SYNTHESIS OF 7-DEHYDROCHOLESTEROL ACETATE

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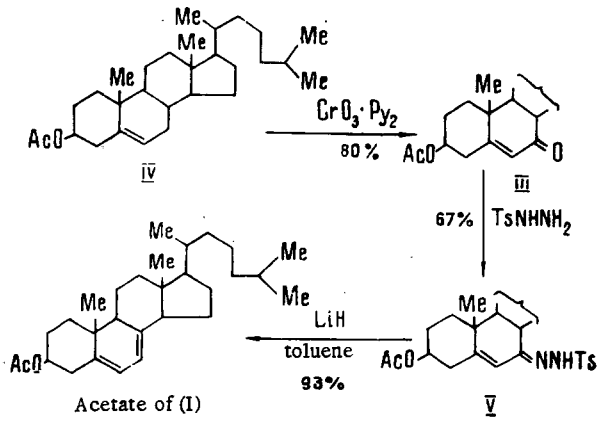
$\Delta^{5,7}$-Steroid dienes are convenient starting materials for the synthesis of 14-hydroxysteroids and are the precursors of the vitamins of the D group. One of them – 7-dehydrocholesterol (I) – is usually obtained by the Wohl–Ziegler reaction followed by dehydrobromination [1]. However, the product formed in this way contains double-bond isomers of (I) as impurities, which complicates the isolation of the pure 7-dehydrocholesterol. Another possible method of synthesizing (I) is the allyl bromination of the benzoate of (I) with the aid of 1,3-dibromo-5,5-dimethylhydantoin (II). This route (after dehydrobromination) also leads to the formation of a complex mixture of compounds from which it has been possible to isolate, in addition to the benzoate of (I) and its isomers, compounds with an aromatic ring A, arising as the result of a dienol–benzene rearrangement [2].

There is information [3] that allyl bromination with the aid of (II) takes place smoothly in the presence of initiators of radical reactions (azoisobutyronitrile). The yield of the corresponding 7-bromo derivative varies between 55 and 66%. Yakhimovich and others [4] have shown that a convenient method for dehydrobromination is the treatment of the 7-bromide with pyrazolinone derivatives. The yield of the benzoate of (I) at this stage amounts to 55%.

It appeared to us to be desirable to test an alternative method of obtaining (I) starting from 7-oxocholesterol acetate (III). The known method for synthesizing (III) by oxidizing cholesterol acetate with chromium trioxide in acetic acid or with tert-butyl chromate is unsatisfactory, since it leads to comparatively low yields of (III) (55-60%) [5]. We have established that the oxidation of cholesterol acetate (III) with the red anhydrous complex of chromium trioxide and pyridine [6] takes place smoothly, giving the 7-oxo acetate (III) with a yield of about 80%. The latter can easily be converted into 7-dehydrocholesterol acetate with an overall yield of 63% calculated on the acetate (IV) by means of the Bamford–Stevens reaction [7] via the corresponding tosylhydrazone (V). A sample of 7-dehydrocholesterol obtained by this method did not contain any $\Delta^{4,6}$ isomer according to UV spectroscopy.



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EXPERIMENTAL

Synthesis of the 7-Oxoacetate (III). At room temperature, in an atmosphere of N_2, 58 g of the complex $CrO_3 \cdot Py_2$ [6] in 70 ml of trichloroethylene was added to a stirred solution of 10 g of cholesterol acetate (IV) in 500 ml of trichloroethylene. The mixture was stirred for 10 h, and then another 43 g of the complex $CrO_3 \cdot Py_2$ in 50 ml of trichloroethylene was added. The reaction mixture was stirred for another 8 h, and the organic layer was washed with water, with a saturated solution of sodium bicarbonate, and again with water. The extract was dried over calcined magnesium sulfate and evaporated in vacuum. The residue obtained was recrystallized from methanol, giving 8.25 g of the oxo acetate (III) with a yield of 80%, mp 160-162.5°C (here and below, the mps were determined on a Kofler block), λ_{max} (in ethanol) 235 nm (ε 12,300). Literature data: mp 161-163°C, λ_{max} (in ethanol) 236 nm (ε 12,400) [6].

The Tosylhydrazone of (III) (V). A. A solution of 7.5 g of the oxo acetate (III) in 70 ml of methanol was boiled (atmosphere of N_2) with 4.6 g of tosylhydrazine for 4.5 h. After cooling, the solution deposited 7.3 g (67%) of the tosylhydrazone (V) with mp 146-148°C, which was used in the subsequent reaction without further purification. Literature data: mp 147-149°C [8].

B. A solution of 5 g of the oxo acetate (III) and 3.1 g of tosylhydrazine in 40 ml of trichloroethylene was boiled for 3 h with the azeotropic distillation of the water formed. The reaction mixture was evaporated and the residue was treated with ethanol. The crystalline product was filtered off, washed on the filter with ethanol, and dried. This gave 6.2 g (85%) of the tosylhydrazone (V) with mp 145-147°C.

7-Dehydrocholesterol Acetate. A solution of 3.5 g of the tosylhydrazone (V) in 100 ml of toluene was boiled (atmosphere of N_2) in the presence of 3.4 g of finely ground lithium hydride for 5 h. After the reaction mixture had been cooled, it was filtered through a paper filter and, with ice-water cooling, the filtrate was carefully acidified with 2% sulfuric acid. The organic layer was washed with water, with saturated sodium bicarbonate solution, and again with water. The extract was dried over calcined sodium sulfate and evaporated in vacuum. After recrystallization of the residue from methanol, 2.25 g of 7-dehydrocholesterol acetate was obtained (yield 93%) with mp 129-130°C, $[\alpha]_D^{21}$ −80° (c 0.3; chloroform), λ_{max} (ethanol) 270, 280 nm (ε 11,000). The absence of absorption in the 230-240 nm region shows that no cholesta-4,6-dien-3β-ol is formed in this reaction. Literature data: melting point for 7-dehydrocholesterol acetate 129°C [8]. The 7-dehydrocholesterol acetate obtained by this method gave no depression of the melting point in admixture with an authentic sample.

SUMMARY

It has been shown that 7-oxocholesterol acetate (III) can easily be converted into 7-dehydrocholesterol acetate by the Bamford–Stevens reaction. The yield of desired product amounts to 79% calculated on the (III) or 63% calculated on the cholesterol acetate.

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