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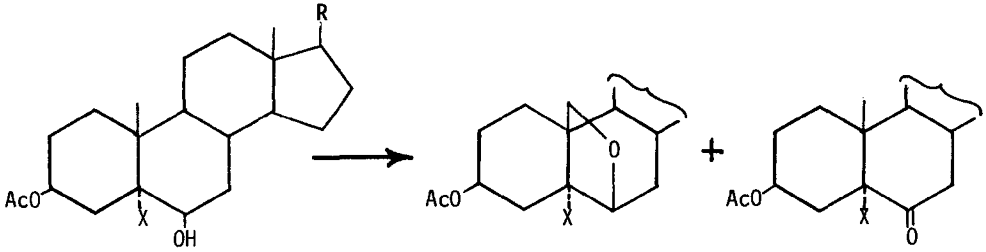
OXIDATIVE CYCLIZATION AND FRAGMENTATION OF STEROIDAL ALCOHOLS INDUCED BY CERIC AMMONIUM NITRATE

Venkataraman Balasubramanian and Cecil H. Robinson*

*Department of Pharmacology and Experimental Therapeutics
The Johns Hopkins University, School of Medicine, Baltimore, Maryland.

Abstract: Oxidative cyclizations of steroidal alcohols (1a-1d) using ceric ammonium nitrate (CAN) in aqueous acetonitrile or aqueous acetic acid gave the corresponding cyclic ethers (2a-2d), whereas the tertiary alcohol (4) gave secosteroid (5).

Tetravalent cerium (ceric ion) is a powerful one electron oxidant with a redox potential[1] comparable to that of lead tetra acetate, and has the ability to oxidize a wide variety of organic compounds.[2] We report here the reaction of ceric ammonium nitrate (CAN) with some conformationally rigid steroidal alcohols in aqueous acetonitrile or aqueous acetic acid at 80°C. Thus the 6β-hydroxy steroids (1a-1d) undergo smooth oxidative cyclization to give the corresponding 6β,19-oxidocompounds (2a-d) in fair to good yield, in addition to some ketone formation (Table I).



1a; X=H; R=OAc
1b; X=H; R=C_8H_{17}
1c; X=Cl; R=OAc
1d; X=Cl; R=O
1e; X=Br; R=OAc

2a-d

3a-e

As seen in Table I (entries 1a, 1c and 1e) the yield of cyclic ether decreases with increasing size of the substituent at C-5 adjacent to the 6β-hydroxy group. Of the organic solvents studied, only acetonitrile and acetic acid were found to favor oxidative cyclization in good yield.

TABLE I

CERIC AMMONIUM NITRATE OXIDATION OF STEROIDAL ALCOHOLS

ALCOHOL	OXIDANT[a] (mmole)	SOLVENT (mL)	TIME[b] (min)	PRODUCTS; Percent Yield[c]		
				CYCLIC ETHER	KETONE	5,10-SECOSTEROID
6β-Hydroxy-3β,17β-diacetoxy-5α-androstane (1a)	2.5	CH_3CN (1.4)	3	2a;55%	3a;34%	——
6β-Hydroxy-3β,17β-diacetoxy-5α-androstane (1a)	2.5	CH_3CO_2H (1.4)	3	2a;63%	3a;22%	——
6β-Hydroxy-3β-acetoxy-5α-cholestane (1b)	3.5	CH_3CO_2H (1.4)	5	2b;60%	3b;30%	——
5α-Chloro-6β-hydroxy-3β,17β-diacetoxy-5α-androstane (1c)	3.5	CH_3CN (2.8)	15	2c;20%[d]	——	——
5α-Chloro-6β-hydroxy-3β-acetoxy-5α-androstan-17-one (1d)	3.5	CH_3CN (2.8)	15	2d;25%[d]	——	——
5α-Bromo-6β-hydroxy-3β,17β-diacetoxy-5α-androstane (1e)	2.5	CH_3CN (1.4)	5	2e;Trace	3e;85%	——
5α-Hydroxy-3β,17β-diacetoxy-5α-androstane (4)	2.5	CH_3CN (1.4)	3	——	——	5;80%

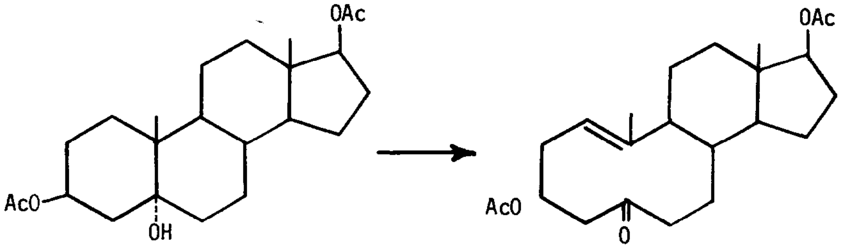
a) 1M-solution of CAN in water added to the steroid (1 millimole) in organic solvent at 80°C.

b) Time taken for the dark red alcohol-Ce ^{IV} complex to dissociate and turn colourless.

c) Isolated yields of pure products after column chromatography. Structural assignments based on spectroscopic and chromatographic comparison with authentic samples.

d) Based on starting material consumed.

Although low yield oxidative cyclization was observed[3] some years ago by the action of ceric ion on n-pentanol, we have seen no subsequent reports on the synthetic exploitation of this process. The reactions shown in Table 1 are analogous to transformations promoted by reagents such as lead tetra acetate,[4,5] iodine/mercuric oxide[6,7] or bromine/silver salts.[8,9] Also listed is the ceric ion-induced oxidative fragmentation of the tertiary alcohol (4) to give the secosteroid (5), in good yield.[10]



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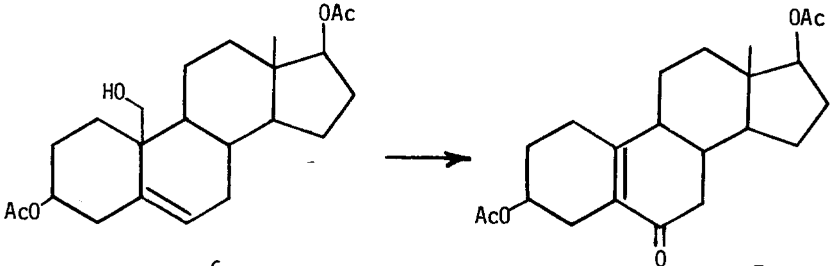
A typical experimental procedure for oxidative cyclization is as follows: To a stirred solution of steroid (1a; 100mg; 1mmole) in acetonitrile (1.4ml) at 80°, was added a solution of ceric ammonium nitrate (375mg; 2.5 mmole) in water. The solution turned dark red immediately and became colorless within five minutes. It was then cooled and poured into water, extracted with methylene chloride and chromatographed on silica gel to give the pure 6β, 19-oxidosteroid (2a, 55mg). The corresponding ketone (3a, 34mg) was also isolated.

Under the same experimental conditions, the tertiary alcohol, 5α-hydroxy-3β,17β-diacetoxy androstane (4) underwent smooth fragmentation to give the 5,10-secosteroid (5) in high yield. Fragmentation is also observed in the ceric ion-induced conversion of the homoallylic alcohol (6) to the conjugated ketone (7) in yields varying between 40% and 60%.



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The initial step in all the above ceric ion-induced reactions is probably an inner sphere process. The dark red alcohol-cerium complex formed initially may dissociate with transfer of one electron from the alcohol to the metal ion, and the resulting electron deficient oxygen may then abstract hydrogen from a conformationally adjacent γ-carbon atom. Finally, it should be pointed out that water is required for successful reaction. In the absence of water, complex reaction mixtures result.

In conclusion, ceric ammonium nitrate offers a simple rapid method for oxidative cyclization or fragmentation. The simplicity and short reaction time of the method, together with ease of work-up, combine to provide a useful alternative to lead tetra acetate and other reagents effecting such transformations.

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