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REACTIONS OF STEROLS WITH PYRIDINIUM CHLOROCHROMATE

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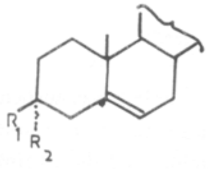
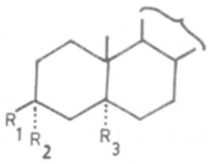
ABSTRACT

Reaction of pyridinium chlorochromate with cyclohexanol and several C_3-sterols have been investigated. It has been found that the equatorieal C_3-sterols are easily oxidised in good yield to give corresponding ketosteroids while the axial sterols give poor yields.

Introduction

In recent years several new oxidation reagents have been developed for example DMSO-DCC (Pfitzner and Moffet 1965) and DMSO-Acetic Anhydride (Albright & Gold-man 1965; Wilson & Ifzal 1967) have been employed in the oxidation of cholesterol and variety of sterols. However, these and many other known and useful oxidising reagents give undesirable side products with steroids. In this communication we wish to report the results of the reaction of Pyridimium chlorochromate with some C_3 sterols of cholestane series.





I. R_1 = OH, R_2 = H

II. R_1 = H, R_2 = OH

III. R_1 = OH, R_2 = H, R_3 = H

IV. R_1 = H. R_2 = OH, R_3 = H

V. R_1 = OH R_2 = H R_3 = OH

I. CHOLESTEROL

II. CHOLEST-5-EN-3α-OL

III. 5α-CHOLESTAN-3β-OL

IV. 5α-CHOLESTAN-3α-OL

V. CHOLEST-3β-5α-DIOL

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Experimental

Preparation of Pyridinium Chlorochromate: (Corey & Sagga 1973)

To 184 ml of 6M HCl (1.1) was added 100 gm (1 mol) of CrO_3 rapidly with stirring. After five minutes the homogenous mixture was cooled to 0°C and 79 ml (I mod) of pyridine was carefully added over 10 minutes. Recooling to 0°C gave a yellow-orange solid which was collected over sintered funnel and dried for one hour. in vacua (yield approx. 175 g; $_{50^{\circ}\mathrm{k}).}$ The solid was stored in a well stoppered bottle at room temperature.

Reaction of Pyridinium Chlorochromate with Cvclohexanol:

To a suspension of pyridinium chlorochromate 22.5 gm in CH_2Cla (100 ml) was added rapidly in one portion cyclohexane (10 ml) and the mixture stirred magnetically for a period of one hour at room temperature. The mixture turned black and the suspension was allowed to stand overnight under refrigeration (to avoid loss of reaction product by evaporation) and then decanted and filtered quickly through a short column of celite. The filterate was transferred to a small distillation flask and the reaction product distilled through a short Vigreux column to separate CH_2Cl_2 from the reaction product. CH_2Cl_2 distilled over between 40-41^{o} and the remaining liquid at 154-156^{o}. It was identified as cyclohexanone on the basis of h.p. and infrared spectrum, $V_{max} = 1715\ cm^{-1}$.

Reaction of Cholesterol with Pyridinium Chlorochromate:

Pyridinium Chlorochromate (3.5 g; approx 0.15 moles) was suspended in CH_2Cl_2 (200 ml) and the suspension stirred rapidly by magnetic stirrer. Cholesterol (3.86 g; approx 1.0 mole) in CH_2Cl_2 (50 ml) was added rapidly and the stirring continued for 1½ hr. The reaction mixture was cooled to 0°C, allowed to stand at this temperature for 30 minutes and the supematent decanted from the dark gum. The insoluble residue was washed thrice with ether 3 x 20 ml; and the washings combined with the decanted supernatent and filtered through a short column of celite. The examination of the clear elutate indicated the formation of ketone with a trace of cholesterol. The elute was therefore concentrated over rotary evaporator under reduce pressure to give a brownish gum which was chromatographed over a short column of silica gel, using pet-ether (40-60/$CHCl_3$ in 9:1 ratio) as elutant.

The elute was concentrated to dryness under reduce pressure to give a white gum and was found on examination by tic and infrared to be a mixture of cholest-4-en-3-one (ir, strong absorption at $V_{max} = 1720\ 1680\ cm^{-1}$). The gum was therefore taken up in methanol 20 ml, 100 mg of oxalic acid added and the mixture refluxed for 30 minutes. The solution was allowed to come to room temperature and then left at 0-5^{o}C in refrigerator overnight whereupon fine yellow needles (2.1 g; m.p. 76-77^{o} raised on cryatallisation to 77-78°) were obtained and shown to be pure cholest-4-en-3-one on the basis of its m.p. (lit. 81-82°), ultravoilet and infrared spectrum: λ_{max} = 241 m, ε-= 16500; V_{max} = 1680, α, β-unsaturated CO str; & 1625 cm^{-1} C = C str.

Reaction of Cholest-5-en-3-α-ol with Pyridinium Chlorochromate:

Pyridinium Chlorochromate (1.3 g; approx 0.05 moles) was added in CH_2Cl_2, (75 ml) and the suspension stirred rapidly over magnetic stirrer. Cholest-5-en-3-a-ol (1.0 g;) was added rapidly and the reaction mixture stirred for 1½ hrs. The reaction mixture was cooled to 0°C and allowed to stand at this temperature for 30 minutes and then worked up as described above as in the case of chloesterol. Tlc examination of the reaction pro-duct indicated mainly the starting alcohol with a slight formation of ketone. The solvent was therefore removed from the crude reaction product and it was subjected to retreatment with double the quantity of pyridinium chlorochromate. Tlc of the work-up again revealed mainly the starting material with trace of ketonic product. The reaction was, therefore not persued further.

Reaction ofCholest-3-β-5-α-diol with Pyridinium Chlorochromate:

The dial (500 mg) in CH_2Cl_2 (25 ml) was treated with pyridinium chlorochromate (650 mg) as described above. Tic examination of the crudreation product revealed formation of ketone with trace of the starting doiol. Recrystallisation of ketone with trace of the starting diol. Recrystallisation of the crude yielded fine yellow needles, m.p. 79-80° and was identified as cholest4-en-3-one on the basis of m.p; comparative tic, infrared and ultravoilet spectral data. (V_{max} = 1680 cm^{-1} ; $\lambda_{max.}$ = 241 m).

Reaction of 5-α-chlestane-3-β-ol with Pyridinium Chlorochromate:

5-*α*-Cholestane-3- *β*-ol (500 mg) was treated with pyridinium chlorochromate (650 mg) as above. Working up the reaction product yielded a dark gum which on tic examination indicated a single compound with a trace of starting alcohol. Chromatography over silica gel using pet-ether/chloroform (9:1) as elutant yielded a light yellow gum, which crystallised out as long colorless nedles, m.p. 127-129° and was identified as 5-*α*-cholestan.3-one on the basis of m.p. and infrared (V_{max} = 1720 cm^{-1}).

Reaction of 5-α-chloestane-3-α-ol with Pyridinium Chlorochromate:

The alcohol 500 mg was treated with the reagent 650 mg as described above. On working up the reaction mixture and examination by tic, and i.r. indicated that the alcohol was unaffected by the reagent.

Discussion of Results

In the present study, reaction of cyclohexanol and five sterols each having the hydroxyl group at position 3 in a different special arrangement with respect to each other have been investigated with pyridinium chlorochromate as the reagent.

Of the five sterols reacted, two of them, namely, cholesterol and S-acholestane-3-β-ol have the hydroxyl group in equatorial position. Cholestan-5-en-3-α-ol and 5-α-cholestane-3-α-ol, on the other hand, have axial hydroxyl group. Cyclohexanol exist in various confirmations, chair form having the hydroxyl group in the equatorial position is the most stable and predominent form, In the present investigation it has been observed that the cholesterol, 5a-cholesten-3-jol and cyclohexanol, all give ketone as a major product. All these three alcohols have the hydroxyl group in the equatorial position. The axial alcohol, i.e., cholestan-5-en-3-α-ol and 5-α-cholestan-3-α-ol, on the other hand yielded none or almost negligibe amount of ketonic product.

Cholestan-3-β-5-α-diol, which contain both the equatorial and an axial hydroxyl group, give the same ketone i.e. cholest4-en-3-one, as that obtained from cholesterol. This is due to the fact that the 5-α-OH in the diol is tertiary in nature and can be easily eliminated under the reaction conditions to give back cholesterol which then react with the reagent. A similar behaviour of cholestan-3-β-5-α-diol has been observed by us in an another study (Wilson & Ifzal 1969), involving DMSO-Acetic Anhydride as an oxidising reagent.

It has also been observed that the double bond in cholesterol has a tendency to migrate from 5,6 position to 4,5 position to form the more stable conjugated ketone. How-ever, it is possible that a use of a suitable buffer alongwith the reagent may prevent or retard the migration and yield the less stable but more important cholest-5-en-3-one. It is suggested that the reaction be investigated further, using several more sterols and varying the reaction condition to draw definite conclusion regarding the utility of Pyridinium-chlorochromate reagent.

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