[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, GETTYSBURG COLLEGE]

The Reactions of α-Halo Keto Steroids with Base. The Preparation of 5β-Cholestane-3β,5β-diol-6-one 3-Monoacetate

ALEX T. ROWLAND

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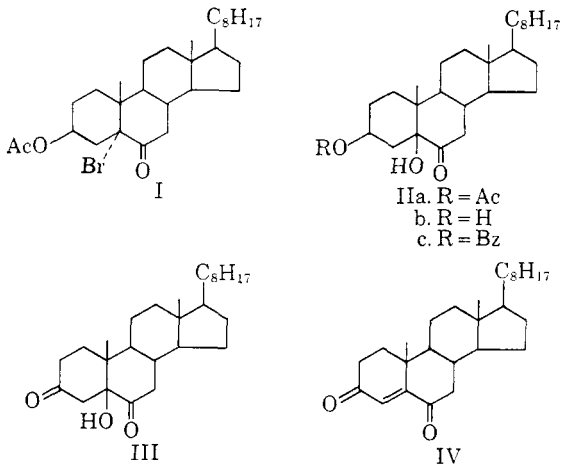
The reaction of 5α-bromocholestane-3β-ol-6-one acetate (I) with sodium ethoxide in ethanol or 5% ethanolic–potassium hydroxide is shown to yield, after acetylation, 5β-cholestane-3β,5β-diol-6-one 3-monoacetate (IIa). The reaction represents formation of an α-hydroxy ketone with inversion of configuration at the carbon bearing the bromine atom in the starting compound. The diolone monoacetate IIa is related to the known Δ^4-cholestene-3,6-dione (IV), and earlier work reporting the preparation of the diolone IIb of IIa is shown to be in error.

The reactions of α-halo keto steroids with alkoxide and hydroxide ions have been noted to yield numerous types of products: esters resulting from rearrangements of carbon skeletons (Favorskiĭ reaction),[1a-d] α-alkoxy ketones,[1e,f] α′-alkoxy ketones and α′-hydroxy ketones,[1g] unsubstituted ketones (halogen replaced by hydrogen),[1e,h] epoxy ethers,[1i] α-diketones,[1e,j,k] *seco* acids,[1e,h] α-hydroxy ketones resulting from isomerization through enediols,[1j-l] normal α-hydroxy ketones,[1a,b,e,h,j,k,m,n] and α-hydroxyketals.[1o] The product(s) obtained from a particular α-halo ketone depends upon the structure of the steroid, the base used, the solvent, the temperature of reaction, and degree of oxygen exclusion. The α-diketones and *seco* acids are probably artifacts formed by air oxidation of products initially produced in the reactions, and their formation can be reduced by variations in experimental conditions.[1e,j]

In order to determine the feasibility of preparing B-norsteroids *via* a Favorskiĭ rearrangement, the reactions of 5α-bromocholestane-3β-ol-6-one acetate (I) with various bases were investigated. Since a facile Favorskiĭ rearrangement apparently depends upon the presence of at least one α′-hyrogen atom in the α-halo ketone,[1a] I appeared to offer possibilities for a model study of this reaction with α-halo keto functions in the B ring of the steroid nucleus. Preliminary evidence[2] indicated that a 5α-chloro-6-ketopregnane derivative gave a small yield of a B-nor ester when treated with sodium ethoxide in ethanol.



The bromo ketone I was first treated with sodium ethoxide in absolute ethanol in order to insure attack by a single basic species ($OC_2H_5^-$) and thus attempt to avoid the formation of compounds (α-alkoxy ketones, α-hydroxy ketones) which are sometimes found as products from the reactions of α-halo ketones with solutions of alkali hydroxides in alcohols.[1e,g] When the reaction was conducted at room temperature for two hours, the crude product showed infrared absorption bands due to hydroxyl functions at 2.75 and 2.90 μ (broad) and carbonyl frequencies at 5.84 (weak-medium) and 5.80 μ (shoulder). The spectrum indicated that little or no Favorskiĭ rearrangement occurred, since a resulting B-nor ester should exhibit a strong carbonyl band at *ca.* 5.74 μ.[1b]

The crude product was acetylated with acetic anhydride–pyridine prior to isolation of the products, which were separated by chromatography on alumina. The first material eluted from the column (as an oil) exhibited no hydroxyl absorption in its

(1) (a) For leading references, see A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959); (c) W. P. Schneider, F. H. Lincoln, G. B. Spero, H. C. Murray, and J. L. Thompson, *J. Am. Chem. Soc.*, **81**, 3167 (1959); (d) A. A. Amos and P. Ziegler, *Can. J. Chem.*, **37**, 345 (1959) [*Chem. Abstr.*, **53**, 22081d (1959)]; (e) H. P. Sigg and Ch. Tamm, *Helv. Chim. Acta*, **43**, 1402 (1960); (f) M. Uskokovic', M. Gut, and R. I. Dorfmann, *J. Am. Chem. Soc.*, **82**, 958 (1960); (g) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960); (h) D. E. Evans, A. C. dePaulet, C. W. Shoppee, and F. Winternitz, *J. Chem. Soc.*, 1451 (1957); (i) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946); (j) S. J. Angyal and R. J. Young, *J. Am. Chem. Soc.*, **81**, 5251 (1959); (k) K. Takeda, T. Komeno, and K. Igarashi, *Pharm. Bull.* (Japan), **2**, 352 (1954) [*Chem. Abstr.*, **50**, 12087i (1956)]; N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959); L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, 1959, p. 639; (l) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 1691 (1959); (m) H. R. Nace, private communication; (n) T. Barr, I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 334 (1938); (o) G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

(2) A. T. Rowland and H. R. Nace, unpublished observations.

TABLE I

PHYSICAL CONSTANTS OF SOME 3,5,6-SUBSTITUTED CHOLESTANES

5α Series[a]	M. P.	$[\alpha]_D$[b]	5β Series[c]	M. P.	$[\alpha]_D$[b]
3β,5α-Diol-6-one	232	+29°	3β,5β-Diol-6-one	Oil	−5°
3β,5α-Diol-6-one 3-monoacetate	233	−56°	3β,5β-Diol-6-one 3-monoacetate	142.5–144.5	−22°
5α-Ol-3,6-dione	232 (253 dec.)	−21°	5β-Ol-3,6-dione	121–122.5	−47°

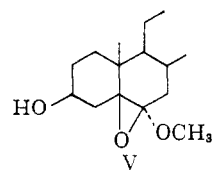
[a] Constants for 5α series given in L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, 1959, p. 192. [b] All rotations in chloroform solution. [c] Constants for 5β series given in Experimental section of this paper.

infrared spectrum but gave carbonyl peaks at 5.75 and 5.80 μ. This material could not be crystallized. The middle fractions showed complex absorption in the region 5.7–5.8 μ and represented an inseparable mixture. Later fractions eluted with 10% ether–benzene mixtures gave a crystalline compound whose infrared spectrum had bands at 2.87, 5.75, and 5.85 μ. It was found that the latter compound could be obtained in pure form by a single crystallization from petroleum ether of the acetylated mixture from the reaction of I with the ethoxide (in 27–36% yield). The infrared spectrum suggested that this product was an α-hydroxy ketone, and this structure was verified by the evidence that follows. The absorption at 2.87 μ in the infrared after acetylation indicated the presence of a *tertiary* hydroxyl group (hydrogen bonded to the C-6 carbonyl oxygen), which can only be located at C-5. Absorption at 5.75 μ is typical of a C-3 acetoxyl carbonyl while the band at 5.85 μ can be assigned to the carbonyl function at C-6. Thus, the α-hydroxy ketone obtained from I must be either 5β-cholestane-3β,5β-diol-6-one 3-monoacetate (IIa) or the epimeric 3β,5α-diol-6-one 3-monoacetate. Since the physical constants of the compound isolated during this study differ from those of the well characterized 3β,5α-steroid (Table I), the α-hydroxy ketone is assigned the structure IIa. IIa was obtained in much better yield (57%) when I was treated with a 5% ethanolic–potassium hydroxide solution, followed by acetylation. The latter represents a simple and direct route to the diolone monoacetate IIa.

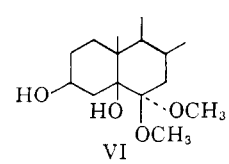
The reaction of I with 10% potassium hydroxide–methanol was investigated some years ago by Heilbron, Jones, and Spring.[3] They isolated, in unstated yield, a compound [m.p. 138° with softening at 128° and $[\alpha]_D$ +29.3° (chloroform)] which was believed to be 5β-cholestane-3β,5β-diol-6-one (IIb). The assignment of this structure was based upon the facts that it formed only a *monobenzoate* (IIc) and its physical constants were different from the known 5α-cholestane-3β,5α-diol-6-one. No analytical values were reported for this compound, and it was stated that it separated from methanol with solvent of crystallization which could not be removed after prolonged desiccation. The saponification of the monoacetate IIa was therefore attempted in order to prepare the diolone IIb and compare it with the compound reported by the English workers. Treatment of IIa at room temperature with a potassium hydroxide–ethanol–water mixture gave an oil which resisted all attempts at crystallization. The infrared spectrum of this oil was consistent with structure IIb, but the specific rotation (−5°) was significantly different from the reported value.[3]

Accordingly, the reaction conditions employed in the earlier work were duplicated in an effort to isolate the material reported and identify it more completely. In one attempt, a small amount of a crystalline compound was obtained which had m.p. 130–140°, with softening at 128°, and $[\alpha]_D$ +23°. These constants were in fair agreement with those reported,[3] but the infrared spectrum exhibited weak bands at 5.85 and 6.01 μ in addition to those at 2.83 and 2.90 (broad shoulder) μ due to hydroxyl absorption. If this compound were IIb, a strong peak should have been observed at *ca.* 5.85 μ due to the C-6 carbonyl group. Further attempts to recrystallize this product were unsuccessful, and after standing for several weeks in a mixture of methanol and water, the infrared of the oil formed had sharp hydroxyl absorption at 2.83 and 2.89 μ and strong carbonyl absorption at 5.85 μ. Benzoylation of this oil gave the reported monobenzoate (IIc).[3]

Evidently the crystalline compound obtained by the English chemists was not the diolone IIb but was, possibly, a precursor such as the epoxy ether V or hydroxy ketal VI:



V



VI

Epoxy ethers and hydroxy ketals are known to be intermediates in the conversions of certain α-halo ketones to α-hydroxy ketones,[4,10] and the benzoylation of the compound isolated by the Heilbron group was apparently accompanied by

(3) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

(4) See the work of Stevens and co-workers: *e.g.*, C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *J. Am. Chem. Soc.*, **77**, 4590 (1955); C. L. Stevens and J. J. De Young, *J. Am. Chem. Soc.*, **76**, 718 (1954); C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **75**, 5975 (1953).

the hydrolysis of the ketal or epoxy ether linkage during the work-up of the reaction mixture. Benzoylation of the oil IIb obtained from the saponification of IIa gave the same monobenzoate IIc.

The structures assigned to the diolone monoacetate IIa and the diolone IIb were substantiated further. IIb was oxidized smoothly by chromic oxide in acetic acid to the previously unknown 5β-cholestane-5β-ol-3,6-dione (III).[5] The dioneol III was then converted by two paths to the known Δ^4-cholestene-3,6-dione (IV): (a) treatment with potassium hydroxide–methanol gave a mixture of IV and some unknown contaminant which was not removed by chromatography; and (b) by reaction with *p*-toluenesulfonic acid in acetic acid and acetic anhydride. The latter procedure gave a pure product which was identical with authentic IV according to melting point, mixture melting point, and infrared determinations.

That the C-3 oxygen function is β-oriented (*axial* to the A ring) in IIa and IIb follows from the facts that IIb did not react with *p*-toluenesulfonyl chloride in pyridine within twenty-four hours at room temperature[6a] and the reaction conditions employed in the conversions (I) → IIa → IIb were not drastic enough to cause epimerization of the 3β-oxygen (*axial* to *equatorial*).[6b]

The formation of IIa from I upon treatment with ethoxide ion in ethanol indicates that the replacement of bromine by hydroxyl proceeded with an inversion of configuration at C-5. Two reasonable paths accounting for the inversion may be considered: (a) direct SN2 displacement of bromine by hydroxyl, and (b) nucleophilic attack at the carbonyl carbon by the ethoxide ion, followed by an inverting displacement of the bromine by backside attack at C-5 by the oxyanion produced at C-6 to yield the epoxy ether V which may be converted to the corresponding α-hydroxy ketal VI or may be hydrolyzed directly to the α-hydroxy ketone when the acetylated mixture is processed. Path (a) does not appear to be likely in this particular reaction since the bromine at C-5 is *tertiary* and a direct displacement would be hindered by the C-10 methyl group. Also, the infrared spectrum of the crude product obtained before acetylation exhibited only weak-medium carbonyl absorption at 5.84 μ. The formation of IIb by an SN2 displacement would not decrease the C-6 carbonyl absorption since the carbonyl group should remain unaltered, and as uncharacterized compounds containing absorption at about 5.80 μ (in addition to that of the 3-acetoxy function at 5.75 μ) were isolated from the chromatogram of the acetylated reaction products, it appears that the band noted at 5.85 μ in the oil obtained from the initial reaction of I with sodium ethoxide–ethanol was due mainly to these unknown components.

In the reaction of I with 5% ethanolic potassium hydroxide, the unacetylated product exhibited an infrared spectrum which was quite similar to that of the diolone IIb (see Experimental). Since there was undoubtedly more water present in the reaction mixture in this case than in the ethoxide–ethanol reaction, hydrolysis of the postulated intermediate V or VI (epoxy*ethyl* ether or hydroxydi*ethyl* ketal) may have occurred to give IIb even before acetylation.

Path (b) is therefore favored for the formation of IIa and is essentially the mechanism proposed by Stevens and Farkas[7] and Mueller and Johns.[1o] In other reactions of α-halo keto steroids, the inversion of configuration was difficult to detect due to the possibility of isomerization of initially formed α-hydroxy ketones to more stable epimers and to different positional isomers by rearrangements through enediols.[1e,j,k] For example, the isolation of 5α-cholestane-2α-ol-3-one from the reaction of 2α-bromocholestane-3-one upon treatment with sodium methoxide–methanol[1h] does not necessarily mean that the initial reaction proceeded with retention of configuration at C-2, since rearrangements may take place to yield more stable isomers[8] under certain conditions. The formation of IIa from I, however, gives an α-hydroxy ketone possessing no α-hydrogen atoms and hence cannot undergo isomerization through an enediol.

EXPERIMENTAL[9]

5α-Bromocholestane-3β-ol-6-one acetate (I).The bromo ketone was prepared in 70% yield by the bromination of 5α-cholestane-3β-ol-6-one acetate according to a reported procedure:[3] m.p. 162–165° dec.; λ_{max} 5.75 (s) and 5.83 (s) μ.

5β-Cholestane-3β,5β-diol-6-one 3-monoacetate (IIa). (A). Ten grams (19.1 moles) of I was added to a solution of sodium ethoxide in ethanol prepared by dissolving 2.74 g. (0.119 g.-atom) of sodium in 175 ml. of absolute ethanol

(5) Erroneously reported previously [B. Ellis and V. Petrow, *J. Chem. Soc.*, 1078 (1939)].

(6) (a) Experiment conducted in this laboratory by Richard Kornmann. 1,3-*axial* interactions between the 3β-hydroxyl group and the C-1 hydrogen and the C-5 hydroxyl group would be expected to inhibit tosylate formation at C-3; (b) Examples are known [*e.g.*, A. T. Rowland and H. R. Nace, *J. Am. Chem. Soc.*, **82**, 2833 (1960)] in which A/B *cis* steroids are formed from A/B *trans* compounds under basic conditions without epimerization of the C-3 hydroxyl group.

(7) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952).

(8) T. Cohen and T. Tsuji, *J. Org. Chem.*, 26, 1681 (1961).

(9) All melting points are uncorrected. Rotations were determined in chloroform solutions at room temperature. Infrared spectra were determined with a Perkin-Elmer Model 21 infrared spectrophotometer in *ca.* 5% carbon tetrachloride solutions using a 0.1 mm. sodium chloride cell and sodium chloride prism; *s*, *m*, and *w* associated with λ_{max} indicate strong, medium, and weak absorptions, respectively. Microanalyses by S. M. Nagy, Microchemical Laboratory, M. I. T. (compound IIa) and Micro-Analysis, Inc., Wilmington, Del. (compound III). Drying of solutions was accomplished with anhydrous sodium sulfate.

(freshly distilled from calcium hydride). The resulting suspension was stirred magnetically at 30° for 2 hr., during which time the steroid dissolved and the solution assumed an orange color. The reaction mixture was diluted with 500 ml. of ether, washed three times with a saturated solution of sodium chloride, and dried. The yellow solution was filtered, the solvent evaporated, and the resulting yellow oil was treated with 35 ml. of pyridine and 55 ml. of acetic anhydride at room temperature for 26.5 hr. The solution was poured into a mixture of crushed ice and concd. hydrochloric acid, and the aqueous phase was extracted three times with ether after being saturated with sodium chloride. The combined ether extracts were washed successively with a saturated saline solution, three times with a 10% sodium bicarbonate solution, and again with a saturated salt solution. The dried solution was filtered and evaporated to yield an oil that crystallized from petroleum ether to yield 2.43 g. (27%) of IIa, m.p. 140.5–143.5°. Recrystallization from methanol gave 2.14 g. of large white plates, m.p. 142.5–144.5°. An additional 525 mg. of IIa was obtained by chromatography of the material from the mother liquors of the initial crystallizations.

From another reaction using 10 g. of the bromo ketone I, 3.17 g. (36%) of IIa, m.p. 142–144°, was obtained by direct crystallization of the oily product from petroleum ether. Recrystallization from methanol gave 2.84 g. with m.p. 142.5–144.5; $[\alpha]_D$ −22° (*c* 1.625), $[\alpha]_D$ −22.5° (*c* 1.29); λ_{max} 2.87 (w), 5.75 (s), and 5.85 (s) μ.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.73; H, 10.51.

B. A suspension of 10 g. (19.1 mmoles) of I in 125 ml. of a 5% solution of potassium hydroxide in commercial absolute ethanol was stirred magnetically at room temperature for 5 hr. After 1 hr., an additional 50 ml. of ethanol was added. The product was isolated as in part A and the oil [λ_{max} 2.83 (w), 2.90 (w), 5.85 (m), 5.77 and 5.80 (shoulders) μ] was acetylated for 46 hr. at room temperature with 45 ml. of pyridine and 37 ml. of acetic anhydride. The acetylation mixture was then added dropwise,with swirling, to a mixture of 100 ml. of concd. hydrochloric acid and crushed ice, and the precipitated product was collected by filtration and recrystallized from an acetone–methanol mixture containing a little water to yield 5.06 g. (57%) of IIa as slightly yellow colored plates, m.p. 139–143°. One recrystallization from methanol gave 4.57 g. of white plates, m.p. 142.5–144.5°.

Reaction of I *with 10% potassium hydroxide–methanol.* A mixture of 1.5 g. (2.88 mmoles) of I and 45 ml. of a 10% potassium hydroxide–methanol solution was boiled under reflux for 2 hr. The dark red colored solution was diluted with water, allowed to stand overnight, and then was saturated with salt and extracted twice with ether. The combined ethereal extracts were washed with a saturated salt solution and dried. About one fifth of this solution was evaporated to dryness; the oily residue was taken up in hot methanol, diluted with water, and refrigerated. The supernatant liquid was decanted from the yellow oil which separated, and this oil was dissolved in hot methanol and refrigerated. A mixture of white and yellow crystals gradually formed, which were separated mechanically. The white crystals had m.p. 124–134°, with previous softening. These were recrystallized from methanol to yield 104 mg. of "rectangular" crystals[3] that had m.p. 130–140° (soften at 128°); $[\alpha]_D$ +23° (*c* 1.40); λ_{max} 2.83 (w), 2.90 (w, shoulder), 5.85 (w), and 6.01 (w) μ [reported[3] for 5β-cholestane-3β,5β-diol-6-one, m.p. 138° (soften at 128°); $[\alpha]_D$ +29.3° (chloroform)]. Further attempts at recrystallization from methanol and methanol–water mixtures were fruitless, and after 3 weeks the material existed as an oil with λ_{max} 2.83 (w), 2.89 (w), 5.85 (s), and 6.01 (vw) μ.

The oil was treated with 1 ml. of pyridine and 0.5 ml. of benzoyl chloride for 18 hr. at room temperature and 1.5 hr. on the steam bath. The product was isolated as in the benzoylation of IIb (*vide infra*) and recrystallized twice from methanol to give 46 mg. of IIc as white needles, m.p. 171–172.5°. This material did not depress the m.p. of IIc prepared from IIb.

5β-Cholestane-5β-ol-3,6-dione (III). One gram (2.17 mmoles) of IIa was dissolved in 40 ml. of 95% ethanol by heating. After cooling to room temperature, a solution of 210 mg. of potassium hydroxide in 6 ml. of water and 10 ml. of 95% ethanol was added, and the mixture was allowed to remain at room temperature for 20 hr. The solution was acidified with 2*N* hydrochloric acid, water was added, and the aqueous phase was extracted three times with methylene chloride. The combined extracts were washed successively with a 10% sodium bicarbonate solution and water and dried. Filtration and evaporation gave an oil [5β-cholestane-3β,5β-diol-6-one (IIb), $[\alpha]_D$ −5° (*c* 2.53), −5° (*c* 1.99); λ_{max} 2.81 (w), 2.87 (w), and 5.85 (s) μ] which could not be crystallized. The oil was dissolved in 15 ml. of glacial acetic acid and treated with a solution of 290 mg. of chromic oxide in 1 ml. of water and 13 ml. of glacial acetic acid. The mixture was stirred magnetically at room temperature for 4 hr., 1 ml. of methanol was added, and the product was precipitated by the addition of water and collected by filtration. The solid was taken up in methylene chloride, and this solution was washed once with a 10% sodium bicarbonate solution (in order to remove some chromium salts), once with water, dried, filtered, and evaporated. Recrystallization of the residue from methanol-water yielded 560 mg. (62%) of III as small white plates, m.p. 121–122.5°; $[\alpha]_D$ −47.5° (*c* 1.263), −47.3° (*c* 1.46); λ_{max} 2.86 (w), 5.81 (s), and 5.84 (s) μ.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.64. Found: C, 77.84; H, 10.61.

5β-Cholestane-3β,5β-diol-6-one 3-monobenzoate (IIc). A solution of 199 mg. (0.476 mmole) of IIb (oil) in 3 ml. of pyridine was treated at room temperature with 0.5 ml. of benzoyl chloride. After 47 hr., the dark red solution was poured into water, and the product was extracted into methylene chloride (twice). The organic extracts were washed successively with water, dilute hydrochloric acid, 10% sodium bicarbonate solution, and water, and then dried. Evaporation of the solvent gave a yellow oil that crystallized upon the addition of methanol to yield white needles with m.p. 170–173°. Recrystallization from acetone–methanol gave 135 mg. (54%) of *IIc* as short white needles, m.p. 172–173.5°; $[\alpha]_D$ +23° (*c* 1.29); λ_{max} 2.89 (w) and 5.84 (s) μ (lit.,[3] m.p. 170° and $[\alpha]_D$ +23°). A further recrystallization from acetone–methanol sharpened the m.p. to 173–174°.

Conversion of III *to* Δ^4*-cholestene-3,6-dione* (IV). (A). To a solution of 175 mg. (0.42 mmole) of III in 10 ml. of methanol was added 50 mg. of potassium hydroxide. The solution was heated under reflux for 5 min., during which time it changed in color from yellow to green. The solution was acidified with 2*N* hydrochloric acid, diluted with water, and extracted twice with methylene chloride. The dried extracts were evaporated to yield an orange colored oil that was crystallized from methanol to give 57 mg. of yellow plates, m.p. 108–119°. Chromatography of this material on alumina (Merck, acid-washed) gave 44 mg. of crystalline product (eluted with benzene) which upon recrystallization from methanol gave 34 mg. (20%) of Δ^4-cholestene-3,6-dione (IV) as pale yellow plates, m.p. 122.5–124°; $[\alpha]_D$ −41° (*c* 0.462). The mixture m.p. with authentic IV (m.p. 123–124.5°) prepared according to Fieser[10] (lit.,[11] m.p. 124–125° and $[\alpha]_D$ −40°) was 122–124°. A further recrystallization gave material that had m.p. 110–135°, with most melting occurring at 120–124°.

(B). A solution of 200 mg. (0.480 mmole) of III and 50 mg. of *p*-toluenesulfonic acid monohydrate in 2 ml. of glacial acetic acid and 1.5 ml. of acetic anhydride was allowed to stand at room temperature for 17.5 hr. The red-

(10) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953).
(11) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

dish orange colored solution was added in portions to a mixture of sodium bicarbonate–ice–water and swirled until gas evolution had ceased. The product was extracted into methylene chloride (twice) and the combined extracts were washed with water and dried. Evaporation of the solvent gave a yellow oil. A solution of the oil in 6 ml. of 10% potassium hydroxide–methanol was warmed on the hot plate for a few minutes, acidified with 2 *N* hydrochloric acid, and extracted twice with methylene chloride. The organic extracts were washed with water, dried, and evaporated to yield semicrystalline material which was crystallized from methanol to give 84 mg. (44%) of IV, m.p. 120.5–122°. Recrystallization from methanol gave 56 mg. of yellow plates, m.p. 123.5–125°. The infrared spectrum [λ_{max} 5.91 (s) μ] of this material was identical to that of authentic IV and no depression in melting point was noted upon admixture with the enedione prepared as reported.[10]

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GETTYSBURG, PA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CXCI.[1] Some Reactions of a 6-Methyl-Δ⁵-3β-hydroxy Steroid System

J. IRIARTE,[2a] J. N. SHOOLERY,[2b] AND CARL DJERASSI[2c]

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Dehydration of 6β,16α-dimethylpregnane-3β,5α-diol-20-one acetate (Ib) gives the corresponding Δ⁵-olefin (III), which upon Jones oxidation yields directly 6α,16α-dimethyl-6β-hydroxyprogesterone (VI). The reaction apparently proceeds through an intermediate oxide and such oxides were actually isolated (XIV, XVII) in related chromium trioxide oxidations of 6-methyl-Δ⁵ (XII) and Δ⁶ (XI) olefins. Epoxidation of the 6-methyl-Δ⁵-3β-ol system (III) with peracid furnishes the 5α,-6α-oxide, which leads to both C-6 epimeric 6-methyl-6-hydroxy-Δ⁴-3-ketones (VI, VII) upon Jones oxidation. 6α- and 6β,16α-Dimethylprogesterones have been prepared from 6β,16α-dimethylpregnane-3β,5α-diol-20-one (Ia). Several structures are based largely on nuclear magnetic resonance measurements, which were performed on nearly all of the steroids recorded in this article and summarized in tabular form.

In connection with work in our laboratory on the synthesis of 6α,16α-dimethyl corticosteroids[3] there were also carried out investigations directed towards 6,16-dimethylated analogs of progesterone.[4] The present paper describes the successful synthesis of these progesterone derivatives and in particular a number of unexpected oxidation reactions, where nuclear magnetic resonance measurements[5] have proved very useful in settling the structures of some of the products.

The starting material for all of the present work was 6β,16α-dimethylpregnane-3β,5α-diol-20-one (Ia),[3] which was oxidized with chromium trioxide to the corresponding 3-ketone and then dehydrated by exposure to dilute base to 6β,16α-dimethylprogesterone. Warming with somewhat stronger alkali or treatment with acid caused inversion with formation of the desired 6α,16α-dimethylprogesterone (II).[3] The substance exhibited the expected ultraviolet and infrared spectral properties and the NMR spectrum was completely consistent with structure II. In particular, all five methyl groups could be located as follows: C-21 (δ,[6] 2.12), C-19 (1.27), C-6 (doublet at 70 and 77 cps (δ = 1.22)), C-16 (doublet at 54 and 61 cps (δ = 0.96) and C-18 (0.72)), while the single olefinic proton at C-4 was responsible for the signal at 5.76.

Acid-catalyzed dehydration of 6β,16α-dimethylpregnane-3β,5α-diol-20-one acetate (Ib) proceeded unidirectionally to give 6,16α-dimethyl-Δ⁵-pregnen-3β-ol-20-one acetate (IIIb), the absence of any Δ⁴-olefinic isomer being demonstrated by the NMR spectrum. This did not contain any signals corresponding to an olefinic proton but again showed complete separation of all methyl peaks

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(1) Paper CXC, P. Crabbé, M. J. Durazo, R. M. Saloma, and P. G. Holton, *Bull. soc. chim. Belge, in press.*

(2) (a) Syntex, S. A., Mexico, D. F.; (b) Varian Associates, Palo Alto, Calif.; (c) Department of Chemistry, Stanford University, Stanford, Calif.

(3) J. Iriarte and M. L. Franco, *J. Org. Chem.*, **26**, 2047 (1961).

(4) One such compound, 6α,16α-dimethylprogesterone (II) has since been synthesized (S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961) and R. P. Graber and M. B. Meyers, *Chem. and Ind.*, 1478 (1960)) by methods different from the one described in the present article.

(5) For general references see (a) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959; (b) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959; (c) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959.

(6) For reasons discussed elsewhere [C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. N. Shoolery, *J. Org. Chem.*, **26**, 1192 (1961)] all peak positions are reported in δ units (c.p.s./60 p.p.m. for a 60 megacycle instrument) rather than as τ(τ = 10 − δ), tetramethylsilane serving as an internal standard. A summary of the shifts observed for methyl groups and olefinic protons appears in Table I.