[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Wolff–Kishner Reduction of 11-Keto Steroids

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Contrary to reports in the literature, it is found that the Wolff–Kishner reduction may give normal reduction products from methyl $3(\alpha)$-acetoxy-11-ketocholanate and $3(\alpha)$-acetoxy-11-keto-24,24-diphenyl-Δ^{23}-cholene.

It is generally believed that a keto group at C-11 of steroids is not removed by the Wolff–Kishner reduction.[1] Huang-Minlon[2] reports that the 11-keto is not attacked in three steroids subjected to his modified procedure. Several workers[3] have subjected $3(\alpha),12(\beta)$-dihydroxy-11-ketocholanic acid to Wolff–Kishner reactions and report principally a mixture of 3,11,12-trihydroxycholanic acids along with some lithocholic and lithocholenic acids. Similarly Wintersteiner and Moore[4] obtained methyl $3(\alpha)$-acetoxy-$11(\beta)$-hydroxycholanate from the 3-acid succinate of methyl $3(\alpha)$-hydroxy-11,12-diketocholanate on Wolff–Kishner reduction followed by esterification and acetylation.

In this work it has been found that under the proper conditions the 11-keto group can be removed in good yields by the Wolff–Kishner reduction. Methyl $3(\alpha)$-acetoxy-11-ketocholanate and $3(\alpha)$-acetoxy-11-keto-24,24-diphenyl-Δ^{23}-cholene have been subjected to this procedure. In each case the only product isolated was the normal desoxo compound, lithocholic acid in the former case and $3(\alpha)$-hydroxy-24,24-diphenyl-Δ^{23}-cholene in the latter.

Experimental[5]

Wolff–Kishner Reduction of Methyl $3(\alpha)$-Acetoxy-11-ketocholanate.—Sodium methoxide was prepared by dissolving 2 g. of sodium in 30 ml. of methanol and concentrating by distillation to about 20 ml. To this was added 0.52 g. (0.0012 mole) of methyl $3(\alpha)$-acetoxy-11-ketocholanate[6] and 2 ml. of anhydrous hydrazine. The resulting solution was sealed in a glass tube which was heated inside a bomb at 200° for 16 hours. Methanol was placed in the bomb outside the glass tube to help equalize the pressure. After cooling, the contents of the tube were diluted with a little water, heated under reflux for one-half hour, and then distilled nearly to dryness on a steam-bath. Water was added, and the suspension of sodium salt was washed with ether. Evaporation of the ether left practically no residue. The basic suspension was heated to boiling and acidified with hydrochloric acid. After cooling the precipitated acid was collected, washed with water and dried. This proved to be nearly pure lithocholic acid; yield 0.36 g. (82.4%), m.p. 181–184°. One crystallization from acetone gave 0.24 g. of nicely crystalline acid, m.p. 187–188°.

The infrared absorption spectrum indicated the absence of a keto group and it was found to be identical to an authentic sample of lithocholic acid[7] by mixed melting point and comparison of infrared absorption spectra.

Wolff–Kishner Reduction of $3(\alpha)$-Acetoxy-11-keto-24,-24-diphenyl-Δ^{23}-cholene.—One gram (0.0018 mole) of this compound[8] was subjected to the Wolff–Kishner reduction under conditions similar to those above, using 2 g. of sodium, 2 ml. of anhydrous hydrazine and 20 ml. of methanol. The contents of the tube were diluted with water and extracted with ether. The ether solution was washed with water, dilute hydrochloric acid, water, very dilute sodium bicarbonate solution and saturated salt solution. After drying over anhydrous sodium sulfate the ether was removed. The amorphous residue crystallized easily from methanol giving 0.56 g. (62.7%) of $3(\alpha)$-hydroxy-24,24-diphenyl-Δ^{23}-cholene,[9] m.p. 108–111° (air-dried). After recrystallization from methanol the melting point was about the same, but when dried at 100° and 0.1 mm. for 1.5 hours it melted at 139–140.5°; $[\alpha]^{24}_{D}$ +56.4° (0.6078 g./100 cc. in $CHCl_3$). Infrared absorption spectrum indicated the absence of a keto group.

Anal. Calcd. for $C_{36}H_{48}O$: C, 87.05; H, 9.74. Found: C, 86.73; H, 9.58.

Acetate.—When 0.29 g. of this compound was acetylated by the method of Long, Marshall and Gallagher,[10] 0.3 g. of product, m.p. 157–158°, was obtained. Recrystallization from acetone gave needles, m.p. 161.5–162.5°, $[\alpha]^{24}_{D}$ +73.1° (0.9124 g./100 cc. in $CHCl_3$). Mixed with an authentic sample of $3(\alpha)$-acetoxy-24,24-diphenyl-Δ^{23}-cholene[7,9] it gave no melting point depression. Infrared absorption spectrum indicated the absence of hydroxyl or keto groups.

Anal. Calcd. for $C_{38}H_{50}O_2$: C, 84.70; H, 9.35. Found: C, 84.72; H, 9.35.

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[1] Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 409–410.

[2] Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

[3] Gallagher, *J. Biol. Chem.*, **162**, 539 (1946); Longwell and Wintersteiner, THIS JOURNAL, **62**, 200 (1940); Wintersteiner, Moore and Reinhardt, *J. Biol. Chem.*, **162**, 707 (1946); Marker, Shabica, Jones, Crooks and Wittbecker, THIS JOURNAL, **64**, 1228 (1942).

[4] Wintersteiner and Moore, *J. Biol. Chem.*, **162**, 725 (1946).

[5] Melting points were taken on a Fisher-Johns block, uncorrected. Analyses are by Mr. William Struck and staff of our Microanalytical Laboratory. Infrared absorption spectra are by Mrs. Agatha R. Johnson of our Physics Department.

[6] Ott and Reichstein, *Helv. Chim. Acta*, **26**, 1799 (1943).

[7] Hoehn and Mason, THIS JOURNAL, **62**, 569 (1940).

[8] Wettstein and Meystre, *Helv. Chim. Acta*, **30**, 1262 (1947).

[9] Meystre and Miescher, *ibid.*, **29**, 33 (1946).

[10] Long, Marshall and Gallagher, *J. Biol. Chem.*, **165**, 197 (1946).