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LEAD TETRAACETATE OXIDATION OF CYCLOOCTANOL.

TRANSANNULAR OXIDE FORMATION.

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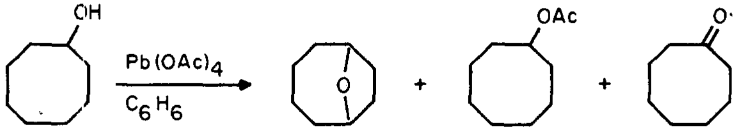
Lead tetraacetate oxidation of monohydric alcohols bearing a carbon-hydrogen bond in the δ - position represents a valuable synthetic route to tetrahydrofurane derivatives [1,2]. The fact that cyclization proceeds via hydrogen abstraction at an unactivated position (i.e., the δ - carbon-hydrogen bond) places this transformation among a class of highly useful reactions for controlled functionalization of remote intramolecular positions [3]. Numerous alcohols of various classes have been used successfully in this oxidative procedure and important mechanistic observations have been made.

Application of the lead tetraacetate oxidation to cyclooctanol appeared to be of interest for three reasons: (a) predominant formation of the five-membered oxide over the six-membered oxide has been explained in terms of the lower activation energy for achieving a six-membered relative to a seven-membered transition state for hydrogen abstraction [4]. In cyclooctanol, however, one must consider that the transition state for five-membered oxide formation involves a bicyclic arrangement of a six- and eight-membered ring while the transition state for six-membered oxide formation consists of a bicyclic seven-seven-membered transition state. Consequently, prior prediction of the reaction course based upon such energy considerations is difficult[5] and (b) due to the well-known transannular effects [6] encountered in the reactions of medium ring compounds, analysis of possible products resulting from transannular hydrogen abstraction might cast some further light upon the mechanism of the lead tetraacetate oxidative cyclization reaction in general. Finally, (c) a favorable entropy situation for oxide formation exists in cyclooctanol relative to n-octanol; hence, high yields of oxide might be anticipated.

Dry lead tetraacetate (0.16 mole) and dry calcium carbonate (0.20 mole) in 250 ml. of anhydrous benzene were kept at reflux for 1 hr. A solution of cyclooctanol (0.15 mole) in 250 ml. of anhydrous benzene was added and reflux was continued for 44 hrs. The crude product was shown by v.p.c. analysis to consist of 1,4-epoxycylooctane (30%) cyclooctanone (6%), cyclooctyl acetate (17%) and cyclooctanol (8%). The latter three products were identified by comparison with known samples. 1,4-Epoxycyclooctane, which could be isolated in 25% yield by direct distillation, had b.p. 50-52° (6.5 mm) and m.p. 30-32° (lit.[7] m.p. 30.8-32.2°).* The infrared spectrum of 1,4-epoxycyclooctane prepared in this investigation was identical with a spectrum of the oxide reported by Cope *et. al.*[7] Minor amounts of higher boiling material were obtained but not characterized. No 1,5-epoxycyclooctane [8] was detected nor were unsaturated acetates isolated.



Formation of only five-membered oxide is in agreement with the result usually obtained in lead tetraacetate oxidative cyclizations. 2-Octanol yields only *cis*- and *trans*-2-methyl-5-propyl tetrahydrofurane [9]. The hydrogen abstraction process appears to be fundamentally similar in both the cyclic and acyclic case. A critical distance factor exists for cyclization; the δ-carbon-oxygen distance must be between 2.5 and 2.8A°.[1] For larger internuclear distances fragmentation and carbonyl formation occur [1]. In the case of cyclooctar conformations of approximately equal stability may be visualized in which the oxygen - δ -

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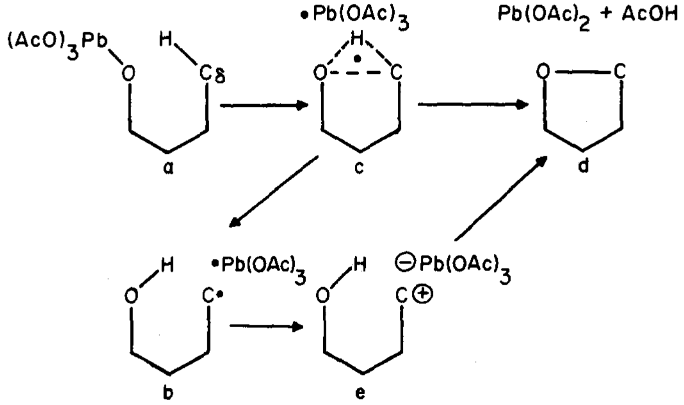
* An acceptable elemental analysis was obtained for the oxide. Prof. A. C. Cope (MIT) has informed us prior to publication that he has obtained the same products.

carbon and oxygen - ε - carbon lengths are 2.6A°. Exclusive formation of the 1,4-epoxycyclooctane must reflect the lower energy of the six-membered transition state (c). A scheme depicting alternative pathways for oxide formation, which has been presented recently, involves steps (a) through (d).[10]



It has been noted that the degree of conformational flexibility of the alcohol has an important effect upon the course of the reaction[10]. In cases involving a rigid conformational relationship between the oxygen and δ-carbon atom, direct formation of oxide occurs (c→d), without the intervention of a carbonium ion intermediate. When the centers are not rigidly fixed, as in acyclic systems, radical pair (c) yields an intermediary organolead ester (b) which in turn gives the ion pair (e). Loss of a proton from (e) may yield an olefin which subsequently reacts intramolecularly with the hydroxy group ultimately yielding an acetoxy-oxide. In the oxidation of cyclooctanol incursion of an intermediate such as (e) appears unlikely since products corresponding to proton loss or solvolysis are not formed in significant amounts. Ring closure to 1,4-epoxycyclooctane must therefore be very close to the transition state for hydrogen abstraction. Finally, formation of cyclooctanone in this reaction is expected due to the strong driving force for $sp^3 \rightarrow sp^2$ type change in the cyclooctane series.

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