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A NOVEL ALUMINA-INDUCED INTRAMOLECULAR CYCLIZATION ACCOMPANIED BY HYDRIDE TRANSFER. FORMATION OF OXEPANE RING FROM 3,4-SECO-4-IODO-CHOLEST-5-EN-3-AL

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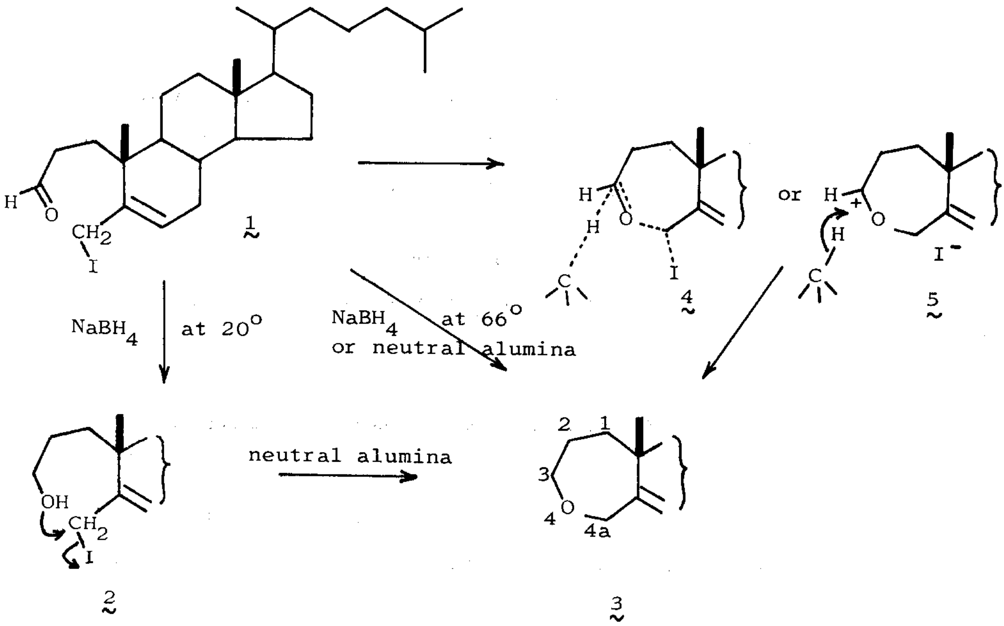
In a previous paper we have shown that one of the major products of the *hypoiodite reaction of cholesterol* was 3,4-*seco*-4-*iodo-cholest*-5-*en*-3-*al* **1**. (1) We wish to report a novel cyclization reactions of **1** which are induced by a solid surface.

When n-hexane solution of **1** was adsorbed on Merck or Woelm neutral alumina (2) and eluted with benzene and n-hexane the eluates contained virtually a single compound **3**, m.p. 75-77°C (Yield 92%). It was apparent that the structure of **3** was 4-oxa-A-homo-cholest-5-ene when an identical compound was obtained by the reduction of **1** with $NaBH_4$ in boiling THF. The elemental analysis, ^{1}H nmr and mass spectra were in agreement with the assigned oxepane structure. (mass. no M^+ peak, m/e 372, 24% (M^+ -14); ^{1}H nmr (100 MHz, $CDCl_3$) τ9.31, s, C-18-H, τ8.90, s, C-19-H, τ5.78- 6.45 (4H) m, C-3-H and C-4-H, τ4.58 (1H), s, C-6-H;) ^{13}C FT nmr spectrum (3) of **3** (25.1 MHz, $CDCl_3$, TMS) together with the ^{1}H off-resonance decoupling fully supported the assigned oxepane structure. Among 27 carbon resonances of **3**, all except two pairs (39.65 and 31.40 or 31.55 ppm) are resolved and these resonances can readily be identified by comparison with cholesterol. Only 7 resonances of **3** were found to differ significantly from those of cholesterol (4) and these resonances are assignable to those due to the oxepane ring of **3** as follows; C-1 (39.65 ppm), C-2 (31.40-31.55), C-3 (64.75), C-4a (70.23), C-5 (139.59), C-6 (121.54), C-10 (35.43), C-19 (18.64). (5)

$NaBH_4$ reduction of **1** in methanol-ether at room temperature readily afforded unstable 3,4-seco-4-iodo-cholest-5-en-3-ol **2**, m.p. 45-48°C. **2** could not be



cyclized to 3 at room temperature without a base and the cyclization was achieved when 2 was treated with a base such as potassium t-butoxide in t-butyl-alcohol. However, when 2 was passed through Merck or Woelm neutral alumina 2 was readily converted into oxepane 3 as a sole product (95% yield). These results indicate that the cyclization is induced by alumina.

We might interpret the pathway of the cyclization of 1 to 3 in terms of the initial transformation of 1 into 2 by alumina-induced Cannizzaro reaction (6), followed by the alumina-induced intramolecular nucleophilic substitution to 3. This is untenable, however, since the yield of 3 exceeds stoichiometric amount required by Cannizzaro disproportionation.

Although it has been proved that Al_2O_3 has a dipolar character and has both electron-donor and acceptor sites on the surface and forms radical anion from an electron deficient olefin, (7) it is very unlikely that the present reaction at room temperature involves the formation of a ketyl radical followed by cyclization and successive electron and proton donations to form 3. The most plausible pathway would be the nucleophilic attack of carbonyl on the iodine-bearing carbon and a hydride transfer from solvent (e.g., 1→5→3). These steps would occur either synchronously (e.g., 4) or stepwise (e.g., 5).

Apart from the alumina-induced Cannizzaro reaction, to our knowledge (8), the present reaction is the first clear example of hydride transfer induced by an alumina surface. In this particular case, the proper geometry between the substrates and the solvents adsorbed on a solid surface should make the cyclization and hydrogen transfer extremely facile, as in the case of the transannular hydrogen shift in solution chemistry (9).

Moreover, no nucleophilic substitution induced by alumina is known and the transformation of 2 into 3 seems to be the first of this sort.

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