Anal. Calcd. for $C_{19}H_{27}BrO_3$: C, 59.53; H, 7.11; Br, 20.85. Found: C, 59.47; H, 7.34; Br, 20.7.

2β-Chloro-1α-hydroxy-5α-androstane-3,17-dione (IXb).—A solution of 5.00 g. of I in 50.0 ml. of dioxane was treated with 7.5 ml. of water, 0.80 ml. of 70% perchloric acid, and finally dropwise with 2.70 g. of N-chlorosuccinimide in 25 ml. of dioxane over 10 min. The mixture was stirred at room temperature for 3 hr., after which time 250 ml. of 10% aqueous sodium sulfite solution was added. Ice water (1000 ml.) was added and the solids were filtered and dried under vacuum at 64° for 2 hr., yielding 3.547 g. of product which was recrystallized several times from methanol in order to obtain 1.610 g. of pure material, homogeneous on thin layer chromatoplates developed with hexane–ethyl acetate (1:1): m.p. 218–222°; $[\alpha]D$ +81.2°; λ_{max}^{KBr} 3.01, 5.75, and 5.81 μ, etc.; δ = 0.80 (C-18 protons), 1.14 (C-19 protons), 2.52 (doublet, J = 2.5 c.p.s., 1α-hydroxyl proton[27]), 4.15 (multiplet, 1β-proton), and 4.84 p.p.m. (doublet, J = 2.5 c.p.s., 2α-proton).

Anal. Calcd. for $C_{19}H_{27}ClO_3$: C, 67.34; H, 8.03; Cl, 10.46. Found: C, 67.77; H, 7.94; Cl, 10.50.

2β-Chloro-1α-hydroxy-5α-androstane-3,17-dione 3,3;17,17-Bisethylene Ketal (IXc).—A mixture of 1.0 g. of IXb, 100 mg. of *p*-toluenesulfonic acid monohydrate, 20 ml. of ethylene glycol, and 125 ml. of benzene was refluxed with continuous removal of water for 13 hr. The cooled mixture was washed with aqueous sodium bicarbonate solution and with water; the benzene layer was dried over anhydrous magnesium sulfate and then evaporated. The residue was crystallized from methanol, yielding 760 mg. of product homogeneous on thin layer chromatoplates: m.p. 224–226°; $[\alpha]D$ −5.1°; λ_{max}^{KBr} 2.88 μ, etc.; δ = 0.84 (C-18 and C-19 protons), 3.06 (doublet, J = 7.5 c.p.s., 1α-hydroxyl proton), 3.68 (doublet, J = 3 c.p.s., 1β-proton), 3.82 (17-ethylene ketal protons), 4.03 (A_2B_2 multiplet, 3-ethylene ketal protons), and 4.28 p.p.m. (doublet, J = 3 c.p.s., 2α-proton).

Anal. Calcd. for $C_{23}H_{35}ClO_5$: C, 64.69; H, 8.26; Cl, 8.35. Found: C, 64.83; H, 8.16; Cl, 8.25.

3-Hydroxy-1-methylestra-1,3,5(10)-trien-17-one (X).—A solution of 50 mg. of VIII in 5 ml. of *t*-butyl alcohol and 0.25 ml. of glacial acetic acid (under nitrogen) was treated with 60 mg. of selenium dioxide, and the mixture was refluxed for 20 hr. The cooled mixture was diluted with ethyl acetate and filtered, and the residue from the evaporated filtrate was chromatographed on six 20 × 20 cm. silica gel thin layer chromatoplates using hexane–ethyl acetate (1:1). The more mobile component (ochre color with phosphoric acid) was eluted with methanol, concentrated, cooled, and diluted with hexane. The crystalline precipitate was filtered, m.p. 243–245°, and identified as 1-methylestrone by thin layer chromatographic and infrared spectral comparisons with authentic material. A second major component (red color with phosphoric acid), more polar than X, was eluted from the chromatoplates. Ultraviolet spectra of this material were essentially the same as spectra of X, but selenium analyses established that the preparation contained organic-bound selenium. This component was not investigated further.

Acknowledgment.—The authors thank Professor Kurt Mislow, New York University, for the optical rotatory dispersion data of VIII.

Studies Related to 2-Keto Steroids

ROBERT L. CLARKE AND SOL J. DAUM

Sterling-Winthrop Research Institute, Rensselaer, New York

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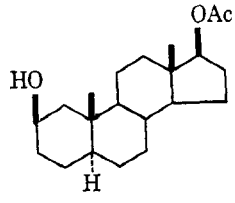
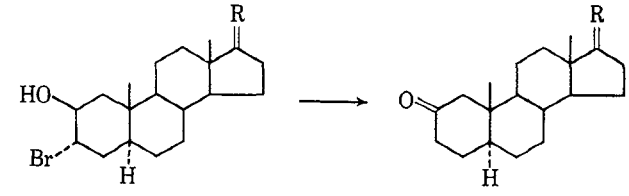
Catalytic debromination of certain steroidal bromohydrins produces ketones instead of the expected alcohols. The rearrangement of 2α-bromo-3-keto steroids to a mixture of 2- and 3-keto steroids has been reported earlier. Applicability of this reaction to certain other steroidal bromo ketones is reported. Several derivatives of 2-keto-androstanes are reported, including a pyrazole and an isoxazole.

A few years ago we desired some 2β(axial)-hydroxy steroids such as 5α-androstane-2β,17β-diol 17-acetate (**1**) for use in preparation of 2,19-oxides, a reaction which has since been reported.[1]



1

An attractive route to **1** appeared to lie through the debromination of 3α-bromo-5α-androstane-2β,17β-diol 17-acetate (**2**).[2] Debromination of this *trans*-diaxial bromohydrin in 95% ethanol with hydrogen in the presence of 30% palladium on strontium carbonate produced, surprisingly, 17β-hydroxy-5α-androstan-2-one acetate (**4**) in 59% yield. These same conditions transformed 3α-bromo-2β-hydroxy-5α-androstan-17-one (**3**)[2] into 5α-androstane-2,17-dione (**5**).[3] Gas

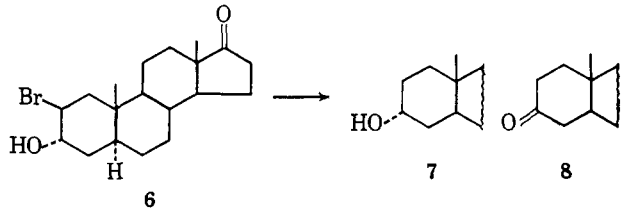


2, R = β-OAc, α-H
3, R = O

4, R = β-OAc, α-H
5, R = O

chromatography indicated that the yield of diketone in this latter reaction was 77%; the yield of purified ketone was 64%. A 4% yield of starting material (**3**) was isolated in pure form as its acetate by careful thick layer chromatography. It appeared that if any normal debromination occurred, the yield of 2β-hydroxy-5α-androstan-17-one was less than 5%.

Another *trans*-diaxial compound, 2β-bromo-3α-hydroxy-5α-androstan-17-one (**6**), was studied, this one with the positions of the hydroxyl and bromine functions simply reversed from those above. Normal de-



6 **7** **8**

(1) *Cf.* R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963); K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2575 (1962); P. N. Rao and J. C. Uroda, *Naturwissenschaften*, **50**, 548 (1963).

(2) P. D. Klimstra and R. E. Counsell, U. S. Patent 3,018,298 (Jan. 23, 1962).

(3) C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, **72**, 5750 (1950).

bromination occurred giving the alcohol, androsterone (7), in 76% yield (purified) and the ketone **8** in about 1% yield. About 4% of less polar materials with apparently no oxygen function in ring A, two other minor impurities of unknown structure, and some unseparated androsterone constituted the remainder of the reaction product.

A third system was then examined, this one with the bromine and hydroxyl groups bearing a *trans*-diequatorial relationship. Debromination of 2α-bromo-3β-hydroxy-5α-pregnan-20-one produced 5α-pregnane-3,-20-dione in 39% yield and 3β-hydroxy-5α-pregnan-20-one in 22% yield.

The only features of this bromohydrin-to-ketone transformation which were determined were that (1) 10% palladium on charcoal serves equally well as 30% palladium on strontium carbonate as catalyst (HBr is evolved and diketone **5** is produced in 78% yield), (2) no reaction occurs until hydrogen is introduced, and (3) the 2β,3β-epoxide is not an intermediate since it can be recovered unchanged when subjected to the reaction conditions. Incidentally, the *trans*-diaxial bromohydrins involved in this study react normally with a strong base; *i.e.*, compound **3** yields the expected 2β,3β-epoxide[2] and compound **6** forms the 2α,3α-epoxide (see Experimental Section).

The preponderance of reactions in the literature involving debromination of bromohydrins are cases where tertiary hydroxyl groups are present which cannot form ketones.[4] James and Shoppee[5] debrominated 7α-bromocholestane-3β,6α-diol, a *cis*-bromohydrin, with hydrogen in the presence of palladium on charcoal and potassium hydroxide to form the normally expected 3β,6α-diol, but the *yield was unspecified* and ketonic material may have been present.

Shoppee, Jones, and Summers[6] report that 2α-bromo-5α-cholestan-3β-ol, a *trans*-diequatorial bromohydrin, is debrominated by hydrogen in the presence of palladium on charcoal and potassium hydroxide to form 5α-cholestan-3β-ol, but again the *yield is unspecified*. This reaction involves exactly the same stereochemistry as present in the pregnane analog described above where we isolated the 3β-ol in 22% yield and the 3-ketone in 39% yield.

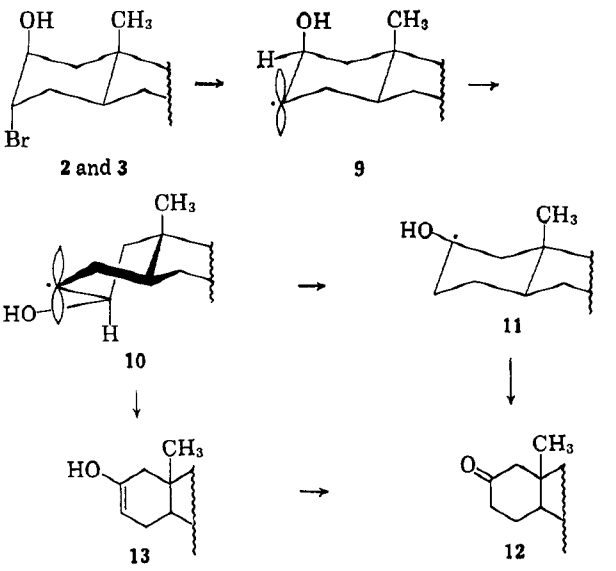
Nambara and Fishman[7] observed that hydrogen in the presence of 25% palladium on calcium carbonate debrominated 16β-bromo-5α,14β-androstane-3β,17α-diol to form 5α,14β-androstane-3β,17α-diol in 86% yield after recrystallization.

Wintersteiner, Moore, and Cohen[8] found that 7α-bromo-6β-hydroxyestradiol 3,17-diacetate, a *trans*-diaxial bromohydrin, is debrominated catalytically to produce 6β-hydroxyestradiol diacetate in 13% yield and its 6α epimer in 44% yield.

It appears that the course of catalytic debromination of cyclic bromohydrins to produce alcohols *vs.* ketones depends upon steric factors other than the particular conformations of the participating bromine and hydroxyl groups. A free-radical mechanism such as is postulated for the conversion of α-mercapto alcohols to ketones

(4) *Cf.* J. A. Zderic, H. Carpio, and D. C. Limon, *J. Org. Chem.*, **27**, 1125 (1962).
(5) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 4224 (1954).
(6) C. W. Shoppee, D. N. Jones, and G. H. R. Summers, *ibid.*, 3100 (1957).
(7) T. Nambara and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961).
(8) O. Wintersteiner, M. Moore, and A. I. Cohen, *ibid.*, **29**, 1325 (1964).

CHART I

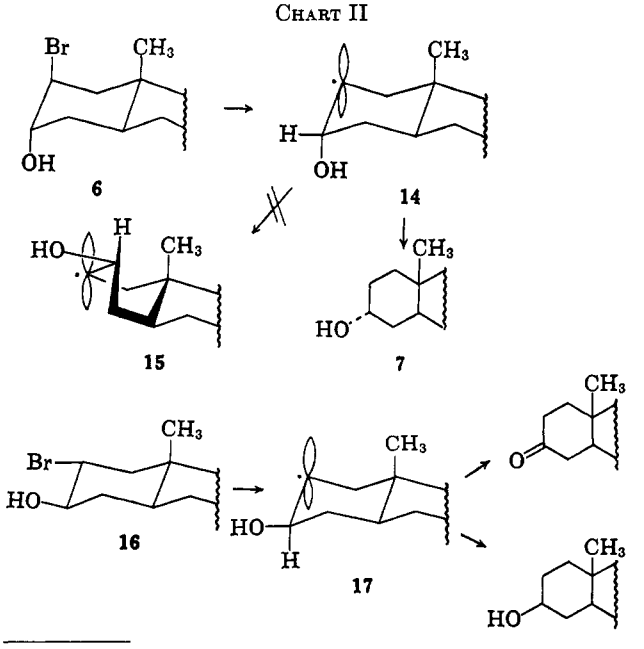


by desulfurization with Raney nickel[9] very nicely explains the divergent courses taken by the reaction under study.

In the case of the 3α-bromo-2β-ols **2** and **3**, the initially formed radical (**9**) (see Chart I) can experience relief of the 1,3-diaxial interaction between the hydroxyl and methyl groups by adoption of a transient boat conformation (**10**) which now has the C-2 hydrogen-to-carbon bond parallel to the single electron orbital at C-3 and thus is in a position favorable for transfer of the radical to C-2 as shown in **11**. Loss of H· from **11** would then produce the observed ketone **12**. An alternate mechanism might involve simple loss of H· from **10** to form an enol precursor (**13**) of ketone **12**.

The failure of the 2β-bromo-3α-ol **6** to form a 3-ketone can be ascribed to the fact that the intermediate radical **14** (see Chart II) cannot assume the boat conformation (**15**) required to bring the C-3 hydrogen

CHART II



(9) C. Djerassi, M. Gorman, and J. A. Henry, *J. Am. Chem. Soc.*, **77**, 4647 (1955); W. A. Bonner, *ibid.*, **74**, 1034 (1952).

bond into parallelity with the electron orbital at C-2 and allow hydrogen transfer or elimination. A methyl group involvement in the prow–stern interaction precludes this conformation. Therefore, the radical **14** simply captures a hydrogen and affords the observed alcohol **7**. In the case of the 2α-bromo-3β-ol **16** where a 39% yield of ketone was produced along with a 22% yield of the 3β-alcohol, the intermediate radical **17** is aligned for rearrangement, but there is no significant strain to be relieved thereby. Hence, competition between rearrangement and H· capture would be expected.

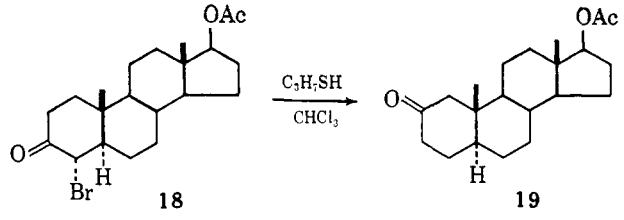
The singularity in the course of debromination of 16β-bromo-5α,14β-androstane-3β,17α-diol reported by Nambara and Fishman[7] is probably related to the difficulty in bringing the single electron orbital of the intermediate radical into parallelity with the bond holding the 17β-hydrogen, an apparent requirement for ketone formation.

In an effort to substantiate the radical nature of this reaction, the debromination was accomplished with tributyltin hydride, a reagent which is known to operate by a radical mechanism.[10] With this hydride, 3α-bromo-2β-hydroxy-5α-androstan-17-one (**3**) was simply debrominated in 95% yield to give 2β-hydroxy-5α-androstan-17-one with 4% recovery of starting material. Tributyltin hydride is an extremely good source of hydrogen for transfer and it apparently donates a hydrogen at C-3 before rearrangement of the radical can occur.

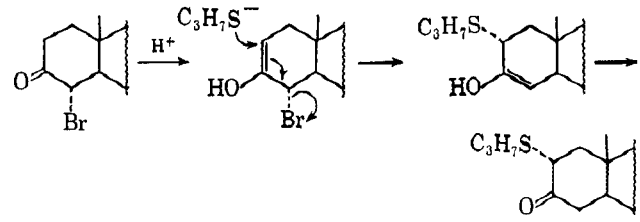
In this paper, which is devoted to some observations on unexpected ketone formation, it appears desirable to record a few further facts about a synthesis of keto steroids reported in 1963.[11]

Treatment of 2α-bromo-3-keto steroids with propylmercaptan in boiling chloroform transforms them into a mixture of 2- and 3-keto steroids. In order to determine the applicability of this reaction where other positions are involved, four different systems were studied.

4α-Bromo-17β-hydroxy-5α-androstan-3-one acetate (**18**)[12] was found to produce 17β-hydroxy-5α-androstan-2-one acetate (**19**), but the yield was only 12%. As reported earlier,[11] the first step in this type of rearrangement apparently involves replacement of Br– by C_3H_7S– with formation of hydrogen bromide. In the present case, under the acidic conditions which develop immediately, it appears that some propylmercapto anion attacks at C-2 as illustrated. The 2-propylmercapto 3-ketone thus formed has already been shown[11] to be an intermediate in the formation of the 2-ketone **19**.

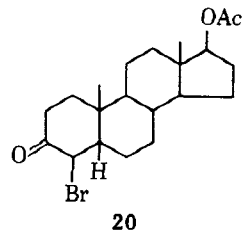


18 19



No pure product could be isolated when the A/B-*cis* compound 4β-bromo-17β-hydroxy-5β-androstan-3-one acetate (**20**)[13] was subjected to the same reaction conditions. 16α-Bromo-3β-hydroxy-5α-androstan-17-one acetate (**21**)[14] was recovered in 72% yield (recrystallized) following a 6.5-hr. reflux period. Indeed, no hydrogen bromide was liberated in this one instance.

Methyl 11α-bromo-3α-hydroxy-12-oxocholanate 3-acetate (**22**)[15] was definitely attacked by propyl mercaptan with formation of sulfur-containing oils, but the only pure product isolated was methyl 3α-hydroxy-12-oxocholanate 3-acetate (**23**)[16] (17%).



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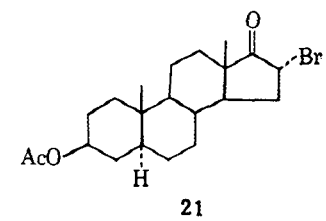

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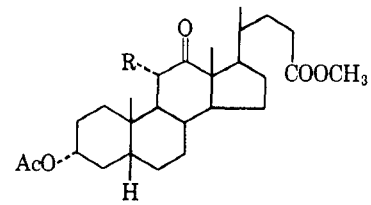
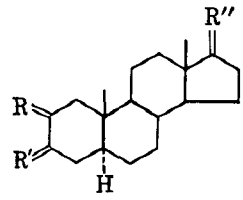


22, R = Br
23, R = H

During the investigation of other routes to 2-keto steroids, consideration was given to the conversion of epoxides to ketones through acid-catalyzed hydride transfer. All examples found in the literature involved cleavage of an oxygen to tertiary carbon bond[17] unless other influences (adjacent carbonyl, for example) were present. In our hands 2β,3β-epoxy-5α-androstan-17β-ol acetate[1] failed to give any 2-ketone when treated with boron trifluoride in benzene.

During the course of these investigations on 2-keto steroids, several derivatives of them were made. Thus, reduction of 17β-hydroxy-5α-androstan-2-one acetate (**19**) with lithium in ammonia afforded 5α-androstane-2α,17β-diol which was purified as its crystalline diacetate (**24**). Reduction of the ketone group with sodium borohydride, lithium aluminum tri-*t*-butoxyhydride, or with hydrogen in the presence of platinum and acetic acid resulted in mixtures of 2α- and 2β-alcohols which we were not able to separate by fractional crystallization or chromatography on silica gel.

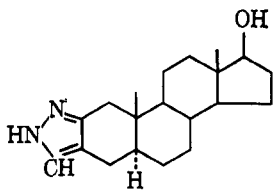
(10) L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964); W. P. Neuman and R. Sommer, *Ann.*, **675**, 10 (1964).
(11) R. L. Clarke, *J. Org. Chem.*, **28**, 2626 (1963).
(12) J. Fajkos and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959).
(13) R. Joly and G. Nominé, *Bull. soc. chim. France*, 1381 (1956).
(14) J. Fajkoš, *Collection Czech. Chem. Commun.*, **20**, 312 (1955).
(15) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).
(16) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 495 (1946).
(17) *Cf.* H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957); J. Elks, R. M. Evans, C. H. Robinson, G. H. Thomas, and L. J. Wyman, *ibid.*, 2933 (1953).



24, R = α-OAc, β-H; R′ = H_2; R″ = β-OAc, α-H
25, R = α-CH_3, β-OH; R′ = H_2; R″ = β-OH, α-H
26, R = α-CH_3, β-OH; R′ = H_2; R″ = O
27, R = α-CH_3, β-OH; R′ = H_2; R″ = α-CH_3, β-OH
28, R = O; R′ = HOCH=; R″ = β-OH, α-H
29, R = O; R′ = Et_2NCH=; R″ = β-OH, α-H

Methylmagnesium bromide converted 17β-hydroxy-5α-androstan-2-one into 2α-methyl-5α-androstane-2β,-17β-diol (**25**) which was oxidized by chromic acid in acetic acid to 2β-hydroxy-2α-methyl-5α-androstan-17-one (**26**). Methylmagnesium bromide then transformed **26** to 2α,17α-dimethyl-5α-androstane-2β,17β-diol (**27**). Attack of the Grignard reagent on the α-face of these molecules is expected. Indeed, this mode of attack at C-2 is confirmed by the work of Rao and Uroda.[18]

Formylation of 17β-hydroxy-5α-androstan-2-one with sodium methoxide and ethyl formate in pyridine furnished 3-(hydroxymethylene)-17β-hydroxy-5α-androstan-2-one (**28**). This compound served as an intermediate in the preparation of 3-(diethylaminomethylene)-17β-hydroxy-5α-androstan-2-one (**29**), 5α-androstano[2,3-*c*]pyrazol-17β-ol (**30**), and 5α-androstano-[2,3-*c*]isoxazol-17β-ol acetate (**31**).



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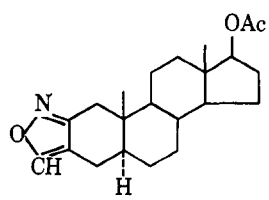

31

Experimental Section[19]

Debromination of 3α-Bromo-5α-androstane-2β,17β-diol 17-Acetate (2).[20]—A mixture of 3.55 g. of the title compound, 3.55 g. of 30% palladium chloride on strontium carbonate, and 300 ml. of undenatured 95% ethanol was treated with hydrogen under 50 p.s.i.g. at room temperature for 24 hr. The mixture was filtered and the filtrate was concentrated to a residue. The product was extracted with methylene dichloride and then was chromatographed on 75 g. of silica gel. Ether–pentane (1:4) eluted 1.69 g. (59%) of **17β-hydroxy-5α-androstan-2-one acetate (4)**, m.p. 144–146°. A single recrystallization from methanol afforded 1.47 g. of material melting at 148–150° (lit.[11] m.p. 149–150°) and undepressed upon admixture with an authentic sample. The infrared spectra of the two samples were identical.

Debromination of 3α-Bromo-2β-hydroxy-5α-androstan-17-one. (3).—A suspension of 1.80 g. of 30% palladium chloride on strontium carbonate in 150 ml. of undenatured 95% ethanol was treated with hydrogen at atmospheric pressure and 25° until no further hydrogen was absorbed. Then 3.30 g. (8.9 mmoles) of 3α-bromo-2β-hydroxy-5α-androstan-17-one[2] was added and the mixture was stirred under the same conditions for 20 hr. Volume measurements on the hydrogen absorbed became meaningless when carbon dioxide was evolved. The mixture was filtered and the filtrate was concentrated to a residue by warming *in vacuo*. Extraction of this residue with methylene dichloride and concentration of the extracts afforded 2.67 g. of crystalline solid.

Vapor phase chromatography (v.p.c.) of this product indicated that it was a complex mixture composed of 77% 5α-androstane-2,17-dione and at least six other components.

The reaction product was chromatographed on 100 g. of silica gel using ether–pentane (15:85) for elution. Some nonpolar material (0.15 g., about 6%) was eluted which was a mixture of three unidentified components (by v.p.c.). The remainder of the products were not separated cleanly on this column.

In order to effect better separation, the remaining mixture was acetylated (acetic anhydride–pyridine, 100°, 1.5 hr.) and this material was chromatographed on 100 g. of silica gel. Elution wth ether–pentane (15:85) afforded 0.44 g. of material which was recrystallized from methanol to give 0.33 g. of crystals, m.p. 118–144°. The major component of this mixture was separated by thick layer chromatography using silica gel with development by *n*-propyl alcohol–benzene–chloroform (3:77:20). This component was **3α-bromo-2β-hydroxy-5α-androstan-17-one acetate**, 132 mg. (3.6%), m.p. 166.5–168°, $[\alpha]^{25}D$ +131° (lit.[2] m.p. 168–169°, $[\alpha]D$ +131°). The minor component represented perhaps 30% of the mixture and was not purified and identified.

Further elution of the column with ether–pentane (3:7) afforded 1.64 g. (64%) of **5α-androstane-2,17-dione (5)**,[3] m.p. 153.5–156°. One recrystallization from methanol raised this melting point to 156–157° (lit.[3] 152.5–154.5°). The identity of this dione was confirmed by mixture melting point together with infrared spectral and v.p.c. comparison with an authentic sample.

Debromination of 3 with Palladium on Charcoal.—When a solution of 54 mg. of bromohydrin **3** in 10 ml. of undenatured 95% ethanol was treated with hydrogen under 30 p.s.i.g. in the presence of 54 mg. of 10% palladium on charcoal for 19 hr., strong acidity developed. The mixture was filtered and the filtrate was concentrated to a residue. Thick layer chromatography on silica gel using pure ether for development and elution of the main product band afforded 33 mg. (78%) of 5α-androstane-2,17-dione melting at 151–153°. One recrystallization from methanol gave material melting at 152–154° and undepressed upon admixture with the sample described above. The infrared spectra of the samples were identical.

Attempted Debromination without Hydrogen.—Bromohydrin **3** (0.50 g.) in 250 ml. of undenatured 95% ethanol was shaken with 0.50 g. of 30% palladium chloride on strontium carbonate and 1.0 g. of 10% palladium on charcoal *without* hydrogen for 18.5 hr. Thin layer chromatography indicated that no reaction had occurred.

Treatment of 2β-Bromo-3α-hydroxy-5α-androstan-17-one with Strong Base.—A solution of 0.20 g. of 2β-bromo-3α-hydroxy-5α-androstan-17-one and 0.20 g. of potassium hydroxide in 10 ml. of methanol was heated under reflux for 4 hr. This solution was diluted with water, the methanol was removed by warming *in vacuo* and the solid precipitate was collected: 0.14 g. (90%), m.p. 126–128°. Recrystallization from methanol gave colorless, six-sided plates, m.p. 127–128°, $[\alpha]^{25}D$ +103.0°, which were identical (mixture melting point and infrared spectra) with a sample prepared by direct epoxidation.[21]

Debromination of 2β-Bromo-3α-hydroxy-5α-androstan-17-one (6).[12]—A solution of 2.42 g. of the title compound in 250 ml. of undenatured ethanol with 2.42 g. of 30% palladium chloride on strontium carbonate added was shaken for 21 hr. in the presence of hydrogen which was under a pressure of 60 p.s.i.g. originally. The mixture was filtered and the filtrate was concentrated to a residue which was extracted twice with methylene dichloride to separate some inorganic material. The extracts were concentrated and the residual solid was chromatographed on 200 g. of silica gel using ethyl acetate–benzene (1:19) for elution.

A nonpolar solid (0.05 g.) was eluted by the first 750 ml. of solvent. In a parallel experiment this solid was shown by gas chromatography to be probably a mixture of **5α-androstan-17-one** and **5α-androst-2-en-7-one**. The yield is close to 3%.

(18) P. N. Rao and J. C. Uroda, *Tetrahedron Letters*, 1117 (1964).

(19) All melting points are corrected and all rotations were measured in chloroform unless noted otherwise. The silica gel used for chromatography (100–200 mesh) was obtained from the Davison Co., Baltimore, Md. The vapor phase chromatography was done using an F & M Model 400 instrument with a flame-ionization detector.

(20) This compound is reported by P. D. Klimstra and R. E. Counsell [*J. Med. Chem.*, **8**, 50 (1965)] as melting at 145–147°. Our sample melted at 169–171.5°. Thin layer chromatography and comparison of the infrared and n.m.r. spectra of the two samples showed that they were the same material with a small difference in purity. Indications are that this is a simple case of dimorphism since a mixture of the two samples melted at the lower range. We thank Dr. Klimstra for making these comparisons.

(21) R. Counsell and P. D. Klimstra, U. S. Patent 3,009,934 (1961).

Further elution gave 0.025 g. of an unidentified solid. After 6 l. of solvent had been put through the column, a mixture began to come off (0.14 g. in 2.5 l. of eluate) which contained 5α-androstane-3,17-dione, an unidentified component, and a trace of androsterone. This 0.14 g. of solid was heated under reflux with 1.0 g. of sodium metabisulfite, 6 ml. of water, and 30 ml. of methanol for 40 min. The methanol was removed by warming *in vacuo* and the residue was partitioned between methylene dichloride and water. The layers were separated and the water layer was extracted with ether to remove a cloudiness. This water layer was then boiled with 2.0 g. of sodium bicarbonate for 3 hr. and the cooled mixture was filtered to give 11 mg. (0.6%) of **5α-androstane-3,17-dione**, m.p. 128–133°. A single recrystallization from aqueous methanol gave material which melted at 133–133.5°. Its identity was established by mixture melting point, infrared spectrophotometry, and both vapor phase and thin layer chromatography.

Further elution of the column gave 1.60 g. of material which, by combined recrystallization (methanol) and rechromatography, afforded 1.36 g. of androsterone (**7**) melting at 184–185° and 0.09 g. of m.p. 181.5–185° (76%). The melting point of this product was undepressed upon admixture with an authentic sample and the infrared spectra and R_f values of the samples were identical.

Debromination of 2α-Bromo-3β-hydroxy-5α-pregnan-20-one.—To a solution of 0.50 g. of the title compound in 40 ml. of undenatured 95% ethanol was added 0.50 g. of 30% palladium chloride on strontium carbonate catalyst. This mixture was treated with hydrogen under 30 p.s.i.g. for 20 hr. and filtered. The filtrate was concentrated to a residue by warming *in vacuo*. This residue was chromatographed on plates coated with a silica gel layer approximately 1 mm. thick. Development of the plates with ether and location of the bands with iodine allowed clean separation of 87 mg. (22%) of 3β-hydroxy-5α-pregnan-20-one, m.p. 191–193.5°, as the most polar product. A single recrystallization from absolute ethanol raised this melting point to 193–195° and it was not depressed upon admixture with an authentic sample. The infrared spectra of the two samples were identical.

It was necessary to rechromatograph all of the other material from the reaction on plates developed with 1:10 ethyl acetate–benzene in order to separate nonpolar products (69 mg.) from 156 mg. (39%) of **5α-pregnane-3,20-dione**, m.p. 182–182.5°. This product is apparently a different polymorphic form than that normally encountered because a mixture of it with an authentic sample of m.p. 198–202° melted at 182–184° and the infrared spectra of the two materials in carbon disulfide were identical.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.20. Found: C, 80.0; H, 10.0.

Debromination of 3α-Bromo-2β-hydroxy-5α-androstan-17-one with Tri-*n*-butyltin Hydride.—A mixture of 0.87 g. (3.0 mmoles) of tri-*n*-butyltin hydride, 1.00 g. (2.7 mmoles) of 3α-bromo-2β-hydroxy-5α-androstan-17-one, 3 ml. of dry ether, and 6 mg. (about 1 mole %) of 2,2′-azobis(2-methylpropionitrile) was warmed at 50° for 3 hr. The ether boiled away immediately. At the end of the first and second hour of heating the mixture was cooled, treated with 3 ml. of ether, and stirred to aid in establishing contact of the reactants before heating was continued.

After 3 hr. the reaction mixture was dissolved in 5 ml. of methylene dichloride and the solution was diluted with 10 ml. of ether and 35 ml. of pentane. This solution was poured onto a column of 100 g. of silica gel and the column was then eluted with a solvent mixture containing 15% ether and 85% pentane. The tin compounds came off the column in the first portions of eluate. Fractions 21–36 (250 ml. each) contained starting material and mixtures of it and 2β-hydroxy-5α-androstan-17-one. Fractions 37–44 contained 0.64 g. of the pure product. The last 0.5 l. of eluting solvent was pure ether. The components of fractions 21–36 were separated cleanly on four 8 × 8 in. thick layer silica plates which were developed with ether–pentane (3:1).

Thus there was obtained 0.037 g. (3.7%) of starting material, m.p. 190–196°, which, upon recrystallization from acetonitrile, afforded heavy needles, m.p. 199–200°, and undepressed upon admixture with starting material. The infrared spectra of these samples were identical.

The total **2β-hydroxy-5α-androstan-17-one** from the column and the plates weighed 0.747 g. (95%) and melted at 191–194.5°. Recrystallization twice from methanol gave material melting at 193.5–195°, $[\alpha]^{25}D$ +101.0°. The n.m.r. spectrum showed the hydrogen on C-2 at 250 c.p.s. which confirms the axial nature of the hydroxyl group.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.6; H, 10.2.

Formation of 17β-Hydroxy-5α-androstan-2-one Acetate (19) from 4α-Bromo-17β-hydroxy-5α-androstan-3-one Acetate (18).—A solution of 1.67 g. (4.1 mmoles) of 4α-bromo-17β-hydroxy-5α-androstan-3-one acetate[12] and 1.23 ml. (13.5 mmoles) of *n*-propylmer captan in 23 ml. of chloroform was heated under reflux in a nitrogen atmosphere for 16.5 hr. At this time, 12 ml. of methanol, 0.5 ml. of concentrated hydrochloric acid, and 0.5 ml. of water were added and refluxing was continued for 4 hr. During this period 0.5 ml. of water was added hourly and at its end 16 ml. of 5% aqueous hydrochloric acid was added. The mixture was concentrated to half its volume by warming *in vacuo*, 60 ml. of 5% hydrochloric acid was added, and the mixture was subjected to steam distillation until no more oily material distilled. Extraction of the still pot contents with three 100-ml. portions of methylene dichloride, drying of the extracts with sodium sulfate, and concentration of the solution gave a solid residue.

The solid product was dissolved in 10 ml. of acetic anhydride and 10 ml. of pyridine and the solution was allowed to stand for 16 hr. at room temperature. It was poured into cold water and the acetylated product was extracted with several portions of ether. The extracts were washed with saturated salt solution, dried over sodium sulfate, and concentrated to give an oily residue which should be largely a mixture of ketones.

In order to remove the 3-ketone present, the residue was dissolved in 32 ml. of methanol, and the boiling solution was treated with a solution of 5 g. of sodium bisulfite in 25 ml. of water. This mixture was allowed to cool to room temperature and was shaken for 15 min. whereupon a solid bisulfite adduct separated. The total mixture was extracted with methylene dichloride and the extracts were washed with saturated salt solution and then dried over sodium sulfate. Concentration of the solution gave an oily residue which crystallized. Two recrystallizations from methanol furnished 100 mg. of **17β-hydroxy-5α-androstan-2-one acetate (19)**, m.p. 148–150°, undepressed upon admixture with an authentic sample. The infrared spectra of the two samples were identical. A second crop of this compound, m.p. 145–147°, amounted to 56 mg. and raised the yield to 12%.

The precipitated bisulfite adduct above and the accompanying aqueous solution were combined with 250 ml. of methylene dichloride and 5.7 g. of sodium bicarbonate and the mixture was heated under reflux for 5 hr. It was cooled, the layers were separated, and the water layer was extracted with methylene dichloride. The combined organic layers were dried over sodium sulfate and concentrated to give a residual solid which was recrystallized from acetone. Crude **17β-hydroxy-5α-androstan-3-one acetate**, m.p. 151–157°, was thus obtained (402 mg., 30%).

Reaction of Methyl 11α-Bromo-3α-hydroxy-12-oxocholanate 3-Acetate (22)[15] with *n*-Propyl Mercaptan.—A solution of 2.62 g. (0.005 mole) of the title compound and 1.52 g. (0.02 mole) of *n*-propyl mercaptan in 50 ml. of chloroform was refluxed for 8.5 hr. and concentrated to a residue by warming *in vacuo*. This residual oil was chromatographed on 100 g. of silica gel. Elution with 1:9 ether–pentane failed to remove anything, but 1:4 ether–pentane washed off 1.15 g. of sulfur-containing oil which was a mixture (infrared bands very broad) and never solidified. Continued elution with the same solvent mixture removed 0.56 g. of solid which was recrystallized from methanol to give 0.37 g. (17%) of **methyl 3α-acetoxy-12-oxocholanate (23)**,[16] m.p. 148–150.5°. A single further recrystallization raised the melting point to 149.5–151° and it was undepressed upon admixture with an authentic sample. The infrared spectra of the two samples were identical. Negligible further material was eluted from the column with pure ether.

5α-Androstane-2α,17β-diol Diacetate (24).—A 3.00-g. sample (9.0 mmoles) of 17β-hydroxy-5α-androstan-2-one acetate (**19**) in 25 ml. of tetrahydrofuran was added with stirring to 0.30 g. (43 mmoles) of lithium in 100 ml. of liquid ammonia in 13 min. The mixture was stirred for 5 min. and 5 ml. of absolute ethanol was added in 6 min. The ammonia was allowed to evaporate, 25 ml. of water was added, and the tetrahydrofuran was removed by warming *in vacuo*. The resulting mixture of oil and water was treated with 10 ml. of 2 *N* sodium hydroxide and 50 ml. of ethanol and heated under reflux for 30 min. Sufficient acetic acid was added to render the mixture acid and the ethanol was removed by warming *in vacuo*. The oily product was extracted

with ether, the solution was dried over sodium sulfate, and the solvent was removed to give an oil which failed to solidify.

The crude product was acetylated by heating it for 1 hr. with 10 ml. of acetic anhydride and 20 ml. of pyridine. The product was precipitated by addition of water, separated with ether, and chromatographed on 75 g. of silica gel. Ether–pentane (1:9) eluted 1.60 g. of crystalline **5α-androstane-2α,17β-diol diacetate (24)** which was recrystallized once from methanol to furnish 1.45 g. (43%) of blade clusters: m.p. 158–159°, unchanged upon further recrystallization; $[\alpha]^{25}D$ −26.5°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.4; H, 9.8.

2α-Methyl-5α-androstane-2β,17β-diol (25).—A stirred solution of 11.1 g. (0.038 mole) of 17β-hydroxy-5α-androstan-2-one[22] in 100 ml. of tetrahydrofuran and 200 ml. of ether was treated dropwise with 60 ml. (0.18 mole) of 3 *M* methylmagnesium bromide in ether and the mixture was stirred under reflux for 2 hr. It was allowed to stand overnight and was then treated with water followed by 2 *N* hydrochloric acid. The layers were separated and the organic layer was washed with saturated salt solution and dried over sodium sulfate. Concentration gave a solid residue which was recrystallized three times to give 7.35 g. of **25** which melted at 196–198° but did not show the proper elemental composition.

The 7.35 g. of nearly pure product was chromatographed on 500 g. of silica gel, the solid's being dissolved in methylene dichloride–ether–pentane (2:1:7). Elution of the column with 1:9 ether–pentane gradually changed to 3:7 ether–pentane afforded the desired product which was recrystallized from methanol to give 5.7 g. of title compound, m.p. 195–198°, $[\alpha]^{25}D$ +15.7°, and a second crop, 0.98 g., m.p. 193–195.5°. Chromatography of the mother liquor residues from the early recrystallizations afforded an additional 0.50 g. of this diol, m.p. 195–197°, giving a total yield of 61%. Analyses were done on the large crop.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.3; H, 11.2.

2β-Hydroxy-2α-methyl-5α-androstan-17-one (26).—A solution of 1.10 g. (3.6 mmoles) of 2α-methyl-5α-androstane-2β,17β-diol (**25**) in 50 ml. of acetic acid was cooled to 16° and treated with 0.39 g. (3.9 mmoles) of chromium trioxide in 1 ml. of water and 25 ml. of acetic acid dropwise with stirring at 16–20° in 30 min. The mixture was stirred for 3 hr. and diluted with 500 ml. of water, and the precipitated solid was collected and air dried. This solid (1.0 g.) was dissolved in 20 ml. of methylene dichloride, 40 ml. of ether, and 55 ml. of pentane and the solution was percolated through 25 g. of silica gel, the column being washed with 2:3 ether–pentane. Concentration of the first 600 ml. of eluate and recrystallization of the residue from methanol afforded 0.80 g. (73% yield) of the desired 17-ketone, m.p. 197–201°. A second recrystallization from methanol involving treatment with Darco G-60 afforded 0.65 g. of colorless, massive prisms, m.p. 198–202.5°, $\alpha^{25}D$ +91.4°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.6; H, 10.5.

2α,17α-Dimethyl-5α-androstane-2β,17β-diol (27).—A solution of 2.93 g. (9.6 mmoles) of 2β-hydroxy-2α-methyl-5α-androstan-17-one in 75 ml. of tetrahydrofuran was treated with 15 ml. of 3 *M* methylmagnesium bromide (45 mmoles) in 5 min. The mixture was allowed to stir at room temperature for 1 hr., refluxed for 1 hr., and allowed to stand overnight. Ammonium chloride solution was added, the layers were separated, and the water layer was extracted with ether. The combined ether solutions were concentrated and the oily residue was chromatographed on 80 g. of silica gel. Elution with 1:4 ether–pentane afforded 0.6 g. of crude starting material which was recrystallized from acetonitrile to give 0.55 g. of massive prisms, m.p. 196–200°, 19% recovery.

Further elution with the same solvent mixture gave the desired diol which was recrystallized from acetone as massive prisms (0.50 g., 16% yield), m.p. 189–190°, with intumescence after being dried at 55° and 15 mm. for 0.5 hr. A second recrystallization from acetone afforded 0.38 g. of material which melted at 190–198°, $[\alpha]^{25}D$ −2.1°, after being dried at 78° and 15 mm. for 8 hr. This material showed a single tight spot when chromatographed on a silica thin layer plate using ether as the solvent.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.9; H, 11.6.

3-(Hydroxymethylene)-17β-hydroxy-5α-androstan-2-one (28).—Sodium methoxide was freshly prepared by dissolving 0.70 g. (0.029 mole) of sodium hydride in 20 ml. of methanol and removing all excess methanol by warming *in vacuo*. Pyridine (37 ml.) was added followed by 1.95 g. (0.0067 mole) of 17β-hydroxy-5α-androstan-2-one and 4 ml. of ethyl formate. This mixture was allowed to stand at room temperature for 18 hr. and then concentrated to a residue by warming *in vacuo*. The residue was partitioned between water and ether and the water layer was separated and treated with carbon dioxide until the pH of the solution fell to 7.5. Extraction with ether separated the product which was then recrystallized twice from acetonitrile to give colorless massive prisms, m.p. 143–145° (evacuated Pyrex capillary), $[\alpha]^{25}D$ +47.4°, λ_{max} 282 mμ (ε 9000).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.6; H, 9.2.

3-(Diethylaminomethylene)-17β-hydroxy-5α-androstan-2-one (29).—A mixture of 2.0 g. (0.0063 mole) of 17β-hydroxy-3-hydroxymethylene-5α-androstan-2-one (**28**), 50 ml. of benzene, and 3 ml. of diethylamine was refluxed for 2 hr. with a water separator attached to the system. Concentration of the reaction mixture by warming *in vacuo* afforded a residue which was recrystallized once from acetonitrile to give 1.80 g. of pale yellow needles, m.p. 229–236° (77% yield). A second recrystallization afforded 1.56 g. of material which melted at 229–237° (immersed at 220° and heated at 3°/min.). This melting point varies with rate of heating and temperature of immersion of the sample. The product showed $[\alpha]^{25}D$ −65.7° and ϵ_{333} 22,600.

Anal. Calcd. for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.52; N, 3.75. Found: C, 77.5; H, 10.4; N, 3.9.

5α-Androstano[2,3-*c*]pyrazol-17β-ol Hemiacetonide (30).—A mixture of 2.00 g. (0.0063 mole) of 17β-hydroxy-3-hydroxymethylene-5α-androstan-2-one (**28**), 2 g. of 100% hydrazine hydrate, and 25 ml. of absolute ethanol was heated under reflux for 20 min., cooled, and diluted with 100 ml. of water. The white solid which separated was collected, air dried, and recrystallized twice from acetone to give 1.60 g. (75% yield) of prisms which melted at 238–239.5° in an evacuated capillary tube. A third recrystallization from acetone did not change this melting point, but the product thus obtained showed a slightly low nitrogen content.

The product was chromatographed on 40 g. of silica gel using 3:2 ether–methylene dichloride for elution and was recrystallized from acetone to give 1.0 g. of the pyrazole, m.p. 238–239.5° (evacuated capillary), $[\alpha]^{25}D$ +50.3° (1% in EtOH), ϵ_{224} 5200. This material proved to be a hemiacetonide, the factor which caused the low nitrogen value in the unchromatographed sample. A weak–medium carbonyl band was present in the infrared spectrum at 5.87 μ.

Anal. Calcd. for $C_{20}H_{30}N_2O \cdot 0.5(CH_3)_2CO$: C, 75.17; H, 9.68; N, 8.16. Found: C, 75.4; H, 9.3; N, 8.3.

5α-Androstano[2,3-*c*]isoxazol-17β-ol Acetate (31).—A mixture of 3.28 g. (0.040 mole) of fused sodium acetate, 2.92 g. (0.042 mole) of hydroxylamine hydrochloride, 8.60 g. (0.027 mole) of 17β-hydroxy-3-hydroxymethylene-5α-androstan-2-one, and 270 ml. of acetic acid was warmed at 65–70° with stirring for 6 hr. and then concentrated by warming *in vacuo*. The residue was partitioned between water and ether, the layers were separated, and the ether layer was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and concentrated.

The 10.68-g. residue present at this point was a mixture of the [2,3-*c*]isoxazole and the [3,2-*d*]isoxazole. It was dissolved in 330 ml. of tetrahydrofuran, 2.65 g. (0.049 mole) of sodium methoxide was added, and the mixture was allowed to stand for 1.5 hr. The mixture was concentrated *in vacuo*, water and ether were added, the layers were separated, and the ether layer was washed with 2 *N* sodium hydroxide, dried over sodium sulfate, and concentrated. Recrystallization of the residue from methanol afforded 5.0 g. (59%) of **31**, m.p. 174–178° after shrinking at about 169°. This product was found to contain methanol of solvation which was difficult to remove entirely, so the compound was converted to its acetate by means of acetic anhydride and pyridine using a 1-hr. heating period followed by dilution with water. Recrystallization from methanol and drying for 6 hr. at 100° and 10 mm. afforded 4.37 g. of 5α-androstano[2,3-*c*]isoxazol-17β-ol acetate, m.p. 178.5–180° (unchanged by further recrystallization), $[\alpha]^{25}D$ +39.2°.

(22) J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibáñez, E. Necoechea, A. de la Roz, E. Segovia, R. Urguiza, and A. Bowers, *J. Med. Chem.*, **6**, 174 (1963).

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.90; H, 8.74; N, 3.92. Found: C, 73.9; H, 8.7; N, 4.2.

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Tumor Inhibitors. X.[1] Photochemical Synthesis of Phenanthrenes. Synthesis of Aristolochic Acid and Related Compounds[2-4]

S. MORRIS KUPCHAN AND HENRY C. WORMSER[5]

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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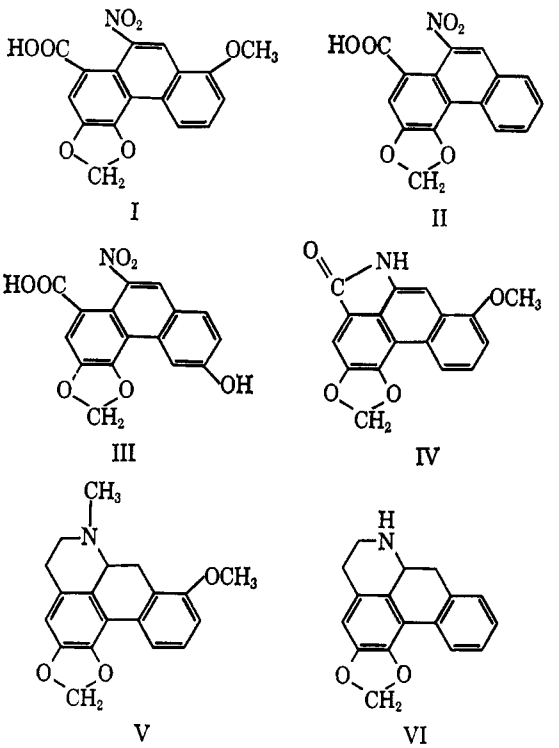
A new general synthesis of substituted phenanthrene derivatives, involving photocyclization of substituted 2-iodostilbenes, is presented herewith. The usefulness of this method for the synthesis of nitrophenanthrenes, not readily accessible by other approaches, is illustrated in an efficient synthesis of the naturally occurring tumor inhibitor, aristolochic acid, and several related analogs.

During the course of a search for tumor inhibitors from plant sources, Kupchan and Doskotch[6] found that *Aristolochia indica* L. possessed reproducible activity against the adenocarcinoma 755 test system. Aristolochic acid I (I) was characterized as the tumor-inhibitory principle. This acid was subsequently tested in mice for carcinogenic activity and was found to produce papillomas when applied topically with croton oil.[7] The structure elucidation of aristolochic acid is credited mainly to Pailer and co-workers.[8] The family *Aristolochiaceae* comprises approximately 180 species. Many of these have played important roles in folk medicine as wound healers, snake bite remedies, fever cures, and as the name itself implies, in childbirth.

Few naturally occurring nitro-containing compounds are known, and these few were discovered relatively recently. The first and, perhaps, best known of this group, chloramphenicol, was fully characterized in 1949.[9] Soon after this discovery, two glycosides, hiptagin and karakin, were isolated and characterized as derivatives of β-nitropropionic acid.[10] Various species of the genus *Aristolochia* have been found to yield substituted nitrophenanthrene derivatives: aristolochic acid I (I), aristolochic acid II (II), aristolochic acid C (III), aristolactam (IV), and three compounds of unknown structure, aristolochic acid B, debilic acid, and aristo-red.[11] It has been postulated that aporphine alkaloids such as stephanine (V) and anonaine (VI) (Chart I) may be biogenetically precursorial to the aforementioned compounds.[11]

CHART I



Kharasch has described a synthesis of polyphenyl compounds by photolysis of the corresponding iodoaromatic compounds in benzene using a cold-cathode, low-pressure mercury arc with Vycor glass housing.[12,13] Photolysis in cyclohexane, methanol, or ethanol causes reductive deiodination, and the reaction appears to have wide applicability. Photolysis in other aromatic solvents such as molten naphthalene and biphenyl gives the isomeric 1- and 2-phenylnaphthalenes and isomeric terphenyls in the ratio expected for homolytic phenylation.

(1) Part IX: S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3933 (1965).

(2) The investigation which forms the subject of this paper was first outlined in part in a preliminary communication: S. M. Kupchan and H. C. Wormser, *Tetrahedron Letters*, 359 (1965).

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(5) American Foundation for Pharmaceutical Education Fellow, 1961–1963; National Institutes of Health Predoctoral Fellow, 1963–1965.

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(7) Appreciation is expressed to Professor R. K. Boutwell of the McArdle Memorial Laboratory at the University of Wisconsin for the study on the carcinogenic activity of aristolochic acid I.

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