STEROIDS

XLIII. STRUCTURE OF THE BY-PRODUCT FROM THE IODINATION OF 17α-HYDROXYPROGESTERONE

L. V. Sokolova, E. M. Dolginova, L. M. Alekseeva, Yu. N. Sheinker, and N. N. Suvorov

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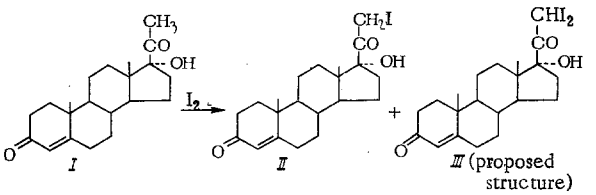
As previously reported [1], the iodination of 17α-hydroxyprogesterone (I) is an important stage in the synthesis of Reichstein's substance S acetate. However, in addition to 21-iodo-17α-hydroxyprogesterone (II) which is the main reaction product, a compound is formed for which a 21,21-diiodide structure is proposed on the basis of elemental analytical data and by analogy with literature data [2-4].



Similar diiodides have been obtained by the iodination, under special conditions, of a series of 3,20-diketones differing from (I) by the presence of additional substituents [2-4] and also certain 3β-hydroxy-20-ketones [4]. According to patent data [2, 3] the 21,21-diiodo derivatives obtained gave, on acetylation, the corresponding 21-monoacetates in yields close to quantitative. No data were given in the patents confirming the constitution of the diiodides. It was proposed [4] that the second iodine atom in the additional compounds was not bonded to carbon but was only retained by molecular forces.

The point of the present work is to establish the constitution of compound (III). The amount of diiodide (III) is dependent upon the conditions of iodinating 17α-hydroxyprogesterone. On iodinating under the conditions described in the literature [1] usually 5-7% diiodide was obtained (according to the data of semiquantitative chromatographic analysis). Iodination in pure methanol leads to the formation of up to 50-60% (III), however much iodoform is formed in this way and compound (III) may only be purified from this by chromatography.

Compound (III) was isolated by us in a homogeneous state by chromatographic resolution on a column of silica gel of the mixture of products formed on iodinating 17α-hydroxyprogesterone under the conditions described in the literature [1].

On acetylating (III) with sodium acetate in dimethylformamide $\Delta^{1,4}$-pregnadiene-17α-,21-diol-3,20-dione 21-acetate (IV) was obtained in quantitative yield. The constitution of (IV) was demonstrated by comparing the IR spectrum and constants of the compound obtained with literature data [5, 6] and also by an alternative microbiological synthesis of compound (IV) by the action of Mycobacterium globiforme 193 on Reichstein's substance S 21-acetate.

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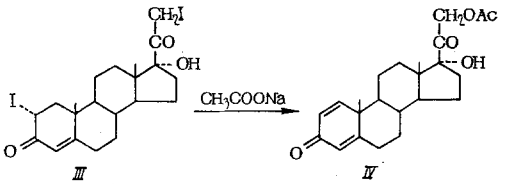

III (established structure)

IV

On the basis of the data given above and also on IR and PMR spectroscopic data we have ascribed the structure 2α,21-diiodo-Δ^4-pregnen-17α-ol-3,20-dione to compound (III).

Signals were observed in the PMR spectrum of compound (III) for protons of angular methyl groups ($\delta_{18\text{-H}}$ = 0.59 ppm, $\delta_{19\text{-H}}$ = 1.25 ppm), a quartet for protons of a methylene group at position 21 (δ = 4.20 ppm, J_{gem} 14 Hz) and a singlet signal for the proton at position 4 (δ = 5.71 ppm). However, there was a quartet (δ = 5.34 ppm) in the PMR spectrum with an intensity of 1 unit which may be ascribed to a 2β-proton split as a consequence of spin-spin interaction with protons of the CH_2 group in position 1 ($J_{aa} \simeq$ 14 Hz, $J_{ae} \simeq$ 6 Hz). Such an interpretation of the signal is in accordance with the assignment made in the spectrum of 2α-bromocholestanone [7]. Signals at 2.65 and 2.25 ppm can be ascribed to the equatorial and axial protons at position 1 respectively.

An increase of 15 cm^{-1} in the vibrational frequency of the conjugated carbonyl group was observed in the IR spectrum of (III) in comparison with the spectrum of compound (II) which also confirms the equatorial orientation of iodine in position 2 [8].

EXPERIMENTAL

IR spectra for substances in the crystalline state were obtained in Nujol mulls with the aid of a UR-10 spectrophotometer. PMR spectra for substances were taken in solution in $CDCl_3$ and in deutero-dimethylsulfoxide in a INM-4H-100 instrument with tetramethylsilane as internal standard.

Thin-layer chromatography used "silufol" as sorbent [9].

2α,21-Diiodo-Δ^4-pregnen-17α-ol-3,20-dione (III). A benzene solution (100 ml) containing a mixture (2 g) of compounds formed on iodination of (I) [1] was put onto a column of SiO_2 (80g) and eluted with a mixture of benzene: chloroform (3:2). Fractions (100 ml) were collected. Fractions were checked by thin-layer chromatography.

Yield of (III) was 0.10 g. After recrystallization from methanol, white crystals (0.09 g) were obtained. Found %: I 43.20. $C_{21}H_{28}I_2O_3$. Calculated %: I 43.57. IR spectrum: 3490 (OH^-), 1705 (unconjugated carbonyl), 1665 (conjugated carbonyl), 1616 cm^{-1} (C=C bond).

Yield of (II) was 1.78 g. After recrystallization from methanol, white crystals (1.5 g) were obtained. Found %: I 27.41. $C_{21}H_{29}IO_3$. Calculated %: I 27.81 [1].

Yield of (I) was 0.12 g. This was 17α-hydroxyprogesterone, a mixing test with an authentic specimen gave no depression of melting point and the IR spectra were completely in accord.

$\Delta^{1,4}$-Pregnadiene-17α,21-diol-3,20-dione (IV). A. From compound (III). To a solution of (III) (0.2 g) in anhydrous dimethylformamide (5 ml) was added fused potassium acetate (0.2 g); the mix was stirred for 2 h at 60° without access to moisture in a stream of nitrogen. The reaction was poured into 10 volumes ice water kept for 2 h at 0° and filtered. White crystals (0.13 g: 98.5%) were obtained which according to thin-layer chromatography did not contain starting (III). After recrystallization from a mixture of acetone and petroleum ether (1:1.5) it had mp 216-218°, $E^{1\%}_{1cm}$ = 390 (alcohol), which coincides with literature data [6]. Found %: C 71.86; H 7.84. $C_{23}H_{30}O_5$. Calculated %: C 71.49; H 7.75. IR spectrum: 3400 (OH^-), 1740, 1715 (20-keto group and ester carbonyl), 1650 (conjugated carbonyl), 1610 cm^{-1} (−C = C− bond) [5].

B. From Reichstein's substance S 21-acetate. The 21-acetate of Reichstein's substance S was fermented with Mycobacterium globiforme 193. The reaction product was isolated by three extractions of the fermentation liquor with chloroform. After evaporation in vacuum and recrystallization of the residue from a mixture of acetone and petroleum ether crystals of mp 218-220° were obtained which gave no depression of melting point in a mixing test with the compound obtained by method A. IR spectra were completely in accord.

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