THE CHEMISTRY AND STRUCTURES OF SOME EUDESMANE SESQUITERPENOID BICYCLIC ORTHOESTERS. IMPLICATIONS FOR THE HYDROLYSES OF β-GLYCOSIDES

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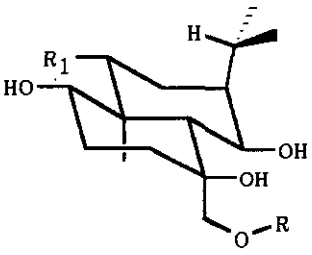
Abstract - The formation of oxonium ions during the acid catalyzed reactions of the tricyclic eudesmanoid orthoesters (3) and (4) is greatly influenced by the overall structural features of the parent molecules. The structures of the reaction products, and molecular modeling of the possible oxonium ions, confirm that the most stable oxonium ion is the most important intermediate. These findings are critical to understanding the hydrolyses of β-glycosides.

The naturally occurring enantio-eudesmane sesquiterpeniods rupestrol[1] (1) and rupestrinol[2] (2) were isolated from *Verbesina rupestris* Urb. (Blake) as their cinnamoyl orthoesters (3) and (4). Their stereostructures were established by chemistry, nmr and CD/ORD spectroscopy. Among the intriguing reactions of these orthoesters were their acidic hydrolyses to give only the esters (5) and (6) respectively. The orthoformate ester (7) was also hydrolysed to the ester[3] (8), showing that the styryl groups of the orthoesters (3) and (4) did not influence the regiochemistry of these reactions.

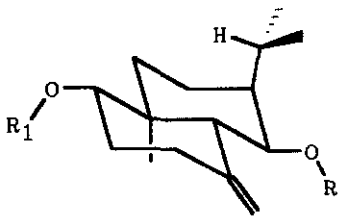
The enantio-eudesmane sesquiterpene chaenocephalol (9) was also isolated as its cinnamate ester (10) from *Verbesina rupestris* and its stereostructure was established by chemical transformations, nmr spectroscopy, and its conversion into rupestrinol (2), by osmium tetroxide catalyzed hydroxylation.[2] Attempts were also made to convert rupestrinol into

chaenocephalol by dehydroxylation[4] using the triethyl orthoformate/benzoic acid procedure.[5] However, although rupestrinol was subjected to prolonged heating with triethyl orthoformate and benzoic acid at 160 °C, this reaction provided only the orthoformate ester (7), in quantitative yield.

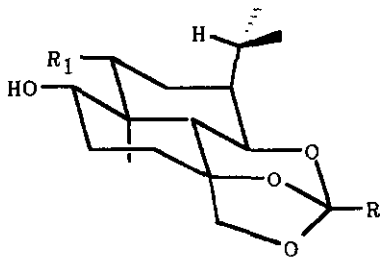
Orthoformate esters of 1,2-diols are converted into alkenes *via* their planar, cyclic formyloxonium ions, Scheme 1. The acid catalyzed reactions of compound (7) described above ought also to proceed *via* the formyloxonium ion (11) or one of the oxonium ions (12) and (13). It seemed logical that the most stable oxonium ion should direct the paths of these reactions.



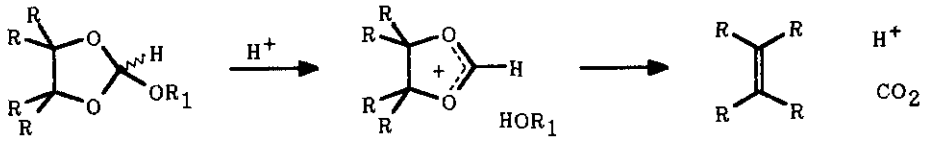
(1) R = H, R_1 = OH
(2) R = H, R_1 = H
(5) R = Cinnamoyl, R_1 = OH
(6) R = Cinnamoyl, R_1 = H
(8) R = formyl, R_1 = H



(9) R = R_1 = H
(10) R = Cinnamoyl, R_1 = H
(22) R = Cinnamoyl, R_1 = Ac



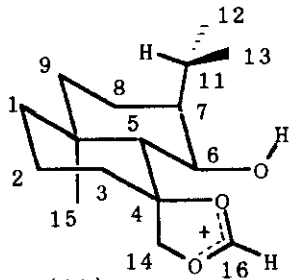
(3) R = styryl, R_1 = OH
(4) R = styryl, R_1 = H
(7) R = R_1 = H



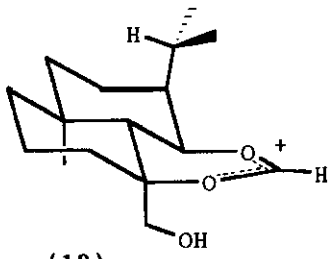
Scheme 1

However, since we did not have any means of estimating the relative stabilities of the oxonium ions (11), (12) and (13), we were unable to convincingly rationalize these reactions with the data then available.

Recently, the molecular modelling of the oxonium ions (11), (12) and (13) was performed[6] and this study suggested that the oxonium ion (13) was about 18 kcal/mol less stable than the isomeric oxonium ion (12), and the oxonium ion (12) was about 2.8 kcal/mol less stable than the oxonium ion (11). An examination of the calculated features of the ions (11) and (12) revealed that the O14-C16 and the O4-C16 bond lengths would be about 128.4 pm in the oxonium ion (11), and the O4-C16 and the O6-C16 bond lengths in oxonium ion (12) would be about 128.8 and 122.8 pm respectively. These bond lengths are



(11)



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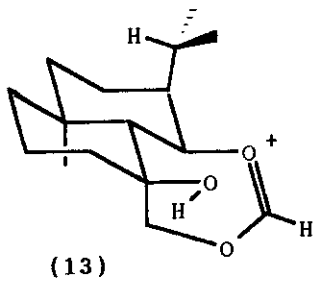

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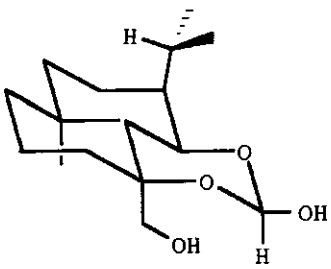
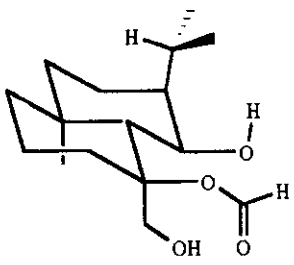
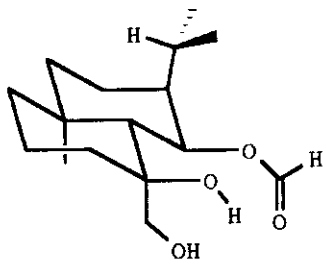


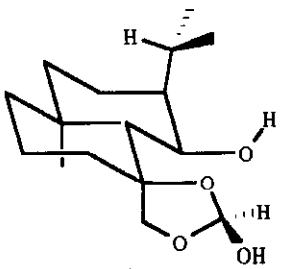
(14A)



(15A)



(16A)



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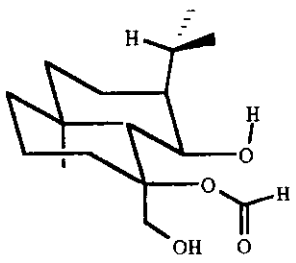

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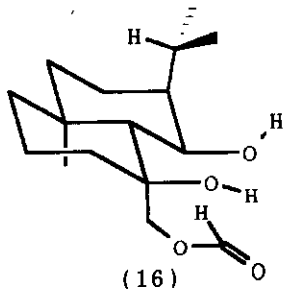

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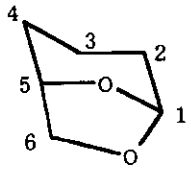

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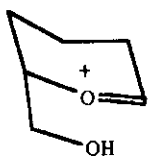

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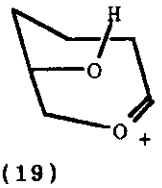


(19)

typical of C-O double bonds[7] and so these ions were predicted to be greatly stabilized by the delocalization of their oxygens' lone pairs into the "empty p" orbital of C16. The distance between O6 and C16 in the oxonium ion (**11**) was about 309.4 pm, while the O14 to C16 distance in the oxonium ion (**12**) was about 308.7 pm. These distances indicate that there would be

minimal through-space, n-p interaction[8] in each of these oxonium ions.

Interestingly, the calculations suggested that the oxonium ion (**13**) should have an O4 to C16 distance of 268.1 pm, small enough for O4 to stabilize the oxonium ion by a through-space n-p interaction.[8] The O14-C16 and O6-C16 bond lengths were suggested to be about 132.0 and 126.5 pm respectively, indicating that the lone pair of O6 would be delocalized in the stabilization of the carbonium ion center,[7] but the lone pair of O14 would not participate. Thus, the oxonium ion (**13**) was suggested to be a less extensively delocalized species than the ions (**11**) or (**12**), but the n-p interaction would play an important role in the stabilization of the ion (**13**).

Thus, during heating with benzoic acid the orthoester (*7*) must have been transformed into the most stable oxonium ion (**11**), rather than into the less stable oxonium ions (**12**) or (**13**). This oxonium ion (**11**) must also have rapidly and efficiently reverted to the starting orthoester (*7*) rather than undergoing conversion into the alkene (**2**).

The conclusion above is dramatically supported by the acidic hydrolysis of the orthoester (*7*). If the oxonium ion (**12**) had participated in the acidic hydrolysis of the orthoester (*7*), then attack by water would have occurred on its *Re* face, so leading to the intermediate (**14A**), which would then have rearranged[9] into either the ester (**15A**) or (**16A**). However, the sterically congested tertiary ester (**15A**) would be a less favoured product than the secondary ester (**16A**), and so the ester (**16A**) would have been the major product of this reaction. The fact that the ester (**16A**) was not formed in this hydrolysis strongly confirms that the oxonium ion (**12**) was not an intermediate in these acid catalyzed reactions.

The hydrolysis of the orthoester (*7*) must therefore have occurred *via* the oxonium ion (**11**). Nucleophilic attack by water on this oxonium ion would have occurred on the *Si* face of the ion (remote to the OH-6, which blocked the *Re* face) and so generated the intermediate (**14**). This intermediate should then rearrange[9] into the primary ester (**16**) rather than to the sterically congested tertiary ester (**15**) and, indeed, the ester (**16**) was the sole product of this reaction. Similar mechanisms must undoubtedly be involved in the quantitative conversions of the orthocinnamate esters (**3**) and (**4**) into the cinnamate esters (**5**) and (**6**).

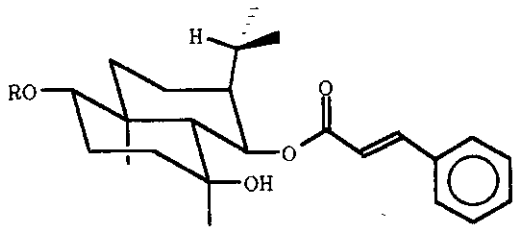
There are many structural similarities between the orthoesters (**3**), (**4**), (*7*) and the 1,6-anhydroglycopyranoses (**17**) which also undergo very facile acid catalyzed hydrolyses. However, the compounds (**17**) show a highly selective cleavage of their C1-O6 bonds[10] (comparable to the O14-C16 bond of the orthoesters above), while the orthoesters above show the selective cleavage of their O6-C16 bonds (comparable to the C1-O5 bonds of the 1,6-anhydroglycopyranoses). The selective cleavage of the

C1-O6 bond of 1,6-anhydroglycopyranoses during their hydrolyses has been attributed to n-σ^* interactions at the anomeric center (postulated to be the principal factors in the anomeric effects[10b]). However, the data above indicate that consideration of these interactions would not have enabled one to accurately predict the paths of the hydrolyses of these orthoesters. Further, these n-σ^* interactions have recently been shown to be transition state effects, rather than ground state features of sugars,[7] (and thus not related to the ground state anomeric effects) and so the suggestion that only n-σ^* interactions had determined the mechanistic pathway for the hydrolyses of 1,6-anhydrosugars must be invalid.

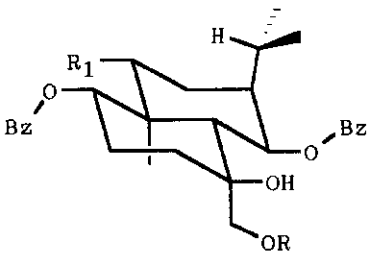
The structures of the orthoesters discussed above show that during their hydrolyses at least one of the lone pairs of O4, O6 and O14 is always properly oriented to participate in the stabilization of a developing carbonium ion at C16, as the molecule moves toward the transition state for the cleavage of a C-O bond. Thus, a mechanistic appreciation of these hydrolyses required an examination of the structural and energetic consequences of the cleavage of each endocyclic C-O bond. Similarly, a more mature appreciation of the hydrolyses of the 1,6-anhydroglycopyranoses must encompass an equilibrium between the protonated sugar and the two possible oxonium ions **(18)** and **(19)**, since each ring oxygen can participate in the stabilization of an incipient carbonium ion at the anomeric center. However, the more stable six-membered ring ion **(18)** is usually formed more rapidly and easily because of the release of strain than the much less stable seven-membered ring ion **(19)**.

Similarly, the mechanistic appreciation of the hydrolyses of α- and β-glycosides must first consider the availability of the lone pairs of the acetal oxygens for participation in the transition state leading to the formation of an oxonium ion. Then, especially if this first condition is met by more than one oxygen, the relative stabilities of the possible oxonium ion intermediates must be determined in order to arrive at any valid conclusion as to which oxonium ion was indeed the most likely intermediate. This approach would also enable researchers to examine the influence of the other substituents on the glycosidic molecule on the path of the reaction.

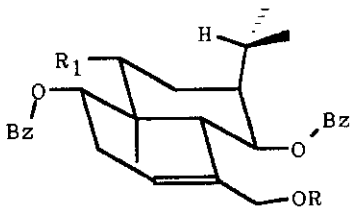
The ester **(20)** had also been isolated[3,11] from *Verbesina rupestris* and its stereostructure was easily established by the dehydration of the diester **(21)** with thionyl chloride in pyridine to give the alkene **(22)** in 97% yield. Hydrolysis of the ester groups of alkene **(22)** gave chaenocephalol **(9)**. This stereospecific dehydration was indicative of an axial methyl group at C4 since it is well known that equatorial, tertiary cyclohexanols are selectively converted into exocyclic alkenes and their axial isomers are selectively converted into endocyclic alkenes, by thionyl chloride (or phosphoryl chloride) in pyridine.[12] The dehydration of the equatorial tertiary alcohol **(23)** produced endocyclic alkenes **(24)** and **(25)**, in 65% and 10% yields,



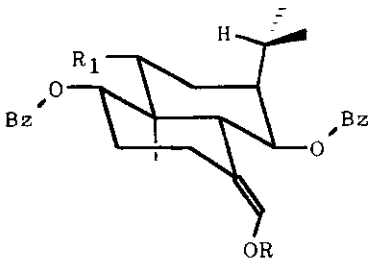
(20) R = H
(21) R = Ac



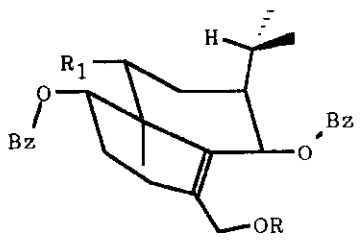
(23) R = cinnamoyl, R_1 = H
(26) R = cinnamoyl, R_1 = OBz



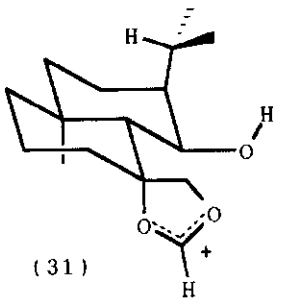
(24) R = Cinnamoyl, R_1 = H
(27) R = Cinnamoyl, R_1 = OBz



(29) R = cinnamoyl, R_1 = H
(30) R = cinnamoyl, R_1 = OBz



(25) R = Cinnamoyl, R_1 = H
(28) R = Cinnamoyl, R_1 = OBz



(31)

respectively. Similarly, the dehydration of the equatorial tertiary alcohol (**26**) produced endocyclic alkenes (**27**) and (**28**), in 75% and 22% yields, respectively. These reactions must have occurred *via* the corresponding oxonium ions (**31**) in which the C4-O4 bond was now axial. These ions were formed by neighbouring group participation in the departure of the chlorosulphite leaving group, and were isomeric with the oxonium ion (**11**) discussed above. The enol esters (**29**) and (**30**)

were produced in 14% and 5% yields respectively.

The oxonium ion (**31**) was calculated to have an O6 to C16 distance of 314.5 pm, too large for O6 to stabilize the oxonium ion by a through- space n-p interaction, and the O4-C16 and O14-C16 bond lengths were predicted to be about 128.4 pm, indicating that these bonds would be delocalized C=O (double) bonds.[7] Although oxonium ion (**31**) was predicted to be only about 0.5 kcal/mole less stable than the ion (**11**), the ion (**31**) was obviously not generated in the hydrolyses of the orthoesters described above, nor was it interconverted with the ion (**11**) *via* the tertiary C4 carbonium ion.

All new compounds gave satisfactory analytical and spectroscopic data, which were completely consistent with their suggested structures.

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7e. Excellent corroboration of these C=O bond lengths in the x-ray crystallographic structures of oxonium ions is found in:

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11. In order to purify the compound (**20**) it was acetylated using acetic anhydride and pyridine. This diester showed: $[\alpha]_D$ = - 24.7 ^{o} (c, 0.97, $CHCl_3$), ν_{max} (film) 3345 (OH), 1720 (C=O), 1635, 1600 cm^{-1}; λ_{max} (EtOH) 281 (ε = 91,900), 224 (ε = 111,000), 205 (ε = 111,000); ^{1}H-nmr (δ, $CDCl_3$, 60 MHz) 0.98 (6H, d, J = 6.0 Hz), 1.13 (3H, s), 1.21 (3H, s), 2.05 (3H, s), 3.75 (1H, s, -O-H), 4.68 (1H, m, H-1), 5.56 (1H, dd, $J_{5,6}$ = 12.0 Hz, $J_{5,7}$ = 5.0 Hz), 6.37 (1H, d, J = 16.0 Hz), 7.68 (1H, d, J = 16.0 Hz), 7.22-7.52 (5H, m). Anal. Calcd for $C_{26}H_{36}O5$: C, 72.86; H, 8.47. Found: C, 2.27; H, 8.44.

Removal of the ester groups by methanolic KOH gave the parent sequiterpene which showed: mp 202-205 ^{o}C; ν_{max} (KBr) 3250 cm-1; ^{1}H-nmr (δ, $CDCl_3$, 60 MHz) 0.92 (6H, d, J = 6.0 Hz), 1.10 (3H, s), 1.30 (1H, s), 3.25 (1H, br s, -O-H), 3.33 (1H, dd, J = 11.0 and 4.0 Hz), 5.15 (1H, d, J = 3.0, -O-H), 5.43 (1H, s, -O-H).

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