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 deStevens 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°, $\lambda_{max}$ 249 mμ (ε 1230) in the ultraviolet spectrum, and $\lambda_{max}$ 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 $\lambda_{max}$ 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°).

**Acknowledgment.**—The author wishes to thank the following members of the staff of the Sterling-Winthrop Research Institute for their contributions to this work: Messrs. K. D. Fleischer, J. D. Grego, and J. M. Lennon for microanalyses; Dr. F. C. Nachod, Dr. R. K. Kullnig, and Miss C. M. Martini and their associates for spectral determinations; and Drs. R. L. Clarke, J. W. Dean, and A. J. Manson for their criticisms of the manuscript.

[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.

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

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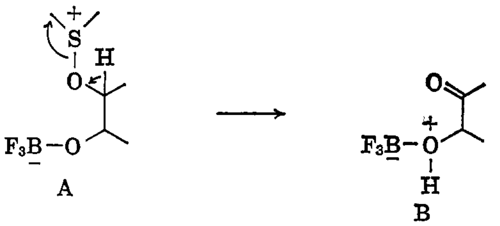
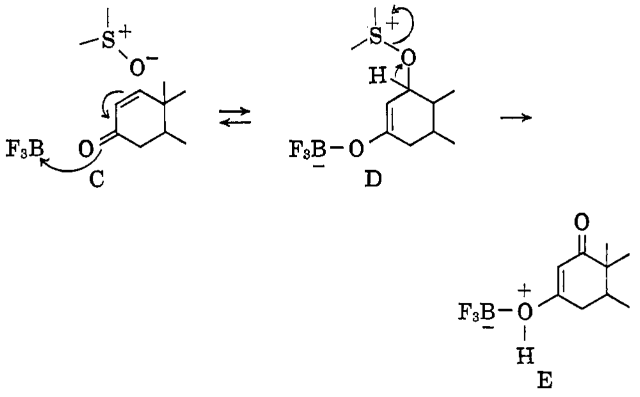
Prolonged refluxing in dimethyl sulfoxide containing boron trifluoride etherate has been found to result in the α- or vinylogously α-methylenation of ketones. The addition of paraformaldehyde to the reaction mixture permits the use of milder conditions and increases the yield. Applications of this novel 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 $\Delta^1$ 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

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

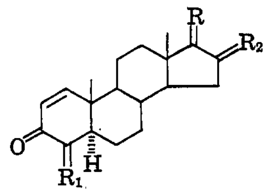
[2] Syntex Postdoctoral Fellow, 1963–1964; Lilly Research Laboratories Ltd., Bromborough Port, New Ferry, Cheshire, England.

[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.



Ia, $R = R_1 = R_2 = H_2$

b, $R = \overset{C_8H_{17}}{\underset{H}{<}}$, $R_1 = R_2 = H_2$

c, $R = R_2 = H_2$, $R_1 = CH_2$

d, $R = \overset{C_8H_{17}}{\underset{H}{<}}$, $R_1 = CH_2$, $R_2 = H_2$

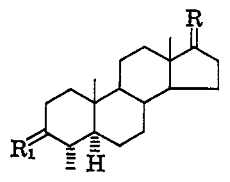
e, $R = O$, $R_1 = R_2 = H_2$

f, $R = \overset{OH}{\underset{H}{<}}$, $R_1 = R_2 = H_2$

g, $R = O$, $R_1 = CH_2$, $R_2 = H_2$

h, $R = O$, $R_1 = R_2 = CH_2$

i, $R = \overset{OH}{\underset{H}{<}}$, $R_1 = CH_2$, $R_2 = H_2$



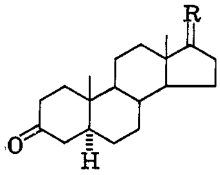
IIa, $R = H_2$, $R_1 = O$

b, $R = \overset{OH}{\underset{H}{<}}$, $R_1 = O$

c, $R = \overset{OH}{\underset{H}{<}}$, $R_1 = \overset{O}{\underset{O}{<}}$

d, $R = O$, $R_1 = \overset{O}{\underset{O}{<}}$

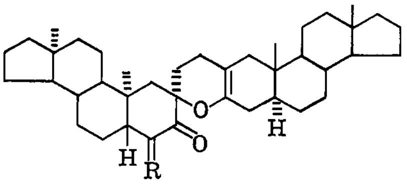
e, $R = H_2$, $R_1 = \overset{O}{\underset{O}{<}}$



IIIa, $R = H_2$

b, $R = O$

c, $R = \overset{OH}{\underset{H}{<}}$



IVa, $R = H_2$

b, $R = CH_2$

extinction coefficient of the former being consistent with the cisoid relationship mentioned above.

Mass spectra of the two products derived from the androstenone and cholestenone precursors are in accord with molecular weights 284 and 397 for Ic and Id, respectively. Confirmatory evidence for the nature of the olefinic protons was provided by n.m.r. spectroscopic studies. An AB pattern, $J = 10$ c.p.s., at 355, 365, 430, and 440 c.p.s., in the spectrum of Ic was assigned to adjacent C-1 and C-2 protons of a $\Delta^1$ 3-ketone system; comparative resonance frequencies were recorded at 346, 356, 425, and 435 c.p.s. for 5$\alpha$-androst-1-en-3-one. One of the *exo*-methylenic protons appeared to be heavily deshielded by the proximate carbonyl group resonating at a frequency (365 c.p.s.) some 50 c.p.s. downfield from the second sterically less proximate methylene proton (312 c.p.s.). Corresponding resonances for 2-methylene-17$\alpha$-methyltestosterone were observed at 356 and 313 c.p.s.[7] The methylene proton resonances displayed a triplet character compatible with a small mutual coupling, $J = ca.$ 1.5 c.p.s., as well as long-range coupling of similar magnitude with an allylic proton.

Hydrogenation of Ic in the presence of palladium on charcoal led to the uptake of 2 moles of hydrogen, thin layer chromatography (t.l.c.) demonstrating the production of an approximately 1:1 two-component mixture. However, chromatography over silicic acid afforded an almost quantitative yield of only one of these components, IIa, isomerization of the 4$\beta$-methyl group to the 4$\alpha$ configuration having presumably occurred on the column. The n.m.r. spectrum of this hydrogenation product exhibited a doublet for the secondary 4$\alpha$-methyl protons signal centered at 59 c.p.s. ($J = ca.$ 6 c.p.s.).

Unequivocal proof for the structure IIa was obtained by its synthesis from the known 17$\beta$-hydroxy analog, IIb.[8] The latter was converted to the cyclic ethylene ketal IIc and then oxidized with chromic oxide in acetone–sulfuric acid reagent[9] to the 17-ketone IId. Wolff–Kishner reduction then led to the 17-desoxy-3-ketal IIe, acid hydrolysis of which furnished 4$\alpha$-methyl-5$\alpha$-androstan-3-one (IIa), identical by melting point, mixture melting point, and infrared spectrum with the product, IIa, derived by hydrogenation of Ia.

Concerning the mode of formation of the 4-methylene ketones, the acid-catalyzed decomposition of DMSO is known[10] to give rise to formaldehyde, among other products. Traynelis and Hergenrother[11] prepared several cyclic ethers of the 1,3-dioxacycloalkane type by heating terminal diols in DMSO, both in the absence and presence of formaldehyde. They suggested that DMSO may serve to facilitate such condensations. Hence, the 4-methylene ketones may be understood to arise *via* dehydration of the 4-hydroxymethyl compounds formed by formaldehyde addition to the 3-ketones.

Indeed, in cogent support of this supposition, it was found that for 5$\alpha$-androst-1-en-3-one (Ia) the addition of paraformaldehyde to the reaction mixture and heating at 160° for 4.5 hr. afforded a 75% yield of Ic. This yield is distinctly higher than the 30% obtained initially by 30-hr. refluxing without paraformaldehyde.

In an attempt to determine whether the DMSO–boron trifluoride etherate mixture was giving rise to a reactive species (other than formaldehyde) which was responsible for the formation of the methylene ketones, the two reagents were refluxed together for 4 hr. and the resultant mixture was distilled. Apart from DMSO there was obtained only a product distilling at 179–181° (15 mm.) and solidifying to a colorless crystalline material, m.p. 60°. This highly hygroscopic substance is assumed to be the 1:1 DMSO–$BF_3$ complex reported[12] to melt at 53°, there being apparently no previous mention of its stability in the vapor phase.

Efforts were next turned toward an examination of the scope of this procedure for the general preparation of steroidal methylene ketones. The diketone, 5$\alpha$-androst-1-ene-3,17-dione (Ie),[13] was obtained in 24% yield by the dehydrogenation of the saturated analog IIIb with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[14] A similar oxidation of IIIc gave a 14% yield of 17$\beta$-hydroxy-5$\alpha$-androst-1-en-3-one (If)[15] together with a small quantity of Ie.

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[7] For similar examples, see L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 123.

[8] (a) H. J. Ringold and G. Rosenkranz, U. S. Patent 2,844,602 (1958); (b) R. E. Schaub and M. J. Weiss, *Chem. Ind.* (London), 2003 (1961).

[9] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Levin, *ibid.*, 2548 (1953).

[10] W. K. Kerney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961).

[11] V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964).

[12] F. A. Cotton and R. Francis, *J. Am. Chem. Soc.*, **82**, 2986 (1960).

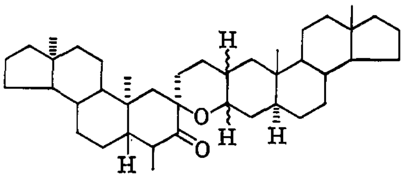
[13] C. Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

[14] H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

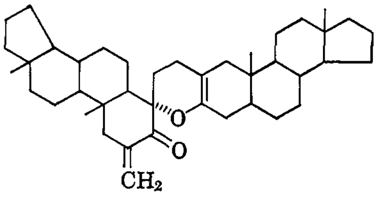
[15] A. Butenandt and H. Dannenberg, *Ber.*, **B73**, 206 (1940).

On being heated at 160° with paraformaldehyde in DMSO containing boron trifluoride (this mixture being henceforth referred to as the reagent), the dione Ie underwent both mono- (C-4) and di- (C-4 and C-16) methylenation. The product of monomethylenation, Ig, absorbed in the ultraviolet at 237 m$\mu$ (log $\epsilon$ 4.03) and in the infrared at 945, 960, 1625, 1675, 3020, and 3090 cm.$^{-1}$ (cisoid conjugated terminal methylenic ketone). Weak overtones at 1900 and 1920 cm.$^{-1}$ were also distinctly visible. The infrared peak at 1745 cm.$^{-1}$ exhibited by both Ie and Ig evidences the absence of methylenation at C-16. In the n.m.r. spectrum of Ig an AB pattern centered at 400 c.p.s., $J$ = 11 c.p.s., for the adjacent C-1 and C-2 protons and terminal methylenic proton signals at 316 and *ca.* 369 c.p.s. (*cf.* Ic, *vide supra*) defined the nature of ring A. The dimorphic dimethylenic product Ih showed an ultraviolet absorption maximum at 233 m$\mu$ (log $\epsilon$ 4.22) and infrared spectral absorption characteristic of the cross-conjugated ring A dienone system, as in Ig. In addition there appeared peaks at 1640 and 1729 cm.$^{-1}$ arising from the ring D enone function. Again, sharp overtones were observed at 1894 and 1920 cm.$^{-1}$, corresponding to the fundamental bands at 947 and 960 cm.$^{-1}$. The two protons of the terminal methylene group at C-16 resonated at 327 and *ca.* 368 c.p.s., the proton resonating at the latter frequency strongly deshielded by the in-plane spatially close carbonyl.[7] Other features of the n.m.r. spectrum were essentially as observed for the product Ig.

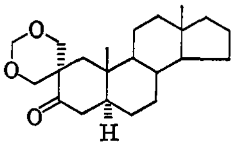
The reaction of 17$\beta$-hydroxy-5$\alpha$-androst-1-en-3-one (If) with the reagent at 160° resulted in methylenation at the 4 position to give Ii, which possesses the expected spectral properties (see Experimental).[16]



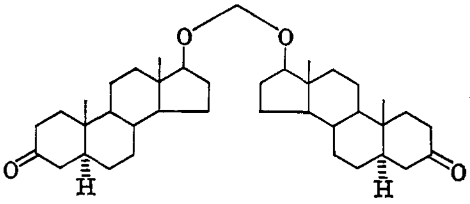
V



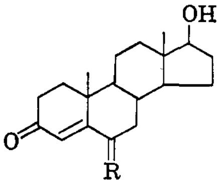
VI



VII



VIIIa
b, 4,5,4′,5′-bisdehydro



IXa, R = H$_2$
b, R = CH$_2$

Attention was focused next on the methylenation of saturated 3-ketones. The reaction of the reagent with 5$\alpha$-androstan-3-one (IIIa) proved to be much more facile than was the case with its $\Delta^1$-unsaturated counterpart: 10 hr. at 60°, or 1.5 hr. at 94°,[17] leading to the disappearance of starting material. Four products were isolated, albeit all in low yields. One of these products was presumed to be dimeric in character by virtue of two 10$\beta$-methyl three-proton resonances at 45 and 55 c.p.s. and a single six-proton 13$\beta$-methyl resonance at 42 c.p.s. in the n.m.r. spectrum which was also devoid of resonance at fields lower than 150 c.p.s. No strong ultraviolet absorption was recorded. The n.m.r. spectrum excludes protons in the environment H–C–O. Structure IVa is tentatively advanced for this product, the absence of a characteristic strong band in the infrared for vinyl ether double-bond stretching constituting an uncertain factor (*vide infra*). An equatorial configuration for the C–O single bond in dimer IVa and related structures (IV–VI) was deduced from the infrared data, $\nu_{C=O}$ 1726 cm.$^{-1}$ being consistent with a six-membered ring ketone bearing an $\alpha$ electronegative substituent.[18] Furthermore, in dimerization, a second molecule of 2-methylene 3-ketone would be expected to approach the 2-methylene group of another molecule from the least hindered $\alpha$ face, leading to IVa. A second methylenation product from the saturated 3-ketone IIIa absorbed in the infrared at 1610 (vinyl ether),[19] 1670 (weak), and 1710 cm.$^{-1}$, and in the ultraviolet at 239 m$\mu$ (lot $\epsilon$ 3.88). In the n.m.r. spectrum there appeared a single methyl resonance peak centered at 42 c.p.s. equivalent to 12 protons which was clearly composed of overlapping signals. The presence of a cisoid terminal methylenic conjugated ketone function was demonstrated by proton resonances at 313 and 361 c.p.s. An area count by integration established the latter signals as equivalent to *one* methylene group in the dimer. Accordingly, this compound is formulated as IVb, the product of methylenation of IVa. Hydrogenation of IVb gave a mixture shown by t.l.c. to contain two components, the less polar predominating. Equilibration with ethanolic potassium hydroxide furnished the more polar component as the stable equatorial 4-methyl epimer, V. The n.m.r. spectrum of this product showed several methyl proton resonances and was in accord with structure V. Structure VI is provisionally assigned to a third product obtained from the reaction with 5$\alpha$-androstan-3-one. The vinylic ether and *cis*-$\alpha$ terminal methylene ketone functions were defined by infrared bands at 1608, 1665, and 1722 cm.$^{-1}$,[18] an ultraviolet maximum at 251 m$\mu$ (log $\epsilon$ 4.02), and n.m.r. signals at 285 and 321 c.p.s. (two protons). The well-defined methyl resonance peaks at 42 and 52 c.p.s. (nine and three

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[16] It is noteworthy that the infrared spectra of all the above methylene ketones exhibit a characteristic intense band, not previously recorded, at 840–860 cm.$^{-1}$. The precise positions of this peak in the various compounds are Ic, 850; Id, 840; Ig, 848; Ih, 847 and 856; and Ii, 842 cm.$^{-1}$.

[17] Steam-bath temperature (Mexico City), 94°.

[18] For collected references on the effect of $\alpha$ electronegative substituents on $\nu_{C=O}$, see D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3906 (1961), footnote 28.

[19] G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

protons, respectively) are in accord with the structure proposed.

The remaining compound derived from this reaction, assigned structure VII, was isolated only for a reaction run at 94°, though t.l.c. indicated its presence at lower reaction temperatures. This fourth product did not absorb strongly in the ultraviolet, but exhibited intense infrared absorption bands at 922, 1020, 1100, 1160, and 1708 cm.$^{-1}$, the first four of these bands being suggestive of the partial structure, $-CH_2-O-CH_2-O-CH_2$.[20] This possibility was supported by an n.m.r. AB pair of doublets at 280, 286, 289, and 295 c.p.s. [*cf.* 289 c.p.s. for $CH_2(OC_2H_5)_2$[21]]. The 1708-cm.$^{-1}$ absorption was indicative of cyclohexanone carbonyl lacking an adjacent equatorial electronegative substituent[18] in contrast to the first three products from this reaction (*vide supra*). Complex n.m.r. resonance in the region 205–253 c.p.s. was analyzed as two overlapping AB patterns corresponding to the $2\alpha$-$CH_2O$ (219, 230, 236, and 247 c.p.s.) and $2\beta$-$CH_2O$ (209, 220, 239, and 250 c.p.s.) methylenes. Molecular models[22] revealed that one of the $2\beta$-$CH_2O$ methylene protons should experience strong long-range shielding by the C-3 carbonyl since it is held over the plane of this double bond.[23]

Treatment of $17\beta$-hydroxy-$5\alpha$-androstan-3-one (IIIc) with the reagent, either at 60° or at room temperature, resulted in condensation of 2 moles of the ketone with 1 mole of formaldehyde to give the methylenedioxy compound VIIIa. The $-O-CH_2-O-$ function was characterized by a two-proton singlet resonance at 278 c.p.s. of *equal* area to the signal for $17\alpha$ protons.

Similarly, at room temperature $17\beta$-hydroxyandrost-4-en-3-one (IXa) afforded the condensate VIIIb, but when the reaction was carried out at 94° there was obtained only the known 6-methylene derivative (IXb).[24] The n.m.r. spectrum of the 6-methylene compound IXb differed significantly from the 2-, 4- and 16-methylene derivatives discussed so far in that the chemical shift between the *exo*-methylene protons was seen to be only 7 c.p.s. This marked reduction from the 40–50-c.p.s. difference observed for the other derivatives reflects the change in net shielding experienced.

One-step $\alpha$-methylenation as described above with dimethyl sulfoxide–boron trifluoride is unique insofar as the solvent is also a vital reagent. The dimeric steroids are considered to be formed by a Diels–Alder addition of an *exo*-methylene group of one steroid molecule to the conjugated *exo*-methylene ketone system of a second molecule. Such dimers have been observed previously as products in amine elimination from 2-dimethylaminomethyl 3-ketones.[25] In this reaction the 2-methylene 3-ketones are the intermediate products which undergo dimerization. $\alpha$-Dialkylaminomethyl ketones are readily available through Mannich condensations. 2-Methylene-$\Delta^4$ 3-ketones have also been synthesized from the $\Delta^4$ 3-ketones *via* the 2-ethoxalyl 3-ketone intermediates.[26]

## Experimental[27]

**Reagent.**—The dimethyl sulfoxide–boron trifluoride mixture (DMSO–$BF_3$ mix) used in all the reactions of ketones with paraformaldehyde was prepared by adding, with caution, boron trifluoride etherate (44 ml.) to dimethyl sulfoxide (660 ml.) and refluxing the mixture under anhydrous conditions with an air condenser until the reflux temperature was in excess of 175° (about 0.5 hr.). In the initial stages of heating, a volatile liquid, presumably ether, was evolved.

**Reaction Conditions.**—Unless otherwise stated, the general procedure used for the reactions of the ketones with paraformaldehyde in the DMSO–$BF_3$ mix was to heat the mixture, using the appropriate temperature and time, cool, dilute with ice–water, water wash the solid thus obtained until acid free, dissolve it in chloroform, dry over sodium sulfate, and evaporate to dryness *in vacuo*.

The mixture of paraformaldehyde, dimethyl sulfoxide, and boron trifluoride is henceforth referred to as the reagent, the volume of DMSO–$BF_3$ mix and mole equivalents of paraformaldehyde being stated in parentheses.

**4-Methylene-5$\alpha$-androst-1-en-3-one (Ic). A. Without Added Paraformaldehyde.**—$5\alpha$-Androst-1-en-3-one (Ia, 3 g.) was refluxed in dimethyl sulfoxide (50 ml.) containing boron trifluoride etherate (2.5 ml.) for 30 hr., whereafter cooling in ice–water and dilution with water deposited a brown oil. The whole was extracted with ether and the etheral solution was washed with 3 vol. of saturated sodium chloride followed by 4 vol. of water, and finally 1 vol. of saturated sodium chloride. After the extract had been dried ($Na_2SO_4$) and the ether had been evaporated, the resultant gum was chromatographed on silicic acid (700 g.) when elution with hexane–benzene (1:1) eluted oily crystals. Recrystallization from cold hexane gave yellow needles which were dissolved in methanol and the solution was filtered to remove a brown sediment, cooling then affording the 4-methylene compound Ic (0.40 g.), m.p. 90–92°. A second crop (0.46 g.), m.p. 89–91°, was obtained on removal of the methanol from the mother liquors and recrystallization from cold hexane. An analytical sample crystallized from methanol exhibited m.p. 92–94°; $[\alpha]_D \pm 0°$; $\lambda_{max}$ 245 m$\mu$ (log $\epsilon$ 3.98) and 345 m$\mu$ (log $\epsilon$ 1.79); $\nu_{max}$ 767, 850, 940, 1630, 1685, and 1880 cm.$^{-1}$; mass spectrum, *m/e* 284 for molecular ion; n.m.r. 45 (18-H), 54 (19-H), 430 and 440, 355 and 365 (1- and 2-protons, AB quartet, $J$ = 10 c.p.s.), 312, and 365 c.p.s. (*exo*-methylene protons).

*Anal.* Calcd. for $C_{20}H_{28}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.45; H, 9.92; O, 5.63.

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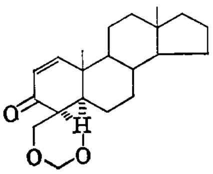
(20) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958, p. 116.

(21) G. V. D. Tiers, "Characteristic Nuclear Magnetic (N.M.R.) Shielding Values, Part I: Table of $\tau$-Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958, p. 9.

(22) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(23) It is pertinent to note that a by-product isolated in small amount from the reaction of the $\Delta^1$ 3-ketone with DMSO–formaldehyde gave an n.m.r. spectrum with the three methylene AB quartet resonances for a fused spiro-1,3-dioxalan ring as in VII. Additionally, the expected olefinic proton resonance AB quartet was present but resonance at *ca.* 130 c.p.s. for the C-4 methylene in VII was absent. These data strongly suggest structure a for this by-product.



**a**

(24) D. Burn, G. Cooley, R. T. Davies, J. W. Ducker, B. Ellis, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, **20**, 597 (1964).

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

(26) *E.g.*, T. R. Carrington, A. G. Long, and A. F. Turner, *J. Chem. Soc.*, 1572 (1962).

(27) Melting points are corrected. Unless stated otherwise, infrared and ultraviolet spectra were determined in potassium bromide and ethanol, respectively. N.m.r. spectra were obtained with 5–8% solutions in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Chemical shifts are quoted as cycles per second downfield from the TMS signal (0 c.p.s.) and are accurate to ±1 c.p.s. Coupling constants, also measured in cycles per second, are accurate to ±0.5 c.p.s. Thanks are due to Mr. E. Diaz and the Universidad Nacional Autónoma de México for the n.m.r. spectra which were recorded on a Varian Associates Model A-60 spectrometer.

**B. With Added Paraformaldehyde.**—The 5α-androst-1-en-3-one (2.18 g.) was treated with the reagents (50 ml., 10 mole equiv.) in a sealed flask for 4.5 hr. at 160° (caution must be used in breaking open the flask as a considerable pressure is developed during the reaction and is later present even after cooling in acetone–Dry Ice). Processing, as above, followed by chromatography on silicic acid (550 g.) and elution with hexane–benzene (3:1) afforded Ic (1.68 g.), m.p. 91–93°.

**4α-Methyl-5α-androstan-3-one (IIa). A. Hydrogenation of Ic.**—A solution of 4-methylene-5α-androst-1-en-3-one (250 mg.) in ethyl acetate (25 ml.) containing 10% palladium-on-charcoal catalyst (50 mg.) was stirred under hydrogen, 2 moles (62 ml.) of which was taken up within 30 min. The catalyst was then removed by filtration and washed with ethyl acetate and the filtrate plus washings were evaporated to dryness at reduced pressure. The resulting oil (256 mg.), shown to consist of approximately equal quantities of two products by t.l.c., was placed on a column of silicic acid (100 g.) and the whole was allowed to stand overnight. Elution with hexane afforded crystals (245 mg.), m.p. 110–112°, which by t.l.c. consisted almost solely of the less polar of the two compounds initially present after hydrogenation. Recrystallization from methanol gave colorless plates (134 mg.), m.p. 131–133°. Concentration of the mother liquors and two crystallizations yielded a second crop (98 mg.), m.p. 129–131°. Analytical material from methanol was characterized by m.p. 132–134°; $[\alpha]_D$ $-3°$; $\nu_{max}$ 1710 cm.$^{-1}$; n.m.r. 44 (18-H), 65 (19-H), and 59 c.p.s. (4α-Me, doublet, $J$ = 6 c.p.s.).

*Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.26; H, 11.18; O, 5.56. Found: C, 82.88; H, 11.36; O, 5.56.

**B. From 17β-Hydroxy-4α-methyl-5α-androstan-3-one (IIb).**—The hydroxy ketone (IIb,[8] 2.60 g.), ethylene glycol (28 ml.), ethyl orthoformate (17 ml.), and *p*-toluenesulfonic acid (0.10 g.) were refluxed gently for 1 hr. with a side-arm condenser to remove the ethanol as it was formed. Cooling, dilution with water, and filtration yielded crystals which were water washed until acid free, then recrystallized from acetone–methylene chloride to give IIc as plates (2.31 g. in two crops) on further concentration. A single crystallization from the same solvent pair afforded an analytical specimen, m.p. 202–204°, $[\alpha]_D$ $-3°$.

*Anal.* Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.57; H, 10.38; O, 13.92.

A small excess of 8 *N* Jones reagent[9] (1.35 ml., 1.2 equiv.) was added to a solution of IIc (1.90 g.) in acetone (300 ml.) and ether (35 ml.), the whole being stirred and maintained below 7°. After a further 5 min. the mixture was poured into ice–water; the crystalline product was collected by filtration, washed free of acid with water, and recrystallized from hexane–dichloromethane to afford IId (three crops totaling 1.58 g.). The analytical sample obtained from the same solvent system exhibited m.p. 243–244°, $[\alpha]_D$ $+74°$, $\nu_{max}$ 1735 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.42; H, 10.16; O, 13.65.

The keto ketal IId (0.80 g.), potassium hydroxide (2.70 g.), hydrazine hydrate (2 ml. of 85%), and ethylene glycol (30 ml.) were refluxed for 1 hr. when t.l.c. demonstrated complete conversion to the hydrazone. Part (6 ml.) of the distillate was then removed and the residue was refluxed with an air condenser for 24 hr. during which time a portion (0.32 g.), m.p. 164–166°, of the product IIe collected in the condenser. The reaction mixture was cooled, diluted with ice–water, and filtered. The resultant solid was triturated with warm methanol and the methanolic solution was filtered and concentrated to give the 17-desoxy compound IIe (0.47 g.), m.p. 156–160°. Recrystallization from methanol resulted in an analytical specimen, m.p. 165–166°, $[\alpha]_D$ $-5°$.

*Anal.* Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92; O, 9.63. Found: C, 79.51; H, 11.05; O, 9.65.

A solution of IIe (0.25 g.) in ethanol (15 ml.), water (2 ml.), and dichloromethane (1.5 ml.) containing hydrochloric acid (0.5 ml. of 36%) was allowed to stand at room temperature for 1 hr. Concentration and precipitation of the product by dilution with water, then filtration and recrystallization from methanol, afforded IIa (0.13 g.) identical by melting point and infrared spectrum with the product from the hydrogenation of Ic (*vide supra*).

**4-Methylene-5α-cholest-1-en-3-one (Id).**—A mixture of 5α-cholest-1-en-3-one (Ib, 1.22 g.), dimethyl sulfoxide (15 ml.), and boron trifluoride etherate (1 ml.) was refluxed for 30 hr., when processing, as described for the 5α-androst-1-en-3-one experiment (A), and chromatography, produced crystals contaminated with a brown gum. Solution in hot methanol, filtration, and cooling gave needles (0.24 g.), m.p. 87–89°. Two recrystallizations from the same solvent yielded a pure sample: m.p. 90–91°; $[\alpha]_D$ $+34°$; $\lambda_{max}$ 245 mμ (log ε 4.0) and 346 mμ (log ε 1.77); $\nu_{max}$ 840, 940, 1630, 1685, and 1880 cm.$^{-1}$.

*Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.78; H, 11.18; O, 4.03. Found: C, 84.96; H, 11.16; O, 4.10.

Concentration of the initial mother liquors and two recrystallizations produced a second crop (0.12 g.), m.p. 86–88°.

**Dehydrogenation of 5α-Androstane-3,17-dione (IIIb) with DDQ.**—5α-Androstane-3,17-dione (28.84 g.), DDQ (36.32 g., 1.6 mole equiv.), and dioxane (600 ml.) were refluxed with stirring for 6 hrs. The bulk of the dioxane was then removed at reduced pressure and the residue was high vacuum dried. The resultant brown solid was triturated with benzene containing 2% ethyl acetate and, after filtration and concentration to 100 ml., the solution was chromatographed on alumina (1500 g.). Fractions eluted by hexane–benzene (1:1 and 1:2), then benzene, afforded the desired unsaturated ketone Ie (5.37 g., 19% yield, in two crops from acetone–hexane). Recrystallization from acetone–hexane gave the pure sample: m.p. 141–143°; $[\alpha]_D$ $+134°$; $\lambda_{max}$ 230 mμ (log ε 4.04); n.m.r. 55 (18-H), 64 (19-H), 349 and 359 (2-H), 429 and 439 c.p.s. (1-H, $J_{1,2}$ = 10 c.p.s.). [Djerassi[13] quotes m.p. 140–142°, $[\alpha]_D$ $+128°$, $\lambda_{max}$ 230 mμ (log ε 4.01)].

For another experiment the reaction mixture after 6 hr. refluxing was cooled in ice–water and filtered and the filtrate was diluted with a large volume of water. Extraction with dichloromethane, several washings of the organic extract with water, and evaporation of the dried extract gave a gum which on chromatography afforded a 24% yield of Ie.

**Dehydrogenation of 17β-Hydroxy-5α-androstan-3-one (IIIc) with DDQ.**—Dihydrotestosterone (29.04 g.) and DDQ (36.32 g., 1.6 mole equiv.) in dioxane (600 ml.) were allowed to react as described above. Chromatography of the crude product over alumina (1500 g.) gave, in hexane–benzene (1:1) eluates, the 17-ketone Ie. Two recrystallizations from acetone–hexane afforded plates (0.53 g.), m.p. 140–142°. Later fractions eluted with benzene and benzene–ethyl acetate mixtures provided the desired enone If. Two recrystallizations from acetone–hexane gave rods (3.90 g. in two crops): m.p. 156–158°; $[\alpha]_D$ $+46°$; $\lambda_{max}$ 230 mμ (log ε 4.0); n.m.r. 47 (18-H), 62 (19-H), 219 (17α-H, ill-resolved triplet), 348 and 359 (2-H), 429 and 440 c.p.s. (1-H, $J_{1,2}$ = 11 c.p.s.) [lit.[15] m.p. 150°, $[\alpha]_D$ $+53.3°$, $\lambda_{max}$ 230 mμ (log ε 4.0)].

**Treatment of 5α-Androst-1-ene-3,17-dione (Ie) with the Reagent.**—The above enedione (Ie, 5.73 g.) and the reagent (15 ml., 10 mole equiv.) were heated for 3 hr. at 160° in a flask with a ball joint retained in position by a spring clip. Dow Corning high vacuum grease was used to complete the seal. After the first 1.5 hr. the flask was removed from the oil bath and allowed to cool for 5 min., and the paraformaldehyde in the neck of the vessel was scraped back into the reaction mixture. The heating was then continued for the remaining 1.5 hr. and the mixture was processed. Chromatography over alumina (500 g.) and elution with hexane–benzene (1:1) gave light yellow crystals. Recrystallization from hexane–acetone yielded the cross-conjugated α-methylene ketone Ih (0.77 g. in two crops). Two recrystallizations from hexane–acetone led to a sample of analytical purity: m.p. 208–210° dec.[28]; $[\alpha]_D$ $+65°$; $\lambda_{max}$ 233 mμ (log ε 4.22) and 344 mμ (log ε 2.08); $\nu_{max}$ 847, 856, 947, 960, 1625, 1640, 1675, 1729, 1894, 1920, 3020, and 3090 cm.$^{-1}$; n.m.r. 57 (18- and 19-H), 316 and 368 (4-$CH_2$=), 327 and 368 (16-$CH_2$=), 358 and 368 (2-H), 432.5 and 443.5 c.p.s. (1-H, $J_{1,2}$ = 11 c.p.s.).

*Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44; O, 10.31. Found: C, 81.35; H, 8.49; O, 10.57.

Later fractions using the same eluent provided Ig, thrice recrystallized from hexane–acetone to provide flat needles (0.89 in two crops), m.p. 150–152°. The analytical specimen obtained by further recrystallization was characterized by m.p. 151–153°; $[\alpha]_D$ $+98°$; $\lambda_{max}$ 237 mμ (log ε 4.03) and 344 mμ (log ε 1.85); $\nu_{max}$ 848, 960, 1625, 1675, 1920, 3020, and 3090 cm.$^{-1}$; n.m.r. 55 and 57 (18- and 19-H), 316 and 369 (4-$CH_2$=), 358 and 369 (2-H), 432 and 443 c.p.s. (1-H, $J_{1,2}$ = 11 c.p.s.).

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(28) The behavior of this compound on melting varies with the rate of heating, a distinct melting point being observed only when the rate was fairly high. Slower heating led first to softening and then hardening to an infusible solid.

*Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.73; H, 8.83; O, 10.50.

In other experiments using a sealed tube submerged[29] in an oil bath at 160° for 3–5 hr., only the dione Ih was obtained, in either the form mentioned above or as long plates, m.p. 192–194° dec.

**4-Methylene-17β-hydroxy-5α-androst-1-en-3-one** (Ii).—A mixture of the hydroxy ketone If (2.88 g.) and the reagent (9 ml., 10 mole equiv.) was heated for 4.5 hr. at 160° in the manner described for the treatment of Ie. Processing and chromatography on alumina (250 g.) using benzene–ethyl acetate (9:1) eluent gave crystals of the dienone Ii (0.8 g. after three crystallizations from hexane–acetone). The analytical sample showed m.p. 178–180°; $[\alpha]_D$ +14°; $\lambda_{max}$ 244 mμ (log ε 3.98) and 344 mμ (log ε 1.83); $\nu_{max}$ 842, 935, 1615, 1670, 1870, and 3450 cm.$^{-1}$; n.m.r. 47 (18-H), 55 (19-H), 220 (17α-H), 314 and 367 (4-$CH_2$=), 357 and 367 (2-H), 433 and 443 c.p.s. (1-H, $J_{1,2}$ = 10 c.p.s.).

*Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.65; H, 9.54; O, 10.72.

**Treatment of 5α-Androstan-3-one (IIIa) with Paraformaldehyde and the Reagent.**—The ketone (IIIa, 3.02 g.) was heated with the reagent (27.5 ml., 5 mole equiv.) at 60° for 10 hr. in a stoppered flask. Work-up in the normal manner and chromatography of the resultant solid on a silicic acid column (760 g.) gave, by elution with hexane–benzene (9:1), a gum. Crystallization of the latter from methanol–hexane furnished the dimer IVb as needles (0.12 g.), m.p. 190–193°. Further crystallizations from the same solvent mixture gave the analytical sample: m.p. 195–197°; $[\alpha]_D$ +92°; $\lambda_{max}$ 239 mμ (log ε 3.88); $\nu_{max}$ 1610, 1670, and 1710 cm.$^{-1}$; n.m.r. 42 (four overlapping three-proton angular methyl singlets), 313, and 361 c.p.s. (4-$CH_2$=).

*Anal.* Calcd. for $C_{41}H_{60}O_2$: C, 84.19; H, 10.34; O, 5.47. Found: C, 84.45; H, 10.51; O, 5.37.

Later hexane–benzene (9:1) fractions gave rise to the highly crystalline product, VI, separating as needles (0.155 g.), m.p. 213–216°, from acetone. Three crystallizations from acetone gave the pure substance: m.p. 220–222°; $[\alpha]_D$ +111°; $\lambda_{max}$ 251 mμ (log ε 4.02); $\nu_{max}$ 1608, 1665, and 1720 cm.$^{-1}$; n.m.r. 42 (nine protons; 18-, 18′-, and 19-H), 52 (19′-H), 285, and 321 c.p.s. (2′-$CH_2$=).

*Anal.* Calcd. for $C_{41}H_{60}O_2$: C, 84.19; H, 10.34; O, 5.47. Found: C, 84.46; H, 10.63; O, 5.33.

Dimer IVa (0.233 g.), m.p. 227–229°, was obtained on crystallization from acetone of the material eluted by hexane–benzene (4:1). Two crystallizations from acetone gave an analytical sample: m.p. 231–232°; $[\alpha]_D$ +60°; $\nu_{max}$ 1690 and 1726 cm.$^{-1}$; n.m.r. 42 (18- and 18′-H), 45 (19-H), and 55 c.p.s. (19′-H).

*Anal.* Calcd. for $C_{40}H_{60}O_2$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.81; H, 10.65; O, 5.68.

In another experiment in which the reaction mixture was heated for 1.5 hr. at 94°, chromatographic separation afforded IVa and IVb and, in benzene eluates, the spiro condensate VII (0.08 g. from 3.02 g. of IIIa). The analytical specimen, obtained by recrystallization from ethanol, showed m.p. 241–242°; $[\alpha]_D$ +41°; $\nu_{max}$ 922, 1020, 1100, 1160, and 1708 cm.$^{-1}$; n.m.r. 43 (18-H) and 56 c.p.s. (19-H), for other resonances see discussion.

*Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.26; H, 9.99; O, 14.01.

**Hydrogenation of IVb.**—The ketone IVb (50 mg.) and 10% palladium-on-charcoal catalyst (15 mg.) were stirred in ethyl acetate (20 ml.) under hydrogen for 1.5 hr. whereafter the catalyst was removed by filtration and washed with ethyl acetate, and the filtrate plus washing were evaporated to dryness under reduced pressure. T.l.c. demonstrated that the oil thus obtained consisted of two products with the less polar one predominating. The mixture was dissolved in ethanol (5 ml., 95%) and potassium hydroxide (0.25 g.) was added. The whole was warmed for 15 min. on the steam bath. Cooling and dilution with water gave gummy crystals which were collected by filtration and passed over a short column of alumina using hexane as eluent. Three recrystallizations from methanol of the product provided analytical material: m.p. 188–192°; $[\alpha]_D$ +49°; n.m.r. 42 (18- and 18′-H), 44 (19-H), 58 (19′-H), 62, and 68 c.p.s. (equatorial 4′-Me).

*Anal.* Calcd. for $C_{41}H_{64}O_2$: C, 83.61; H, 10.95. Found: C, 83.59; H, 10.99.

**Methylenedioxy Compounds VIIIa and VIIIb. A.**—The hydroxy ketone IIIb (7.26 g.) and the reagent (20 ml., 5 mole equiv.) were kept together at room temperature in a stoppered flask with occasional shaking over a period of 30 days during which time solidification commenced. Normal work-up followed by chromatography over alumina (250 g.) and benzene elution provided crystals of the condensate VIIIa. Recrystallization of VIIIa from dichloromethane–benzene provided the analytical sample (0.64 g.) with m.p. 284–286° dec.; $[\alpha]_D$ +45°; $\nu_{max}$ 1710 cm.$^{-1}$; n.m.r. 47 (18- and 18′-H), 61 (19- and 19′-H), 213 (17α- and 17α′-H), and 278 c.p.s. ($OCH_2O$).

*Anal.* Calcd. for $C_{39}H_{60}O_4$: C, 79.00; H, 10.20; O, 10.79. Found: C, 78.51; H, 10.11; O, 10.93.

**B.**—In a similar manner testosterone (IXa, 7.21 g.) and the reagent (40 ml., 5 mole equiv.) yielded the condensate VIIIb which by recrystallization from benzene furnished an analytical sample (0.90 g.): m.p. 225–227°; $[\alpha]_D$ +136°; $\lambda_{max}$ 241 mμ (log ε 4.21); $\nu_{max}$ 1620 and 1675 cm.$^{-1}$; n.m.r. 48 (18- and 18′-H), 72 (19- and 19′-H), 216 (17α- and 17α-′H), 280 ($OCH_2O$), and 343 c.p.s. (4- and 4′-H).

*Anal.* Calcd. for $C_{39}H_{56}O_4$: C, 79.54; H, 9.59; O, 10.87. Found: C, 78.88; H, 9.49; O, 10.91.

**17β-Hydroxy-6-methyleneandrost-4-en-3-one** (IXb).—Testosterone (14.7 g.) and the reagent (270 ml., 10 mole equiv.) were heated in a closed vessel for 3 hr. at 94°. Normal work-up and chromatography of the product over silicic acid (2900 g.) yielded by elution with benzene–ethyl acetate (3:1) the 6-methylene derivative IXb (1.52 g.), m.p. 167–172°. Recrystallization from acetone provided a pure sample: m.p. 174–176°; $[\alpha]_D$ +286°; $\lambda_{max}$ 261 mμ (log ε 4.06); n.m.r. 47.5 (18-H), 66 (19-H), 221 (17α-H), 298 and 305 (4-$CH_2$=), and 355.5 c.p.s. (4-H) [lit.[24] (for 6-methylene-testosterone) m.p. 175°, $[\alpha]_D$ +292°, $\lambda_{max}$ 259 mμ (log ε 4.04)].

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(29) Differences were encountered according to the vessel used for the reaction. A closed or sealed flask partly immersed in an oil bath led to the collection of a considerable proportion of the paraformaldehyde on the walls of the exposed part of the flask, the amount depending on the temperature of the bath. When the vessel was totally submerged there was a greater tendency for the paraformaldehyde to remain in solution. In the case of the closed flask using a spring-clipped ball-joint seal, only high vacuum stopcock grease was found to close the vessel efficiently at high temperature and maintain a pressure such that paraformaldehyde, sufficient for reasonable reaction rates, was kept in solution.