A RELIABLE SYNTHESIS OF 3β-ACETOXY-6-NITROCHOLEST-5-ENE

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ABSTRACT

A consistently reproducible method for the preparation of the title compound by the nitration of cholesteryl acetate is given.

The preparation of 3β-acetoxy-6-nitrocholest-5-ene (6-nitrocholesteryl acetate) is a valuable, yet often frustrating, synthesis. The nitro compound is readily converted to the 6-oxo steroid [1a], thus providing a two-step synthesis of the 6-one from 3β-acetoxycholest-5-ene (cholesteryl acetate). The sequence is the most important one for the preparation of a 6-one containing an A/B trans ring juncture.

Unfortunately, the syntheses of 6-nitrocholesteryl acetate reported in the literature have been characterized by an unacceptable degree of reliability. We and others have found that the treatment of solid cholesteryl acetate with nitric acid and an alkali nitrite [1b, c, d] produces a reaction that often "takes off" with violent evolution of nitrogen oxides and destruction of the product. Fieser's modification [2] utilizing fuming nitric acid in ether solution is reported to give a good yield of the 6-nitro derivative on a small scale but also results in product

decomposition during the work-up of some runs. A similar occasional tendency toward an uncontrolled reaction was noted in the nitration of an androst-5-ene derivative [3]. The nature of the "abnormal" products obtained from the nitration of cholesteryl acetate has been the subject of recent investigations [4].

Since we were interested in large-scale preparations of 5β-hydroxy-6-oxo-cholestanes [5] that included the synthesis of 6-nitrocholesteryl acetate as one of the intermediates, a reliable nitration procedure was developed by modification of the reported methods.

Treatment of unrecrystallized cholesteryl acetate in a 1/1 mixture of concentrated nitric acid/absolute ether with potassium nitrite at 5°, followed by a rapid work-up, gave the 6-nitro product in 61% yield after one crystallization. The procedure reported in the Experimental section has been followed dozens of times and in no case did an uncontrolled reaction occur. However, when the cholesteryl acetate was recrystallized from acetone-methanol prior to use, the familiar vigorous evolution of nitrogen oxides occurred with concomitant destruction of the product by an uncontrollable temperature rise. Whether residual methanol in the recrystallized material activates the side reaction, or residual acetic acid in the unrecrystallized acetate suppresses it, is not known.

We have carried out the nitration on 5/3 the scale given below with no problems. The method described has the following advantages: (1) large amounts of the nitro compound can be made in a short time [cf. 2], (2) pure product is obtained by a single

crystallization, (3) the preparation and use of fuming nitric acid is avoided [3], (4) the cholesteryl acetate need (should) not be recrystallized, saving time and solvents, (5) the yield is good, and (6) the method works consistently.

In view of the increased interest in the chemistry of 6-nitrocholesteryl acetate [6, 7], this nitration method should be of interest.

EXPERIMENTAL

3β-Acetoxycholest-5-ene. -- A suspension of 500 g (1.30 mol) of cholesterol in 1.3 ℓ of acetic anhydride was heated under reflux for 1.5 hr. The resulting orange colored solution was allowed to cool for 0.5 hr and then was poured slowly, with stirring, into a 5-gallon crock containing 2 gal of chopped ice and 100 ml of conc. hydrochloric acid. After 1 hr the white precipitate was collected, washed with much water, and allowed to air dry for several days after being spread on paper. The cholesteryl acetate was used without recrystallization.

3β-Acetoxy-6-nitrocholest-5-ene. -- (The reaction must be carried out in an efficient hood with appropriate hand and eye protection.) A charge of 90 g (0.21 mol) of unrecrystallized cholesteryl acetate was placed into a 3-ℓ, 3-necked round bottomed flask equipped with an efficient mechanical stirrer, condenser, thermometer (suspended into the flask through the condenser), and a glass stopper. The flask was surrounded by a bath containing a large quantity of crushed ice. Nine hundred milliliters of anhydrous ether was added and rapid stirring was commenced. When the internal temperature reached 10°, 900 ml of white conc. nitric acid (d 1.42) was slowly added. The temperature gradually rose to 30-35° by the end of the addition and the mixture developed a dark blue color which gradually faded when the temperature decreased. At 15° some steroid precipitated and the suspension had a "muddy" gray color.

When the temperature reached 5°, 11 g of potassium nitrite was added (through the side arm) in small portions over a period of ca. 25 min to the rapidly stirred mixture. No significant rise in temperature was noted. After stirring for an additional 10 min, the green solution was poured immediately into a 4-ℓ separatory funnel containing 600 ml of an ice-water mixture. The aqueous layer was removed as soon as the layers had separated (no shaking) and the ether solution was washed successively with 600 ml of ice water, 600 ml of cold 2.5% aqueous sodium hydroxide solution, and 500 ml of ice water.

The ether solution was drained through anhydrous sodium sulfate and the drying agent was rinsed with 300 ml of absolute ether. The solution was concentrated by boiling to a volume of 200 ml and then diluted with 500 ml of methanol. After a short time at room temperature the nitro product separated as small white needles. The flask was cooled in the refrigerator for a few hours and the product was collected and washed with cold methanol, yielding 60 g (61%) of 3β-acetoxy-6-nitrocholest-5-ene with mp 102.5-103°; $[\alpha]_D$ -77 ± 2° ($CHCl_3$, c 1.00); nmr ($CDCl_3$, 60 MHz) 42 (s, 3, 18-H), 69 (s, 3, 19-H), 122 (s, 3, $CH_3C=O$), and 278 (m, $W_{1/2}$ ~22, 1, 3α-H) Hz (lit. mp 103-104° [2]; $[\alpha]_D$ -80° [2], -78° [7]; nmr 41.4 (18-H), 69 (19-H) Hz [8]).

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