2α,2′α-Methylenebis(17β-hydroxy-5α-androstan-3-one) and 17β-Hydroxy-2-methylene-5α-androstan-3-one Dimer

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2α,2′α-Methylenebis(17β-hydroxy-5α-androstan-3-one) (**1a**) was unexpectedly obtained when a solution of 17β-hydroxy-2-(hydroxymethylene)-5α-androstan-3-one (**3a**) and a catalytic amount of *p*-toluenesulfonic acid in 2-(dimethylamino)ethanol was heated at steam-bath temperature. Compound **1a** was characterized by conversion into its diacetate ester **1b** and into bis(5α-androstano[3,2-*b*:2′,3′-*e*])pyridine-17β,17′β-diol diacetate (**5b**). The compound earlier reported as **1a** by deStevens and Halamandaris was shown to be 17β-hydroxy-2-methylene-5α-androstan-3-one dimer (**2a**). Investigation of the reaction which afforded **1a** with the aid of thin layer chromatography revealed that **1a** was produced by the reaction of **3a** with formaldehyde formed from an impurity in the particular 2-(dimethylamino)ethanol used. The finding that both **1a** and **2a** were formed by the reaction of **3a** with added formaldehyde in 2-(dimethylamino)ethanol was interpreted in terms of the partitioning of the intermediate, 17β-hydroxy-2-methylene-5α-androstan-3-one (**6**), between condensation with **3a** to form **1a** and Diels–Alder dimerization to form **2a**.

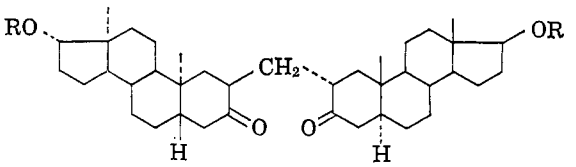
The purpose of this paper is to report an unexpected synthesis of 2α,2′α-methylenebis(17β-hydroxy-5α-androstan-3-one) (**1a**), to demonstrate that the compound earlier reported as **1a** by deStevens and Halamandaris[1] was in fact 17β-hydroxy-2-methylene-5α-androstan-3-one dimer (**2a**),[2] and to show that the formation of both **1a** and **2a** from the reaction of 17β-hydroxy-2-(hydroxymethylene)-5α-androstan-3-one (**3a**)[3] and formaldehyde in 2-(dimethylamino)ethanol may be interpreted in terms of the partitioning of the intermediate, 17β-hydroxy-2-methylene-5α-androstan-3-one (**6**), between condensation with **3a** to form **1a** and Diels–Alder dimerization to form **2a**.

When a solution of 17β-hydroxy-2-(hydroxymethylene)-5α-androstan-3-one (**3a**) and a catalytic amount of *p*-toluenesulfonic acid in an old batch of commercial grade 2-(dimethylamino)ethanol was heated overnight at steam-bath temperature, the product isolated was not the expected enol ether (**3b**) but was **1a**. It will be shown later in the discussion that the **1a** thus formed resulted from the reaction of **3a** and formaldehyde, the latter formed from an impurity in the particular 2-(dimethylamino)ethanol used.

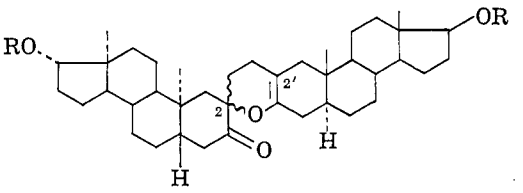
Compound **1a** was characterized as a diol by pyridine–acetic anhydride acetylation, which afforded 2α,2′α-methylenebis(17β-hydroxy-5α-androstan-3-one) diacetate (**1b**), and as a 1,5-dione by cyclization with hydroxylamine hydrochloride in refluxing pyridine–ethanol, which gave bis(5α-androstano[3,2-*b*:2′,3′-*e*])pyridine-17β,17′β-diol (**5a**). While **5a** was amorphous, its diacetate ester (**5b**) was crystalline.

The dimeric nature of **1a** was established by a molecular weight determination. Infrared absorption, ultraviolet absorption, and proton magnetic resonance spectral data on **1a**, **1b**, and **5b** corroborated their structures.

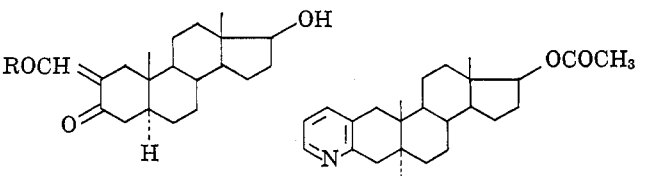
In the infrared spectrum of **1a**, absorption bands attributed to the 17β-ol and the 3-one functions were observed. The integrated intensity of the 3-one absorption band at 5.86 μ was 5.12 intensity units, about the value observed for a 5α steroid 3-one,[4] thus confirming the presence of *two* 3-one groups in the molecule. No hydroxyl group absorption was evident in the spectrum of the diacetate **1b**; however, the 3-one absorption band at 5.86 μ and acetate group absorption bands at 5.78 and 8.07 μ were present. The 5.86-μ band was absent in the spectrum of the pyridine **5a**. Both the pyridine **5a** and its diacetate **5b** exhibited aromatic ring absorption bands in the 6.0–6.5-μ region of their spectra.



1a, R = H
b, R = $COCH_3$
c, R = $COCH_2CH_3$

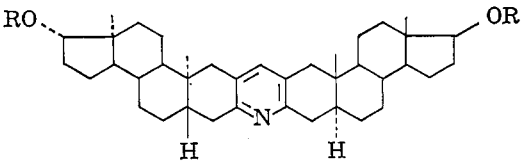


2a, R = H
b, R = $COCH_3$
c, R = $COCH_2CH_3$



3a, R = H
b, R = $(CH_3)_2NCH_2CH_2$

4



5a, R = H
b, R = $COCH_3$

(1) G. deStevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1614 (1961).

(2) R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5494 (1960).

(3) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *ibid.*, **83**, 1478 (1961).

(4) R. N. Jones and C. Sandorfy in "Technique of Organic Chemistry," Vol. IX, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 465.

Ultraviolet absorption at λ_{max} 284 mμ (ε 64.2) in the spectrum of **1a** was also consistent with the presence of two unconjugated 3-one groups in the molecules.[5] A comparison of ultraviolet absorption spectra of pyridine, 5α-androstano[3,2-*b*]pyridin-17β-ol acetate (**4**),[6,7] and **5b** is shown in Table I. Interestingly, there was an additive effect of 12 mμ/ring in the absorption maxima of **4** and **5b** resulting from the fusion, respectively, of one and two steroid A-rings to the pyridine nucleus. While both fusions also resulted in increased absorption intensities, the increments were not additive in this parameter. These changes evidently reflect the out-of-plane distortions of the α- and β-substituent bonds of the singly and doubly fused pyridine rings.[8]

TABLE I

ULTRAVIOLET SPECTRA OF PYRIDINES

Compd.	λ_{max}, mμ	$\Delta\lambda_{max}$, mμ	ε	Δε
Pyridine[a]	257		2600	
4[b]	269	12	5630	3030
5b	281	12	9700	4070

[a] M. J. Kamlet, Ed., "Organic Electronic Spectral Data," Interscience Publishers, Inc., New York, N. Y., 1960, p. 43. [b] See ref. 6 and 7.

Table II represents an interpretation of the proton magnetic resonance spectra of **1a**, **1b**, and **5b**. The most significant feature of these spectra was the singlet aromatic proton signal at 7.02 p.p.m. in the spectrum of **5b**. The areas of this signal and of that at 4.66 p.p.m. attributed to the protons at the 17 and 17′ positions were in the ratio of 1:2. Thus, the bridge between the 5α-androstane moieties in **1a** and **1b** was definitely established as being a methylene group and not an ethylidene group, which could not be distinguished from the methylene group by other means. Another interesting feature of the spectrum of **5b** was the shielding effect of the pyridine ring on the C-19 protons.[9]

TABLE II

INTERPRETATION OF PROTON MAGNETIC RESONANCE SPECTRA

Compd.	δ, p.p.m.	Splitting	Assignment
1a	3.64	Multiplet	C-17 H
	2.52	Singlet	OH
	1.08	Singlet	C-19 H_3
	0.77	Singlet	C-18 H_3
1b	4.59	Multiplet	C-17 H
	2.03	Singlet	$OCOCH_3$
	1.07	Singlet	C-19 H_3
	0.81	Singlet	C-18 H_3
5b	7.02	Singlet	Aromatic H
	4.66	Multiplet	C-17 H
	2.04	Singlet	$OCOCH_3$
	0.82	Singlet	C-18 H_3
	0.76	Singlet	C-19 H_3

The assignment of configuration at C-2 in the 5α-androstane moieties of **1a** and **1b** was that of the more thermodynamically stable 2α configuration[10] and was based on the assumption that **1a** was formed under equilibrating conditions.

The synthesis and proof of structure of **1a** described herein require a reinterpretation of the findings of deStevens and Halamandaris,[1] who claimed to have obtained **1a** and its dipropionate ester **1c** from the reaction of 17β-hydroxy-5α-androstan-3-one (or its propionate ester), dimethylamine hydrochloride, and 37% formaldehyde in refluxing ethanol. While the physical and spectral properties of the "**1a**" of deStevens and Halamandaris disagree with those of the **1a** described herein, they may be logically accommodated by **2a**. The dipropionate ester "**1c**" of deStevens and Halamandaris, then, would be **2c**. Compound **2a** has been reported by Mauli, Ringold, and Djerassi[2] and by Knox and Velarde,[11] who characterized it as its diacetate ester **2b**. Compound **2a** was prepared according to the method of deStevens and Halamandaris[1] and its diacetate ester **2b** was prepared by acetylation of **2a**. Both had physical properties corresponding to those reported for **2a** and **2b** and differing decidedly from those of **1a** and **1b**.[12]

An investigation was undertaken to determine the nature of the reaction which produced **1a** from **3a**, 2-(dimethylamino)ethanol, and *p*-toluenesulfonic acid catalyst.

The original experiment involved heating a solution of **3a** and a catalytic amount of *p*-toluenesulfonic acid in an old batch of 2-(dimethylamino)ethanol for 16 hr. on the steam bath. Compound **1a** was obtained in 28% yield by direct crystallization of the crude neutral product. Only additional **1a** and 17β-hydroxy-5α-androstan-3-one, formed by hydrolytic or alcoholytic deformylation of **3a**, could be isolated by elution chromatography of the residue from the mother liquors. Subsequent experiments were aided by the advent of thin layer chromatography (t.l.c.). It was found convenient to run the reactions for 2 hr. in refluxing 2-(dimethylamino)ethanol (b.p. 135°) rather than for 16 hr. at steam-bath temperature. Thus, using the old batch of 2-(dimethylamino)ethanol, **1a** was obtained in 27% yield and a trace of **2a** was indicated by t.l.c. When a new batch of 2-(dimethylamino)ethanol was used, only trace amounts of **1a** and **2a** were indicated by t.l.c. and 17β-hydroxy-5α-androstan-3-one was isolated in 27% yield. Repetition of the last experiment using the new batch of 2-(dimethylamino)ethanol and adding the theoretical quantity of paraformaldehyde required to produce **1a** resulted in a mixture of **1a** and **2a**. Yields of about 50% of **1a**, 20% of **2a**, and 10% of 17β-hydroxy-5α-androstan-3-one were estimated by t.l.c. Fractional crystallization permitted a partial separation of **1a** and **2a**, affording **1a** in 30% yield. The **2a** thus obtained was identical with that prepared according to the method of deStevens and Halamandaris.[1] When the reaction was repeated with the new

(5) L. Dorfman, *Chem. Rev.*, **53**, 50 (1953).
(6) T. C. Miller, unpublished work.
(7) G. Ohta, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), [1] **12**, 77 (1964).
(8) G. Uhta, K. Ueno, and M. Shimizu, *ibid.*, [1] **12**, 87 (1964).
(9) N. A. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, pp. 13–40.
(10) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).
(11) L. H. Knox and E. Velarde, *J. Org. Chem.*, **27**, 3925 (1962).
(12) A discrepancy involving the analogs of **1** and **2** in the 5α-cholestane series also exists in the literature. The physical properties of the compound reported independently by deStevens and Halamandaris[1] and by T. H. Waid and A. Taurins [*Can. J. Chem.*, **38**, 1983 (1960)] as 2ξ,2′ξ-methylenebis-(5α-cholestan-3-one) disagree with those reported by C. S. Barnes and A. Palmer [*Australian J. Chem.*, **12**, 751 (1959)] for the same compound. It would appear from the deStevens–Halamandaris and the Waid–Taurins data and from the analogs of the 5α-androstane series that their compound was, in fact, 2-methylene-5α-cholestan-3-one dimer. Barnes and Palmer offered no proof for the structure of their compound.

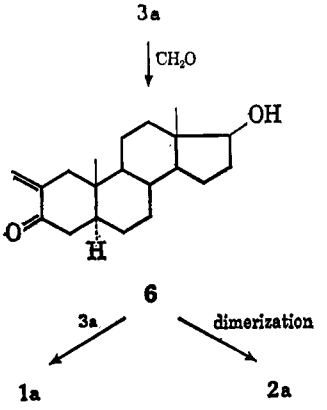
batch of 2-(dimethylamino)ethanol and without the *p*-toluenesulfonic acid, the yields estimated by t.l.c. were 40% of **1a** and 30% of **2a**.

These results provide presumptive evidence that formaldehyde or a compound which could react to form formaldehyde was present as an impurity in the old batch of 2-(dimethylamino)ethanol. However, the formaldehyde was not formed by a reaction of 2-(dimethylamino)ethanol itself. Although the accidental conditions for the preparation of **1a** were approximated by adding paraformaldehyde to uncontaminated 2-(dimethylamino)ethanol, the accidental conditions were superior in that they provided **1a** essentially free of **2a**. While *p*-toluenesulfonic acid was not essential to the formation of **1a**, use of it gave relatively more **1a** than **2a**.

The old batch of 2-(dimethylamino)ethanol was examined for the presence of formaldehyde by the chromotropic acid test.[13] While prior to heating a negative test was observed, a strong positive test was seen after heating the sample on the steam bath for 5 min. Thus, a compound which could react to produce formaldehyde, perhaps paraformaldehyde, which also gave a positive test only after heating, was present as an impurity. Further confirmation of a formaldehyde-forming impurity in the old batch of 2-(dimethylamino)ethanol was obtained by heating it with 5,5-dimethylcyclohexane-1,3-dione (dimedone) and isolating 2,2′-methylenebis-(5,5-dimethylcyclohexane-1,3-dione).

Formation of both **1a** and **2a** by the reaction of **3a** with formaldehyde may be interpreted in terms of the scheme shown in Chart I, in which the intermediate, 17β-hydroxy-2-methylene-5α-androstan-3-one (**6**), is partitioned between condensation with **3a** to form **1a** and Diels–Alder dimerization to form **2a**.

CHART I



It should be mentioned here that the interesting question of the configuration of the dimer **2** at C-2 remains to be settled. The configuration is determined by the stereochemistry of the dimerization of **6**.

Experimental

General.—Melting points were taken in evacuated capillaries and are uncorrected. Thin layer chromatograhic (t.l.c.) plates were coated with silica gel supplied by Merck A. G. (GF_{254}). The spots were brought out on the plates by spraying with 20% sulfuric acid, then heating on a hot plate. Infrared spectra were determined on 1% potassium bromide pellets on a Perkin-Elmer Model 21 spectrophotometer, unless otherwise noted. Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer on 95% ethanol solutions. Proton magnetic resonance spectra were determined on deuteriochloroform solutions on a Varian Model A-60 spectrometer using tetramethylsilane as an internal reference.[14] Rotations were determined on 1% chloroform solutions.

2α,2′α-Methylenebis(17β-hydroxy-5α-androstan-3-one) (1a). A.—A solution of 17β-hydroxy-2-(hydroxymethylene)-5α-androstan-3-one (**3a**)[3] (3.00 g., 0.00942 mole) and *p*-toluenesulfonic acid monohydrate (0.30 g.) in an old batch of commercial grade 2-(dimethylamino)ethanol (30 ml., about 0.3 mole), later shown to be contaminated by a formaldehyde-forming impurity, was heated for 16 hr. on the steam bath, then quenched in water (about 1 l.) containing potassium carbonate (10 g.). The resulting solid was collected, washed with water, dried (2.69 g.), and recrystallized twice from methanol, affording colorless needles, 0.77 g., 28% yield, m.p. 313–315°, $[\alpha]^{25}D$ −0.4°. The infrared integrated intensity determination was done on a chloroform solution.

Anal. Calcd. for $C_{39}H_{60}O_4$: C, 79.01; H, 10.20; mol. wt., 593. Found: C, 78.90; H, 10.10; mol. wt. (cryoscopic determination in dioxane), 575.

Elution chromatography of the residues from the mother liquors of several such runs on silica gel (Davison Chemical Co., 100–200 mesh) afforded only 17β-hydroxy-5α-androstan-3-one and additional **1a** and no **2a**.

B.—A solution of **3a** (3.18 g., 0.0100 mole) and *p*-toluenesulfonic acid monohydrate (0.38 g.) in the old batch of 2-(dimethylamino)ethanol (20 ml., about 0.2 mole) was refluxed for 2 hr. and quenched in dilute sodium hydroxide (0.1 *N*, about 200 ml.). One recrystallization of the resulting solid (2.86 g.) from methanol gave 0.81 g. (27% yield) of **1a** having m.p. 309–311°. Examination of the mother liquors by t.l.c. revealed the presence of additional **1a**, 17β-hydroxy-5α-androstan-3-one, and a trace of **2a**.

C.—Repetition of experiment B using identical quantities of materials and a new batch of commercial grade 2-(dimethylamino)ethanol afforded 17β-hydroxy-5α-androstan-3-one (identified by mixture melting point and t.l.c.) in 27% yield by recrystallization of the crude product (2.40 g.) from methanol. Additional 17β-hydroxy-5α-androstan-3-one and trace amounts of **1a** and **2a** in the mother liquors were indicated by t.l.c. examination.

D.—Experiment B was repeated using identical quantities of materials and the new batch of 2-(dimethylamino)ethanol and adding paraformaldehyde (95%, 0.158 g., 0.00500 mole) to the reaction. Recrystallization of the crude product (2.77 g.) from methanol (about 50 ml.) with seeding by **1a** and decantation of the mother liquor when the first granules of **2a** appeared afforded **1a**, 0.89 g., 30%, m.p. 309–311°, undepressed on admixture with **1a** from experiment A. A second crop (0.31 g.) contained about 10% of **1a** and 90% of **2a** as estimated by t.l.c. A third crop of dense granules was nearly pure **2a**, 0.11 g., m.p. 263–265°, undepressed by **2a** prepared by the method of deStevens and Halamandaris,[1] and identical with that **2a** by t.l.c. and infrared spectral comparison. The mother liquor was estimated to contain 40% of **1a**, 20% of **2a**, and 20% of 17β-hydroxy-5α-androstan-3-one. Thus, the total estimated yields were about 50% of **1a**, 20% of **2a**, and 10% of 17β-hydroxy-5α-androstan-3-one.

E.—Experiment D was repeated leaving out the *p*-toluenesulfonic acid monohydrate. The crude product (2.76 g.) was estimated by t.l.c. to contain 45% of **1a**, 35% of **2a**, and 10% of 17β-hydroxy-5α-androstan-3-one, indicating yields of 40, 30, and 10%, respectively.

2α,2′α-Methylenebis(17β-hydroxy-5α-androstan-3-one) diacetate (1b) was prepared in 90% yield by acetic anhydride–pyridine acetylation of **1a** followed by recrystallization from methanol and had m.p. 303–305°.

Anal. Calcd. for $C_{43}H_{64}O_6$: C, 76.29; H, 9.53. Found: C, 76.01; H, 9.33.

Bis(5α-androstano[3,2-*b*:2′,3′-*e*])pyridine-17β,17′β-diol Diacetate (5b).—A solution of **1a** (1.31 g., 0.00221 mole), hydroxyl-

(13) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., Amsterdam, 1960, p. 349. The author thanks Mr. W. R. Wiehler for performing this test.

(14) The author wishes to thank Professor W. S. Johnson and Dr. K. L. Williamson of Stanford University for recording the proton magnetic resonance spectra of compounds **1a**, **1b**, and **5b**.

amine hydrochloride (0.61 g., 0.0088 mole), pyridine (20 ml.), and absolute ethanol (20 ml.) was heated for 4 hr. at reflux and quenched in water (300 ml.). The resulting solid could not be induced to crystallize. Therefore, a solution of it in pyridine (16 ml.) and acetic anhydride (8 ml.) was warmed for 2 hr. on the steam bath and quenched in water (200 ml.). Two recrystallizations of the resulting solid from methylene dichloride–methanol gave the product as colorless plates, 0.95 g., 65% yield, m.p. >330°, $[\alpha]^{25}D$ +53.9°.

Anal. Calcd. for $C_{43}H_{61}NO_4$: C, 78.73; H, 9.37; N, 2.14. Found: C, 78.86; H, 9.24; N, 2.26.

17β-Hydroxy-2-methylene-5α-androstan-3-one dimer (2a) was prepared in 22% yield exactly according to the procedure of de-Stevens and Halamandaris[1] and had m.p. 264–265.5° and infrared and ultraviolet spectral characteristics which were also in agreement with those reported by those authors for it.

17β-Hydroxy-2-methylene-5α-androstan-3-one dimer diacetate (2b), obtained by acetic anhydride–pyridine acetylation of **2a** in 89% yield, had m.p. 268–272° with an allotropic transformation at 250–255°, λ_{max} 249 mμ (ε 1230) in the ultraviolet spectrum, and λ_{max} 5.78 μ in the infrared spectrum. The ultraviolet maximum at 249 mμ was a resolved shoulder on an intense end absorption. Mauli, Ringold, and Djerassi[2] reported m.p. 249–250°, "no selective absorption in the ultraviolet," and λ_{max} 5.81 μ in the infrared spectrum.

2,2′-Methylenebis(5,5-dimethylcyclohexane-1,3-dione).—A solution of 5,5-dimethylcyclohexane-1,3-dione (2.20 g., 0.0157 mole) and *p*-toluenesulfonic acid monohydrate (0.22 g.) in the old batch of 2-(dimethylamino)ethanol (50 ml.) was heated for 15 min. on the steam bath. Distillation of most of the solvent and treatment of the residue with dilute hydrochloric acid afforded a solid (0.45 g.) which was recrystallized from 95% ethanol to give 2,2-methylenebis(5,5-dimethylcyclohexane-1,3-dione), 0.11 g., 7% yield, m.p. 191–194° (undepressed on admixture with authentic material[15] having m.p. 192–194°).

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(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p. 254.

Steroids. CCLXXVI.[1] The Acid-Catalyzed Reaction between Ketones and Formaldehyde in Dimethyl Sulfoxide

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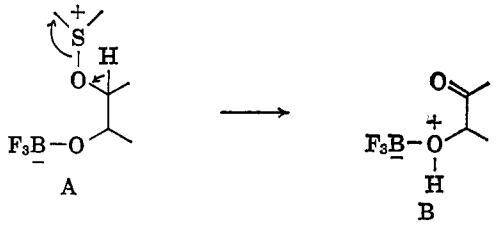
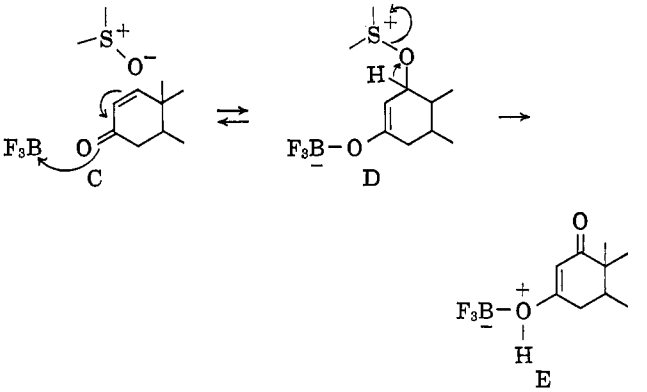
Prolonged refluxing in dimethyl sulfoxide containing boron trifluoride etherate has been found to result in the α- or vinylogously α-methylenation of ketones. The addition of paraformaldehyde to the reaction mixture permits the use of milder conditions and increases the yield. Applications of this novel reaction to saturated and conjugated steroidal ketones are described.

Dimethyl sulfoxide (DMSO) by virtue of its nucleophilic character has been used in several instances to introduce a ketone group.[3] The general course of the reaction is exemplified by the opening of epoxides with DMSO and boron trifluoride[3a] to form the reactive intermediate A, which undergoes loss of a proton from the site of attack to give a ketone B.



In connection with our current interest in the reactions of C-1 oxygenated steroids[4] the possibility of obtaining 1,3-diketones according to the sequence C → E was investigated.

When 5α-androst-1-en-3-one (Ia) or cholest-1-en-3-one (Ib) was dissolved in DMSO containing boron trifluoride etherate and the mixtures were maintained under prolonged reflux there could be isolated, in



both cases, products for which elemental analyses were in accord with a net introduction of one carbon atom. These products are formulated as Ic and Id, respectively, on the basis of the data given below. Strong infrared spectral absorptions were observed at 940, 1630, and 1685 cm.$^{-1}$, with a weak overtone at 1880 cm.$^{-1}$, characteristic[5] of a terminal methylene group conjugated and cisoid to a ketone function. A strong absorption at 767 cm.$^{-1}$ indicated the retention of the Δ^1 double bond. Furthermore, both compounds absorbed strongly in the ultraviolet at 245 mμ (log ε 4.0), close to the value of 244 mμ (log ε *ca.* 4.2) characteristic of steroid 1,4-dien-3-ones,[6] the lower

(1) Steroids. CCLXXV: F. S. Alvarez and A. B. Ruiz, *J. Org. Chem.*, **30**, 2047 (1965).

(2) Syntex Postdoctoral Fellow, 1963–1964; Lilly Research Laboratories Ltd., Bromborough Port, New Ferry, Cheshire, England.

(3) (a) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961); (b) H. R. Nace and J. J. Monagle, *ibid.*, **24**, 1792 (1959).

(4) G. von Mutzenbecher and A. D. Cross, *Steroids*, in press.

(5) J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **6**, 178 (1963), and references cited therein.

(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 20.