# The Preparation of 2-Methylene-$\Delta^4$-3-keto Steroids

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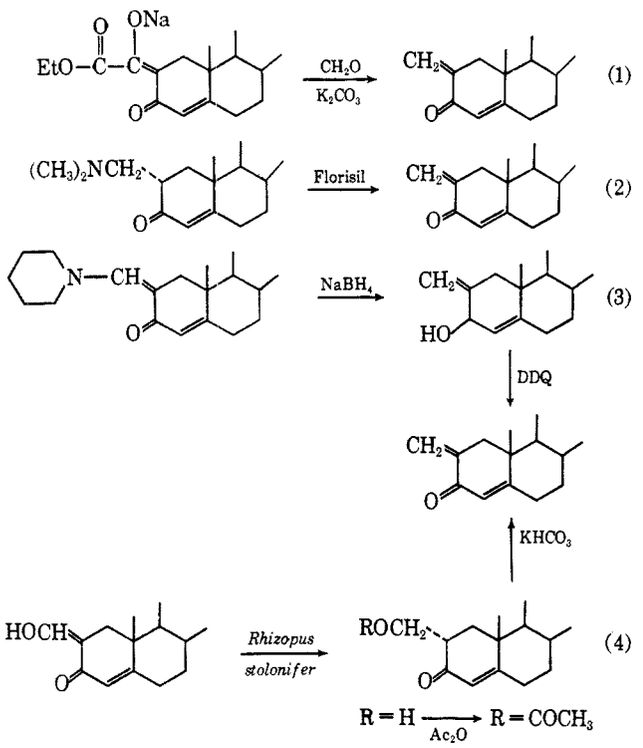
A practical synthesis of 2-methylene-$\Delta^4$-3-keto steroids from 2-hydroxymethylene-$\Delta^4$-3-keto steroids is presented. It is demonstrated that this conversion proceeds through a 2-spirodioxane-$\Delta^4$-3-keto steroid intermediate.

The study of the effect of substituents at position 2 of steroid molecules on their physiological profile has been a subject of intense interest to pharmaceutical chemists. An approach to this study which has received only limited attention involves the synthesis of 2-methylene-$\Delta^4$-3-keto steroids. Four methods have been reported for the preparation of these compounds.




Beal, Lincoln and Hogg[2] synthesized 2-methylenehydrocortisone and its 21-acetate by treatment of their key intermediate, the sodium salt of a 2-ethoxyoxalyl-$\Delta^4$-3-keto steroid, with aqueous formaldehyde in the presence of potassium carbonate (eq 1). This reaction yielded the 2-methylene-$\Delta^4$-3-keto intermediate needed to complete their synthesis. Evans, Evans, Lewis, and Palmer[3] also used this method for the preparation of a variety of 2-methyleneandrostenes.

Carrington, Long, and Turner[4] synthesized 2-methylenecortisone by subjecting cortisone to the Mannich reaction, followed by a $\beta$ elimination of the resulting amino group (eq 2).

Edwards, Calzada, and Bowers[5] prepared the 2-methylene analogs of 17$\alpha$-methyltestosterone and hydrocortisone by sodium borohydride reduction of the appropriate 2-aminomethylene-$\Delta^4$-3-keto steroids, followed by oxidation of the resulting 2-methylene-$\Delta^4$-3-hydroxy steroids (eq 3).

Manson, Sjogren, and Riano[6] reported the microbiological reduction of 2-hydroxymethyleneethisterone [17-hydroxy-2-(hydroxymethylene)-17$\alpha$-pregn-4-en-20-yn-3-one] and conversion of the resulting 2$\alpha$-hydroxymethyl derivative, *via* its acetate, to 2-methyleneethisterone (eq 4). Its structure was confirmed by its synthesis using the method depicted in eq 2.

For any of these methods the average yield of 2-methylene-$\Delta^4$-3-keto steroids is less than 20%; hence, none provides a practical synthesis. This paper reports the development of a practical synthesis of these compounds.

For some time our laboratories have been interested in the variety of reactions that can be accomplished with 2-hydroxymethylene-3-keto steroids.[6,7] This interest led to an investigation of the reaction of formaldehyde with 2-hydroxymethylene-$\Delta^4$-3-keto steroids.

When a 2-hydroxymethylene-$\Delta^4$-3-keto steroid, for example, 17-hydroxy-2-(hydroxymethylene)-17$\alpha$-pregn-4-en-20-yn-3-one (I), was mixed at room temperature with an excess of formaldehyde, either as formalin or paraformaldehyde, in such solvents as ether, tetrahydrofuran, or ethanol, thin layer chromatography (tlc) indicated the formation of a product, but the equilibrium of this reaction lay greatly on the side of the starting material. However, when pyridine was used as the solvent, the equilibrium was shifted so that this product was formed in yields of 70–80%. A reaction time of at least 24 hr was required for optimum yields. The structure of this product was shown to be the spirodioxane II by elemental analyses and spectral data. (See eq 5).

The most convincing data for the spirodioxane structure were provided by the nuclear magnetic resonance spectra of these compounds. In the case of the monoacetate III, for example, the characteristic signals of the dioxane ring are illustrated in Figure 1. The $J$ values for AB patterns, c and d, 6Hz and 12Hz, respectively, are in accord with the expected values.[8]

These spirodioxanes are relatively unstable compounds. Mild acid, *e.g.*, acetic acid or silica gel, readily converts them back to the 2-hydroxymethylene-$\Delta^4$-3-keto steroids. Purification was best accomplished by precipitation of the crude product with water, followed by direct recrystallization. In one run, an attempt was made to purify the spirodioxane II by

(1) Ayerst Laboratories, Montreal, Canada.

(2) P. F. Beal, F. H. Lincoln, and J. A. Hogg, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1957, p 12-O. See also P. F. Beal, U. S. Patent 2,847,430.

(3) D. D. Evans, D. E. Evans, G. S. Lewis, and P. J. Palmer, *J. Chem. Soc.*, 4312 (1963).

(4) T. R. Carrington, A. G. Long, and A. F. Turner, *ibid.*, 4312 (1963).

(5) J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **6**, 178 (1963); J. A. Edwards, M. C. Calzada, and A. Bowers, *ibid.*, **7**, 528 (1964).

(6) A. J. Manson, R. E. Sjogren, and M. Riano, *J. Org. Chem.*, **30**, 307 (1965).

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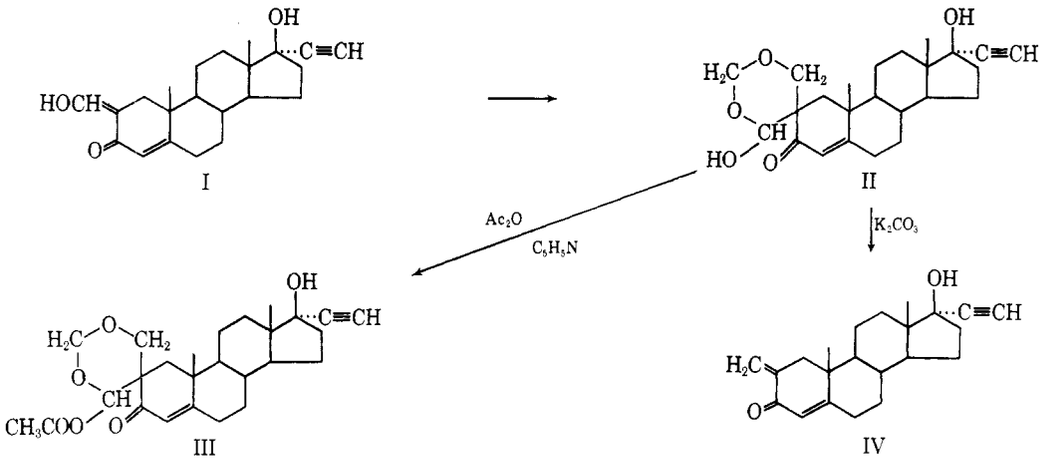
(8) C. Barbier, M. Davidson, and C. Delmau, *Bull. Soc. Chim. France*, 1046 (1946); T. A. Crab and R. C. Cookson, *Tetrahedron Letters*, 679 (1964).




(5)

TABLE I

SPIRODIOXANES AND 2-METHYLENE $\Delta^4$-3-KETONES

| Name | Yield,[a] % | Mp, °C | $[\alpha]_D$ | $\lambda_{max}$ m$\mu$ | $\epsilon$ | Formula | Analyses, % Calcd | Found |
|---|---|---|---|---|---|---|---|---|
| 4′-17$\beta$-Dihydroxy-17-methylspiro[androst-4-ene-2,5′-*n*-dioxan]-3-one | | 142–143 | 12.9 | 247 | 13,400 | $C_{23}H_{34}O_5$ | C 70.74 | 70.66 |
| | | | | | | | H 8.78 | 8.49 |
| 4-Hydroxyspiro-[*m*-dioxane-5,2′-pregn-4′-ene]-3′,20′-dione | | 208–209 | 134.6 | 246 | 13,800 | $C_{24}H_{34}O_5$ | C 71.61 | 71.64 |
| | | | | | | | H 8.51 | 8.26 |
| 17$\beta$-Hydroxy-17-methyl-2-methyleneandrost-4-en-3-one[b,c] | 40 | 179–181 | 143.8 | 260 | 14,600 | $C_{21}H_{30}O_2$ | C 80.21 | 80.28 |
| | | | | | | | H 9.62 | 9.64 |
| 2-Methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal)[d] | 84 | 167–170 | 146.8 | 260 | 14,300 | $C_{24}H_{34}O_3$ | C 77.80 | 77.74 |
| | | | | | | | H 9.25 | 9.28 |
| 17-Hydroxy-2-methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal)[e] | 63 | 213–217 | 99.1 | 259 | 14,100 | $C_{24}H_{34}O_4$ | C 74.57 | 74.47 |
| | | | | | | | H 8.87 | 8.94 |

[a] Based on 2-hydroxymethylene-$\Delta^4$-3-keto steroid. [b] Reported in ref 3. [c] For the preparation of the 2-hydroxymethylene compound, see R. O. Clinton, *et al.*, *J. Am. Chem. Soc.*, **83**, 1478 (1961). [d] For the preparation of the 2-hydroxymethylene compound, see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961). [e] For the preparation of the 2-hydroxymethylene compound, see J. A. Edwards, *et al.*, *ibid.*, **29**, 3481 (1964). These authors reported 17-hydroxy-2-hydroxymethylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal) as a crude product. In our laboratory, recrystallization from methylene dichloride yielded the pure compound as pale orange crystals, mp 219–221°, $[\alpha]_D$ 9.1, $\lambda_{max}$ 252 m$\mu$ ($\epsilon$ 12,500) and 307 (6200). *Anal.* Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.75; H, 8.55.

chromatography using Florisil. 17-Hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one (IV), obtained in a 10% yield, was the only isolable compound. On the basis of this experiment the total crude product from the spirodioxane formation was treated with potassium carbonate in acetone. After 3 hr at room temperature, the 2-methylene derivative IV was isolated in 86% yield.

Application of this two-step reaction to other 2-hydroxymethylene steroids has given yields ranging from 40 to 84% (see Table I).

Since triethylamine, like pyridine, is a basic, aprotic solvent, the condensation of formaldehyde with I was repeated using triethylamine as solvent. (A small portion of tetrahydrofuran was used as co-solvent.) After 2 hr, tlc indicated only traces of starting material. Partial precipitation with water afforded directly a 55% yield of the 2-methylene derivative IV. Tlc indicated that the main constituent in the remaining portion of the reaction mixture was the known 17-hydroxy-2$\alpha$-hydroxymethyl-17$\alpha$-pregn-4-en-20-yn-3-one (VI).[6]

Greater insight into this reaction was gained when I was allowed to react with excess formaldehyde in the presence of only 4 molar equiv of triethylamine with tetrahydrofuran as a diluent. This diminution of the amount of triethylamine present in the reaction slowed the reaction rate. The course of the reaction was followed by tlc (see Table II).

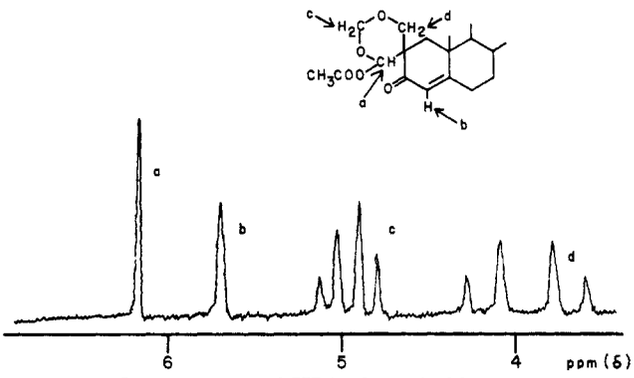



Figure 1.—Nmr spectrum of III in deuteriochloroform (internal standard, TMS) recorded on a Varian A-60 spectrometer.

The most interesting new information provided by this reaction is the increase in concentration of the unknown substance at $R_f$ 0.6 in the first 6 hr of the reaction and its subsequent decrease in concentration relative to the formation of the 2$\alpha$-hydroxymethyl derivative. An attempt to isolate this unknown by a water quench of the reaction mixture resulted instead in an immediate conversion of the unknown to the 2$\alpha$-hydroxymethyl derivative VI, which was characterized *via* its acetate (see Experimental Section). Therefore, the labile unknown is a precursor of the 2$\alpha$-hydroxymethyl derivative.

The unknown was isolated by interrupting the preceding experiment after 6 hr and subjecting the total

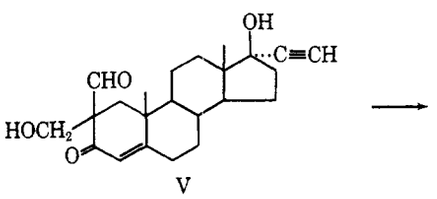
TABLE II

RELATIVE AMOUNTS[a] OF MATERIAL ON TLC PLATES OF ALIQUOTS FROM THE REACTION MIXTURE OF 17-HYDROXY-2-(HYDROXYMETHYLENE)-17α-PREGN-4-EN-20-YN-3-ONE (I) AND FORMALDEHYDE IN PRESENCE OF TRIETHYLAMINE

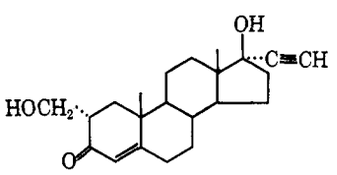
| | $R_f$ | | | |
|---|---|---|---|---|
| Time | 0.0–0.15 | 0.2 | 0.6 | 0.7 |
| 0 | 4 | | | |
| 45 min | 3 | Trace | 1 | 1 |
| 6 hr | 2 | 1 | 4 | 4 |
| 24 hr | 1 | 1 | 2 | 4 |
| 5 days | | 2 | | 4 |

[a] Estimated after the $SiO_2$ plate was developed in ether, sprayed with sulfuric acid–water (1:1), and charred. [b] The $R_f$ values were assigned as follows: $R_f$ 0.0–0.15, either I or II (the hydroxymethylene derivative I and the spirodioxane II are indistinguishable since the II decomposes rapidly to I on silica gel); $R_f$ 0.2, 17-hydroxy-2α-(hydroxymethyl)-17α-pregn-4-en-20-yn-3-one (VI); $R_f$ 0.6, unknown; $R_f$ 0.7, 17-hydroxy-2-methylene-17α-pregn-4-en-20-yn-3-one (IV).

reaction mixture to preparative tlc. The unknown, $R_f$ 0.6, was isolated as an oil (*ca.* 90% pure); the contaminants were VI and IV. This oil exhibited all the behavior expected for an aldehyde (*i.e.*, characteristic signal at 8.08 ppm in the nmr, $\lambda_{max}^{KBr}$ 5.79 μ in the infrared spectrum, and a positive Tollen's test). All the accumulated data can best be explained by assigning structure V to the unknown.




V



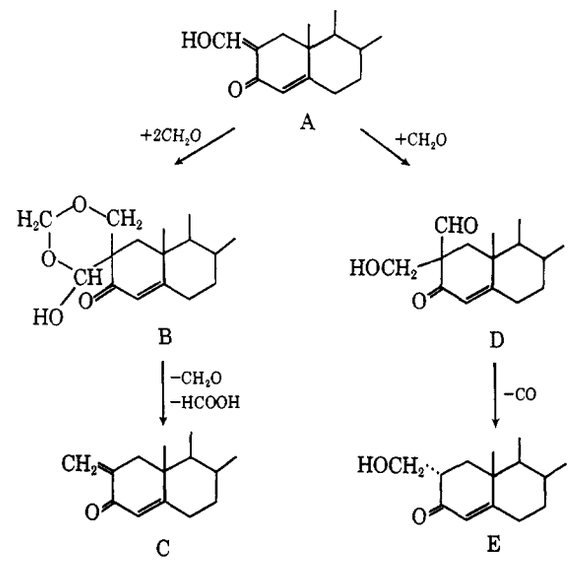

VI

Conclusive proof that the spirodioxane III plays a role in this reaction was demonstrated by tlc using a system of chloroform–methanol–glacial acetic acid (48:1:1). The preceding experiment was repeated. Aliquots from the reaction mixture were neutralized with acetic acid and spotted on a silica gel plate, which was developed *without delay* in order to prevent the conversion of the spirodioxane back to the starting material. Using this technique it could be shown that the concentration of the spirodioxane builds up to and remains constant at about 40% of the steroidal material during most of the reaction, then finally disappears at the same time as the starting material.

A third modification of this reaction was realized when a solution of I in acetone was treated with excess aqueous formaldehyde in the presence of potassium carbonate. Tlc indicated that conversion to the 2-methylene derivative IV was complete after 4 min at room temperature. Subsequent quenching in water afforded pure IV in 80% yield. Again, tlc was used to demonstrate the presence of the spirodioxane in this reaction. (It was observed to be present in a concentration of 30–40% at the end of 1 min.) The more rapid conversion of the spirodioxane II to the 2-methylene-Δ⁴-3-ketone IV in this reaction compared to the previously described conversion of II to IV in the presence of anhydrous potassium carbonate in acetone (*i.e.*, 4 min *vs.* 3 hr) was shown experimentally to be due to water in the aqueous formaldehyde. Similarly, 17-hydroxy-2-methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal) was prepared in 86% yield.

The simplicity and efficiency of this third modification represents a vast improvement over the literature preparations of 2-methylene-Δ⁴-3-keto steroids.

The results of these investigations into the base-promoted reactions of formaldehyde with 2-hydroxymethylene-Δ⁴-3-keto steroids are summarized as shown below.




In separate experiments it has been observed that under the reaction conditions of the last two modifications (*i.e.*, promoting the reaction with triethylamine or with potassium carbonate) *the reactions designated by B → C and D → E occur readily and that compounds C and E are stable to these conditions.* Therefore, A → B → C and A → D → E represent two different pathways for the reaction of formaldehyde with 2-hydroxymethylene-Δ⁴-3-keto steroids.

## Experimental Section[9]

Three methods for the preparation of 17-hydroxy-2-methylene-17α-pregn-4-en-20-yn-3-one (IV) are given to illustrate the three general methods for the conversion of 2-hydroxymethylene-Δ⁴-3-keto steroids to 2-methylene-Δ⁴-3-keto steroids.

**Method A. Two-Step Process Involving the Isolation of the Intermediate 2-Spirodioxane Derivative. Step I.**—A solution of 50.0 g of 17-hydroxy-2-(hydroxymethylene)-17α-pregn-4-en-20-yn-3-one (I) and 50 ml of 35–40% aqueous formaldehyde in 200 ml of pyridine was allowed to stand for 48 hr at room temperature. Dilution of the reaction mixture with 300 ml of water precipitated the crude product as an oil which solidified after standing for an hour. The granular solid was collected, washed well with water, and air dried to constant weight, 53.0 g (90%), mp 100–111°. This material was suitable for conversion into the 2-methylene derivative, see below. A sample of this material was recrystallized twice from acetone to afford 4,17′-

(9) All melting points were taken on a Hershberg-type apparatus and are corrected. Rotations were measured in chloroform solution at 25°, $c \sim 1\%$, ultraviolet spectra in 95% ethanol (Cary) (ε values are given in parentheses following the wavelengths of the maxima), and infrared spectra in a KBr disk (Perkin–Elmer 21). Nuclear magnetic spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard; the signal assignments were consistent with the line shapes.

**dihydroxyspiro[*m*-dioxane-5,2′-17′$\alpha$-pregn-4′-en-20′-yn]-3′-one (II)** as colorless needles: mp 146–150° dec; $[\alpha]_D$ −10.9°; $\lambda_{max}$ 248 m$\mu$ ($\epsilon$ 13,800); $\lambda_{max}$ 2.95 (OH), 3.05 (≡CH), 6.09 and 6.18 $\mu$ ($\Delta^4$-3-ketone).

*Anal.* Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.03; H, 8.07.

The 4-acetate III was prepared by treating II with acetic anhydride and pyridine for 24 hr at room temperature. After a water quench, the isolated crude product was recrystallized from acetone to give a 40% yield of the acetate, colorless crystals: mp 226–229° (change in crystalline form noted at 169–172°); $[\alpha]_D$ 0°; $\lambda_{max}$ 248 m$\mu$ ($\epsilon$ 15,500); $\lambda_{max}$ 2.98 (OH); 3.06 (≡CH); 4.75 (C≡C); 5.68 (C=O of acetate); 6.09 and 6.19 $\mu$ ($\Delta^4$-3-ketone); $\delta_{max}$ (20% $CDCl_3$), 6.27 (singlet, CH—OAc), 5.70 (singlet, =CH), 5.06, 4.85 ($J$ = 6 Hz; AB quartet, —$OCH_2O$—), 4.14, 3.66 ($J$ = 12 Hz; AB quartet, —$OCH_2$—C), 2.57 (singlet, ≡CH), 2.08 (singlet, $CH_3CO$), 1.37 (singlet, $C_{19}$-$CH_3$), 0.92 ppm (singlet, $C_{18}CH_3$).

**Step II.**—The crude precipitated product (21.2 g) from the preparation of the spirodioxane (see above) was dissolved in 1200 ml of acetone and 15.0 g of powdered, anhydrous potassium carbonate was added. The slurry was stirred at room temperature with a Hershberg stirrer for 16 hr and allowed to stand for 32 hr.[10] Careful addition of water first dissolved the solid potassium carbonate, then precipitated the product. The white solid was collected and dried at 60° to give 14.0 g (85%) of product, mp 146–156°, which on tlc ($SiO_2$–ether) showed essentially one spot (>90%) with $R_f$ and color identical with those of authentic 2-methylene derivative IV.[6] A sample of this material was recrystallized from acetone to yield pure 17-hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one, mp 182–184°, as demonstrated by mixture melting point and ultraviolet and infrared spectral comparison with an authentic sample.[6]

Application of this two-step reaction to various 2-hydroxymethylene steroids has given the spirodioxanes and 2-methylen-$\Delta^4$-3-ones shown in Table I. (Note: The 2-spiro derivative of 17-hydroxypregn-4-ene-3,20-dione cyclic 20-(ethylene acetal) was not purified, but total crude product was converted into the 2-methylene derivative using step II.)

**Method B. Utilizing Triethylamine.**—A stirred suspension of 5.00 g of 17-hydroxy-2-(hydroxymethylene)-17$\alpha$-pregn-4-en-20-yn-3-one (I) in 30 ml of triethylamine and 30 ml of tetrahydrofuran was treated dropwise with 10 ml of 35–40% aqueous formaldehyde at such a rate (*ca.* 3 ml/min) that the temperature of the reaction mixture was kept below 35°. The undissolved portion of the steroid quickly went into solution. After 2 hr, the reaction mixture was diluted with 2 l. of water. There resulted a solid precipitate which was collected, washed well with water, and dried at 60°. The crude product (4.37 g) had mp 166–172°. Tlc ($SiO_2$–ether) examination of this crude product indicated that it contained greater than 80% of the expected 2-methylene derivative and that the major contaminant (*ca.* 10%) was 17-hydroxy-2$\alpha$-(hydroxymethyl)-17$\alpha$-pregn-4-en-20-yn-3-one (VI).[6] (For characterization of the latter compound, see below.) The crude product was recrystallized from methanol to afford 2.99 g (63%) of the 2-methylene derivative IV, mp 183–184°. The identity of this product was established by mixture melting point and infrared and ultraviolet spectral comparisons.

**Method C. Utilizing Potassium Carbonate.**—A solution of 0.50 g of 17-hydroxy-2-(hydroxymethylene)-17$\alpha$-pregn-4-en-20-yn-3-one (I) in 40 ml of acetone was vigorously stirred with 1.0 g of powdered potassium carbonate and 1.0 ml of 35–40% aqueous formaldehyde at room temperature for 30 min. The reaction mixture was then gradually diluted with 120 ml of water. The potassium carbonate dissolved, and then a solid white precipitate formed. The solid was collected, washed with water, and dried at 60° to a constant weight of 0.39 g. The solid had mp 180–181°, which was not depressed when mixed with an authentic sample of 17-hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one.[6] Also, the infrared and ultraviolet spectra and tlc behavior of this material were identical with those of the authentic sample. Similarly, 17-hydroxy-2-methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal) was prepared in 86% yield.

**Modification of Method B and Isolation of 17-Hydroxy-2$\alpha$-(hydroxymethyl)-17$\alpha$-pregn-4-en-20-yn-3-one (VI) and 17-Hydroxy-2$\xi$-(hydroxymethyl)-3-oxo-17$\alpha$-pregn-4-en-20-yne-2$\xi$-carboxaldehyde (V).**—A solution of 6.80 g (20 mmoles) of 17-hydroxy-2-(hydroxymethylene)-17$\alpha$-pregn-4-en-20-yn-3-one (I), 8.20 g (80 mmoles) of triethylamine, and 4 ml of 35–40% aqueous formaldehyde in 80 ml of tetrahydrofuran was allowed to stand at room temperature. The progress of the reaction was followed by tlc (see Table II). After standing 12 days the reaction mixture was evaporated to dryness under reduced pressure and the residue was subjected to chromatography on 250 g of silica gel. Elution with 4:1 benzene–ether gave 1.87 g of a solid which was recrystallized from acetone to yield 1.02 g of 17-hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one (IV), mp 180–182°. Further elution with 1:1 benzene–ether afforded 2.98 g of an oil [$\lambda_{max}$ 242 m$\mu$ ($\epsilon$ 12,300)]. Tlc examination of this oil indicated that it was a 19 to 1 mixture of the 2$\alpha$-hydroxymethyl derivative VI and the 2-methylene derivative IV, respectively. The crude oil was treated with acetic anhydride–pyridine for 24 hr. A water quench and extraction with methylene dichloride afforded an oil which was subjected to chromatography on 60 g of silica gel. Elution with 9:1 pentane–ether gave 0.81 g of an oil which was a 19:1 mixture of 17-hydroxy-2$\alpha$-(acetoxymethyl)-17$\alpha$-pregn-4-en-20-yn-3-one and 17-hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one (IV) as indicated by tlc ($SiO_2$–ether). Further purification by preparative tlc ($SiO_2$–50% ether in benzene) gave the acetate (99% pure, by tlc) as an oil: $\lambda_{max}$ 242 m$\mu$ ($\epsilon$ 15,000); $\delta_{max}$ (16% $CDCl_3$), 5.77 (singlet, =CH), 4.37 (complex signal, $CH_2O$), 2.64 (singlet, ≡CH), 2.05 (singlet, $CH_3CO$), 1.15 (singlet, $C_{19}CH_3$), 0.90 ppm (singlet, $C_{18}CH_3$). The infrared spectrum and behavior on tlc ($SiO_2$–ether or ethyl acetate) of this oil were identical with those of the authentic 2$\alpha$-acetoxy derivative.[6] (Note: Reexamination of the authentic 2$\alpha$-acetoxy derivative, mp 86–89°, reported in ref 6, indicated that this material was amorphous; consequently the oil obtained here could not be induced to crystallize even when seeded.)

**17-Hydroxy-2$\xi$-(hydroxymethyl)-3-oxo-17$\alpha$-pregn-4-en-20-yne-2$\xi$-carboxaldehyde (V)** was obtained by interrupting the preceding experiment after 6 hr and subjecting an aliquot of the total reaction mixture to preparative tlc ($SiO_2$–30% ether in pentane). Elution of a second less polar spot with ethyl acetate afforded V as a glass (positive Tollen's test): $\lambda_{max}$ 2.78 and 2.92 (OH), 3.04 (≡CH), 5.79 (CHO), 6.02 and 6.18 $\mu$ ($\Delta^4$-3-one); $\delta_{max}$ (10% $CDCl_3$), 8.08 (singlet, CHO), 5.67 (singlet, =CH), 3.92 (broad, $CH_2O$), 2.60 (singlet, ≡CH), 1.23 (singlet, $C_{19}CH_3$), 0.90 ppm (singlet, $C_{18}CH_3$). Tlc ($SiO_2$–ether) inspection of this oil indicated it to be *ca.* 85% pure; the contaminants were 17-hydroxy-2$\alpha$-(hydroxymethyl)-17$\alpha$-pregn-4-en-20-yn-3-one (VI) and 17-hydroxy-2-methylene-17$\alpha$-pregn-4-en-20-yn-3-one (IV).

**Registry No.**—II, 13758-83-3; III, 13758-84-4; IV, 2137-41-9; V, 13942-84-2; VI, 2787-03-3; 4,17$\beta$-dihydroxy-17-methylspiro[androst-4-ene-2,5′-*m*-dioxan]-3-one, 13758-87-7; 4-hydroxyspiro-[*m*-dioxane-5,2′-pregn-4′-ene]-3,20′-dione, 13942-85-3; 17$\beta$-hydroxy-17-methyl-2-methyleneandrost-4-en-3-one, 2137-39-5; 2-methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal), 13758-89-9; 17-hydroxy-2-methylenepregn-4-ene-3,20-dione cyclic 20-(ethylene acetal), 13758-90-2.

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(10) When this reaction was repeated on 1.0 g of steroid, a reaction time of only 3 hr was required.