[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

Chemical Studies with 11-Oxygenated Steroids. II. 11β-Hydroxyprogesterone[1]

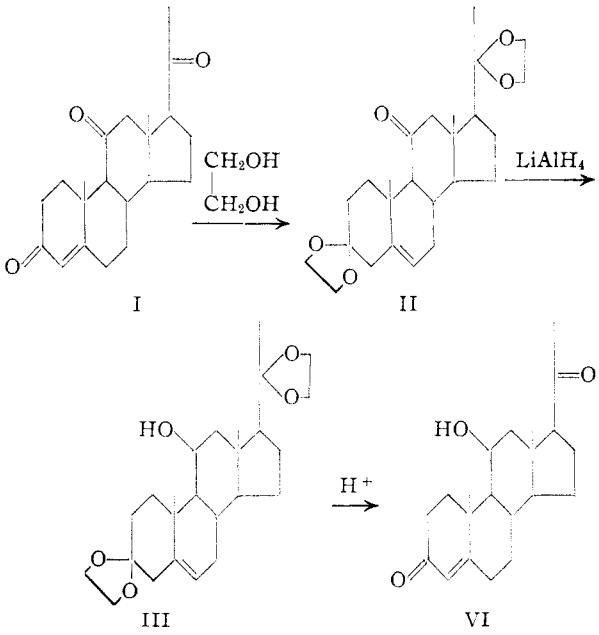
BY BARNEY J. MAGERLEIN AND R. H. LEVIN

RECEIVED APRIL 23, 1953

A novel synthesis of 11β-hydroxy-4-pregnene-3,20-dione (11β-hydroxyprogesterone) from the now readily available 11α-hydroxyprogesterone is described.

A facile synthesis of 11β-hydroxy-4-pregnene-3,20-dione (11β-hydroxyprogesterone) (IV) from the readily available 11α-hydroxyprogesterone produced by the microbiological oxygenation of progesterone[2] was of interest from both the chemical and biological standpoint.[3]

Reichstein and Fuchs[4] originally prepared 11β-hydroxyprogesterone from corticosterone. However their method of synthesis is not adaptable to large scale preparations. A recent synthesis by Rosenkranz, Pataki and Djerassi[5] from 3α-hydroxypregnane-11,20-dione entails a selective Oppenauer oxidation of the 3-hydroxy group over the 11β-hydroxy and the introduction of the Δ^4-3-keto system in the A-ring as well as conversion of the 11-ketone to a hydroxyl. In this Laboratory with 11-ketoprogesterone easily prepared from 11α-hydroxyprogesterone,[2] the following synthesis of 11β-hydroxyprogesterone was achieved.



The over-all yield of 11β-hydroxyprogesterone (IV) from 11-ketoprogesterone (I) was 55–60%.

While the intermediates II and III were originally isolated, in practice only the ketal II was isolated. The oily mother liquors after the removal of a 60% yield of crystalline II were treated with dilute sulfuric acid to give a 15% recovery of I. Papergram analysis[6] of the crude 11β-hydroxyprogesterone showed that 3–5% of 11α-hydroxy isomer was formed in the lithium aluminum hydride reduction. Our observation is in accord with recent reports that lithium aluminum hydride reduction of 11-ketopregnanes gives varying amounts of 11α-hydroxypregnanes.[7] The physical constants of our 11β-hydroxyprogesterone are in good agreement with those of Reichstein and Fuchs[4] and Rosenkranz, Pataki and Djerassi.[5]

Acknowledgment.—The authors are indebted to G. Beyer, V. R. Shellman and J. L. Thompson for technical assistance; to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies: to W. A. Struck and associates for microanalyses; and to L. M. Reineke and associates for papergram analyses.

Experimental[8]

5-Pregnene-3,11,20-trione 3,20-Bis-(ethylene ketal) (II).—A mixture of 500 ml. of benzene, 5.0 g. of *p*-toluenesulfonic acid monohydrate and 200 ml. of distilled ethylene glycol was heated to boiling. Over a period of 2 hours a solution of 100 g. (0.305 mole) of 11-ketoprogesterone (free of 11α-hydroxyprogesterone) in 1.5 l. of benzene was added. During the time of addition and for 6 hours afterwards the reaction mixture was heated under reflux and vigorously stirred. The water formed in the reaction was codistilled with the benzene and removed in a water trap. The solution was cooled, washed with cold $NaHCO_3$ and water and dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude product was recrystallized from 0.5 l. of ethyl acetate to give 66.8 g. of product (52.6%), m.p. 171–176°. A second crop of crystals weighed 10.8 g. (8.5% yield), m.p. 170–172°. After several recrystallizations this material melted 176–179°, $[\alpha]_D$ +2.5° (acetone). Material melting over 170° is of satisfactory purity for subsequent steps.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.95; H, 8.64.

While the addition of all of the reactants at the beginning of the experiment gave good yields with 10–15 g. runs, better yields were obtained on larger runs using the modified procedure described above.

Recovery of 11-Ketoprogesterone.—The mother liquors after crystallization of the diketal II as described above (138 g.) was dissolved in a solution of 600 ml. of acetone, 150 ml. of water and 25 ml. of concentrated sulfuric acid. After 16 hours at 26° the solution was neutralized with sodium bicarbonate, diluted with 4 l. of water and extracted with methylene dichloride. The extract, after removal of the solvent, was crystallized from acetone and Skellysolve B[9]

(1) Preceding paper in this series, R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri and E. S. Gutsell, THIS JOURNAL, **75**, 503 (1953).

(2) D. H. Peterson and H. C. Murray, *ibid.*, **74**, 1871 (1952); D. H. Peterson, H. C. Murray, S. H. Epstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, *ibid.*, **74**, 5933 (1952); U. S. Patent 2,602,769 (July 8, 1952).

(3) The biological testing of 11β-hydroxyprogesterone will be reported elsewhere by K. J. Olson, R. O. Stafford, W. W. Byrnes, *et al.*, of our Department of Endocrinology.

(4) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(5) G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

(6) L. M. Reineke, *et al.*, to be published shortly; see also A. Zaffaroni, R. B. Burton and E. H. Keutmann, *Science*, **111**, 6 (1950).

(7) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953). Unpublished data from this Laboratory.

(8) Melting points are uncorrected, and taken in capillary tube.

(9) A saturated hydrocarbon fraction, b.p. 60–71°.

to give 42.0 g. of 11-ketoprogesterone, m.p. 167–171°. Infrared analysis and papergram analysis showed this material to be 11-ketoprogesterone of greater than 90% purity.

11β-Hydroxy-5-pregnene-3,20-dione 3,20-Bis-(ethylene ketal) (III).—Ten grams (24 millimoles) of 5-pregnene-3,11,-20-trione 3,20-bis-(ethylene ketal) (II) in 500 ml. of anhydrous ether was added to 10 g. of lithium aluminum hydride partially dissolved in 800 ml. of anhydrous ether. After stirring at 26° for 45 minutes and heating under reflux for one hour, water was added until a thick white precipitate was formed. The ether was decanted. The precipitate was washed with ether. Evaporation of the solvent gave crude III which after crystallization from 2-propanol weighed 6.5 g. (60.5% yield), m.p. 137–140°. Two recrystallizations from 2-propanol gave an analytical sample, m.p. 138–140°, $[\alpha]_D$ −23° (chloroform).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.71, 71.53; H, 9.03, 9.29.

11β-Hydroxy-4-pregnene-3,20-dione (11β-Hydroxyprogesterone) (IV). (a) **From Diketal III.**—Two grams (4.8 millimoles) of crude ketal III, m.p. 165–170°, was dissolved in 75 ml. of acetone and 25 ml. of water containing 1 ml. of concentrated sulfuric acid. After heating under reflux for 50 minutes the acid was neutralized and 75% of the acetone distilled under vacuum. Dilution of the residue with water gave 1.42 g. (89.9% yield) of crystals, m.p. 165–173°. Papergram analysis using a propylene glycol–toluene system[6] showed the presence of about 5–10% of 11α-hydroxyprogesterone. Several recrystallizations from acetone–ether gave 0.50 g., m.p. 186–188°, $[\alpha]_D$ +212° (acetone). Reichstein and Fuchs reported m.p. 187–188°, $[\alpha]^{17}_D$ +222.2 ± 4° (acetone).[4]

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.37. Found: C, 76.50, 76.44; H, 9.48, 9.07.

Oxidation of 11β-hydroxyprogesterone with chromic acid gave 98% yield of 11-ketoprogesterone, m.p. 171–174°, which when recrystallized melted 172.5–173°. This material was identical with a known sample of 11-ketoprogesterone.

(b) **From Diketal II.**—To a partial solution of 9 g. of lithium aluminum hydride in 2.8 l. of anhydrous ether there was added a solution of 50 g. (0.12 mole) of 5-pregnene-3,11,20-trione 3,20-bis-(ethylene ketal) (II), m.p. 170–176°, in 0.8 l. of benzene. After stirring at 26° for one hour and heating under reflux for one hour, a solution of 0.6 l. of concentrated hydrochloric acid and 0.6 l. of water was added to the cooled solution. The mixture was stirred at 26° for 16 hours. The crystals which formed were recovered by filtration. They weighed 17.0 g. (43.0% yield), m.p. 178–182°. After refrigeration of the ether solution for 8 hours a second crop of crystals, m.p. 182–185°, was obtained (8.0 g., 20.2% yield). The ether solution was concentrated to give an additional 11.2 g. (28.4% yield) of crystals, m.p. 174–177°. Recrystallization of this material from methylene dichloride–Skellysolve B gave 9.35 g., m.p. 178–181° (23.6% yield). The over-all yield of 11β-hydroxyprogesterone from II is therefore 86.8%.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FLORIDA STATE UNIVERSITY]

Sodium Hydride as a Condensing Agent with Acylaminomalonates in the Synthesis of Amino Acids[1,2]

BY JACOB SHAPIRA, RAYMOND SHAPIRA AND KARL DITTMER

RECEIVED JANUARY 12, 1953

Sodium hydride in inert solvents has been employed in the synthesis of α-amino acids to effect the condensation between alkyl halides and diethyl formamidomalonate, diethyl acetamidomalonate and ethyl acetamidocyanoacetate. The use of toluene or benzene as solvent readily permits the removal of traces of water from the solvents, reagents, or apparatus by azeotropic distillation. This procedure has been found to be more convenient than the use of sodium ethoxide in absolute ethanol under conditions where high humidity is a problem. The liberation of hydrogen indicates whether the condensation has started and its progress. When dimethylformamide is used as the solvent, a solution of the sodium salt of diethyl formamidomalonate is readily obtained and permits the condensation with isopropyl bromide.

The use of specially dried ethanol in condensations between acyl derivatives of diethyl aminomalonate and primary or secondary halides in ethanolic sodium ethoxide has often been stressed.[3] Yields are drastically lowered or become nonexistent when traces of water are present in the reagents. Sodium in *t*-butyl alcohol can be used to advantage but when xylene or dioxane were used as solvents, tarry by-products and decreased yields resulted.[4] Sodium in refluxing toluene has been reported to effect the condensation between diethyl formamidomalonate and benzhydryl bromide in 25% yield accompanied by considerable coupling of the halide.[5]

Sodium hydride has been shown to have no effect on a wide variety of alkyl halides in an inert solvent even at elevated temperatures and after prolonged exposure.[6] It can also be used to effect a number of condensations with active methylenic compounds.[7]

In this paper is reported the use of sodium hydride in the condensation between various alkyl bromides or chlorides and diethylformamidomalonate (I), diethyl acetamidomalonate (II) and ethyl acetamidocyanoacetate (III). The reaction involves refluxing an equimolar mixture of the halide and amide with a slight excess of sodium hydride in a solvent such as toluene until the evolution of hydrogen has ceased, usually a few hours (Fig. 1).

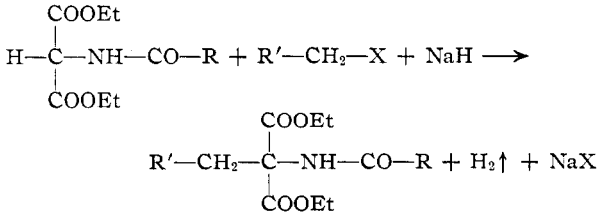


Fig. 1.

(1) Presented in part before the Meeting-in-Miniature of the Florida Section of the American Chemical Society on May 3, 1952 in Jacksonville, Florida.

(2) This work was supported in part by a research contract with the Office of Naval Research, Research Grant 2714 from U. S. Public Health Services, and a Parke, Davis and Company Research Grant.

(3) N. F. Albertson, THIS JOURNAL, **68**, 450 (1946); E. P. Painter, *ibid.*, **62**, 232 (1940); C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(4) D. Goldsmith and M. Tishler, THIS JOURNAL, **68**, 144 (1946).

(5) Z. J. Vejdelek and M. Protiva, *Chem. Listy*, **45**, 44 (1951).

(6) S. J. Cristol, J. W. Ragsdale and J. S. Meek, THIS JOURNAL, **71**, 1863 (1949).

(7) V. J. Hansley and P. J. Carlisle, *Chem. Eng. News*, **23**, 1332 (1945); F. W. Swamer and C. R. Hauser, THIS JOURNAL, **72**, 1352 (1950); N. Green and L. B. LaForge, *ibid.*, **70**, 2287 (1948); G. H. Daub and W. S. Johnson, *ibid.*, **72**, 501 (1950).