Tetrahedron Letters No.15, pp. 1157-1158, 1969. Pergamon Press. Printed in Great Britain.

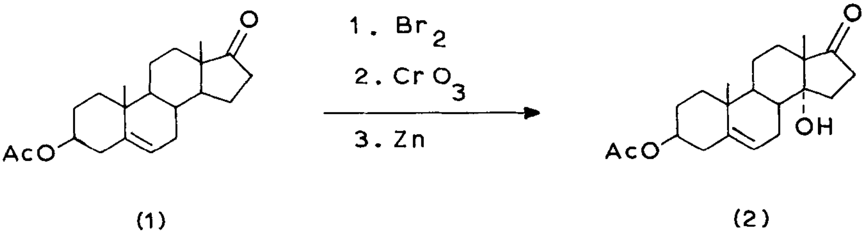
INFLUENCE OF WATER ON THE CHROMIC ANHYDRIDE OXIDATION OF ANDROSTENOLONE ACETATE.

C.M. Hol, M.G.J. Bos and H.J.C. Jacobs.

(Laboratory of Organic Chemistry, The University, Postbus 75, Leiden, The Netherlands)

(Received in UK 28 January 1969; accepted for publication 27 February 1969)

In 1952 St. Andre et al[1] described the preparation of 3β-acetoxy-14α-hydroxyandrost-5-en-17-one (2) from 3β-acetoxy-androst-5-en-17-one (1) by chromic anhydride oxidation of the dibromide in acetic acid. This reaction has since been extensively used for the direct introduction of an α-hydroxyl group at C-14 in the steroid nucleus[2,3]. In a recent paper Sykes and Kelly[3] report that for a successful oxidation to take place it is necessary to have hydrobromic acid present in the reaction mixture. In this paper we report on the remarkable influence of water on this reaction.



To investigate this influence a series of experiments was carried out with equal amounts of steroid. Bromination took place in acetic acid containing less that 0.2% of water. Prior to the addition of chromic anhydride to the dibromide solutions, varying quantities of water were added. The reaction was allowed to proceed during 30 minutes at 25°C. After debromination and working up the reaction mixtures were analysed by GLC. The results are collected in Table I.

Table I. Influence of varying quantities of water on the chromic anhydride oxidation of androstenolone acetate in acetic acid.

% H_2O added	% 14α-H unreacted	% 14α-OH a	% 14α-OH b
0	73	4	15
0.5	56	13	34
1	33	26	39
1.5	28	30	42
2	34	29	44
3	34	24	36
5	78	7	31
7	79	6	29
10	86	3	21

a. percentage yield 14α-OH calculated upon the total amount of starting material.

b. percentage yield 14α-OH calculated upon consumed starting material.

The table clearly indicates that the formation of the 14α-hydroxy-compound (2) is critically dependent on the percentage of water present in the solvent. Maximum and optimum yields are obtained when oxidation is performed in the presence of 1.5 to 2 % of water.

The effect of the water content of the solvent on the course of a CrO_3/HOAc oxidation was first noted by Fieser[4]. An explanation of the favourable influence of low water concentration in chromic acid oxidations is offered by Wiberg and Evans[5].

References.
1. A.F. St. Andre, H.B. MacPhillamy, J.A. Nelson, A.C. Shabica and C.R. Scholz, J.Am.Chem.Soc. 74, 5506 (1952).
2. a. F. Sondheimer, S. Burstein and R. Mechoulam, J.Am.Chem.Soc. 82, 3209 (1960).
   b. S.H. Eppstein, P.D. Meister, D.H. Peterson, H.C. Murray, H.M.L. Osborn, A. Weintraub, L.M. Rieneke and R.C. Meeks, J.Am.Chem.Soc. 80, 3382 (1958).
   c. T. Nambara, Chem.Pharm.Bull. (Tokyo) 12, 1253 (1964).
3. P.J. Sykes and R.W. Kelly, J.Chem.Soc. (C) 1968, 2346.
4. L.F. Fieser, J.Am.Chem.Soc. 70, 3237 (1948).
5. K.B. Wiberg and R.J. Evans, Tetrahedron 8, 313 (1960).