Communications TO THE EDITOR

The Wolff-Kishner Reaction with α-Oximinoketones

Sir:

The Wolff-Kishner reaction is usually a very reliable and useful method for converting a carbonyl group to methylene. However, when applied to α- or β-substituted ketones and aldehydes,[1] some other structural change may occur as well. We have found that α-oximinoketones, when subjected to this reaction, may lead to a number of products, including in one instance normal reduction to the methylene group.

When 1,2-indanedione 2-oxime (I) was exposed to the usual Wolff-Kishner reaction conditions (hydrazine, potassium hydroxide, diethylene glycol, 190°) a 73% yield of indano[1,2]-v-triazole (II) resulted (m.p. 140–141°. *Anal.* Found: C, 68.8; H, 4.4; N, 26.8). The hydrazone of I (m.p. 240–

I II

242°, *Anal.* Found: C, 61.9; H, 5.2; N, 24.1) gave the same product when exposed to the action of alkali in diethylene glycol. This appears to be a possible method for preparing v-triazoles in which the nitrogen is unsubstituted.[2] However, the reaction is far from general.

When α-oximinoacetophenone was treated under the same conditions, the only product isolated was phenylacetic acid (in 70% yield). From 2,3-butanedione 2-oxime, 2,3-butanedione 3-hydrazone-2-oxime was obtained in 65% yield with no evidence of any triazole formation. And from 2,3-octanedione 3-oxime a 90% yield resulted of the normal reduction product, 3-octanone oxime (b.p. 115°/14 mm., n_D^{25} 1.4492; reported[3] b.p. 92°/5 mm., n_D^{20} 1.4517. *Anal.* Found: C, 67.4; H, 11.7; N, 9.5).

The mechanism of this reaction and its application to α-oximinoketones in general is under further study.

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(1) D. Todd, *Org. Reactions*, **IV**, 378 (1948); R. B. Turner, R. Anliker, R. Heibling, J. Meier, and H. Heusser, *Helv. Chim. Acta*, **38**, 411 (1955); R. Fischer, G. Lardelli, and O. Jeger, *Helv. Chim. Acta*, **34**, 1577 (1957).

(2) A number of *N*-phenyltriazoles have been obtained by the action of acids or acetic anhydride on oxime-phenylhydrazones [F. R. Benson and W. L. Savell, *Chem. Revs.*, **46**, 1 (1950)]. Also, M. Ruccia and D. Spinelli, [*Gazz. chim. ital.*, **89**, 1654 (1959)] have considered the reaction with hydrazone-oximes.

(3) F. Asinger, G. Geiseler, and P. Laue, *Ber.*, **90**, 485 (1957).

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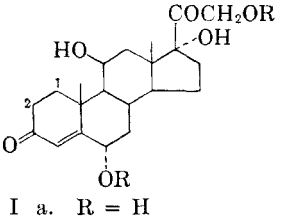
C6-Hydroxylated Steroids. I. Preparation of 6α- and 6β-Hydroxyhydrocortisone and 6α-Hydroxyprednisolone

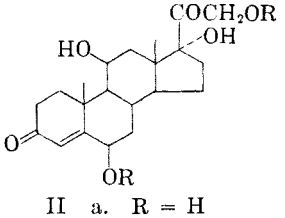
Sir:

We wish here to describe the first chemical preparation of 6α- and 6β-hydroxyhydrocortisone (Ia, IIa) and 6α-hydroxyprednisolone (Ic).[1]

6β-Hydroxyhydrocortisone (IIa) has been established as a metabolite of hydrocortisone in animal and human studies.[2a] Burstein and Dorfman[2b] have speculated that 6α-hydroxyhydrocortisone (Ia) may also be a metabolite of hydrocortisone in the guinea pig.



I a. R = H
b. R = Ac
c. Δ^1, R = H
d. Δ^1, R = Ac



II a. R = H
b. R = Ac

The 5α,6α-epoxide III of hydrocortisone bisethylene ketal[3] on treatment with either perchloric

(1) F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954), have described the preparation of 6β-hydroxycortisone. Also the 6α-hydroxy analogs of cortisone and prednisone have been prepared, J. A. Edwards, J. Iriarte, C. Djerassi, and H. J. Ringold, forthcoming publication, as cited by A. Bowers and co-workers, *J. Am. Chem. Soc.* **81**, 5233 (1959).

(2) (a) S. Burstein, R. Dorfman, and E. Nadel, *Arch. Biochem. and Biophys.*, **53**, 307 (1954); (b) S. Burstein and R. Dorfman, *J. Biol. Chem.*, **213**, 581 (1955), and (c) E. Colle, R. A. Ulstrom, J. Burley, and R. Gunville, Abstracts of the 41st Meeting of the Endocrine Society, Atlantic City, N. J., June 4–6, 1959. See also, (d) M. Hayano and R. Dorfman, *Arch. Biochem. and Biophys.*, **50**, 218 (1954).

(3) R. Littell and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 984 (1956).

or sulfuric acid in aqueous acetone gave 5α,6β,-11β, 17α,21-pentahydroxypregnane-3,20-dione (IV) [m.p. 273–274° dec., $[\alpha]_D^{25}$ +35° (pyridine). *Anal.* Found: C, 63.44; H, 8.46]. Acetylation of IV at room temperature gave a separable mixture of 21-monoacetate V [m.p. 280–282°, $[\alpha]_D^{25}$ +35° (pyridine). *Anal.* Found: C, 62.62; H, 8.00], and the 6,21-diacetate VI [m.p. 145–155°,[4] $[\alpha]_D^{25}$ +6° (pyridine). *Anal.* Found: C, 62.46; H, 7.81]. Acetylation at 100° provided exclusively the 6,21-diacetate VI.[5]

Treatment of the 6,21-diacetate VI in methylene chloride with hydrogen chloride at 0° provided a mixture of 6α-hydroxyhydrocortisone 6,21-diacetate (Ib) and 6β-hydroxyhydrocortisone 6,21-diacetate (IIb) separated by chromatography on magnesium silicate. This gave the 6α,21-diacetate Ib [m.p. 128–130°, $\lambda_{max}^{CH_3OH}$ 236 mμ (ϵ 12,800), $[\alpha]_D^{25}$ +107° (chloroform). *Anal.* Found: C, 64.72; H, 7.69] and the *impure* 6β,21-diacetate IIb. When the reaction was performed in methylene chloride containing ethanol only the thermodynamically more stable 6β,21-diacetate Ib was obtained. Saponification of Ib with potassium carbonate gave 6α-hydroxyhydrocortisone (Ia) as a solvate [m.p. 220–222°, $\lambda_{max}^{CH_3OH}$ 241 mμ (ϵ 13,300), $[\alpha]_D^{25}$ +122° (pyridine). *Anal.* Found: C, 64.42; H, 7.96]. Impure 6β,21-diacetate IIb on saponification followed by partition chromatography on diatomaceous earth provided 6β-hydroxyhydrocortisone (IIa) [m.p. 241–243°, $\lambda_{max}^{CH_3OH}$ 234–235 mμ (ϵ 12,000), $[\alpha]_D^{25}$ +90° (methanol)].[2b,d] Acetylation gave the 6β,21-diacetate IIb [m.p. 148–150°, $\lambda_{max}^{CH_3OH}$ 235–236 mμ (ϵ 12,100), $[\alpha]_D^{25}$ +89° (methanol)].[2b,d;6]

Finally, 6α-hydroxyhydrocortisone 6,21-diacetate (Ib) on selenium dioxide dehydrogenation in *t*-butyl alcohol and acetic acid[7] gave 6α-hydroxyprednisolone 6,21-diacetate (Id) [m.p. 146–148°, $\lambda_{max}^{CH_3OH}$ 241–242 mμ (ϵ 13,900), $[\alpha]_D^{25}$ +80° (chloroform). *Anal.* Found: C, 65.08; H, 7.48]. Saponification gave 6α-hydroxyprednisolone (Ic) as a solvate [m.p. 248–250°, $\lambda_{max}^{CH_3OH}$ 242 mμ (ϵ 13,800), $[\alpha]_D^{52}$ +88° (methanol). *Anal.* Found: C, 66.28; H, 7.97].

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(4) All attempts to obtain a sample with a sharp m.p. were unsuccessful. However, the compound was shown to be homogeneous by paper strip chromatographic analysis. In fact, all compounds reported herein were similarly shown to be homogeneous.

(5) The 6,21-diacetate VI usually proved difficult to obtain in a crystalline form, and generally was used as an oil in subsequent transformations. The oil was demonstrated by paper chromatographic analysis to be practically homogeneous.

(6) The infrared absorption spectra of IIa and b were identical with those of the Worcester samples. We are indebted to Dr. S. Burstein for these comparisons.

(7) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. Szpilfogel, T. Posthumus, M. De Winter, and D. Van Dorp. *Rec. Trav. Chim.*, **75**, 475 (1956).