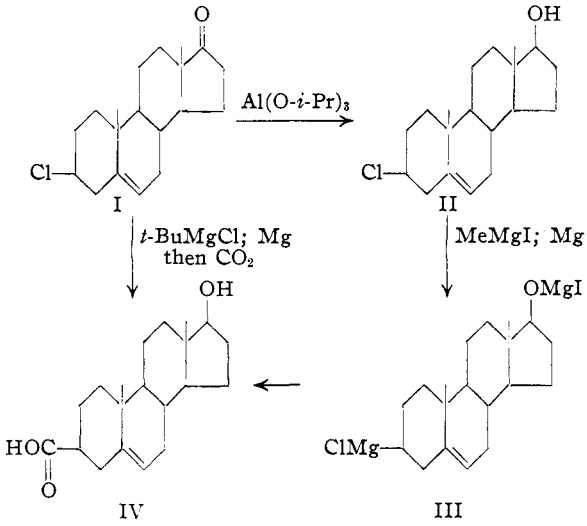
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Derived Steroids. III. 5-Androsten-17-ol-3-carboxylic Acid[1]

BY ROBERT H. BAKER AND EDWARD N. SQUIRE[2]

Marker[3] prepared 17-androstanone-3-carboxylic acid and found that it had estrogenic properties. We now report the synthesis of a similar compound (IV) with the additional feature of a double bond in the 5,6-position.

Two methods were used to prepare IV. Since the steroid halides form Grignard reagents only in the presence of preformed Grignards, it appeared that *t*-butylmagnesium chloride would serve both this role and as reducing agent for the 17-keto group.[4] This route produced only an 8% yield of the acid and it proved better to reduce the ketone by standard procedures and proceed by the longer route.



The ketone (I) is reduced only slowly and crystallization of the product gives what appears to be a molecular compound of I and II. This substance, m. p. 134°, resists separation by chromatography on alumina, but after acetylation the ester and ketone may be separated by either crystallization or chromatography. So prepared, II and its acetate agree in m. p. with the products prepared by Kuwada[5] by the action of thionyl chloride on 17-acetoxy-5-androsten-3-ol.

Because of the low solubility of II in ether, and the still lower solubility of III, the treatment with methyl Grignard was best carried out on the more soluble acetate of II. This produced a fine suspension of III which even then required a prolonged contact with carbon dioxide. Maximum yields of the acid (IV) were not obtained with less than eighteen hours for Grignard formation and eight hours for carbonation.

Experimental[6]

3-Chloro-5-androsten-17-one (I).—This was prepared essentially by the method of Wallis and Fernholz[7] except that the phosphorus pentachloride was added slowly and the product was purified by absorption from chloroform solution on alumina, m. p. 154–154.4°.

3-Chloro-5-androsten-17-ol (II).—A solution made from 60 ml. of isopropyl alcohol containing 0.037 mole of aluminum isopropoxide and 1.15 g. (0.0037 mole) of I was refluxed for fourteen hours, and then slowly distilled to a residue of 15 ml. This was hydrolyzed with hydrochloric acid, extracted with ether and crystallized from methanol, m. p. 128–138°. The solid was dissolved in 10 ml. of benzene, diluted with 40 ml. of petroleum ether (b. p. 60–70°) and passed through a column containing 15 g. of alumina. Elution with the same solvent, 50 ml., produced 390 mg., m. p. 120–135°. The next four fractions, eluted with benzene, gave 650 mg. of the chloro alcohol, m. p. 162.5–165.5°, lit.[5] 163°.

3-Chloro-17-acetoxy-5-androstene.—This could be prepared by heating (95°) the 120–135°-melting product with acetic anhydride and pyridine for two hours. Repeated crystallization from methanol gave m. p. 182–184°, lit.,[5] 183°. For preparative purposes the pure chloro alcohol was used.

5-Androsten-17-ol-3-carboxylic Acid (IV).—To a mixture of methylmagnesium iodide and magnesium, made from 2.28 g. (1.6×10^{-2} mole) of the iodide and 1.0 g. (4.1×10^{-2} mole) of metal, in 5 ml. of ether there was added a solution of 0.702 g. (2×10^{-3} mole) of 3-chloro-17-acetoxy-5-androstene in 35 ml. of ether. This mixture was refluxed under nitrogen and stirred for twenty-four hours. The mixture was then cooled by a dry ice-acetone bath and subjected to 790 mm. pressure of dry carbon dioxide during sixteen hours, then for two more hours at room temperature. The reaction mixture was decomposed with 10% hydrochloric acid and extracted with 50 ml. of ether. The carboxylic acid was extracted from the ether with four 25-ml. portions of 5% potassium hydroxide. The alkaline solution, after extraction with ether, was acidified to precipitate the acid which was then crystallized from ether to give four fractions, 0.540 g., m. p. 220–243° (top fraction 240–243°). Crystallization from benzene gave m. p. 239–242°. The analytical sample was dried four days at 100° *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.96, 75.45; H, 9.92, 9.74.

The ether washes contained suspended solid which was removed by filtration, 20 mg., m. p. *ca.* 300°. This is probably 3,3'-bis-5-androsten-17-ol formed similarly to the bicholesteryl.[1]

Evaporation of the neutral ether washes left a product which did not crystallize well from methanol, 0.2 g., m. p. 138–154°. In this was identified **5-androsten-17-ol** by conversion into the acetate, 0.1 g., m. p. 135–136°, lit.,[8] 133–135°.

The acid (IV) was also prepared directly from 3-chloro-5-androsten-17-one. To 1.0 g. (3.2×10^{-3} mole) of the

(1) Preceding papers Baker and Squire, THIS JOURNAL, **70**, 1487 (1948); **70**, 4134 (1948).

(2) Junior Fellow of the National Institute of Health. Present address Franklin and Marshall College, Lancaster, Pa.

(3) Marker, Kamm, Oakwood and Laucius, THIS JOURNAL, **58**, 1948 (1936).

(4) Ruzicka and Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936), used propylmagnesium iodide for the reduction of 17-ketosteroids.

(5) Kuwada and Miyasaka, *J. Pharm. Soc. Japan*, **57**, 232 (1937).

(6) Microanalyses by Margaret Hines and Jean Gibbs.

(7) Wallis and Fernholz, THIS JOURNAL, **59**, 764 (1937).

(8) Marker and Wittle, U. S. Patent 2,397,424-5-6; *Chem. Abs.*, **40**, 3570 (1946).

chloroketone in 50 ml. of ether there was added 0.243 g. (1×10^{-2} mole) of magnesium powder and 10 ml. of 2 *N* *t*-butylmagnesium chloride. The mixture was refluxed for four hours, and carbonated as previously described to give 83 mg. of the acid, m. p. 243°.

3-Carbomethoxy-5-androsten-17-ol.—A solution of 10 ml. of absolute methanol, 110 mg. (3.4×10^{-4} mole) of IV and 6 drops of concd. sulfuric acid was refluxed for twenty-four hours. The mixture was poured into water, extracted with ether and washed free of acid by alkali. Crystallization from methanol–petroleum ether followed by chromatography over alumina from benzene–petroleum ether gave 80 mg., m. p. 141–142°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.73. Found: C, 75.20; H, 9.79.

17-Acetoxy-5-androsten-3-carboxylic Acid.—A crude sample, 250 mg., of the acid (IV) was heated at 100° for two hours with excess acetic anhydride in pyridine. The product obtained by pouring into water was dissolved in acetone and filtered to remove some insoluble material. Slow crystallization from acetone gave 110 mg., m. p. 211–213°, $[\alpha]^{23}D$ −40.6 (*C*, 4.90 in chloroform).[9]

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.00; H, 8.99.

Acknowledgment.—We wish to thank Dr. Wayne Cole of the Soya Products Division of the Glidden Co. for supplying the dehydroisoandrosterone.

Summary

5-Androsten-17-ol-3-carboxylic acid has been prepared by carbonation of a Grignard reagent. Its acetate and methyl ester are described.

(9) The specific rotations of the intermediates and other compounds in this series will appear in a future publication by Dr. Squire.

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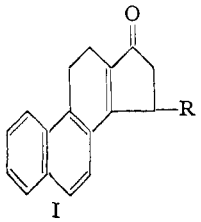
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

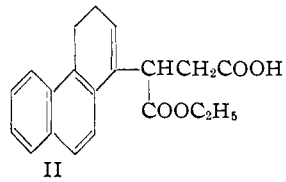
The Stobbe Condensation with 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene. A New Approach to β-17-Equilenone[1]

BY WILLIAM S. JOHNSON, VERNER L. STROMBERG AND JACK W. PETERSEN[2]

A few years ago we described a convenient synthesis of the ketone I (R = H) by the cyclization of the half-ester II produced by a Stobbe condensation with III (R = H), followed by hydrolysis and decarboxylation of the resulting keto ester I (R = $COOC_2H_5$).[3] Since then this scheme has been applied successfully by Riegel, Siegel and Kritchevsky[4] to the synthesis of a number of derivatives of I (R = H) containing alkyl substituents at the 3-position of the phenanthrene nucleus.



I



II

It seemed of particular interest to extend the synthesis to the homologous ketone III (R = CH_3) containing the methyl substituent at the 2-position, since if the cyclization proceeded into the alicyclic ring, a substance IV (R = $COOC_2H_5$) would be produced which is known to be convertible by hydrolysis, decarboxylation and hydrogenation into the 17-equilenones (3-desoxyequilenins).[5] The results of such an investigation are reported in this communication.

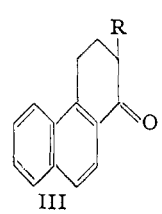
(1) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) W. A. R. F. Research Assistant, 1943–1945. Deceased, January 29, 1948.

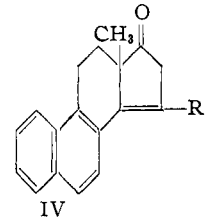
(3) Johnson and Petersen, THIS JOURNAL, **67**, 1366 (1945).

(4) Riegel, Siegel and Kritchevsky, *ibid.*, **70**, 2950 (1948).

(5) Johnson, Petersen and Gutsche, *ibid.*, **69**, 2942 (1947).

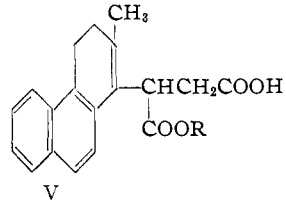


III

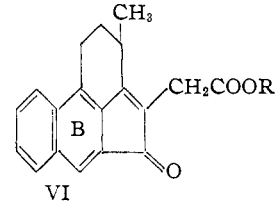


IV

The Stobbe condensation with III (R = CH_3) proceeded less readily than with the unsubstituted ketone III (R = H), but by altering conditions a non-homogeneous half-ester V (R = CH_3)[6] was obtained in excellent yield, from which a pure crystalline isomer was isolated in 61% yield.



V



VI

Cyclization of the crude half-ester V (R = CH_3 or C_2H_5) with a mixture of zinc chloride, acetic acid and acetic anhydride gave a neutral crystalline product of the expected composition. Because of its bright yellow color, however, it was presumed to be the indenone derivative VI produced by cyclization accompanied by ester exchange as observed in other studies.[7] That the ring had indeed closed into the aromatic nucleus was proved by oxidative degradation to benzenepentacarboxylic acid evidently arising from ring B (formula VI).

(6) The formulation of the ethylenic bond in the endocyclic position is tentative. *Cf.* the structure of the lower homolog, ref. 3.

(7) Johnson and Goldman, THIS JOURNAL, **67**, 430 (1945).