Tetrahedron Letters No.22, pp. 1399-1402, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE WESTPHALEN REARRANGEMENT

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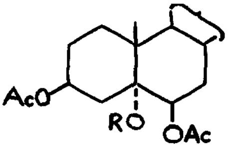
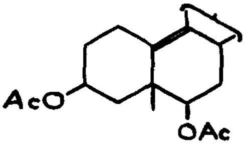
(Received 30 March 1964)

Westphalen in 1915 reported[1] the dehydration of 3β, 6β-diacetoxycholestan-5α-ol (1a) by acetic anhydride-sulphuric acid to give a diacetate which was shown by later workers[2] to be 3β, 6β-diacetoxy-5β-methyl-19-norcholest-9-ene(2).





1 a R, H
b R, Ac
c R, CH_3
d R, SO_3H
e R, SO_2OAc

2

The only other reported[3] procedure for the dehydration of 6β-substituted-5α-hydroxy compounds (1a) to give the rearranged product (2) involves reaction with potassium hydrogen sulphate-acetic anhydride. The use of other catalysts of varied acidity for the reaction in acetic anhydride, e.g. hydrogen chloride[4], toluene-p-sulphonic acid[5], and in this work perchloric acid and hydrofluoroboric acid, has been shown to give only the 5α-acetate(1b). Reaction of the 5α-acetate(1b) with sulphuric acid-acetic anhydride at 45° for 5 min., conditions for the smooth conversion of the 5α-alcohol(1a) into the rearranged diacetate (2), gave only starting material. Furthermore, extension of the reaction time to 2 hr. did not affect the recovery (ca. 95%) of the 5α-acetate(1b). This result excludes the possibility of the formation of the rearranged diacetate (2) via the 5α-acetate using sulphuric acid-acetic anhydride, even though the extreme conditions of hydrofluoroboric acid-acetic anhydride at 90° for 15 min. did convert the 5α-acetate to the rearranged diacetate (2) in low yield (ca. 20%).

The possibility that the dehydration of the 5α-hydroxy compound(1a) proceeded via protonation of the hydroxyl group followed by loss of a molecule of water and migration of the C_{19} methyl group was excluded by a comparison of the reactions of the 5α-hydroxy-(1a), 5α-methoxy-(1c) and 5α-acetoxy-(1b) compounds with sulphuric acid-acetic anhydride at 20°. Had protonation of the C_5-oxygen atom, followed by loss of water or methanol, been involved then the reactions of the 5α-hydroxy-(1a) and the 5α-methoxy-(1c) compounds should have been comparable. However, while the reaction of the 5α-hydroxy compound(1a) to give the rearranged diacetate (2) was complete in 1 min., the 5α-methoxy-compound(1c) could be isolated in good yield (> 90%) from the corresponding reaction after 24 hr.

Reaction of cholesterol with sulphuric acid-acetic anhydride under the conditions used above gave after 1 min. cholesteryl hydrogen sulphate isolated as the potassium salt in

75% yield in addition to a small amount of cholesteryl acetate (13%). The sulphonating properties of the sulphuric acid-acetic anhydride system are also revealed in the formation[6] of sulpho-acetic acid from the sulphuric acid-acetic anhydride alone and in the formation[7] of the 6-sulphonic acid on reaction of cholest-4-en-3-one with the system.

It is proposed that the Westphalen rearrangement of the 5 -hydroxy compound(1a) proceeds <u>via</u> sulphonation of the 5 -hydroxy group followed by loss of $HO{-}SO_2{-}O^-$ ion or $CH_3{-}CO{-}O{-}SO_2{-}O^-$ ion and migration of the C_{19} methyl group. In sulphuric acid-acetic anhydride the following equilibria are established[8] :-

$$H_2SO_4 + Ac_2O \rightleftharpoons HO{-}SO_2{-}O{-}Ac + AcOH$$

$$HO{-}SO_2{-}O{-}Ac + Ac_2O \rightleftharpoons Ac{-}O{-}SO_2{-}O{-}Ac + AcOH$$

followed by breakdown of the mixed anhydride species:-

either $HO{-}SO_2{-}O{-}Ac \longrightarrow SO_3 + AcOH$

or $HO{-}SO_2{-}O{-}Ac \longrightarrow HSO_3^+ + AcO^-$.

The nature of the sulphonating species is not known but it is possible that any one of SO_3, HSO_3^+, $HO{-}SO_2{-}O{-}Ac$ and $Ac{-}O{-}SO_2{-}O{-}Ac$ may be involved.

$$(1a) + \text{sulphonating species} \longrightarrow (1d) \xrightarrow{Ac_2O} (1e)$$

either $(1d) \longrightarrow (2) + HSO_4^-$

or $(1e) \longrightarrow (2) + Ac{-}O{-}SO_2{-}O^-$

It is not known which of the above steps in the reaction sequence is rate-determining, neither is the nature of the leaving group (HSO_4^- or $Ac{-}O{-}SO_2{-}O^-$) certain. A detailed kinetic study of the system is now being undertaken, although it is already known that the rate of the reaction is markedly dependant upon the sulphuric acid + steroid ratio.

When the effect of the potassium hydrogen sulphate-acetic anhydride system on the 5α-hydroxy compound(1a) was examined it was found that the rate of conversion of the alcohol(1a) into the rearranged diacetate (2) was comparable with those reactions using sulphuric acid-acetic anhydride where the sulphuric acid : steroid ratio was low. If an initial equilibrium can be postulated :-

$$HSO_4^- + Ac_2O \rightleftharpoons Ac{-}O{-}SO_2{-}O^- + AcOH$$

then the otherwise identical courses of the sulphuric acid- and potassium hydrogen sulphate-acetic anhydride reactions may be explained.

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