroxyl group at a bridgehead position of a bicyclic compound[8], polyclyclic compounds[9], naturally occurring products of some lupane, friedelane derivatives[10], and dammarane derivatives[11]. We wish to report here the oxidation reactions of sesquiterpenes, cedrol 1a and cedrol acetate 1b, with m-CPBA.

Cedrol acetate 1b, prepared from cedrol 1a in isopropenyl acetate with catalytic amount of p-toluenesulfonic acid, was treated with m-CPBA and $NaHCO_3$(1:1) in chloroform under reflux. The usual work up and column chromatography on silica gel gave five products, 2a (1.8%), 3a (11.8%), 4a (38%), 4b (44%), and 5a (28%)[12]. Under the same oxidation condition, cedrol 1a yielded five corresponding products, 2b (20%), 3b (10.5%), 4c (35%), 4d (27%) and 5b (1.8%)[12]. The structural elucidation of every product was shown as follow[13].

The presence of hydroxyl group in 4b at C-2 position was revealed by the fact that C-2 methyl gives a singlet at δ 1.18 instead of a doublet as in 1b.

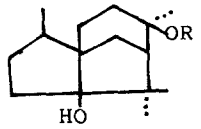
1a R_1=H

1b R_2=Ac



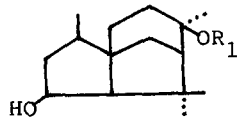
2a R=Ac

2b R=H



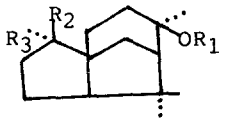
3a R=Ac

3b R=H



5a R_1=Ac

5b R_1=H

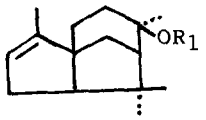


4a R_1=Ac R_2=OH R_3=CH_3

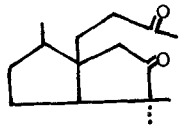
4b R_1=Ac R_2=CH_3 R_3=OH

4c R_1=H R_2=OH R_3=CH_3

4d R_1=H R_2=CH_3 R_3=OH



6 R_1=Ac



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The α-configuration of C-2 hydroxyl group was assigned according to Ourisson's report[14]. Compound 4a is an epimer of 4b by comparison of their ^{1}H NMR spectra. Furthermore, 4a and 4b gave the same dehydration product 6[14] upon treatment with thionyl chloride in pyridine. In the ^{1}H NMR spectrum of 5a, a multiplet centred at δ 4.15 ($W_{\frac{1}{2}}$=15Hz) was observed. This result indicated that a secondary alcohol was formed in 5a. Treatment of 5a with methanolic NaOH solution gave the known 4β-hydroxycedrol, 5b, by comparison with the reported physical data of 5b[15]. No signal appeared between 3.0 and 5.0 in the ^{1}H NMR spectrum of 3a indicated that it contained a tertiary hydroxyl and a tertiary acetoxyl groups (νmax 3530 and 1725 cm^{-1}) without regard to the secondary hydroxyl group. A doublet presented at 0.91 suggests that the hydroxyl group can not be located at C-2 position. Compound 2a showed similar NMR spectrum pattern with that of 3a. The possibility of a C-2 hydroxyl group can be excluded due to the presence of a doublet signal at δ 0.87 in the ^{1}H NMR spectrum of 2a. Therefore, the structure of 2a or 3a can be assigned as 5β-hydroxycedrol acetate or 7β-hydroxycedrol acetate. Compound 4c and 4d are epimers by comparison of their ^{1}H NMR spectra. The hydroxyl groups were introduced into 4c and 4d at C-2 positions since the C-2 methyl showed its singlet signal at δ 1.16 and 1.17 in 4c and 4d, respectively. The correct structures of the two epimers were confirmed by the treatment of 4a and 4b in methanolic NaOH solution to give 4c and 4d, correspondingly.

Compounds 3b and 2b, also showed signals with doublet at δ 0.92 and 0.86, respectively. Therefore the structure of 3b and 2b can be assigned as 5β-hydroxycedrol and 7β-hydroxycedrol, individually. The correlation among 2a, 3a, 2b, and 3b was demonstrated by the conversion of 2a and 3a to 2b and 3b, respectively, via saponification. By the observation chemical shift of C-2 methyl in 1a (δ 0.84), 1b (δ 0.86), 2a (δ 0.87), 2b (δ 0.86), 3a (δ 0.91), and 3b (δ 0.92), the downfield shift of C-2 methyl groups in 3a and 3b leads us to conclude that the hydroxyl groups in 3a and 3b must be located at C-5 with a β-orientation due to the fact that C-2 methyl group was deshielded by the diamagnetic effect from hydroxyl group[16]. Meanwhile, 2b yielded 7 by reaction with lead tetraacetate in refluxing benzene. This result confirmed the above conclusion. From the formation of 4a, 4b, 4c and 4d, it seems likely that the hydroxylation reaction with m-CPBA is via a radical mechanism[17]. The hydroxylation of cedrol by dry ozonization[14], microbial[18] and mammals[19] has been reported. This paper describes the first hydroxylation reaction with m-CPBA to sesquiterpenoid. Further applications to other sesquiterpenes and using this method for synthesis in related sesquiterpenoid are under way.

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References and Notes

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12. Base on 1a or 1b consumed.
13. All compounds were characterized by Infrared and 200MHz ^{1}H NMR spectra plus microanalytic evidence. 2a:νmax 3434 and 1727 cm^{-1}; δ $CDCl_3$ 0.89 (3H,d,J=6.6Hz), 1.14, 1.26 and 2.03 (each 3H,s); 2b:mp 60-62°C; νmax 3440 cm^{-1}; δ $CDCl_3$ 0.86(3H,d,J=6.6Hz), 0.96, 1.21, 1.34 (each 3H, s);

3a: νmax 3520 and 1725 cm^{-1}; $\delta CDCl_3$ 0.91(3H,d,J=6.5Hz),1.07, 1.13, 1.55 and 1.94(each 3H,s); 3b: νmax 3440 cm^{-1}; $\delta CDCl_3$ 0.92(3H,d,J=6.8Hz), 1,10, 1,28 and 1.28(each 3H, s); 4a: νmax 3160, 1715 and 1730cm^{-1};$\delta CDCl_3$ 0.97, 1.15, 1.15, 1.54 and 1.94 (each 3H, s);4b: mp 59-60°C; νmax 3450 and 1725 cm^{-1}; $\delta CDCl_3$ 1.02,1.14,1.17,1.54 and 1.96(each 3H, s); 4c: mp 78-80°C; νmax 3397 cm^{-1}; $\delta CDCl_3$ 1.00, 1.16,1.28 and 1.32(each 3H, s); 4d: mp 80-82°C; νmax 3397 cm^{-1}; $\delta CDCl_3$ 1.03, 1.17, 1.28 and 1.30 (each 3H, s); 5a:νmax 3420, 1710 and 1725 cm^{-1}; $\delta CDCl_3$ 0.91(3H,d,J=6.8Hz), 1.13, 1.26, 1.53 and 1.96 (each 3H, s); 5b: mp 133-135°C; νmax 3600 and 3400 cm^{-1};$\delta CDCl_3$ 0.91 (3H,d,J=6.8Hz), 1.15, 1.25 and 1.51 (each 3H, s), 4.16 (1H,m,$W_{\frac{1}{2}}$=14Hz); 7: νmax 1730 and 1715 cm^{-1}; $\delta CDCl_3$ 0.95(3H,d,J=6.6Hz), 1.03, 1.09 and 2.17 (each 3H, s).

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