

3% of IV. Analytical absorption bands for *endo*-IV were found at 613 and 622 cm^{-1} , while those for *exo*-III were at 506, 521, 598, 622, and 651 cm^{-1} . Solutions of the bromides in tetrachloroethylene were used. This procedure was much more satisfactory than that described earlier.² The infrared spectrum of the mixture, both in the sodium chloride and potassium bromide regions, was essentially identical to that of a synthetic mixture which contained 31% IV and 69% III. *exo*-Bromide III was found not to isomerize to *endo*-bromide IV under the bromination conditions. (The solvent was saturated with hydrogen bromide at the start.)

Bromination of a mixture of dihydroaldrin (VI) and *endo*-(IV) or *exo*-(III) aldrin hydrobromide. A mixture of 1.835 g. (5.00 mmoles) of VI and 21.2 mg. (0.050 mmole) of IV was brominated as described above for VI. There was recovered 1.802 g. (98.2%) of VI and 77.2 mg. of aldrin hydrobromides. The latter corresponds to an increment of 56.0 mg. (2.5%) of bromination product plus 21.2 mg. of added IV. The mixture gave an analysis corresponding to 46% *endo* product (calcd., 49%) indicating that *endo* material IV survived further bromination (within experimental error). A similar experiment with *exo* bromide gave similar results (found: 11% *endo*; calcd.: 10% *endo*).

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Steroids and Related Natural Products. IX. Selective Osmium Tetroxide Oxidation of Olefins^{1,2}

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Addition of osmium tetroxide to an olefin usually yields a cyclic osmium ester and this reaction may be accelerated by employing solvents such as pyridine.^{3,4} A *cis*-glycol derivative of the original olefin can be prepared by treating the osmic acid ester with one of several reagents. Hydrogen sulfide or sodium sulfite in aqueous ethanol are commonly used for this purpose.^{5,6} Recently, Baran

(1) The preceding contribution in this series was prepared by G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

(2) This investigation was supported by PHS Research Grants CY-4074(C1) and CY-4074(C2) from the National Cancer Institute, Public Health Service.

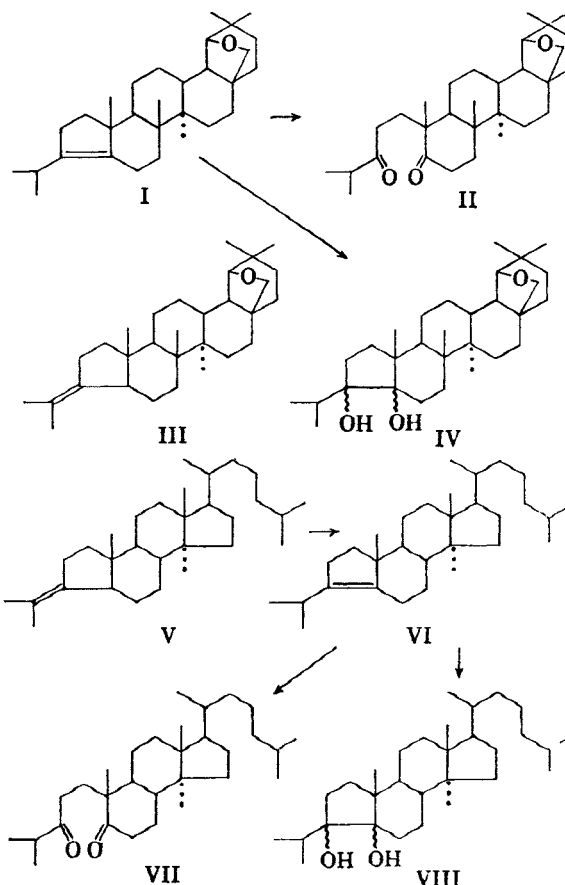
(3) A recent review of this reaction has been prepared by F. D. Gunstone, *Advances in Organic Chemistry: Methods and Results*, Vol. I, R. A. Raphael, E. C. Taylor, and H. Wynberg, eds., Interscience, New York, 1960, p. 110.

(4) Compare the observations of: G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4377 (1955); J. A. Zderic, H. Carpio, and C. Djerassi, *J. Org. Chem.*, **24**, 909 (1959); and E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5953 (1960).

(5) Alternatively, the osmium intermediate may be oxidized with periodate to a dicarbonyl derivative of the original olefin. Cf. R. Pappo, D. S. Allan, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956); and N. A. Nelson and R. B. Garland, *J. Am. Chem. Soc.*, **79**, 6313 (1957).

has recommended an osmium tetroxide hydroxylation procedure utilizing pyridine as solvent for the initial reaction and sodium bisulfite in aqueous pyridine for generating the *cis*-glycol.^{6,7}

During a previous study concerned with the structure of α -apoallobetulin (I)⁸ we found that oxidation of this substance using the osmium tetroxide-pyridine-sodium bisulfite technique⁶ yields diketone II. When exocyclic olefin III was oxidized under the same conditions only a glycol derivative was obtained. Similarly, glycol IV was readily prepared from the endocyclic isomer (I) using an osmium tetroxide (benzene solution)-hydrogen sulfide procedure.



Information derived from these experiments suggested that the Baran procedure⁶ might provide a method for selectively oxidizing certain tetra-substituted olefins. Several transformations of the Δ -norsteroid (V)⁹ arising from phosphorus pentachloride dehydration of 3 β -hydroxy-5 α -lanostane

(6) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

(7) Cf. also, B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2226 (1958).

(8) Evidence in support of this structure has been summarized by G. R. Pettit, B. Green, and W. J. Bowyer, *J. Org. Chem.*, **26**, 2879 (1961). The NMR spectrum of α -apoallobetulin is also consistent with formulation I. We are indebted to Dr. George Slomp, Research Division, the Upjohn Company, for providing this information.

(9) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

lend additional support to this proposal. Acid-catalyzed isomerization of 3-isopropylidene- α -norlanostane (V) yielded the isomeric olefin VI. Oxidation of 3-isopropyl- α -norlanost-3(5)-ene (VI) employing the osmium tetroxide-sodium bisulfite reaction⁶ resulted in oxidative cleavage to diketone VII. Although the ketone was obtained in rather poor yield (7%) following chromatographic separation, it appeared to represent the major product. An identical specimen of the diketone (VII) was isolated following ozonization of olefin VI. As previously observed in the case of α -apoallobetulin, cyclopentene VI was easily converted to a glycol (VIII) by successive treatment with osmium tetroxide-benzene and hydrogen sulfide.

Interestingly, an osmium tetroxide (pyridine)-hydrogen sulfide reaction sequence¹⁰ was also found to convert α -apoallobetulin (I) to glycol IV. The product (IV) was recovered in quantitative yield following treatment with sodium bisulfite in aqueous pyridine. Consequently, the unusual oxidation of endocyclic olefins I and IV by osmium tetroxide-sodium bisulfite does not appear to depend on initial presence of pyridine or simple oxidative cleavage of a glycol intermediate.^{11,12}

EXPERIMENTAL¹³

3-Isopropylidene- α -norlanostane (V). A pure sample (2.5 g.) of 3 β -hydroxy-5 α -lanostane¹⁴ in benzene solution was dehydrated with phosphorus pentachloride as described by Barton.⁹ After recrystallization from chloroform-methanol the product (1.9 g.) melted at 112–113° (lit.,⁹ m.p. 114°).

3-Isopropyl- α -norlanost-3(5)-ene (VI). A solution composed of 3-isopropylidene- α -norlanostane (V, 3.4 g.), ethyl alcohol (750 ml.), carbon tetrachloride (30 ml.), and concd. hydrochloric acid (30 ml.) was heated at reflux for 3 hr. After cooling, the reaction mixture was concentrated to ca. 200 ml. *in vacuo* and the crystalline product (2.5 g.), m.p. 84–86°, which separated was collected. Two recrystallizations from methanol gave colorless needles melting at 88.5–89.5°, $[\alpha]_D^{25} + 72.9^\circ$.

Anal. Calcd. for C₃₀H₅₂: C, 87.30; H, 12.70. Found: C, 87.11; H, 12.61.

Oxidation of 3-isopropyl- α -norlanost-3(5)-ene (VI). Osmium tetroxide (0.6 g.) was added with stirring to a solution of

(10) Recent applications of a similar hydroxylation reaction have been described by: D. H. R. Barton and A. S. Kende, *J. Chem. Soc.*, 688 (1958); and P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 42, 2122 (1959).

(11) Apparently, an osmium-containing intermediate is necessary for further oxidation.

(12) Several oxidation reactions involving sulfite have recently been described by W. G. Toland, *J. Am. Chem. Soc.*, 82, 1911 (1960).

(13) All melting points are uncorrected and were determined in a silicone oil bath, using open Kimble glass capillaries. Elemental analyses were provided by Dr. A. Bernhardt, Mülheim, Germany. The infrared data was recorded by Dr. R. A. Hill of this department and the optical rotation (chloroform solution) measurements were performed in the laboratory of Drs. Weiler and Strauss, Oxford, England. Activated alumina refers to Merck aluminum oxide, "suitable for chromatography."

(14) C. S. Barnes and A. Palmer, *Australian J. Chem.*, 10, 334 (1957).

olefin VI (1.0 g.) in dry pyridine (16 ml.). The reaction mixture rapidly became dark brown and warm. Following a 3-day period at room temperature a solution prepared from water (18 ml.), sodium bisulfite (1.2 g.) and pyridine (8 ml.) was added to the dark-colored mixture. Stirring was continued for 20 min., before extracting the mixture with chloroform. The combined chloroform extract was dried (sodium sulfate) and concentrated to a dark purple oil (1.4 g.). A solution of the residue in petroleum ether (b.p. 65–70°) was chromatographed on activated alumina. A portion (0.035 g.) of the oily fraction (VII, 0.09 g.) eluted with benzene was crystallized from methanol; yield, 0.020 g., m.p. 64–65°, $\nu_{\max}^{\text{CHCl}_3}$ 1695 and 1700 cm.⁻¹ The specimen of diketone VII obtained by this procedure was found (mixture melting point determination and infrared spectral comparison in chloroform) to be identical with the ozonolysis product described in the following experiment.

Several attempts to isolate a glycol derivative from the remaining mixture of dark-colored oxidation products were unsuccessful.

Ozonization of 3-isopropyl- α -norlanost-3(4)-ene (VI). A solution of olefin VI (0.6 g.) in methylene chloride (75 ml.) cooled to -70° was treated with a stream of ozone in oxygen until oxidation appeared complete (potassium iodide indicator). The reaction mixture was then diluted with acetic acid (10 ml.) and stirred for 1 hr. with zinc dust (2 g.) at 0°. After filtration the solution was washed with dilute sodium bicarbonate solution and water. Removal of dry (sodium sulfate) solvent left a viscous oil which was dissolved in petroleum ether (b.p. 65–70°) and chromatographed on activated alumina. The fraction (0.47 g.) eluted with benzene was dissolved in methanol. The higher melting (127–133°) side-product¹⁵ (0.13 g.) which crystallized first was not further investigated. A second crop (0.2 g.), m.p. 62–64°, was found to be diketone VII. An analytical sample recrystallized from methanol as colorless prisms, m.p. 64–65°, $[\alpha]_D^{25} + 48.6^\circ$ (c, 1.30), $\nu_{\max}^{\text{CHCl}_3}$ 1695 and 1700 cm.⁻¹

Anal. Calcd. for C₃₀H₅₀O₂: C, 81.02; H, 11.79; O, 7.20. Found: C, 80.80; H, 11.90; O, 6.99.

Osmium tetroxide hydroxylation of 3-isopropyl- α -norlanost-3(5)-ene (VI). A solution of osmium tetroxide (0.23 g.) in benzene (8 ml.) was added with stirring to cyclopentene VI (0.36 g.) in benzene (15 ml.). After 3 days at room temperature the brown solution was treated with a stream of hydrogen sulfide for 10 min. After removal of the black precipitate the filtrate was concentrated to dryness. The colorless crystalline residue weighed 0.16 g., m.p. 125–135°, following recrystallization from methanol. A pure specimen crystallized from petroleum ether as colorless needles; yield, 0.10 g., m.p. 151–152°, $[\alpha]_D^{25} + 41.7^\circ$ (c, 1.32), ν_{\max}^{KBr} 3300 cm.⁻¹

Anal. Calcd. for C₃₀H₅₄O₂: C, 80.65; H, 12.18; O, 7.17. Found: C, 80.65; H, 12.01; O, 7.04.

Osmium tetroxide hydroxylation of α -apoallobetulin (I). A reaction mixture prepared from α -apoallobetulin (I, 1.0 g.),⁸ osmium tetroxide (0.6 g.), and pyridine (20 ml.) was stirred at room temperature for 2 hr. Following an additional 20-hr. period at room temperature a stream of hydrogen sulfide was conducted into the solution for 15 min. The precipitate was removed and the dark-colored solution was then diluted with benzene and washed with 2N hydrochloric acid and water. The resulting green solution was dried (sodium sulfate) and concentrated to a semisolid (0.85 g.) which was dissolved in benzene and chromatographed on activated alumina. Following recrystallization from methanol the fractions (0.22 g. and 0.40 g., respectively) eluted with benzene and 1:1 chloroform-methanol melted at 225–230°, and weighed 0.50 g. One additional recrystallization from methanol led to a pure sample of glycol IV, m.p. 229–230°. The product was found (mixture melting point and infrared spectral comparison in potassium bromide) to be identical with an authentic sample (IV, m.p. 230°).⁸

(15) Cf., ref. 8, footnote 10.

Attempted oxidation of glycol IV. The glycol (IV, 0.25 g.) was dissolved in pyridine (11 ml.) and treated with a solution of sodium bisulfite (0.3 g.) in water (5 ml.). After 45 min. the solution was diluted with water and filtered. The colorless solid weighed 0.25 g. and melted at 228°. A mixture of the product and glycol IV melted at 228–230°.

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Optical Rotatory Dispersion Studies. LVI.¹ Thiones²

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The success of our initial studies³ on the optical rotatory dispersion behavior of carbonyl-containing substances encouraged us to examine other chromophores⁴ which may exhibit anomalous optical rotatory dispersion. From a theoretical standpoint,⁵ a comparison of the rotatory dispersion curves of ketones and thiones would be most instructive. The anomalous rotatory dispersion of a variety of C=S containing chromophores—such as dithiocarbamates,⁶ xanthates,^{6,7} thionocarbalkoxy derivatives,⁸ thiohydantoin⁸ and trithiones⁹—have already been recorded and in a number of instances valuable correlations could be made between these Cotton effect curves and certain stereochemical features.

Simple thio ketones, however, are essentially unavailable,¹⁰ largely because of their instability in the monomeric state. Recently, Dodson and Sollman¹¹ have reported that certain steroidal

(1) Paper LV, C. Djerassi, *Pure and Appl. Chem.*, **2**, 475 (1961).

(2) Supported by grant No. CRTY-5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) For pertinent references see C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1960.

(4) Our most recent papers in this area are summarized in ref. 1, as well as in C. Djerassi, *Endeavour*, **20**, 138 (1961). See also C. Djerassi, E. Lund, E. Bunnenberg, and B. Sjöberg, *J. Am. Chem. Soc.*, **83**, 2307 (1961) and C. Djerassi, E. Lund, E. Bunnenberg, and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961).

(5) See J. W. Sidman, *Chem. Revs.*, **58**, 702 (1958).

(6) B. Sjöberg, A. Fredga, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5002 (1959).

(7) T. M. Lowry and H. Hudson, *Phil. Trans. Roy. Soc. London*, **232A**, 117 (1933).

(8) C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry, and B. Sjöberg, *Acta Chem. Scand.*, **16**, July (1961).

(9) C. Djerassi and A. Lüttringhaus, *Ber.*, **94**, 2305 (1961).

(10) For leading references see N. Lozac'h, *Rec. Chem. Progress*, **20**, 23 (1959); A. Schönberg in E. Müller (ed.) *Methoden der Organischen Chemie*, George Thieme, Stuttgart 1955, Vol. IX, pp. 704–737.

(11) R. M. Dodson and P. B. Sollman, U. S. Patents 2,763,669 and 2,837,539. We are indebted to these investigators for additional experimental details.

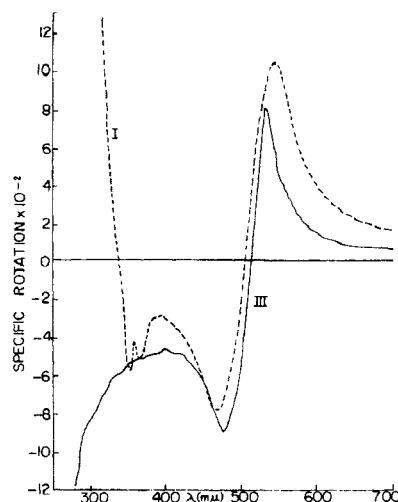


Fig. 1.—Optical rotatory dispersion curves (dioxane solution) of Δ^4 -pregnen-3-one-20-thione (I) and Δ^4 -androsten-3 β -ol-17-thione (III).

dibenzylmercaptals upon reduction with sodium in liquid ammonia produce relatively stable monomeric thiones and through their cooperation, a sample of Δ^4 -pregnen-3-one-20-thione (I) was obtained. Its rotatory dispersion curve is reproduced in Fig. 1 and it will be noted that the two individual chromophores produce completely separate Cotton effects. The fine structure in the 350–400 $m\mu$ region is typical¹² of the Δ^4 -3-keto moiety, while the positive Cotton effect in the visible is clearly associated with the low-intensity absorption maximum at 493 $m\mu$ of the 20-thiono function. The rotatory dispersion curve of this 20-thiono analog I of progesterone (II) is thus completely different from that¹³ of progesterone (II), since the latter's 20-keto function exhibits a strongly positive Cotton effect with a peak near 320 $m\mu$, which already makes itself felt in the rotatory dispersion of the Δ^4 -keto grouping, whose multiple Cotton effect now appears at a much more positive rotation value as compared to an ordinary Δ^4 -3-ketone.

In order to secure a thione containing no other chromophoric substituent, the dibenzylmercaptal¹⁴ of Δ^5 -androsten-3 β -ol-17-one was reduced with sodium in liquid ammonia to yield Δ^5 -androsten-3 β -ol-17-thione (III), whose physical constants were in reasonable agreement with those reported in the patent literature.¹¹ This thio ketone exhibits a high intensity absorption maximum at 237.5 $m\mu$ ($\log \epsilon$ 4.06) and a low intensity one (dioxane solution) at 492.5 $m\mu$ ($\log \epsilon$ 1.15). As shown in Fig. 1, it is this latter absorption band which gives rise to the positive Cotton effect in the 500- $m\mu$ region. The corresponding rotatory dispersion figures in

(12) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(13) E. W. Foltz, A. E. Lippman, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4359 (1955).

(14) R. H. Levin and J. L. Thompson, *J. Am. Chem. Soc.*, **70**, 3140 (1948).