iodide, 20 g. of potassium carbonate, 225 ml. of methanol and 75 ml. of water was boiled under reflux for 11 hours. After removal of most of the methanol, the mixture was diluted with water and cooled. The solid which separated was recrystallized from hexane and yielded 13.2 g. (55%) of white crystals, m.p. 144–146.5°. Further recrystallization gave a sample melting at 148–149°.

Attempts to carry out a Willgerodt reaction with XXII gave only dithioöxalodimorpholide, a compound previously observed in this type of reaction by McMillan and King.[15]

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.08; H, 6.75.

1-(β,γ-Epoxypropyl)-3,4-dimethoxy-7,8,9,10-tetrahydro-6-dibenzopyrone (XXIII).—To a solution of 11.3 g. of XXII in 200 ml. of chloroform there was added 100 ml. of a 0.374 *M* chloroform solution of perbenzoic acid and the mixture was allowed to stand for 3 days. The chloroform solution was then extracted with sodium bicarbonate solution, washed with water and dried over sodium sulfate. After removal of the chloroform, the residue was extracted with hot hexane to remove any starting material and recrystallized from ethanol. There resulted 7.4 g. (62%) of white crystals, m.p. 144–148°. Further recrystallization from ethanol gave a sample melting at 149–150°.

Attempts to rearrange XXIII in the usual way[16] did not yield aldehydic material.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.60; H, 6.36.

(15) F. H. McMillan and J. A. King, THIS JOURNAL, **69**, 1207 (1947).

(16) M. Tiffeneau, P. Weill and B. Tchoubar, *Compt. rend.*, **205**, 54 (1937); R. A. Barnes and W. M. Budde, THIS JOURNAL, **68**, 2339 (1946); and E. Mosettig, *Ber.*, **62**, 1274 (1929).

ROCHESTER, NEW YORK RECEIVED SEPTEMBER 19, 1951

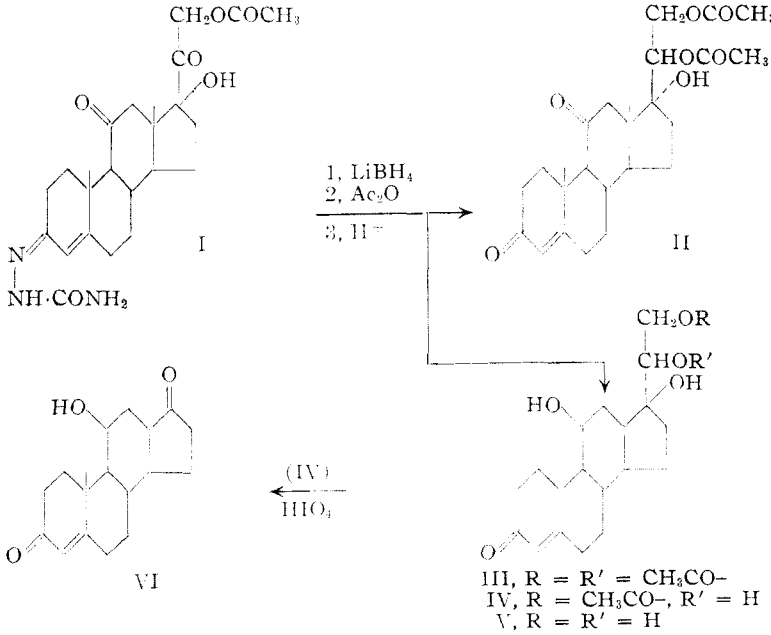
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

A Further Study on the Reduction of Steroid Semicarbazones

BY HUANG-MINLON AND RUSSELL H. PETTEBONE

A product isolated from the reaction mixture of cortisone acetate 3-semicarbazone after $LiBH_4$ reduction followed by acetylation and regeneration has been proved to be 4-pregnane-11,17,20,21-tetrol-3-one-21-acetate (Reichstein's substance E 21-acetate). The route to the formation of this new substance has been studied.

The synthesis from cortisone of 4-pregnene-11,-17,20,21-tetrol-3-one 20,21-diacetate and 4-pregnene-17,20,21-triol-3,11-dione 20,21-diacetate (Reichstein's Substances E and U diacetate) was the subject *inter alia* of a recent communication.[1] This transformation consisted in the reduction of cortisone acetate 3-semicarbazone (I) with lithium borohydride and subsequent acetylation and removal of the semicarbazone grouping. Since the time of the completion of this work a third substance has been isolated from this reaction sequence and identified as 4-pregnene-11,17,20,21-tetrol-3-one 21-acetate (IV), previously not described in the literature. This substance has been found, moreover, to be the predominant product from this synthesis under properly chosen conditions.



Saponification of (IV) yielded 4-pregnene-11,17,-20,21-tetrol-3-one (V) and acetylation produced the diacetate (III). Periodic acid oxidation converted (IV) to 11-dihydroadrenosterone[2] (VI) thereby establishing the structure of this compound.

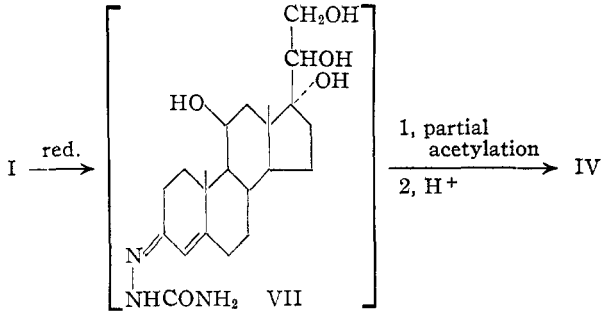
It seemed desirable to ascertain whether the acetyl group of (IV) originated from the starting material (I) or had been replaced by the subsequent acetylation step following the hydride reduction of (I). The latter possibility implies that the 21-acetyl group of (I) was lost during the treatment with lithium borohydride. In support thereof it was found that omission of the acetylation step produced (V) as the major product. Furthermore, when the crude reduction product obtained from (I) was acetylated under *mild* conditions there resulted a twofold increase of (IV) in the final product. It therefore appears that the 21-acetyl group of (IV) arises through partial acetylation of an intermediate tetrol (VII) which we have not been able to obtain in crystalline form.

Experimental

4-Pregnene-11,17,20,21-tetrol-3-one 21-Monoacetate (IV).—A solution of 1.00 g. of cortisone acetate 3-semicarbazone (I) in 175 cc. of dry tetrahydrofuran was added with stirring

(1) N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951).

(2) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937).



at 25° to a solution of 0.80 g. of lithium borohydride in 50 cc. of tetrahydrofuran over a period of ¾ hr. The mixture was further stirred at room temperature for 4 hr. and then the excess lithium borohydride was decomposed under cooling with 40 cc. of 20% aqueous acetic acid. The resulting acidic solution was evaporated *in vacuo* to nearly dryness and after trituration with water the separated solid was filtered, washed with saturated sodium chloride solution and dried at 80° *in vacuo*. This crude product was acetylated with 10 cc. of pyridine and 10 cc. of acetic anhydride either at steam-bath temperature for 7 minutes or better at room temperature for 15 minutes. The excess of acetic anhydride was immediately decomposed by treatment with 10 cc. of water and the solvents were removed *in vacuo*. For the regeneration it was dissolved in 15 cc. of acetic acid. After addition of 4.6 cc. of water, 2.55 g. of anhydrous sodium acetate and 2.4 cc. of 90% pyruvic acid the mixture was heated at 75° under nitrogen for 4 hr. At the end of this period the solvents were removed *in vacuo* and the residue was extracted with ethyl acetate. The ethyl acetate solution was washed with 5% aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the dry residue (0.832 g.) was dissolved in benzene–chloroform and chromatographed on acid-washed alumina. Fractional elution with benzene–chloroform afforded, as described previously,[1] 4-pregnene-17,20,21-triol-3,11-dione 20,21-diacetate (II) and 4-pregnene-11,17,20,21-tetrol-3-one 20,21-diacetate (III) melting first at 235–245° (about 60 mg.) and at 223–226° (about 100 mg.), respectively. Recrystallization from ethyl acetate gave the pure substances. Further elution with chloroform–methanol (1:1) gave the crude compound (IV) melting at 219–230° (350–465 mg.). Recrystallization from acetone–ethyl acetate or from acetone raised the melting point to 235–237° depressed by admixture with (II) or (III), λ_{max} 2425, E% 399 (ethanol).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.99; H, 8.38; $[\alpha]^{24}D$ +99 ± 1° (1% acetone).

Another run under essentially the same condition, but without the acetylation step, gave 4-pregnene-11,17,20,21-tetrol-3-one (V) as major product.

4-Pregnene-11,17,20,21-tetrol-3-one and Its Diacetate from (IV).—To a solution of 40.0 mg. of (IV) in 5 cc. of methanol was added at 40°, 1 cc. of water containing 30 mg. of potassium carbonate and 50 mg. of potassium bicarbonate. After standing at room temperature for 72 hr. the reaction mixture was acidified with acetic acid and concentrated *in vacuo* nearly to dryness. The residue was extracted with ethyl acetate and the ethyl acetate solution after washing with saturated sodium chloride solution and 5% sodium bicarbonate solution was dried over anhydrous sodium sulfate. Concentration of the filtrate and addition of ether afforded 4-pregnene-11,17,20,21-tetrol-3-one (V) melting at 126–127° not depressed by admixture with an authentic specimen. Infrared spectra confirm the identity in every respect.

Acetylation of (IV) by pyridine and acetic anhydride gave 4-pregnene-11,17,20,21-tetrol-3-one 20,21-diacetate melting at 228–230°. A mixed melting point of this material with an authentic specimen was not depressed.

11-Dihydroadrenosterone (VI) from (IV).—To a solution of 50 mg. of IV in 4 cc. of methanol was added a solution of 80 mg. of periodic acid in 0.6 cc. of water. After standing for 21 hr. at room temperature the reaction mixture was diluted with a few cc. of water, concentrated *in vacuo* to remove methanol and extracted with ethyl acetate–ether. The extract, after washing with 5% soda solution and then with water, was dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated *in vacuo* yielding a brownish powder. On high vacuum sublimation at 170° (0.035 mm.), 26 mg. of crystalline sublimate was obtained; which after two recrystallizations from ether melted at 195.5–197° not depressed by admixture with an authentic sample of 11-dihydroadrenosterone prepared according to Reichstein[2] from 4-pregnene-11,17,20,21-tetrol-3-one (V). Infrared spectra confirm the identity in every respect.

RAHWAY, N. J. RECEIVED SEPTEMBER 4, 1951

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

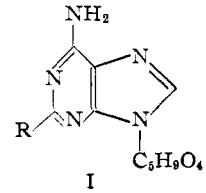
Some Synthetic Analogs of the Natural Purine Nucleosides[1]

BY JOHN DAVOLL[2] AND BERTRAM A. LOWY

The synthesis of a number of 9-glycosylpurines is reported. These include the pyranosyl analogs of the natural purine nucleosides, and the 2-methyl, 2-methylthio and 2-chloro derivatives of adenosine. The structure of Fischer and Helferich's "trichloropurine tetraacetyl glucoside"[3] has been determined.

The chloromercuri derivatives of purines form convenient starting materials for the synthesis of the 9-β-D-ribofuranosyl derivatives of adenine, 2,6-diaminopurine, guanine[3] and isoguanine.[4] These methods have now been applied to the preparation of various analogous glycosylpurines of possible biological interest.

9-β-D-Ribopyranosyladenine, 9-β-D-ribopyranosylguanine and 2,6-diamino-9-β-D-ribopyranosylpurine were prepared by replacing the triacetyl D-ribofuranosyl chloride used in the synthesis of the ribofuranosylpurines[3] by its pyranose isomer. Treatment of 2,6-diamino-9-β-D-ribopyranosylpurine with nitrous acid under the conditions used for the synthesis of crotonoside[4] appeared to give 9-β-D-ribopyranosylisoguanine, though this compound could not be obtained in a pure condition. 2,6-Diamino-9-β-D-xylofuranosylpurine was prepared by deacetylation of the condensation product of chloromercuri-2,6-diacetamidopurine and triacetyl D-xylofuranosyl chloride.



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(1) This investigation was supported by grants from the National Cancer Institute, of the National Institutes of Health, Public Health Service, from the Atomic Energy Commission, Contract AT-(30-1)-910 and from the Nutrition Foundation, Inc.

(2) Fellow of the United States Public Health Service.

(3) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(4) J. Davoll, *ibid.*, **73**, 3174 (1951).