

$m\mu$  ( $\log \epsilon$ ) at 235 (4.26), 327 (3.78), 368 (3.59) and 392 (3.11) and minima at 273 (3.25), 363 (3.57) and 387 (3.30). II absorbs four molar equivalents of hydrogen in ethanol with platinum oxide giving an oil oxidized with permanganate to pimelic acid, m. p. 99–102° (m. p. 100–102° in admixture with authentic material, m. p. 101–102°). These facts are consistent with the assignment of tropolone (IIa) as the structural hypothesis for II but do not completely exclude IIb.

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THE ACTION OF METHANOLIC POTASSIUM HYDROXIDE ON A  $\Delta^{16}$ -20-KETOSTEROID: ISOLATION OF  $3\beta$ -ACETOXY-16-METHOXY- $\Delta^6$ -PREGNEN-20-ONE

Sir:

The reaction recently described by Marker<sup>1</sup> for the introduction of a 17-hydroxyl group could have great significance in the synthesis of adrenal cortical hormones. Since no evidence was offered for the presence of a 17-hydroxyl group other than failure to acetylate the newly introduced oxygen function, and since the reaction postulated was improbable, we have investigated the problem and have arrived at a completely different conclusion.

$3\beta$ -Acetoxy- $\Delta^{6,16}$ -pregnadien-20-one was refluxed with a solution of potassium hydroxide in methanol. As evidenced by the ultraviolet absorption spectrum,  $E_{1\text{ cm.}}^{1\%} = 121$  at 2390 Å., approximately half the product no longer contained the  $\alpha, \beta$ -unsaturated carbonyl group of the initial compound. Acetylation followed by chromatography resulted in the separation of  $3\beta$ -acetoxy- $\Delta^{6,16}$ -pregnadien-20-one and a compound, m. p. 158.5–159.5°;  $[\alpha]^{25\text{D}} - 28.5^\circ$  (chloroform), which showed no absorption in the ultraviolet above 2250 Å. The possibility that the compound was a  $3\beta$ -acetoxy-17-hydroxy- $\Delta^6$ -pregnen-20-one was readily eliminated by comparison of the physical constants with the known epimers ( $17\alpha$ -<sup>2</sup> m. p. 234–235°;  $[\alpha]_{\text{D}} - 41.8^\circ$  [dioxane];  $17\beta$ -<sup>3</sup> m. p. 187–188°;  $[\alpha]_{\text{D}} - 61.3^\circ$  (chloroform)). A  $\delta$ -homosteroid was similarly discarded as a possible interpretation. The most important evidence against these structures was provided by infrared spectrometry<sup>4</sup> which revealed that no free hydroxyl group was present in the product.

The elementary analysis conformed to the

- (1) Marker, *THIS JOURNAL*, **71**, 4149 (1949).
- (2) Hegner and Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).
- (3) Shoppee and Prins, *ibid.*, **26**, 201 (1943).

(4) We wish to express our appreciation to Dr. Konrad Dobriner of this Institute, who determined and interpreted the infrared spectra for us.

molecular formula  $\text{C}_{24}\text{H}_{36}\text{O}_4$ . *Anal.* Calcd.: C, 74.29; H, 9.34. Found: C, 74.53; H, 9.18. The additional carbon atom was shown to be in a methoxyl group by Zeisel determination (calcd. 7.99; found 8.59). When an ethanol solution of potassium hydroxide was used for the reaction a different product, the corresponding ethoxy compound, was obtained, m. p. 143–144.5°,  $[\alpha]_{\text{D}} - 30.6^\circ$  (chloroform). These results clearly prove that the reaction led to the formation of an ether rather than an alcohol. An examination of Marker's analytical data shows that there is equally good agreement for a methoxy derivative.

The addition of alcohol to an  $\alpha, \beta$ -unsaturated 20-ketosteroid is entirely analogous to the base-catalyzed addition of alcohols to methyl acrylate or acrylonitrile to yield  $\beta$ -alkoxy propionic acid derivatives.<sup>5</sup> The product formed from  $3\beta$ -acetoxy- $\Delta^{6,16}$ -pregnadien-20-one upon treatment with methanolic potassium hydroxide is therefore  $3\beta$ -hydroxy-16-methoxy- $\Delta^6$ -pregnen-20-one. The reaction is reversible, and an equilibrium mixture containing 69% of the 16-methoxy compound spectrophotometrically is reached from either compound at 23° in 3% methanolic potassium hydroxide in about two hours.

(5) Koelsch, *THIS JOURNAL*, **65**, 437 (1943).

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A NEW ROUTE TO 11-KETOSTEROIDS

Sir:

Whereas 3-hydroxyl groups usually resist attack by N-bromosuccinimide in aqueous acetone,<sup>1</sup> methyl  $3\alpha$ -hydroxy-9 $\alpha, 11\alpha$ -oxidocholanate (I, from the 9,11-ethylene,<sup>2,3</sup> m. p. 135.4–136.4°,  $[\alpha]^{25\text{D}} + 22^\circ$  Chf.<sup>4</sup> *Anal.*  $\text{C}_{25}\text{H}_{40}\text{O}_4$ : C, 74.21, H, 9.97. Found: C, 74.51; H, 10.09) is oxidized to the 3-ketone (II, m. p. 129–130°,  $[\alpha]^{25\text{D}} + 4^\circ$  Di.<sup>4</sup> *Anal.*  $\text{C}_{25}\text{H}_{38}\text{O}_4$ : C, 74.52; H, 9.52. Found: C, 74.34; H, 9.38. Semicarbazone, m. p. 209–210°; Wolff-Kishner reduction to 9 $\alpha, 11\alpha$ -oxidocholanate, m. p. 158–159°,  $[\alpha]^{22\text{D}} + 17^\circ$  Di.<sup>5</sup> *Anal.*  $\text{C}_{24}\text{H}_{38}\text{O}_3$ : C, 76.96; H, 10.23. Found: C, 76.93; H, 10.42). Chromic acid oxidation of I or II gives the hemiketal III, m. p. 119–120° (variable),  $[\alpha]^{23\text{D}} + 102^\circ$  Chf.,  $\lambda_{\text{Max}}^{\text{Chf.}}$  2.85, 5.78, 5.85 $\mu$ . *Anal.*  $\text{C}_{25}\text{H}_{38}\text{O}_5$ : C, 71.66; H, 9.16. Found: C, 71.89; H, 9.20. Acetate ( $\text{BF}_3\text{-Ac}_2\text{O}$ ), m. p. 148.6–149.8°,  $[\alpha]^{24\text{D}} + 100.3^\circ$  Chf. *Anal.*  $\text{C}_{27}\text{H}_{40}\text{O}_6$ : C, 70.38; H, 8.77. Found: C, 70.27; H, 8.76. Methyl ether ( $\text{CH}_3\text{OH-HBr}$ ), m. p. 124.8–125.5°,  $[\alpha]^{18\text{D}} + 92.3^\circ$

(1) Fieser and Rajagopalan, *THIS JOURNAL*, **71**, 3935, 3938 (1949).

(2) Seebeck and Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).

(3) Mattox, Turner, Engel, McKenzie, McGuckin and Kendall, *J. Biol. Chem.*, **164**, 569 (1946).

(4) Chf. = chloroform; Di. = dioxane; An. = acetone.

(5) Alther and Reichstein, *Helv. Chim. Acta*, **26**, 492 (1943), give  $[\alpha]_{\text{D}} + 18.8^\circ$  An. for the methyl ester.