ACIDOLYSIS OF CHOLESTERYL ETHERS; A SIMPLE REMOVAL OF ETHEREAL PROTECTING GROUPS

By

J. A. SZABÓ

Department of Organic Chemistry, Attila József University, Szeged, Hungary

(Received 5th May 1980)

The acidolysis of aliphatic and alicyclic ethers of cholesterol has been studied in acetic anhydride + perchloric acid media with the aid of IR spectroscopy. The reaction seems useful for the removal of ethereal groupings from the steroidal 3-*beta* position.

The simplicity and success of preparing ethers by solvolyzing the steroidal *delta*-5-3-*beta*-ol tosylates with alcohols is well known [1]. There are also several methods for the removal of the protecting ethereal groupings from the same position [2], but in some cases difficulties arise from the protracted reaction time and from the unavoidable by-products.

On the basis of our preliminary results, the acidolysis of cholesteryl ethers (I) seems to be simple, when an acyl cation is readily produced. We have therefore investigated the solvolysis of such compounds with acetic anhydride in the presence of small amounts of perchloric acid, because this has been found to be superior to other acids for the hydrolysis of carboxylic acid anhydrides [3].

It may be seen in the experimental section that this acidolysis procedure is an extremely simple one; the cholesteryl ether (I) is dissolved at room temperature in

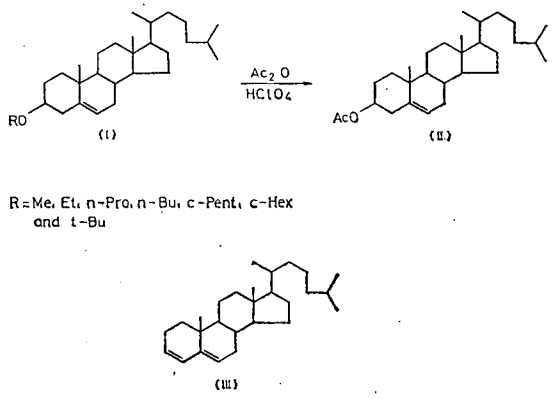

Fig. 1

acetic (or propionic) anhydride and a small amount of 70% aqueous perchloric acid is added to the stirred solution. After some seconds the mixture turns dark, and after some minutes the reaction is complete.

The course of the reaction has been studied by means of IR spectroscopy. Only the amount of the steroidal ester (II) has been established, based upon the intensity of the ester carbonyl stretching band. Our TCL investigations revealed that cholesta-3,5-diene (III) and some coloured steroidal by-products are also present at low concentrations in the solvolyzed mixture (max. 1—2%).

Table I

Percentage yields of cholesteryl acetate

Compound	Reaction temperature, °C	Percentage yield of cholesteryl acetate after		
		1 min	2 min	4 min
cholesteryl methyl ether	21.5	27.5	34.7	45.9
cholesteryl ethyl ether	22	24.3	37.4	48.8
cholesteryl *n*-propyl ether	22	24.4	41.5	52.8
cholesteryl *n*-butyl ether	19.5	24.3	55.7	62.2
cholesteryl cyclopentyl ether	22	18.7	34.8	45.7
cholesteryl cyclohexyl ether	24	13.3	36.2	60.2
cholesteryl *tert*-butyl ether	24	100	100	100

The pathways of the reaction are complicated. The reaction order is found to be fractional for ester formation, and therefore only the percentage production of the ester (II) is recorded (Table I).

The data in Table I show that the acidolysis is fastest for the *tert*-butyl ether, but this derivative can be prepared only in moderate yields (30—50%) and it is thus unsuitable as a protecting group. All other derivatives tested undergo acidolysis almost equally well. Therefore and because of the highest yields of preparation the methyl ether seems to be the most convenient protecting group.

Acetolysis of this type is applied for the transformation of dehydroepiandrosterone ethers [4].

There are also some data on the acidolysis of the title compounds in propionic anhydride + perchloric acid, but the amount of the propionic acid ester differs only slightly from that of the acetate under similar conditions.

Experimental

The preparation and physical properties of the cholesteryl ethers have been reported elsewhere [5]. The analytical data on the compounds are shown in Table II.

The proton resonance spectra have been recorded in carbon tetrachloride solution relative to TMS with a JEOL 60 HL type spectrometer. The IR spectra have been made in Merck Uvasol carbon tetrachloride and potassium bromide with a UNICAM SP 1000 spectrometer.

Table II

Analytical data on cholesteryl ethers

Compound	Mp °C	$[\alpha]_D^*$	Anal. calcd. C	Anal. calcd. H	Anal. found C	Anal. found H
cholesteryl methyl ether	83.5	−45.8	83.93	12.07	83.65	11.93
cholesteryl ethyl ether	89	−39.4	83.99	12.15	83.88	11.89
cholesteryl *n*-propyl ether	101	−34.8	84.05	12.23	84.07	11.98
cholesteryl *n*-butyl ether	79.5 (87)	−28.8	84.09	12.29	84.01	12.15
cholesteryl cyclopentyl ether	149	−25.0	84.51	11.97	84.34	11.64
cholesteryl cyclohexyl ether	142	−32.0	84.55	12.04	84.65	11.97
cholesteryl *tert*-butyl ether	156	−36.0	84.09	12.29	83.88	11.80

* Measured in chloroform solution at about c=1, d=1, at 24—26 °C.

Analytical technique

At room temperature 0.001 mole cholesteryl ether is dissolved in 5 ml A. R. grade acetic anhydride and 15 ml A. R. benzene, and under vigorous stirring with a magnetic stirrer 0.2 ml 70% aqueous perchloric acid is added rapidly. After the predetermined reaction time, 2 ml aliquots are transferred from the stirred solution to 30 ml stirred solution of 1 M aqueous sodium carbonate, and this mixture is extracted twice with 50 ml A. R. benzene. The extracts are combined, and washed with an equal amount of distilled water, dried over anhydrous magnesium sulphate, and evaporated to dryness on a rotary evaporator. The glassy solid residue is dissolved in 2 ml carbon tetrachloride (Merck Uvasol) and investigated by IR spectroscopy at a thickness of 0.1 mm, relative to standard samples prepared from cholesteryl acetate.

A typical experiment in the preparative range:

4.2 g (0.1 mole) cholesteryl methyl ether is dissolved in 40 ml practical grade acetic anhydride and 0.5 ml 70% aqueous perchloric acid is added to the stirred solution. After five minutes the reaction mixture is poured into 250 ml 20% aqueous sodium carbonate solution and extracted with benzene (3×150 ml). The combined extracts are washed with equal volumes of water, 2% aqueous hydrochloric acid and water, respectively, dried over anhydrous magnesium sulphate and filtered through a short silica gel (*e.g.* Merck Kieselgel 100) column, and the eluates is evaporated *in vacuo*. Crystallization from rectified spirit yields colorless crystals of 3-b*eta*-acetoxy-cholest-5-ene, 3.96 g (mp: 115 °C).

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The author is grateful to Mr. Gy. Maknics and Mrs. J. Csányi—Kertész for technical assistance.

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АЦИДОЛИЗ ЭФИРОВ ХОЛЕСТЕРИНА, ПРОСТОЕ УДАЛЕНИЕ ЭФИРНЫХ ЗАЩИТНЫХ ГРУПП

Й. А. Сабо

Изучен ацидолиз алифатических и алициклических эфиров холестерина в среде ангидрида уксусной и прехлорной кислоты методом ИК-спектроскопии. Показано, что применение изученной реакции удобно для удаления эфирных групп с положения 3 β стероидов.