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LEAD TETRAACETATE OXIDATION OF UNSATURATED ALCOHOLS. OXIDE FORMATION AND FRAGMENTATION

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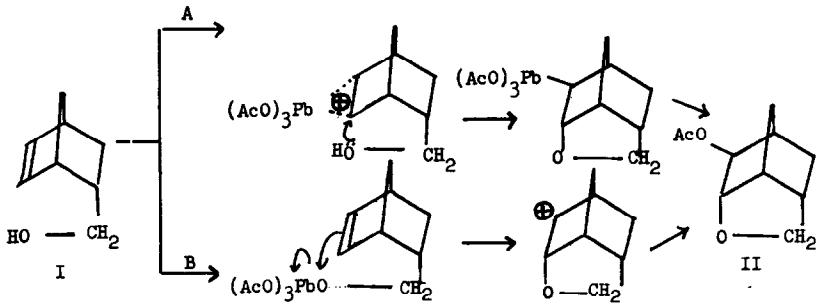
Lead tetraacetate is known to interact with both the carbon-carbon double bond[1] and the isolated hydroxyl group[2]. Oxidation of the double bond results in either allylic acetoxylation as observed with cyclohexene[3], α - cyclogeraniolene[4] and α - pinene[5] or formation of a saturated diacetate as in the case of norbornene[6]. Both reaction pathways probably involve initial addition of ⊕ $Pb(OAc)_3$[7] to the double bond yielding either an open or bridged intermediary organo-lead carbonium ion[5] which may lose a proton, react with the solvent, or undergo rearrangement. Solvolysis of the Pb-C bond yields the corresponding product. Oxidation of monohydric alcohols proceeds via initial formation a lead ester[2]. Homolytic or heterolytic decomposition, depending upon the reaction conditions[2], results in the formation of an electron deficient oxygen (ion or radical); subsequent reactions of which include insertion into a C-H bond to form a five[7] or six-membered cyclic oxide[9], loss of the carbinyl hydrogen to yield a carbonyl compound[10], rearrangement[11] or fragmentation[12].

Application of this oxidative procedure to 2α - hydroxymethylbicyclo-[2.2.1.] -hept-5-ene(I)[13] appeared of interest in that this molecule possesses both a reactive double bond and a primary hydroxyl group. Either set of reaction steps, i.e., initial reaction of the lead tetra-acetate with the double bond of I or with the primary hydroxyl group could, in principle, lead to the same product. These possibilities are represented by pathways A or B:



In agreement with this prediction we wish to report the formation of 6-oxatricyclo [3.2.1.1$^{3.8}$] nonan-4β-ol-acetate (II) from the action of the lead tetraacetate on I. 2α-Hydroxymethylbicyclo[2.2.1]-hept-5-ene(I), lead tetraacetate (molar ratio 1:1), and calcium carbonate in boiling benzene were allowed to react for 12 hours. Distillation of the crude product afforded a 57% yield of II, m.p. 50-51° ; $\lambda_{MAX}^{CCl_4}$ 5.77μ , C=O, 8.68μ, C-O-C of tetrahydrofuranyl ring; N.M.R. (60.0Mc, T.M.S./CCl_4), δ= 2.00 ($\underline{CH_3}CO$), δ=3.72 (-$\underline{CH_2}$-O-multiplet), δ= 3.65 (-$\underline{CH}$-O-multiplet), δ=4.30 (-$\underline{CH}$-OAc, multiplet). 6-Oxatricyclo[3.2.1.1.$^{3.8}$]-nonan- 4β - ol-acetate (II) was synthesized according to the method of Henbest and Nicholls[14] using the reaction of 2α-hydroxymethylbicyclo [2.2.1] - hept-5-ene(I) with perphthalic acid in ether; 6-oxatricyclo [3.2.1.1$^{3.8}$] -

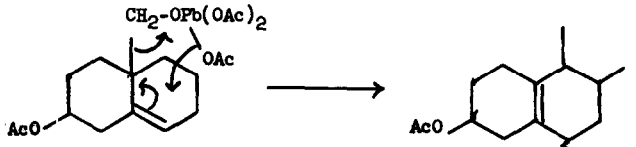
nonan-4β-ol is formed directly rather than the alternative 5α,6α oxido-alcohol. Acetylation yielded a compound identical in all respects with II. Further confirmation of the structure of II was obtained by oxidation (Jones reagent) to the corresponding acetoxylactone m.p.95-96°. This material was also identical with the same acetoxylactone previously described by Henbest and Nicholls[14].

Formation of only one isomer at the C_4 appears somewhat more compatible with mechanism A, i.e., initial addition of $\oplus$ $Pb(OAc)_3$ to the double bond followed by trans opening of this bridged ionic species by the hydroxyl group acting as an internal nucleophile.

The balance of materials from the lead tetraacetate oxidation of I was composed of more highly acetylated products (NMR analysis) which probably derive from Wagner Meerwein rearrangement of carbonium ion intermediates. Pertinently, norbornene itself yields, upon treatment with lead tetraacetate, exo-2-syn-7-dihydroxynorbornene[6].

In order to test the generality[16] of the synthesis of acetoxyoxide derivatives by lead tetraacetate oxidation of appropriately unsaturated alcohols, the reaction was applied to Δ^5-cholestene-3β, 19-diol-3-acetate (III) in the hope of analogously producing the corresponding 5-acetoxy-6β, 19-oxido derivative. In this system, however, the reaction took a different course. Oxidative fragmentation resulted in the loss of the C19 hydroxymethyl group, yielding a product tentatively identified as 19-nor-$\Delta^{5(10)}$cholestene-3β,6λ-diol diacetate (IV)[18], m.p. 92-94°; $[\alpha]_D$ +86 (C,0.46). The NMR spectrum revealed both the absence of the C19 methylene quartet present in III, as well as any vinylic protons.

The two methine protons bound to C_3 and C_6 were unresolved, centered at δ= 5.1, $W_{1/2} \sim$ 15cps. Saponification yielded the diol (IVa), m.p.174-75°; $[\alpha]_D$+111 (C,0.5); N.M.R., C_3-H, δ= 3.82, C_6-H, δ= 4.10 (both multiplets). Allylic oxidation with manganese dioxide in chloroform gave 19-nor-$\Delta^{5(10)}$-cholestene-3β-ol-6-one, m.p. 147-48°, λ_{max}^{EtOH} 250 mμ (e.13,700), $\lambda_{MAX}^{CCl_4}$ 2.67,2.86,6.05,6.17μ. These results are taken to establish the constitution of IV. Furthermore, an analogous fragmentation reaction has been observed by Jeger,et.al[12] in the formation of 3,17-diethylenedioxy-19-nor-$\Delta^{5(10)}$-androstene-6-ol from the lead tetraacetate oxidation of 3,17-diethylene dioxy-Δ^5-androstene-19-ol. Since several steroidal examples exist in which a C5-6 double bond is uneffected by lead tetraacetate[2], a probable intermediate in the above reactions is the C19 lead ester which subsequently decomposes, perhaps via concerted intramolecular allylic transfer of an acetoxy group from Pb to C6. The stereochemical consequence of such a reaction would require an axial conformation of the C6 hydroxyl group.



III IV

Non-formation of the C6β,19-oxide may be due to the strain present in this ring system. For example, buffered solvolysis of Δ^5-cholestene-3β, 19-diol-3p-toluenesulfonate yields no 3α,5α-cyclo-6β, 19-oxidocholestane[15]. Further work is aimed at delineating those structural types which favor intramolecular oxide formation and those which are prone to undergo fragmentation.

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(15) Unpublished result, T.D. Silva, this laboratory.

(16) One example has been reported of acetoxy-oxide formation with an unsaturated steroidal alcohol upon lead tetraacetate treatment. Jeger et.al. have observed the formation of 20-ethylenedioxy-3α, 9α-oxidopregnane-11β-ol-11-acetate from 20-ethylenedioxy-pregnene-3α-ol in 18% yield.

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