Improved Synthesis of 7-Dehydrositosterol[1,2]

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ABSTRACT

Sitosteryl acetate was brominated in petroleum ether by the gradual addition of N-bromosuccinimide to a refluxing, illuminated solution and dehydrobrominated by the dropwise addition of the bromo derivative to a refluxing solution of collidine in mesitylene to give a 38% yield of 7-dehydrositosteryl acetate.

INTRODUCTION

7-Dehydrositosterol (trivial name for 5,7-stigmastadien-3β-ol) was first prepared in Windaus' laboratory in 1936, in 2% yield from sitosteryl acetate to test the antirachitic properties of its irradiated products (1). 7-Dehydrositosteryl benzoate has been prepared in unspecified yield by the photo bromination and dehydrobromination of sitosteryl benzoate (2); the purity of this material, however, is in doubt. A mp of 153-4 C was reported (lit [1] 149 C), and the authors mention the presence of tachysteryl derivatives in the product. Our recent isolation of 99.5% pure sitosteryl acetate (3), together with an improved method for the preparation of 5,7-dienes from Δ^5-steryl acetates (4), enabled us to prepare chromatographically pure 7-dehydrositosterol in good yield.

EXPERIMENTAL PROCEDURES

Petroleum ether (Skellysolve B) was stirred a week with 1% $KMnO_4$ in water, several days with conc. H_2SO_4, shaken with 0.1% $KMnO_4$ to remove SO_2, dried ($MgSO_4$), and distilled, bp 65-67 C. Collidine and mesitylene were distilled under N_2 and dried over KOH. Reagent grade acetone, absolute ethanol, and N-bromosuccinimide (NBS) were used as obtained. The sitosteryl acetate used, mp 120.8-121.5 C, was a portion of fraction 42 mentioned in a previous communication (3). Mp's were taken in vacuo and are corrected. All crystallizations and reactions of the $\Delta^{5,7}$ derivatives were performed in solvents flushed with nitrogen and in a nitrogen atmosphere.

7-Dehydrositosteryl acetate: A 1 cm bore stopcock topped with a powder funnel was cemented (GE Silicone RTV) to a 24/40 glass joint and placed in the center opening of a 1 liter 3-necked flask equipped with a reflux condenser and nitrogen inlet. The lower stem of the stopcock protruded ca. one fourth of the way into the flask. The flask was clamped over a magnetic stirrer and was heated and illuminated by 2 GE DSB Photospot bulbs 5 cm away. Sitosteryl acetate (65 g, 0.142 mole) was dissolved and brought to a reflux in 350 ml Skellysolve B under N_2 with rapid stirring. NBS (32 g, 0.187 mole, 30% excess) was added in small portions during 30 min through the stopcock with the aid of 5-10 ml solvent for each addition. The lights were removed 5 min later and replaced with an ice bath. The cooled mixture was filtered into a 2 liter suction flask that contained 35 ml mesitylene and a magnetic stirring bar and the contents of the flask evaporated with an oil pump at 30-40 C until a thick, honey-colored syrup remained. Too high a temperature during this step results in low yields of product.

The bromosteryl acetate was transferred to a dropping funnel with 130 ml mesitylene and added during 30 min to a well stirred, refluxing solution of 50 ml collidine in 300 ml mesitylene. Five min later the mixture was cooled in an ice bath, low-boiling petroleum ether was added (400 ml) and the mixture filtered and evaporated at 50-60 C in vacuo. The resulting brown semisolid was brought to boiling under N_2 with 250 ml acetone. After cooling to room temperature, 31.0 g 7-dehydrositosteryl acetate that contained small amounts of sitosteryl and 4,6-stigmastadienyl acetate was filtered off (thin layer chromatography: 10% $AgNO_3$-SiO_2 plates, 1:1 $CHCl_3/CCl_4$, R_f: $\Delta^5 > \Delta^{4,6} > \Delta^{5,7}$ acetates). An additional 9.4 g less pure product precipitated from the acetone filtrate in the refrigerator; this was recrystallized from 150 ml acetone to give 3.8 g purer material. The combined products (34.8 g) were recrystallized again from acetone (900 ml) and then from Skellysolve B (200 ml) to yield 17.0 g 7-dehydrositosteryl acetate, mp 146.5-147.2 C (lit. [1] 151-2 C). An additional 7.7 g material, mp 146-7 C precipitated from the Skellysolve B filtrate in the refrigerator.

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[1] One of eight papers presented in the symposium "Phytosterols," AOCS Spring Meeting, New Orleans, April 1973.

[2] Contribution 2015, Arizona Agricultural Experiment Station.

7-Dehydrositosterol: A solution of sodium ethoxide (1.5 g Na plus 300 ml absolute ethanol) was added to a suspension of 25 g 7-dehydrositosteryl acetate in 1 liter ethanol, and the mixture was stirred at room temperature 20 hr under N_2. Acetic acid (7 ml) was added and the mixture cooled several hours in a refrigerator. The precipitated 7-dehydrositosterol was washed thoroughly with methanol and dried in vacuo; wt 17.5 g, mp 145-145.5 C (lit. [1] 144-5 C), single spot on thin layer chromatography (10% $AgNO_3$-SiO_2 plate, 95:5 $CHCl_3$/acetone), single peak on gas liquid chromatography (5% OV-101, 260 C). A benzoate was prepared, mp 149-149.2 C (lit [1] 149 C).

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