Preparation of 7-Dehydrocholesterol (Provitamin D_3)

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Summary: Some of the methods available for converting cholesterol into 7-dehydrocholesterol are reviewed for improving the yield of final product by modifying different steps. The allylic bromination of cholesteryl benzoate was done with 1,3-dibromo-5,5-dimethylhydantoin. In the dehydrobromination of 7-bromocholesteryl benzoate an advantageous solvent namely ethyl benzoate was used for the isolation of 7-dehydrocholesteryl benzoate. The yield of provitamin D_3 was 43% based on cholesteryl benzoate.

It is well known that 7-dehydrocholesterol being an unstable compound is frequently synthesised from cholesterol[1-5]. In this work, the allylic bromination of cholesteryl benzoate was done with 1,3-dibromo-5,5-dimethylhydantoin[6] in petroleum ether (b.p. 40-60°C) at reflux in the presence of dibenzoyl peroxide. The bromination of cholesteryl benzoate with 1,3-dibromo-5,5-dimethylhydantoin was effected by a number of factors such as the purity of cholesteryl benzoate; molar ratio of 1,3-dibromo-5,5-dimethylhydantoin; the presence of catalyst,[7] type of solvent and reaction temperature. Dehydrobromination of 7-bromocholesteryl benzoate was extensively studied with various bases in ethyl benzoate as a solvent given in (Table-1). The product obtained was hydrolysed to get 7-dehydrocholesterol.

It was found that ethyl benzoate was a choice of solvent to effect the better yield of 7-dehydrocholesteryl benzoate in the dehydrobromination of 7-bromocholesteryl benzoate. The use of ethyl benzoate as solvent in dehydrobromination of 7-bromocholesteryl benzoate served two main objectives. Firstly being a high boiling solvent it can be used easily upto 140°C and secondly it was found that the solubility of 4,6-cholestadienyl benzoate in ethyl benzoate at room temperature was more than 7-dehydrocholesteryl benzoate. Consequently almost pure 7-dehydrocholesteryl benzoate separated out as crystalline product from ethyl benzoate.

The diluent ethyl benzoate could not be used for the dehydrobromination of 7-bromocholesteryl acetate because all the products formed during dehydrobromination were soluble in ethyl benzoate at room temperature.

Experimental

All yields are based on ultraviolet spectroscopic analysis. The value of molecular extinction coefficient at the λ_{max}. 282 mμ was taken as a measure of the purity, of the products and was based on the following standard.

7-Dehydrocholesteryl benzoate ϵ_{282} = 13,580.

7-Bromocholesteryl Benzoate:

Cholesteryl benzoate (24.5 gm; 0.05 mole), 1,3-dibromo-5,5-dimethylhydantoin[6] (8.6 gm; 0.03 mole), petroleum ether (200 ml; b.p. 40-60°C) and dibenzoyl peroxide (0.015 gm) were heated under reflux for 30 minutes with vigorous stirring. The mixture was cooled, washed with water (3x50 ml), dried over anhydrous sodium sulphate and distilled under reduced pressure at temperature below 10°C. The orange gum so obtained was crystallised from acetone to furnish crude 7-bromocholesteryl benzoate (21.3 gm). The crude 7-bromocholesteryl benzoate was used directly for dehydrobromination.

Table I *Dehydrobromination of 7-bromocholesteryl benzoate.*

Dehydrobromination solvent: Ethyl benzoate

S.No.	Dehydrobrominating agent	Product	Yield %
1.	2,4,6-Collidine	7-dehydrocholesteryl benzoate.	58
2.	2,6-Lutidine	"	46
3.	Quinaldine	"	37
4.	Isonicotinic acid	"	34
5.	Ephedrine	"	34
6.	Nicotine	"	39
7.	Urea	"	17

Dehydrobromination:

A mixture of 7-bromocholesteryl benzoate (16.0gm), 2,4,6-collidine (12 ml), ethyl benzoate (75 ml) and anhydrous sodium carbonate (8 gm) were heated quickly on a hot plate to 140°C with vigorous stirring and kept at this temperature for 15 minutes. After the reaction, the mixture was filtered hot with suction. The filterate was kept at 20°C for 24 hours and a colourless crystalline product separated out was collected and washed with cold ethyl benzoate (5 ml). A crystalline solid (9.6 gm; 85% pure), m.p. 135-146°C was obtained. Recrystallization from ethyl benzoate afforded pure 7-dehydrocholesteryl benzoate (6.4 gm); m.p. 139-140°C.

Saponification:

A mixture of 7-dehydrocholesteryl benzoate (5.0 gm) and 5% methanolic potassium hydroxide (50 ml) was heated under reflux on a steam bath for one hour. After cooling to 0°C, the resulting crystalline product was collected, washed with cold methanol (5 ml) and water (2x30 ml). Recrystallisation from acetone furnished 7-dehydrocholesterol (3.25 gm; yield 43% based on cholesteryl benzoate) m.p. 148-150.5°C; λ_{max} (in ether) 272,282 and 294 mμ[8].

The dehydrobromination with other bases was carried out under similar conditions.

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