

A New Synthesis of Cyclic Ketones¹

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Cyclopentanone, cyclohexanone, and cycloheptanone have been obtained by reaction of the appropriate ω -iodo esters **3** with triphenylphosphine followed by treatment of the phosphonium salts **4** with base and subsequent hydrolysis of the ylids **6**. Reaction of the ylid **6b** with peracetic acid produced adipic acid and triphenylphosphine oxide.

The successful acylation of alkylidetriphenylphosphoranes (Wittig reagents) with esters, thioesters, and acid chlorides² suggested that the intramolecular application of this reaction, like the intramolecular reaction of a Wittig reagent with an aldehyde or ketone,³ might provide a useful route to cyclic ketones. The results of our exploration of this idea are summarized in Chart I,

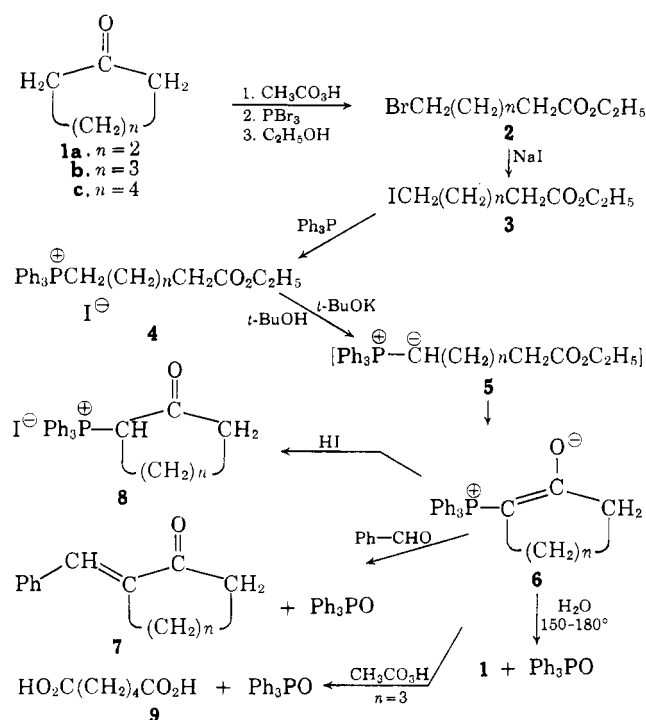
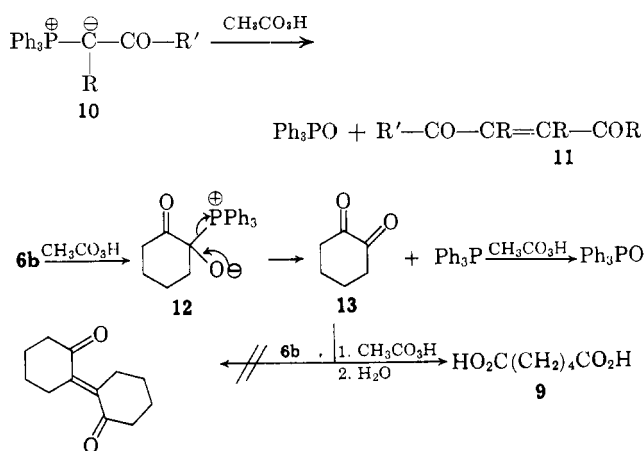


Chart I

wherein the ring closure step (*i.e.*, **5** \rightarrow **6**) may be considered mechanistically comparable to a Dieckman condensation.⁴ Subsequent hydrolytic cleavage⁵ furnished the appropriate ketones. A noteworthy by-product of this study is a ready preparative route for the α -ketocycloalkylidetriphenylphosphoranes **6** which are not accessible^{6,7} *via* the reaction of the α -halocyclo-

alkanones with triphenylphosphine. The formation of the *trans*-2-benzylidenecycloalkanones **7** from reaction of the ylids with benzaldehyde is in agreement with the expected stereochemical course of Wittig reactions involving relatively stable phosphorus ylids.⁸ The ylid **6b** (or its conjugate acid) was found to undergo a rapid reaction with three molar equivalents of peracetic acid to form adipic acid (**9**) and triphenylphosphine oxide. Since attempts to intercept possible intermediates in this oxidative cleavage by use of less than a stoichiometric quantity of peracid led only to the isolation of **6**, **9**, and triphenylphosphine oxide, we conclude that the first step in this oxidation is rate determining. In the light of the reported⁹ conversions of acyclic phosphoranes **10** to diketone ethylene derivatives **11** by reaction with one molar equivalent of peracetic acid, it seems probable that both reactions involve formation and cleavage of the alkoxide—*e.g.*, **12**—to form an α -diketone—*e.g.*, **13**. In the case reported here the diketone **13** is apparently sufficiently reactive that it is intercepted by peracetic acid to form an anhydride more rapidly than it reacts with an additional molecule of the ylid **6**.

Experimental¹⁰

The ω -Halo Esters 2 and 3.—Following the general procedures previously summarized,¹¹ each of the ketones **1** was allowed to react with peracetic acid in refluxing chloroform. The crude

(1) This research has been supported by Grant No. RG-8761 from the National Institutes of Health and Grant No. 594-A from the Petroleum Research Fund.

(2) (a) H. J. Bestmann, *Tetrahedron Letters*, No. 4, 7 (1960); (b) H. J. Bestmann and B. Arnason, *ibid.*, No. 14, 455 (1961); (c) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961); (d) S. T. D. Gough and S. Trippett, *ibid.*, 2333 (1962).

(3) (a) T. I. Bieber and E. H. Eisman, *J. Org. Chem.*, **27**, 678 (1962); (b) C. E. Griffin, K. R. Martin, and B. E. Douglas, *ibid.*, **27**, 1627 (1962).

(4) C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, **1**, 266 (1942).

(5) (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957); (b) R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **45**, 1137 (1962); (c) α -Ketoalkylidene triphenylphosphoranes have also been reductively cleaved with zinc and acetic acid (ref. 2c).

(6) (a) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

(7) (a) I. J. Borowitz and L. I. Grossman, *Tetrahedron Letters*, No. 11, 471 (1962); (b) H. Hoffmann and H. J. Diehr, *ibid.*, No. 13, 583 (1962).

(8) H. O. House and G. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

(9) D. B. Denny and L. C. Smith, *J. Am. Chem. Soc.*, **82**, 2396 (1960).

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined on a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954).

lactones produced were heated on a steam bath with excess phosphorus tribromide¹² for 12 hr. and then treated with ethanol to produce the bromo esters **2** in over-all yields ranging from 53 to 95%. Each of the esters exhibited a single peak on gas chromatography¹³ and had infrared and n.m.r. absorption consistent with the assigned structure. Reaction of the bromo esters **2** with sodium iodide in acetone produced the iodo esters **3** in yields ranging from 89 to 97%.

The Phosphonium Salts 4.—A solution of 21 g. (0.078 mole) of the iodo ester **3b** and 21 g. (0.080 mole) of triphenylphosphine in 150 ml. of benzene was refluxed for 12 hr. and then cooled. The benzene solution was decanted from the crude salt **4** which had separated as a pale yellow oil and the residual oil was extracted with three 100-ml. portions of boiling benzene. The residual oil was heated to 100° under reduced pressure for 1 hr. to leave 42.5 g. (100%) of the crude salt **4b** whose thin-layer chromatogram¹⁴ showed only one spot and indicated the absence of either starting material. The product, which gave an immediate precipitate with methanolic silver nitrate, has infrared absorption¹⁵ at 1722 cm.⁻¹ (ester C=O) with n.m.r. absorption¹⁶ in the region 2.0–2.5 τ (15H, aryl C—H), a quadruplet ($J = 7$ c.p.s.) centered at 5.93 τ (2H) with a triplet ($J = 7$ c.p.s.) at 8.79 τ (3H) attributable to an ethoxyl function, a very broad peak centered at 6.35 τ (2H, $\text{—}\overset{\ominus}{\text{P}}\text{—CH}_2\text{—}$), and a triplet ($J = 6$ c.p.s.) at 7.74 τ (2H, $\text{—CH}_2\text{—CO—}$) and broad absorption in the region 8.0–8.6 τ (6H, $\text{—CH}_2\text{—}$).

Similarly, reaction of 50.2 g. (0.194 mole) of the iodo ester **3a** with 52.4 g. (0.20 mole) of triphenylphosphine in 300 ml. of benzene followed by the previously described purification procedure yielded 98 g. (97%) of the crude salt **4a** as a pale yellow oil which showed only a single spot (not starting materials) on thin-layer chromatography¹⁴ and has infrared absorption¹⁵ at 1722 cm.⁻¹ (ester C=O) with n.m.r. absorption¹⁶ in the region 2.0–2.5 τ (aryl C—H) with a quadruplet ($J = 7$ c.p.s.) at 5.95 τ and a triplet ($J = 7$ c.p.s.) at 8.82 τ (OCH₂CH₃) as well as broad absorption at about 6.3 τ ($\text{—}\overset{\ominus}{\text{P}}\text{—CH}_2\text{—}$) and broad absorption in the region 7.5–8.4 τ .

The same procedure employing 57 g. (0.20 mole) of the iodo ester **3c**, 53 g. (0.20 mole) of triphenylphosphine, and 200 ml. of benzene yielded 90 g. (90%) of the crude salt **4c** as a colorless oil which exhibits a single spot on thin-layer chromatography¹⁴ and has infrared absorption¹⁵ at 1720 cm.⁻¹ (ester C=O) and n.m.r. absorption¹⁶ in the region 1.9–2.5 τ (aryl C—H), a broad band

centered at about 6.3 τ ($\text{—}\overset{\ominus}{\text{P}}\text{—CH}_2\text{—}$), broad absorption in the region 7.4–8.6 τ and a quadruplet ($J = 7$ c.p.s.) at 5.84 τ with a triplet ($J = 7$ c.p.s.) at 8.75 τ (OCH₂CH₃).

α -Ketocyclohexylidetriphenylphosphorane (6b).—A solution of 42 g. (0.078 mole) of the salt **4b** in 300 ml. of *t*-butyl alcohol was placed in a flask fitted with a Soxhlet extractor containing 3.4 g. (0.085 g.-atom) of potassium.¹⁷ The mixture was refluxed, with stirring and conversion of the potassium to the potassium alkoxide, for 12 hr. After the reaction mixture had been concentrated under reduced pressure and partitioned between water and chloroform, the chloroform solution was dried and diluted with ethyl acetate to precipitate 22.1 g. (79%) of the ylid **6b** as yellow prisms, m.p. 243–245°. Recrystallization from an ethyl acetate–chloroform mixture raised the melting point to 245–247° (sealed capillary). The product has infrared absorption¹⁸ at 1507 cm.⁻¹ with intense end absorption (ϵ 5,200 at 210 $m\mu$) and a shoulder with no distinct maxima in the region 250–280 $m\mu$ of the ultraviolet.¹⁹ The material has complex n.m.r. absorption in regions 2.0–3.0 τ (aryl C—H) and 7.5–8.5 τ (aliphatic C—H) with no other absorption.

(12) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(13) A column packed with Dow-Corning silicone fluid, no. 710, suspended on ground firebrick was employed.

(14) A Silica Gel coating was employed with a 1:1 (by volume) mixture of methanol and ethyl acetate as the solvent system.

(15) Determined in chloroform solution.

(16) Determined in deuteriochloroform.

(17) An attempt to achieve cyclization with ethanolic sodium ethoxide was unsuccessful, the bulk of the starting material being recovered.

(18) α -Ketoalkylidene ylids are reported (ref. 5a) to have infrared absorption in the region 1515–1530 cm.⁻¹ with ultraviolet maxima in the region 268–288 $m\mu$.

(19) Determined in 95% ethanol.

Anal. Calcd. for C₂₄H₂₃PO: C, 80.34; H, 6.47. Found: C, 80.03; H, 6.47.

To a solution of 1.72 g. (5 mmoles) of the ylid **6b** in 25 ml. of boiling methanol containing a few crystals of sodium bisulfite was added 1.4 ml. (10 mmoles) of hydriodic acid. The solution was cooled and filtered to separate 1.98 g. (81%) of the iodide **8b** as yellow crystals, m.p. 235–240° dec. Repeated attempts to purify the salt **8b** resulted in conversion back to the ylid **6b**. The crude salt **8b** has infrared absorption¹⁵ at 1698 cm.⁻¹ (C=O).

A solution of 7.168 g. (0.020 mole) of the ylid **6b** and 2.12 g. (0.020 mole) of benzaldehyde in 50 ml. of benzene was refluxed for 24 hr. and then concentrated under reduced pressure. Distillation of the residue (125° at 0.3 mm.) and subsequent recrystallization from pentane afforded 3.41 g. (91.5%) of benzaldehyde (7b), m.p. 54–55°, identified with an authentic sample²⁰ by a mixed melting-point determination and comparison of infrared spectra.

A mixture of 3.560 g. (0.01 mole) of the ylid **6b**, 1.470 g. of *o*-dichlorobenzene (as an internal standard), and 12 ml. of a 2:1 (by volume) ethanol–water mixture containing a small amount of sodium hydroxide to bring the pH of the mixture to 10–11 was heated to 150° in a sealed tube for 3 days. After the reaction mixture had been partitioned between chloroform and water, the chloroform solution was distilled. Gas chromatographic analysis¹³ of the distillate indicated a quantitative yield of cyclohexanone (1b). A portion of the distillate was converted to cyclohexanone 2,4-dinitrophenylhydrazine, m.p. 159–160°, identified by a mixed melting-point determination. Sublimation (200° at 0.3 mm.) of the residue from the hydrolysis mixture separated 2.35 g. (85%) of triphenylphosphine oxide, m.p. 154–156°.

α -Ketocyclopentylidetriphenylphosphorane (6a).—Reaction of 98 g. (0.188 mole) of the phosphonium salt **4a** with 8.5 g. (0.21 g.-atom) of potassium and 250 ml. of *t*-butyl alcohol as previously described was followed by acidification of the crude product with 20 ml. (0.24 mole) of concentrated hydrochloric acid and concentration. The residue was partitioned between water and methylene chloride and the methylene chloride phase was dried, concentrated, and diluted with ethyl acetate to separate 70 g. of crude phosphonium salt. A solution of this salt in ethanol was made basic with aqueous sodium hydroxide and concentrated to precipitate 54.5 g. (84%) of the ylid **6a** as pale yellow crystals, m.p. 243–245° dec. (sealed capillary). This product, whose decomposition point was not altered by recrystallization from aqueous ethanol or a methylene chloride–ethyl acetate mixture, has infrared absorption¹⁵ at 1545 cm.⁻¹ with ultraviolet¹⁹ end absorption (ϵ 5200 at 210 $m\mu$) and a shoulder in the region 250–280 $m\mu$.

Anal. Calcd. for C₂₃H₂₁PO: C, 80.21; H, 6.15. Found: C, 80.14; H, 6.04.

A 3.58-g. sample of the ylid **6a** was converted to the 4.79 g. of the iodide **8a** as colorless needles, m.p. 243–254° dec. Recrystallization from methanol separated the pure salt **8a**, m.p. 245–248° dec., with infrared absorption¹⁵ at 1740 cm.⁻¹ (cyclopentanone C=O).

Anal. Calcd. for C₂₃H₂₂IPO: C, 58.49; H, 4.70; I, 26.87. Found: C, 58.75; H, 4.86; I, 26.87.

Reaction of 6.848 g. (0.02 mole) of the ylid **6a** with 2.12 g. (0.02 mole) of benzaldehyde in 50 ml. of benzene as previously described afforded 5.35 g. (96.5%) of triphenylphosphine oxide, m.p. 155–156°, and 3.26 g. (95%) of benzaldehyde (7a), m.p. 67–69°, identified with an authentic sample²⁰ by comparison of infrared spectra.

Hydrolysis of a 3.24-g. (0.01 mole) sample of the ylid **6a** employing 1.265 g. of *o*-chlorotoluene (as an internal standard) and 12 ml. of 2:1 (by volume) ethanol–water (adjusted to pH 10–11) at 180° for 3 days afforded 2.52 g. (92%) of triphenylphosphine oxide, m.p. 153.7–155°. The calculated¹⁸ yield of cyclopentanone (1a) was 93%. A portion of the volatile product was converted to cyclopentanone 2,4-dinitrophenylhydrazone, m.p. 145–145.5°, identified by a mixed melting-point determination.

α -Ketocycloheptylidetriphenylphosphorane (6c).—Reaction of 90 g. (0.18 mole) of the phosphonium salt **4c** with 6.9 g. (0.17 g.-atom) of potassium and 250 ml. of *t*-butyl alcohol as described in the previous case afforded 32.8 g. (52%) of the crude ylid **6c**, m.p. 210–216°. Recrystallization from an ethyl acetate–methylene chloride mixture separated 26.8 g. (41%) of the pure ylid, m.p. 205–208°, with infrared absorption¹⁵ at 1508 cm.⁻¹ and ultraviolet¹⁹ end absorption (ϵ 3,900 at 210 $m\mu$) with a series of maxima (ϵ 770–460) in the region 250–280 $m\mu$.

(20) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **78**, 4394 (1956).

Anal. Calcd. for $C_{25}H_{25}PO$: C, 80.62; H, 6.77. Found: C, 80.40; H, 6.68.

A 3.75-g. sample of the ylid **6c** gave 4.95 g. (98%) of the iodide **8c** as yellow prisms from methanol, m.p. 206–208°, dec., with infrared absorption at 1695 cm^{-1} ($C=O$).

Anal. Calcd. for $C_{25}H_{25}IPO$: C, 60.01; H, 5.24; I, 25.36. Found: C, 59.72; H, 5.11; I, 25.63.

From the reaction of 7.410 g. (0.02 mole) of the ylid **6c** with 2.12 g. (0.02 mole) of benzaldehyde in 50 ml. of benzene was isolated 4.10 g. (74%) of triphenylphosphine oxide, m.p. 154–156°, and 3.08 g. (82.5%) of benzaldehyde (7c), b.p. 200° (0.5 mm.), in a short-path still. Recrystallization gave 2.66 g. (71%) of the pure benzylidene derivative **7c**, m.p. 37–39°, identified with an authentic sample²⁰ by comparison of infrared spectra.

Hydrolysis of 3.7052 g. (0.01 mole) of the ylid **6c** in the presence of 1.265 g. of *o*-chlorotoluene (as an internal standard) and 12 ml. of 2:1 ethanol–water at 160° for 3 days produced 2.48 g. (84%) of triphenylphosphine oxide, m.p. 154.5–156°. The calculated yield of cycloheptanone (**1c**) was 90%; a portion of the volatile product was converted to cycloheptanone 2,4-dinitrophenylhydrazone, m.p. 147.5–148°, identified by a mixed melting-point determination.

Reaction of the Ylid 6b with Peracetic Acid.—To a cold (0°) solution of 3.44 g. (0.01 mole) of the ylid **6b** in 50 ml. of methanol was added, dropwise and with stirring, a solution containing from 0.01 to 0.04 mole of peracetic acid in a mixture (1:1 by volume) of

TABLE I

REACTION OF 0.01 MOLE OF THE YLID **6b** WITH PERACETIC ACID

Peracetic acid, mole	Ylid 6b , %	Ph_3PO , %	Acid 9 , %
0.01	54	..	20
0.02	35	36	33.5
0.03	..	75	66
0.04	..	88	71

methanol and methylene chloride. The resulting mixture was stirred for 1.5 hr. at 0° and then concentrated under reduced pressure and partitioned between methylene chloride and sodium bicarbonate. The adipic acid, recovered from the bicarbonate solution in the usual way, was recrystallized from an acetone–methylene chloride mixture to give the pure acid (**9**), m.p. 151–153°, identified by a mixed melting-point determination. Concentration of the methylene chloride solution followed by extraction with ether separated the unchanged ylid **6b** (recrystallized from an ethyl acetate–methylene chloride mixture, m.p. 243–245° dec.) and triphenylphosphine oxide (recrystallized from an acetone–pentane mixture, m.p. 152–156°). The yields as a function of quantity of peracid used are summarized in Table I.

C-6 Hydroxylated Steroids. IV.¹ 6-Hydroxylated 17 α -Acetoxypregesterone, 17 α -Acetoxy-6-methylprogesterone, and Related Compounds

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The preparation of the 6 α - and 6 β -hydroxy derivatives of 17 α -acetoxypregesterone and 17 α -acetoxy-6-methylprogesterone by a variety of methods is described. Certain transformations (dehydrogenation, elimination, and isomerization) of these C-6 oxygenated steroids have been studied.

Our interest in the various methods for the synthesis of steroids containing a 6-hydroxyl group has been centered about the study of the conversion of Δ^4 -3-ones to the corresponding 6-hydroxy- Δ^4 -3-ones.^{2–4} In this paper we wish to report on the preparation of a number of 6-hydroxy compounds related to 17 α -acetoxypregesterone and 17 α -acetoxy-6-methylprogesterone.

We have previously demonstrated a general utility for the preparation of 6-hydroxy- Δ^4 -3-ones through the reaction of Δ^3 -enol ethers with peracid.¹ Accordingly, when 17 α -acetoxy-3-methoxypregna-3,5-dien-20-one (**I**) was oxidized with monopero-phthalic acid there were isolated by chromatography two crystalline fractions. The less polar material was readily identified as 17 α -acetoxy-6 β -hydroxypregna-4-ene-3,20-dione (**III**). The second fraction isolated in much smaller yield proved to be 17 α -acetoxy-6 α -hydroxypregna-4-ene-3,20-dione (**IV**).⁵ As in other series we have studied, a mixture of the 6-hydroxylated compounds is encountered with the β -epimer predominating.¹

When the 6 β ,17 α -diacetate **V** was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone,⁶ there was obtained 6 β ,17 α -diacetoxypregna-1,4-diene-3,20-dione (**VI**). Under the vigorous reaction conditions required for 1,2-dehydrogenation, protection of the 6-hydroxyl group was mandatory.⁷ Selective hydrolysis of **VI** afforded 17 α -acetoxy-6 β -hydroxypregna-1,4-diene-3,20-dione (**VII**). The latter was converted into its crude 6-mesylate, which on attempted recrystallization led to the formation of the $\Delta^{1,4,8}$ -trienone **VIII**.⁸ Chromic acid oxidation of **VII** yielded the $\Delta^{1,4,3,6}$ -dione **IX** with an ultraviolet absorption maximum at 250 $m\mu$ (ϵ 14,800). Under basic conditions it exhibited a more intense maximum at 253 $m\mu$ (ϵ 18,000) and a second broad maximum centered at 393 $m\mu$ (ϵ 9650).⁹

The preparation of 6-hydroxy-6-methyl compounds was also undertaken and was approached through a number of pathways. Peracid attack on 3,17 α -diacetoxy-6-methylpregna-3,5-dien-20-one (**X**)¹⁰ was selected for one study. When an ethereal solution of the latter

(1) Previous paper in this series, *J. Org. Chem.*, **27**, 4046 (1962).

(2) S. Bernstein, W. S. Allen, C. E. Linden, and J. Clemente, *J. Am. Chem. Soc.*, **77**, 6612 (1955).

(3) S. Bernstein and R. Littell, *J. Org. Chem.*, **25**, 313 (1960).

(4) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *ibid.*, **26**, 974 (1961).

(5) (a) The 6 β -hydroxy compound **III** has been previously prepared by acetic acid opening of the appropriate 5 α ,6 α -epoxide and subsequent hydrolysis [R. Sciaky, *Gazz. chim. ital.*, **91**, 545 (1961)]; and (b) through the reaction of peracid on the corresponding Δ^3 -enol acetate [H. Mori, *Chem. Pharm. Bull. Japan*, **9**, 328 (1961)]. The 6 α -hydroxy compound **IV** has been obtained by epimerization of the 6 β -acetoxy derivative **IV** followed by 6-deacetylation (ref. 5a).

(6) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(7) Although the selective oxidation of Δ^4 -3 β ,6 β -diols to 6 β -hydroxy- Δ^4 -3-ones by the quinone reagent has been successfully executed [D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. 9, 14 (1960)] the conditions used were considerably milder than those employed here for 1,2-dehydrogenation.

(8) W. Hiersemann, E. Kaspar, and U. Kerb, U.S. Patent 2,962,510 (November 29, 1961).

(9) In the cholesterol series, this chromophore [λ_{max} 251 $m\mu$ (ϵ 14,800)] has been generated by quinone oxidation of the Δ^4 -3,6-dione; D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, 29 (1962).

(10) H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959).