Chemistry of Natural Compounds, Vol. 37, No. 1, 2001

SIMPLE SYNTHESIS OF 17α,20β-DIHYDROXYPREGN-4-EN-3-ONE

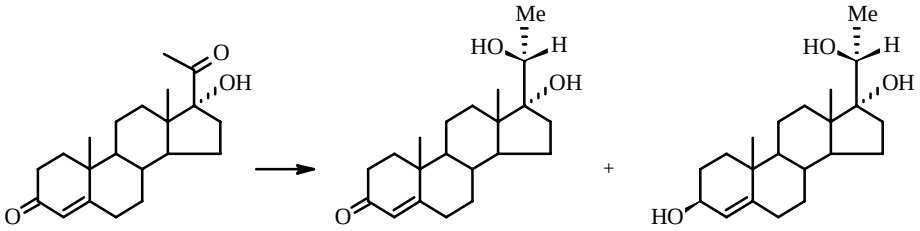
N. V. Kovganko, Zh. N. Kashkan, and V. M. Shkumatov

UDC 547.92

*Reduction of 17α-hydroxyprogesterone (**1**) with $NaBH_4$ produces 17α,20β-dihydroxypregn-4-en-3-one (**2**) and pregn-4-en-3β,17α,20β-triol (**3**).*

Key words: 17α-hydroxyprogesterone, 17α,20β-dihydroxypregn-4-en-3-one, pregn-4-en-3β,17α,20β-triol.

The steroid 17α,20β-dihydroxypregn-4-en-3-one (**2**) is a common natural derivative of 17α-hydroxyprogesterone (**1**). It has been isolated several times from various natural sources [1-3]. Scientific interest in this compound has recently increased significantly because, primarily, it acts as a fish sex pheromone [4, 5]. Convenient methods of synthesizing **2** from available steroids, for example, **1**, are necessary for broad research of its biological functions. A key step in the synthesis of **2** in the literature [6, 7] is the reduction of the corresponding pregnan-20-ones by $LiAlH_4$. Naturally, the 3-ketone is also reduced. This makes it necessary to protect the 3-ketone, which increases significantly the number of synthetic steps and reduces the overall yield of the desired product. Furthermore, reduction of 17α-hydroxy-20-ketosteroids with $LiAlH_4$ or $LiAl(t\text{-}OBu)_3H$ produces the usual 17α,20β-diols and their 20α-isomers [7, 10]. This also decreases the yield of the desired compounds.



We developed a new method for synthesizing 17α,20β-dihydroxypregn-4-en-3-one (**2**) that is based on reduction of **1** by $NaBH_4$, which is less reactive and more selective than $LiAlH_4$. It was found that reduction of **1** by $NaBH_4$ in methanol gives **2** in ~30% yield. The second product is 3β,17α,20β-triol **3** in 70% yield.

The structure of **2** was proved using ^1H NMR spectra. The spectrum contains a signal for the methine proton H-20 geminal to the hydroxyl. The presence of the 20-hydroxyl was confirmed by the fact that the signal for the 21-methyl protons appears as a doublet with splitting constant J = 6 Hz, which is due to vicinyl coupling with H-20. Furthermore, the characteristic shift of the signal for the 21-methyl to strong field at δ 1.18 ppm compared with its position in the spectrum of starting **1** (δ 2.30 ppm) is interesting. The presence of the 17α-hydroxyl in **2** is inferred from the magnitude of the chemical shift of H-20 (δ 4.04 ppm). It is known [11] that this signal is observed at δ 3.72-3.73 ppm in the corresponding 20-hydroxypregnane steroids that lack the 17α-hydroxyl. The shapes and positions of the signal for vicinyl proton H-4 in spectra of **1** and **2** are identical, suggesting that the Δ^4-3-ketone is retained in the latter. The 20β-configuration of the newly formed chiral center in **2** was confirmed by the similarity of its ^1H NMR spectrum with that described in the literature [3].

The ^1H NMR spectrum of **3** exhibits characteristic signals for the H-20 and H-21 methyl protons, the position and multiplicity of which agree with analogous signals in the spectrum of **2**. Hence, it can be concluded that **3** is a 17α,20β-diol. Furthermore, the spectrum of **3** also contains a signal for methine proton H-3 (δ 4.15 ppm), which indicates the presence of a 3-hydroxyl. The quasi-equatorial (i.e., β) orientation is consistent with the half-width of the H-3 signal (W/2 = 19 Hz).

Institute of Bioorganic Chemistry, National Academy of Sciences, Belarus, 220141, Belarus, Minsk, ul. Akad. Kuprevicha, 5/2. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 51-52, January-February, 2001. Original article submitted February 6, 2001.

0009-3130/01/3701-0055$25.00

In conclusion, it should be noted that although the yield of **2** from reduction of **1** by $NaBH_4$ is moderate, the simplicity of the method and the lack of 20α-epimers among the products gives this method an advantage over those known previously.

EXPERIMENTAL

Melting points were determined on a Kofler block. ^{1}H NMR spectra of $CDCl_3$ solutions were obtained on a Bruker AC-200 NMR spectrometer at working frequency 200 MHz. Chemical shifts are given relative to TMS internal standard.

Reduction of 17α-Hydroxyprogesterone (1) by $NaBH_4$. A solution of **1** (50 mg) in methanol (7 mL) was treated with $NaBH_4$ (6 mg), stirred with cooling on an ice bath for 1.5 h, treated with acetic acid (0.3 mL), and evaporated under vacuum. The solid was dissolved in $CHCl_3$. The solution was filtered through a layer of silica gel and evaporated under vacuum. Yield of products, 64 mg. The mixture was separated by preparative TLC on silica-gel plates with elution by $CHCl_3$:CH_3OH (20:1).

Yield of **2** in fraction 1, 14 mg (28%). ^{1}H NMR (δ, ppm): 0.85 (3H, s, 18-Me), 1.18 (3H, d, J = 6 Hz, 21-Me), 1.19 (3H, s, 19-Me), 4.04 (1H, q, J = 6 Hz, H-20), 5.74 (1H, br. s, H-4).

Yield of **3** in fraction 2, 35 mg (70%). ^{1}H NMR (δ, ppm): 0.82 (3H, s, 18-Me), 1.06 (3H, s, 19-Me), 1.17 (3H, d, J = 6 Hz, 21-Me), 4.02 (1H, q, J = 6 Hz, H-20), 4.15 (1H, m, W/2 = 19 Hz, H-3α), 5.28 (1H, d, J = 1 Hz, H-4).

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