Notes

A department for short papers of immediate interest.

A Novel Fission of Steroidal Semicarbazones

Eugene P. Oliveto, Hershel L. Herzog, Lois Weber, Maryann E. Tully, and E. B. Hershberg

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The regeneration of steroidal ketones from their semicarbazone derivatives is an important step in the preparation of hormones and hormone intermediates.[1] This has been accomplished in the past by hydrolysis with strong acids,[2] exchange with another aldehyde or ketone,[1] or fission with nitrous acid.[3] In the course of our investigations on steroidal semicarbazones we found that a mixture of pyridine and acetic anhydride would remove these protective groups and regenerate the ketone functions at C-3 and at C-20.

In an attempt to prepare cortisone acetate 3,20-bis-semicarbazone, cortisone 3,20-bis-semicarbazone[4] was warmed with acetic anhydride-pyridine for one hour at 75°, then allowed to stand 18 hours at 25°. A 35% yield of crude cortisone acetate 3-mono-semicarbazone was isolated. Increasing the time of heating to six hours resulted in substantial removal of both semicarbazone groups to give a 5–10% yield of cortisone acetate after chromatography. Treatment of hydrocortisone 3,20-bis-semicarbazone (prepared by reduction of cortisone 3,20-bis-semicarbazone with potassium borohydride) with acetic anhydride and pyridine on the steam-bath for two hours gave, after chromatography, a 16% yield of pure hydrocortisone 21-acetate.

Similar results were obtained when 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione 3,20-bis-semicarbazone (I) and 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione bis-semicarbazone (II)[3c] were treated with acetic anhydride and pyridine giving, respectively, 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione 21-acetate (III) and 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (IV). While these yields were low (5–10%), they were higher than those obtained by the use of nitrous acid,[3c] pyruvic acid,[2] or hydrochloric acid at room temperature[5] on the same starting materials. In our hands the first reagent gave *ca.* 5% yield of IV from II, while the latter two gave no isolable III from I.

In one experiment with I, in which the pyridine was omitted, III was formed, but in lower yield. A mixture of pyridine and acetic acid gave essentially no reaction, and starting material was recovered.

EXPERIMENTAL

All m.p. are corrected. Optical data were obtained by the Micro-analytical and Physical Chemistry Departments of these laboratories.

Cortisone acetate 3-monosemicarbazone from cortisone 3,20-bis-semicarbazone. A solution of 2.0 g. of cortisone 3,20-bis-semicarbazone[4] in 15 ml. of acetic anhydride and 40 ml. of pyridine was warmed for one hour at 75°, allowed to stand 18 hours at 25°, then poured into water to give 0.68 g. (35%) of material, m.p. 195° dec., λ_{max}^{EtOH} 270 mμ (ϵ 22,200) which was identified as crude cortisone acetate 3-monosemicarbazone by comparison of its infrared spectrum with that of an authentic sample. Lit.[4] m.p. 218–220°.

Cortisone acetate from cortisone 3,20-bis-semicarbazone. A solution of 2 g. of cortisone 3,20-bis-semicarbazone in 15 ml. of acetic anhydride and 40 ml. of pyridine was warmed for 6 hours at 75°, poured into water, and filtered to give 0.92 g. (54%) of material, m.p. 190° dec., λ_{max}^{EtOH} 238 mμ (ϵ 12,600). Cortisone acetate (m.p. 222–225°) could be obtained in 5–10% yield after chromotography and crystallization. It was identified by comparison of its infrared spectrum with that of an authentic sample.

Hydrocortisone acetate from hydrocortisone 3,20-bis-semicarbazone. A suspension of 1 g. of hydrocortisone 3,20-bis-semicarbazone, 20 ml. of pyridine, and 7.5 ml. of acetic anhydride was heated on the steam-bath for two hours, at which time solution was complete. The mixture was poured into about 120 ml. of ice-water, and the pyridine was neutralized with hydrochloric acid. The water then was extracted with methylene chloride, and the organic extracts were washed to neutrality, dried, and evaporated to yield a residue of 0.6 g. This was chromatographed on Florisil to give 0.35 g. of crude product. Recrystallization from acetone-hexane gave 0.14 g. (16%) of pure hydrocortisone 21-acetate, m.p. 217–220°, identical in all respects with an authentic sample (mixture m.p. and infrared spectrum).

17α,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione 21-acetate (III) *from 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione 3,20-bis-semicarbazone* (I). *A.* A mixture of 1 g. of I, 7.5 ml. of acetic anhydride, and 20 ml. of pyridine was heated on the steam-bath for 2 hours, then poured into ice-water. About 25 ml. of concentrated hydrochloric acid was added, the mixture was extracted with methylene chloride, and the organic extracts were washed to neutrality with water, dried, and evaporated to give 0.68 g. of an oil.

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[1] See, for example: (a) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948); (b) V. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); (c) B. Koechlin, T. Kritchevsky, and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950); (d) N. Wendler, R. Graber, R. Jones, and M. Tishler, *J. Am. Chem. Soc.*, **74**, 3630 (1952).

[2] See ref. 1a for leading references.

[3] (a) S. Goldschmidt and W. Veer, *Rec. trav. chim.*, **65**, 796 (1946); (b) D. H. Hey and D. S. Morriss, *J. Chem. Soc.*, 2319 (1948); (c) H. L. Herzog, *et al.*, *J. Am. Chem. Soc.*, **77**, 4781 (1955).

[4] N. L. Wendler, Huang-Minlon, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951).

[5] *Cf.* J. Demaecker and R. H. Martin, *Nature*, **173**, 266 (1954).

Chromatography of 0.57 g. on Florisil gave 0.13 g. of crude III. Crystallization from acetone-hexane gave 90 mg. of III, m.p. 220–226°, identical in its infrared spectrum with an authentic sample. Lit.[3c] m.p. 226–232°.

B. A mixture of 1 g. of I and 25 ml. of acetic anhydride was heated on the steam-bath for 2 hours, then worked up in the usual way to give 0.52 g. of an oil. This was triturated with ether to give 0.34 g. of a solid, m.p. 200° dec.; chromatography of 0.3 g. on Florisil gave 60 mg. of crude III. Crystallization from acetone-hexane gave 30 mg. of III, m.p. 220–225° (structure confirmed by infrared spectrum and mixture m.p.).

11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (IV) *from 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione bis-semicarbazone* (II). A mixture of 0.5 g. of II, 3.75 ml. of acetic anhydride, and 10 ml. of pyridine was heated on the steam-bath 2 hours, then worked up as in the previous experiment to give 0.49 g. of an oil. Chromatography of 0.40 g. on Florisil gave 50 mg. of crude IV. Crystallization from acetone-hexane gave 20 mg. of IV, m.p. 220–229°, identical in its infrared spectrum with an authentic sample. Lit.[3c] m.p. 237–239°.

CHEMICAL RESEARCH AND DEVELOPMENT DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

Reaction of Paraoxon with Hydrogen Peroxide in Dilute Aqueous Solution

JOSEPH EPSTEIN, MARY M. DEMEK, AND DAVID H. ROSENBLATT

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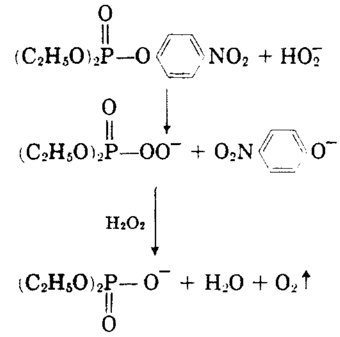
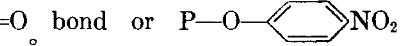
The perhydroxyl ion reacts with suitable substrates, such as benzonitrile[1] and isopropyl methylphosphonofluoridate[2] to produce unisolable[3] perhydroxylated intermediates; the latter are capable of further reaction with hydrogen peroxide, whereby oxygen and hydrolysis products of the substrates are formed. The net effect is to accelerate markedly the basic hydrolysis of the substrates at a given *p*H. In the present report it is shown that the hydrolysis of paraoxon (O,O-diethyl O-*p*-nitrophenyl phosphate) is similarly accelerated by hydrogen peroxide, *i.e.*, *via* the perhydroxyl ion, most likely according to the following equation (by analogy with reactions of alkaline hydrogen peroxide with isopropyl methylphosphonofluoridate):



The reaction, which can be followed through appearance of the strongly colored *p*-nitrophenoxide ion, is of first order with respect to both substrate and perhydroxyl ion, as in the previously cited instances. Although perhydroxyl is a less basic ion than hydroxyl,[4] its reaction rate with paraoxon is about 10^2 times as rapid as that of hydroxyl ion. Interatomic distances[5] between the hydrogen and the charged oxygen of the perhydroxyl ion (1.91 Å) and between the phosphorus and oxygen[6] of either the P═O bond or  groups (1.55–1.76 Å) are sufficiently close to permit the operation of a push-pull mechanism, such as has been used to explain the extraordinary reactivities of catecholate ions with isopropyl methylphosphonofluoridate.[7] It is visualized that an attack by the negatively charged perhydroxyl ion upon the phosphorus atom simultaneous wth a pull on the phosphoryl oxygen (or the *p*-nitrophenoxide oxygen) by the perhydroxyl hydrogen facilitates the cleavage of the phosphorus to oxygen (phenoxide) bond.

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(1) Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); **77**, 2519 (1955).

(2) Wilson, Gehauf, and Rueggeberg, *Abstracts of the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy*, Feb. 27, 1956, p. 23; J. Epstein and V. E. Bauer, *Abstracts of the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy*, Feb. 27, 1956, p. 24.

(3) The existence of the perhydroxylated intermediate has been postulated through its ability, in the case of the isopropyl methylphosphonofluoridate derivative, to oxidize certain amines, such as *o*-tolidine, rapidly to yellow dyes.[2]

(4) Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954), has pointed out the importance of two factors in the rates of displacement reactions, namely, the relative basicity of the attacking anion toward protons and a parameter, E_n (the "nucleophilic constant"), related to the electrode potential of the anion. For displacements on phosphorus in aqueous solution, E_n may be assumed to be rather unimportant, as compared to the influence of the basicity of the anion. Thus, we have observed that the thiosulfate ion which, according to Edwards, has a very high nucleophilic constant, has scarcely any effect on the rate of decomposition of isopropyl methylphosphonofluoridate in aqueous solution. Hence, in comparing the activity of two anions, only "basic" strength should be important, and greater reactivity might be expected of the anion possessing higher basicity.

(5) The distance between the hydrogen and charged oxygen was calculated on the basis of data taken from Milas, in Kirk and Othmer, *Encyclopedia of Chemical Technology*, Interscience Encyclopedia, Inc., New York, 1951, Vol. 7, p. 729. The H—O—O bond angle was taken as 101.5°, the O—O bond distance as 1.48 Å and the O—H bond distance as 1.01 Å.

(6) Van Wazer, in Kirk and Othmer, *Encyclopedia of Chemical Technology*, Interscience Encyclopedia, Inc., New York, 1953, Vol. 10, p. 466.

(7) Epstein, Rosenblatt, and Demek, *J. Am. Chem. Soc.*, **78**, 341 (1956).