[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Preparation of a Pregnane Compound from Dehydroandrosterone

BY H. E. STAVELY

The preparation of Δ^5-17-ethynylandrostenediol-3,17 (II) from dehydroandrosterone (I) was reported almost simultaneously by Ruzicka and Hofmann,[1] and Kathol, *et al.*[2] The methods employed were identical and involved the condensation of dehydroandrosterone and acetylene in a solution of potassium in liquid ammonia. β-Ionone[3] and cyclohexanone[4] have been condensed with acetylene to form hydroxyethynyl derivatives without the use of liquid ammonia. By a similar method dehydroandrosterone has been condensed with acetylene at room temperature.

Some time ago it was decided to attempt to hydrate this acetylene compound, and in this manner to obtain a compound of the C_{20} ketopregnane series. Nieuwland and co-workers[5] were successful in adding acetic acid or methanol to the acetylene bond of alkyl acetylene derivatives in the presence of boron fluoride–ether and mercuric oxide catalysts. Subsequent hydrolysis yielded the ketone.

$$R{-}C{\equiv}CH + CH_3COOH \longrightarrow R{-}C(OOCCH_3){=}CH_2 \xrightarrow{H_2O} R{-}C(=O){-}CH_3$$

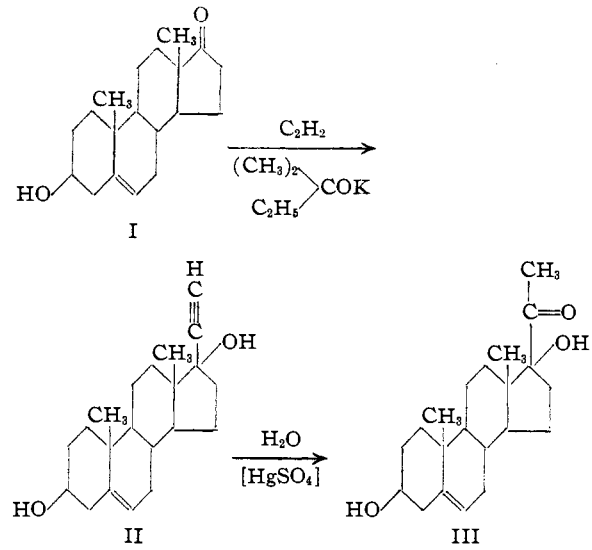
$$R{-}C{\equiv}C{-}H + 2CH_3OH \longrightarrow R{-}C(OCH_3)_2{-}CH_3 \xrightarrow{H_2O} R{-}C(=O){-}CH_3$$

As an alternate and simpler method, the addition of water to the triple bond in the presence of mercuric salts was attempted, analogous to the hydration of acetylene to form acetaldehyde.

$$R{-}C{\equiv}CH + H_2O \longrightarrow R{-}C(=O){-}CH_3$$

While this work was in progress a note by Ruzicka and Meldahl[6] appeared. These workers were able to prepare Δ^5-pregnenediol-3,17-one-20 (III) by the addition of acetic acid to Δ^5-17-ethynylandrostenediol-3,17 (II) and subsequent hydrolysis, using the method of Nieuwland.[5] In attempting to add methanol to Δ^5-17-ethynylandrostenediol-3,17 (II), by the method of Nieuwland and co-workers,[5] non-crystalline, insoluble products were obtained which contained mercury. Experimental conditions were varied in several ways without altering the result. A small amount of mercury free product could sometimes be obtained, which melted over a 30–40° range, and was extremely hard to purify. In view of the work of Ruzicka and Meldahl[6] this phase of the problem was dropped.

It was found, however, that Δ^5-pregnenediol-3,-17-one-20 (III) can be prepared from Δ^5-17-ethynylandrostenediol-3,17 (II) in one step by heating it with water and mercuric sulfate in a sealed tube at 110–120° for twenty-four hours. This method is more successful than one employing acetic acid–water mixtures. The ether extract yielded about 10% of almost pure Δ^5-pregnenediol-3,17-one-20 (III). The aqueous layer contained an insoluble residue suspected of being a complex of mercury salt and organic compound. When this was made alkaline with sodium hydroxide, saturated with hydrogen sulfide and again extracted with ether, a further quantity of Δ^5-pregnenediol-3,17-one-20 (III) was obtained, about 20% of the starting material. After standing several days a little more of the product could be obtained in the same manner.



(1) Ruzicka and Hofmann, *Helv. Chim. Acta*, **30**, 1280 (1937).
(2) Kathol, Logemann and Serini, *Naturwissenschaften*, **25**, 682 (1937).
(3) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935).
(4) Pinkney, Nesty, Wiley and Marvel, *ibid.*, **58**, 974 (1936).
(5) Hennion, Killian, Vaughn and Nieuwland, *ibid.*, **56**, 1130 (1934).
(6) Ruzicka and Meldahl, *Nature*, **142**, 399 (1938).

Experimental

Preparation of Δ^5-17-Ethynylandrostenediol-3,17.—Purified and dried acetylene was bubbled through 50 cc. of dry ether in a flask with a mercury-sealed stirrer for one-half hour. Solutions of 1 g. of potassium in 15 cc. of dry tertiary amyl alcohol, and of 1 g. of dehydroandrosterone in 50 cc. of dry ether and 5 cc. of dry benzene were added dropwise during one-half hour, and stirring continued for five hours longer, acetylene being bubbled through the reaction mixture during the whole period and the reaction flask being maintained at room temperature. The reaction mixture was then acidified with saturated ammonium chloride solution containing a little hydrochloric acid and thoroughly extracted with ether. The ether was washed, dried over sodium sulfate, and evaporated under reduced pressure. The last traces of alcohol were removed in a stream of carbon dioxide. The residue was crystallized twice from methanol or aqueous methanol; yield 80–85%; m. p. 240–242°, $[\alpha]^{25}D$ −119° (chloroform).

Besides avoiding the use of liquid ammonia, this method has several other advantages over the methods of Ruzicka and Hofmann[1] and Kathol, *et al.*[2] The reaction time is less, and the use of Girard's ketone reagent for removing dehydroandrosterone is unnecessary.

Preparation of Δ^5-Pregnenediol-3,17-one-20 (III).—A mixture of 800 mg. of Δ^5-17-ethynyl-3,17-androstenediol (II), 1 g. of mercuric sulfate and 15 cc. of distilled water, previously boiled to remove oxygen, was heated in a sealed tube at 110–120° for twenty-four hours. The tube's contents were thoroughly extracted with ether, the ether washed with dilute sodium carbonate solution and water, dried over sodium sulfate and evaporated to dryness. The residue was crystallized from acetone, yield 10%. After two recrystallizations the melting point was constant at 276–278°; $[\alpha]^{23}D$ −106° (dioxane).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71. Found: C, 76.11; H, 9.90.

The aqueous layer containing a precipitate was made alkaline with sodium hydroxide and thoroughly saturated with hydrogen sulfide. The next morning the mixture was extracted with ether and worked up as before, giving 180 mg. of product. After standing for several days 50 mg. more of the product was obtained in the same way; total yield 35%.

Oxime of Δ^5-Pregnenediol-3,17-one-20.—From 30 mg. of Δ^5-pregnenediol-3,17-one-20 the oxime was prepared in the usual manner; recrystallized from aqueous methanol or chloroform, m. p. 245–246°.

Anal. Calcd. for $C_{21}H_{33}O_3N$: C, 72.56; H, 9.58. Found: C, 72.63; H, 9.37.

Summary

Δ^5-17-Ethynylandrostenediol-3,17 has been prepared, without recourse to liquid ammonia, by condensing acetylene and dehydroandrosterone in the presence of potassium tertiary amylate at room temperature.

Δ^5-Pregnenediol-3,17-one-20 has been prepared from Δ^5-17-ethynylandrostenediol-3,17 in one step by the addition of the elements of water in the presence of mercuric sulfate. This provides a method for changing a member of the androstane series into a pregnane derivative with a ketone group at carbon atom 20.

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A Synthesis of Aryl Sulfonium Salts

BY GREGG DOUGHERTY AND P. D. HAMMOND

Sulfonium compounds in which all three hydrocarbon radicals are aryl in nature have not been prepared by the direct method of adding an aryl halide to an aryl sulfide. The usual methods of obtaining these compounds have involved the condensation of a sulfoxide with a hydrocarbon or derivative in the presence of sulfuric acid or aluminum chloride. In some cases the sulfoxide was not used as starting material but was formed in the course of the reaction.[1]

Leicester and Bergstrom[2] were able to form aryl selenonium compounds by the interaction of diphenyl selenide dichloride with benzene and aluminum chloride

$$(C_6H_5)_2SeCl_2 + C_6H_6 + AlCl_3 \longrightarrow (C_6H_5)_3SeCl + HCl + AlCl_3$$

A search of the literature failed to disclose any attempt to use this method in the preparation of sulfonium compounds. It was thought that the synthesis would have certain advantages in the preparation of halogenated aryl sulfonium salts, and those containing cyclic aryl sulfides. These syntheses may be represented by the equations

$$(C_6H_5)_2S + 2Br_2 \longrightarrow (p\text{-}Br\text{-}C_6H_4)_2S + 2HBr$$

$$(p\text{-}Br\text{-}C_6H_4)_2S + Cl_2 \longrightarrow (p\text{-}Br\text{-}C_6H_4)_2SCl_2$$

$$(p\text{-}Br\text{-}C_6H_4)_2SCl_2 + C_6H_6 + AlCl_3 \longrightarrow (p\text{-}Br\text{-}C_6H_4)_2\text{—}\underset{\displaystyle Cl}{\overset{\displaystyle |}{S}}\text{—}C_6H_5 + HCl + AlCl_3$$

(1) Michaelis and Godchaux, *Ber.*, **24**, 757 (1891); Smiles and Le Rossignol, *J. Chem. Soc.*, **89**, 696 (1906); **93**, 745 (1908); Courtot, *Compt. rend.*, **200**, 1541 (1935).

(2) Leicester and Bergstrom, THIS JOURNAL, **51**, 3587 (1929).