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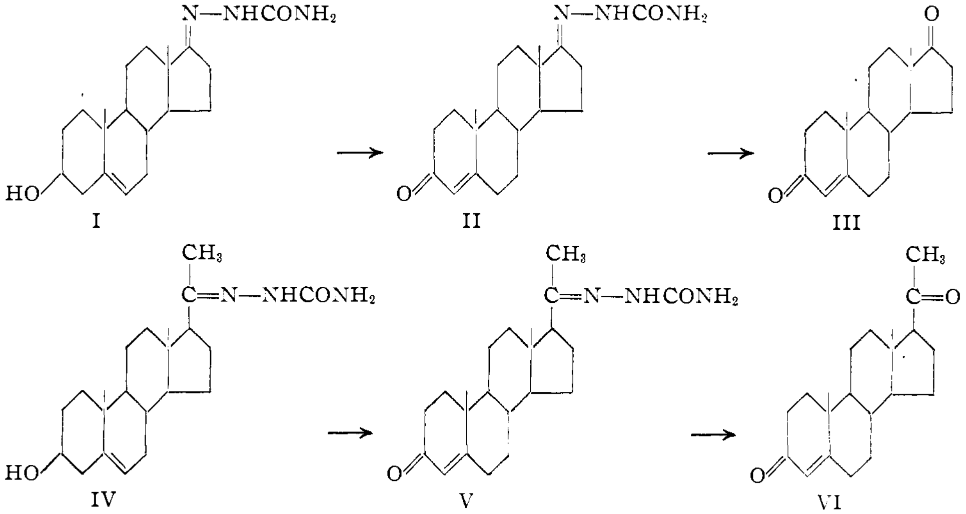
The Oppenauer Oxidation of Steroid Semicarbazones

BY CLARENCE H. GLEASON AND GEORGE W. HOLDEN

In the synthesis of testosterone from cholesterol one of the important intermediates, Δ^4-androstenedione-3,17 (III), is prepared from dehydroepiandrosterone[1] by means of an Oppenauer oxidation. This reaction involves the migration of the double bond from the 5,6- to the 4,5-position and a removal of two hydrogen atoms from the secondary alcohol group at C-3, resulting in an α,β-unsaturated ketone. These changes are effected by using as the hydrogen acceptor a ketone such as cyclohexanone having a high oxidation potential, in the presence of an alkoxide such as aluminum *t*-butoxide. Since dehydroepiandrosterone possesses a carbonyl group at C-17 it is conceivable that this grouping could function as a hydrogen acceptor thereby inhibiting the reaction to some extent. This assumption is supported by the fact that Oppenauer[2] isolated 5–7% testosterone which he postulates as having arisen from the dismutation of dehydroepiandrosterone under the influence of aluminum alcoholate. Moreover, the possibility of the free carbonyl entering into side reactions, such as condensation, would tend to further lower the yield. Indeed, in our experience with commercial quantities, it was found that improved yields of (III) were obtained when the semicarbazone of dehydroepiandrosterone (I) instead of the free ketone was submitted to the Oppenauer oxidation. The product, androstenedione-17-monosemicarbazone (II), has not been reported previously although the 3-mono-[3] and the 3,17-disemicarbazones[4] of androstenedione have been reported. On hydrolysis with dilute hydrochloric acid in the presence of benzene, (II) readily yielded (III) in good yield and of high purity.

Following the same line of reasoning this method was extended to the oxidation of pregnenolone-20-monosemicarbazone (IV) with the object of preparing progesterone (VI) *via* the intermediate progesterone-20-monosemicarabazone (V). Although considerable difficulty was encountered in the isolation of (V) a small quantity was finally obtained as an amorphous powder. Inasmuch as there is no previous mention of this compound in the literature, its physical properties are described in spite of the questionable purity of the sample. In this respect, it is noteworthy that Wintersteiner and Allen[5] were unable to prepare the 3,20-disemicarbazone of progesterone in a crystalline state and the impurity of their material was illustrated by the analytical results. In practice, however, it was found unnecessary to isolate (V) in the crystalline state and satisfactory yields of good quality progesterone could be obtained by direct hydrolysis of the mother oil.

A major obstacle in the preparation of (III) and (VI) from dehydroepiandrosterone and pregnenolone, respectively, lies in the separation of the latter, either as the free ketones or as the semicarbazones as obtained from the oxidation products of cholesterol. During the course of the present investigation it was observed that (V) was completely soluble in the oxidation mixture whereas (II) was insoluble. Hence, by direct oxidation of the mixed semicarbazones, (I) and (IV), a preliminary separation is circumvented, since the end-products are obtained separately as the desired (III) and (VI).



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(1) Fieser and Fieser, "Natural Products Related to Phenanthrene," Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 363.

(2) Oppenauer, *Acta brevia Neerl*, **7**, 176 (1937).

(3) Butenandt and Peters, *Ber.*, **71**, 2690 (1938).

(4) Hershberg, *J. Org. Chem.*, **13**, 545 (1948).

(5) Wintersteiner and Allen, *J. Biol. Chem.*, **107**, 324 (1934).

Experimental

In a preliminary trial using methyl ethyl ketone and benzene (a mixture which had given satisfactory results with the oxidation of the free ketone and other sterol ketones) completely unchanged (I) was recovered. Since it was observed that the semicarbazone remained suspended throughout the reaction period it was thought that if the temperature were increased by the introduction of higher-boiling solvents, solubility of the semicarbazone might be achieved and thereby bring about reaction. When a mixture of cyclohexanone and benzene (solution temperature approx. 100°) was used, there was no apparent change in the solubility of (I) but (III), after the appropriate hydrolysis of (II), was obtained in a yield of 47.6%. Further increases in temperature were achieved by the use of cyclohexanone–toluene (approx. 112°) and cyclohexanone–xylene (approx. 120°) and, although still no apparent solubility changes were observed, the yields were 78.0 and 46.7%, respectively. The reflux time was investigated for the cyclohexanone–toluene system and the yield was found to be constant for periods of eighteen, twenty-four and forty-eight hours.

Δ^4-Androstenedione-(3,17)-17-monosemicarbazone (II).—Twenty grams of (I), m. p. 267–270°[6]; $[\alpha]^{25}\text{D}$ − 18.55° (1% in acetic acid) was refluxed for eighteen hours with a mixture of cyclohexanone (380 ml.), toluene (955 ml.) and aluminum *t*-butoxide[7] (70.0 g.). The reaction mixture was cooled and the gray, gelatinous aluminum-steroid complex filtered and washed with toluene and methanol. The filtrate was discarded and the steroid complex decomposed by suspending with stirring in dilute aqueous hydrochloric acid for thirty minutes and the product then filtered and washed with water, methanol and finally isopropyl ether. (II) was thus obtained as small, colorless crystalline plates showing no definite m. p. up to 350° but undergoing gradual decomposition starting at around 275° and exhibiting insolubility in most organic solvents except glacial acetic acid; $[\alpha]^{25}\text{D}$ + 155.8° (1% in acetic acid), yield 16.9 g. (84.5%). *Anal.* Calcd. for $C_{20}H_{29}O_2N_3$: C, 69.97; H, 8.45; N, 12.24. Found: C, 70.50, 70.74; H, 8.08, 8.12; N, 11.80, 11.82.

Δ^4-Androstenedione-3,17 (III).—Ten grams of (II) was refluxed until solution was complete (overnight) with a mixture of alcohol (160 ml.), water (160 ml.), benzene (320 ml.) and concd. hydrochloric acid (40 ml.). The benzene was separated, the aqueous phase further extracted with benzene and the combined benzene solution was then washed with 10% sodium carbonate and finally with water. After drying over sodium sulfate and filtering with charcoal, the product was crystallized by concentration of the benzene and addition of isopropyl ether; yield 6.5 g. (78%), $[\alpha]^{25}\text{D}$ + 185.2° (1% in alc.), m. p. 172–173°; mixed m. p. with authentic Δ-^{4}androstenedione-3,17 was undepressed. The filtrate yielded an additional 0.37 g. of slightly impure product which was found to be contaminated with dehydroepiandrosterone.

Progesterone-20-monosemicarbazone (V).—Twenty grams of (IV), m. p. 258–261°, $[\alpha]^{25}\text{D}$ − 10.6° (1% in acetic acid), was refluxed for eighteen hours with a mixture of cyclohexanone (380 ml.), toluene (955 ml.) and aluminum *t*-butoxide (70.0 g.). The reaction mixture was cooled and the gray, gelatinous precipitate, unlike the product from the oxidation of (I), on decomposition with dilute hydrochloric acid yielded no steroid and was therefore discarded. The light-yellow filtrate was then acidified with dilute hydrochloric acid to decompose the soluble aluminum-steroid complex and the organic layer separated, washed with water and steam distilled *in vacuo* until the distillate was free of oil. In two of the above oxidations under identical conditions, the residual gum, following the steam distillation, amounted to (a) 24.0 and (b) 25.1 g.

(a) No attempt was made to crystallize the semicarbazone (V) from (a), but the gum was hydrolyzed directly with dilute hydrochloric acid as previously described for the hydrolysis of (II). The yield of progesterone (VI) was 10.4 g. (62.0%), m. p. 120–121°, $[\alpha]^{25}\text{D}$ + 192.3° (1% in alc.). A mixed m. p. with authentic (VI) was undepressed.

(b) After unsuccessful attempts from a variety of solvents, (V) was finally isolated in the solid state by dissolving residue (b) in ether and refrigerating for two weeks. At the end of this time, the gelatinous mass was slurried with ether and filtered and washed to a creamy-colored amorphous solid. The yield was 3.64 g. (18.2%). As thus obtained the m. p. was 177–186° (dec.), $[\alpha]^{25}\text{D}$ + 239.2° (1% in acetic acid) and + 226.5° (1% in chloroform). The ultraviolet absorption maximum (25 mg. (V) dissolved in 1 ml. of chloroform and made up to 0.001% with alcohol) was found to be at 240–241 mμ, characteristic of α,β-unsaturated ketones. Hydrolysis of 1.0 g. of (V) yielded 0.42 g. (50%) of progesterone (VI), m. p. 126–128°, $[\alpha]^{25}\text{D}$ + 191.8° (1% in alc.). The product (V) dissolved readily in cold benzene and chloroform with production of a brown solution further substantiating the impurity of the material as indicated by the melting point. Repeated attempts at recrystallization of (V) were unsuccessful. Treatment with Girard reagent "P" in order to eliminate any possible non-ketonic material simply resulted in the hydrolysis of the semicarbazone group, since pure progesterone (44%) was isolated.

Oxidation of a Mixture of Dehydroepiandrosterone- and Pregenolone Semicarbazones.—Thirty grams of a mixture of (I) and (IV), m. p. 251–259°, $[\alpha]^{25}\text{D}$ −15.8° (1% in acetic acid), obtained by saponification of the mixed acetate semicarbazones from a cholesterol oxidation, was refluxed for eighteen hours with cyclohexanone (570 ml.), toluene (1433 ml.) and aluminum *t*-butoxide (105.0 g.). The insoluble product was filtered after cooling and worked up for Δ^4-androstenedione (III) as described above for the oxidation of (I) to yield 9.17 g. (30.6% by weight), m. p. 170–171°, $[\alpha]^{25}\text{D}$ + 188.7° (1% in alc.). The filtrate was worked up for progesterone (VI) as described above for the oxidation of (IV) to yield 5.38 g. (17.9% by weight), m. p. 119–121°, $[\alpha]^{25}\text{D}$ + 189.9° (1% in alc.).

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Summary

1. By the Oppenauer oxidation of dehydroepiandrosterone and pregnenolone semicarbazones two previously unreported steroid derivatives, namely, Δ^4-androstenedione-17- and progesterone-20-monosemicarbazones have been prepared.

2. In comparison with the method of oxidizing the free ketones, the oxidation of the semicarbazones of dehydroepiandrosterone and pregnenolone results in improved yields of androstenedione and progesterone, respectively, as well as greater facility of operation.

3. Difficultly separable mixtures of dehydroepiandrosterone and pregnenolone can be effectively processed by direct oxidation of their semicarbazones.

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(6) All m. p.'s were carried out on the Fisher-Johns melting point apparatus.

(7) Aluminum isopropoxide was found to give equally good results.