λ_{max} 246 mμ (ε 9900); λ_{max} 2.75 (w), 2.90 μ (w, broad, 3β-OH), 6.22 (m), and 6.63 μ (m, pyrazole ring); $R_{cholesterol}$, 0.93; relative retention time, 3.20.

Anal. Calcd for $C_{28}H_{34}N_2O$: C, 81.11; H, 8.27; N, 6.76. Found: C, 80.75; H, 8.06; N, 6.89.

17-[3(5)-Pyrazolyl]-5,16-androstadien-3β-ol (25).—The benzene solution of β-ketoaldehyde **20** (100 ml) was treated with 85% hydrazine (4.0 g); a solid separated which redissolved after adding acetic acid (30 ml). After 24 hr the solution was evaporated to dryness and the gummy residue was chromatographed on alumina, using ethyl acetate as the eluent. A gum was obtained which, after rechromatography and trituration with methanol yielded crystals. Four recrystallizations from methanol gave analytical **25**: 500 mg; mp 222–223.5°; $[\alpha]_D$ −40°; λ_{max} 247 mμ (ε 11,000); λ_{max}^{KBr} 3.02 (m, broad, 3β-OH, ring NH), 6.11 (w), and 6.43 μ (w, pyrazole ring); $R_{cholesterol}$, 0.43; relative retention time, 1.25.

Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.84; H, 8.97; N, 7.82.

17-(1-Methyl-5-pyrazolyl)-5,16-androstadien-3β-ol (26).—The benzene solution of the β-ketoaldehyde **20** (100 ml) was treated with methylhydrazine (4.0 g). A precipitate formed which was redissolved by the addition of acetic acid (30 ml). After 24 hr the benzene layer was washed twice with water (50 ml), dried over anhydrous sodium sulfate, and chromatographed on alumina, using benzene as eluent. The product was recrystallized from ethanol (four times) to give analytical **26**: 1.7 g; mp 242–244°; $[\alpha]_D$ −33°; λ_{max} 241 mμ (ε 10,300); λ_{max} 2.75 (w), 2.90 (w, broad, 3β-OH), and 6.62 μ (w, pyrazole ring); $R_{cholesterol}$, 0.44; relative retention time, 0.93.

Anal. Calcd for $C_{23}H_{32}N_2O$: C, 78.36; H, 9.15; N, 7.95. Found: C, 78.25; H, 9.28; N, 7.93.

17-(1-Methyl-5-pyrazolyl)-5,16-androstadien-3β-ol Acetate (22).—Pyrazole **26** (700 mg) was dissolved in a 1:1 mixture (80 ml) of pyridine and acetic anhydride, by warming. After keeping it at room temperature for 24 hr, evaporation *in vacuo* and chromatography on alumina, using benzene as eluent, gave pyrazole **22**. Recrystallization from acetonitrile yielded the analytical sample: 450 mg; mp 165–168°; $[\alpha]_D$ −28°, λ_{max} 241 mμ (ε 8600); λ_{max} 5.78 (s), 7.95 (s, 3β-acetate), and 6.63 μ (w, pyrazole ring); $R_{cholesterol}$, 0.88; relative retention time, 1.36.

Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 75.88; H, 8.51; N, 7.12.

Hydrogenation of Pyrazole 21.—A solution of pyrazole **21** (200 mg) in glacial acetic acid (20 ml) was hydrogenated at room temperature and 60 psi for 3 hr, using 10% palladium-on-charcoal (100 mg) catalyst. After filtration, the catalyst was washed with acetic acid (10 ml) and the combined filtrates were evaporated *in vacuo*. A gum was obtained, which crystallized from acetone. Two recrystallizations from this solvent gave a compound (mp 222–224°; melting point obtained by heating very slowly), which proved to be identical with pyrazole **15** by mixture melting point, tlc, vpc, and comparison of infrared and ultraviolet spectra.

Hydrogenation of Pyrazole 22.—A solution of compound **22** (200 mg) in glacial acetic acid (50 ml) was hydrogenated at room temperature and 60 psi for 17 hr, using 10% palladium-on-charcoal (400 mg) as the catalyst. After filtration and evaporation *in vacuo*, the residue was chromatographed on alumina, using benzene as eluent. Recrystallization from acetonitrile gave pyrazole **13**, mp 196–199°. The identity of this product was confirmed by mixture melting point and comparison of tlc, vpc, and infrared and ultraviolet spectra.

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Selenium Dioxide Oxidation of 5α-Androstane-3,17-dione. The Stereochemistry of Dehydrogenation

ROBERT A. JERUSSI[1] AND DANIEL SPEYER[2]

Department of Chemistry, New York University, New York 53, New York

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Oxidation of 5α-androstane-3,17-dione with selenium dioxide produced 5α-androst-1-ene-3,17-dione, androst-4-ene-3,17-dione, and androsta-1,4-diene-3,17-dione. Oxidation of 1α-deuterio-5α-androstane-3,17-dione to 5α-androst-1-ene-3,17-dione proceeded with 93% loss of dueterium and apparently with a small isotope effect. The androst-4-ene-3,17-dione also isolated from the isotope reaction contained almost all of the original deuterium, indicating that it was not formed by isomerization of the Δ^1 compound.

Since Riley's introduction of selenium dioxide as an oxidant for organic compounds,[3] it has been the subject of many investigations.[4] Although it was soon applied to steroids,[5] a major contribution to its use in steroid chemistry came with the discovery that oxidation of a 12-keto steroid produced the $\Delta^{9,11}$-12 ketone, not the 11,12 diketone.[6] Subsequently, this finding was used in the synthesis of 11-dehydrocorticosterone.[7] In 1956 two groups reported that selenium dioxide in refluxing tertiary alcohols introduced a double bond at the 1,2 position in either 5α-3-keto steroids or Δ^4-3-keto steroids.[8,9] This fact coupled with the information that the introduction of a double bond at the 1,2 position in cortisone increased its antirheumatic and antiallergic activity[10] promoted interest in this reagent. However, since the mechanism and steric course of the reaction had not been completely elucidated, we undertook a study of the stereochemistry of the dehydrogenation reaction.

Results and Discussion

Oxidation of 5α-androstane-3,17-dione with 1 equiv of selenium dioxide in refluxing *t*-amyl alcohol gave a complex mixture of products, which were separated by preparative thin layer chromatography. In addition to 4.8% recovered starting material, 5α-androst-1-ene-3,17-dione in 13.3% yield, androst-4-ene-3,17-dione in 8.1% yield, and androsta-1,4-diene-3,17-dione

(1) To whom inquiries should be addressed at the General Electric Research and Development Center, General Chemistry Laboratory, Schenectady, New York 12301.

(2) Undergraduate summer research participant, 1965.

(3) H. L. Riley, J. F. Morley, and N. A. Friend, *J. Chem. Soc.*, 1875 (1932).

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(5) R. K. Callow and O. Rosenheim, *J. Chem. Soc.*, 387 (1933); E. T. Stiller and O. Rosenheim, *ibid.*, 353 (1938).

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(9) S. A. Szpilfogel, T. A. P. Posthumus, M. S. deWinter, and D. A. vanDorp, *Rec. Trav. Chim.*, **75**, 475 (1956).

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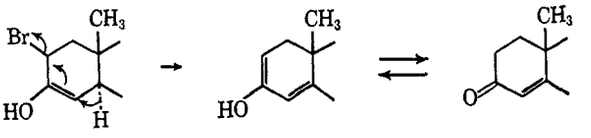
in 5.3% yield were isolated.[11] An oil was also obtained which contained a five-membered ring ketone, $\lambda_{max}^{CHCl_3}$ 1735 cm^{-1}, and a conjugated six-membered ring ketone, $\lambda_{max}^{CHCl_3}$ 1660 and 1590 cm^{-1}. In addition, its infrared spectrum contained a complex pattern of bands between 1300 and 900 cm^{-1}. This material was very likely an organoselenium compound similar to those reported by Florey and Restivo,[12] and by Baran[13] since it was converted to 5α-androst-1-ene-3,17-dione by treatment with ammonium polysulfide. The latter has been shown effective in substituting hydrogen for selenium in a C–Se bond.[14] We did not realize the high yield of dehydrogenated product obtained with other steroid systems.[8,9] However, this is the first report of double-bond introduction at the 4,5 position in a 19-methyl-5α-3-keto steroid using selenium dioxide.

Several reports have been made of both Δ^1- and Δ^4-3-ketone formation from the dehydrohalogenation of 2 halo-5α-3-keto steroids.[15-17] Warnhoff has shown that in the γ-picoline dehydrobromination of 2α-bromo-5α-cholestan-3-one, where both products were isolated, both 5α-cholest-1-en-3-one and cholest-4-en-3-one were stable under the reaction conditions and were not interconvertible.[18] He suggested that the Δ^4 compound was produced directly from the 2α-bromo compound. Kuehne has formulated a mechanism for Δ^4 production by 1,4 dehydrobromination of the 2-bromo-Δ^3-enol, partial structure 1.[19]



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Definitive proof that the Δ^4 compound isolated by us was not produced by isomerization was obtained from an experiment in which 1α-deuterio-5α-androstane-3,17-dione was oxidized. The purpose of the latter experiment was to determine the stereochemistry of the dehydrogenation at C-1. Although selenium dioxide dehydrogenation of steroids to introduce a double bond conjugated with a carbonyl group will remove an α- or β-situated hydrogen atom on the β carbon if only one hydrogen atom is present there,[9,20] no evidence is available as to which hydrogen atom will be removed if two sterically nonidentical hydrogens are present at the β carbon atom.

Oxidation of 1-deuterio-5α-androstane-3,17-dione (0.856 atom of deuterium, 96% 1α and 4% 1β)[21] using the same conditions as for the nondeuterated compound gave 5α-androst-1-ene-3,17-dione containing 7.0% monodeuterated species by mass spectral analysis and 2.2% of an M + 3 material which is either trideuterated Δ^1 compound or starting deuterioandrostanedione. The former appears unlikely since the Δ^1 compound is only slightly more polar than the saturated compound on thin layer chromatography and it is possible that a small amount of the latter remained in the dehydrogenated compound even after thin layer chromatography and recrystallization. However, even assuming that the M + 3 peak is trideuterated 5α-androst-1-ene-3,17-dione containing deuterium at C-1, the stereoselectivity of the reaction using an iterated calculation is 93% removal of deuterium from the 1α position. Thus the stereochemistry of the selenium dioxide dehydrogenation at C-1 parallels that of the dichloro, dicyanoquinone dehydrogenation[22] and also the *Bacillus sphaericus* mediated dehydrogenation.[23]

Androst-4-ene-3,17-dione was also obtained from the oxidation of deuterioandrostanedione. It exhibited an infrared band at 2160 cm^{-1} indicative of an axial C-D bond[23b,24] and mass spectral analysis revealed the presence of 83.2% monodeuterated species and 2.8% of dideuterated material. These results indicate that the Δ^4 compound was produced directly from the androstanedione and that only a small percentage, if any, arose by isomerization of 5α-androst-1-ene-3,17-dione since the Δ^4 compound produced in this manner should have contained less than 10% deuterium. The dideuterated material may have arisen by deuterium incorporation *via* enolization of the monodeuterated Δ^4 dione since the deuterium removed from the 1α position in Δ^1 formation must be incorporated into the solvent.

Mass spectral analysis of the recovered starting dione indicated the presence of 86.6% monodeuterated species and an infrared peak at 2148 cm^{-1} indicated that the deuterium remained at the 1α position.[23b] Since the starting dione analyzed for 85.3% monodeuterated content by mass spectroscopy (0.856 g-atom of deuterium by combustion[21]) and since the mass spectral measurement error is probably not more than ±0.5%, it appears that a small amount of enrichment does occur and that removal of deuterium from the 1α position proceeds with a small isotope effect. However, since the effect appears small and since a precise value cannot be arrived at, no further adjustment in the stereospecificity percentage has been made.

That the selenium dioxide oxidation of ketones to α diketones and the dehydrogenation to α,β-unsaturated ketones are related reactions has been recognized for some time. Corey and Schaefer found the rate of diketone formation dependent on both the ketone and selenium dioxide concentrations and observed a primary deuterium isotope effect.[25] They ruled out enolization as a step in the reaction and proposed the formation of an enol selenite ester as the rate-limiting step by attack of selenious acid on the ketone. They also suggested that such an intermediate may be involved in the dehydrogenation reaction. Best, Littler, and Waters have pointed out that Corey and Schaefer's data is not inconsistent with enolization being a distinct step in the reaction sequence since a reaction proceeding

(11) All yields are of partially purified products.
(12) K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957).
(13) J. S. Baran, *J. Am. Chem. Soc.*, **80**, 1687 (1958).
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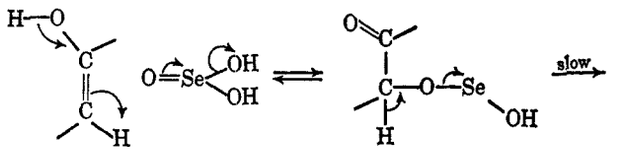
through an enol which is slower than the enolization step should also occur less readily with a deuterated ketone until the unreacted ketone has attained isotopic equilibrium with the solvent.[26] Waters considers the slow step to be decomposition of a selenium(II) intermediate, partial structure 2, which is formed by direct



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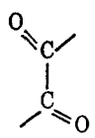
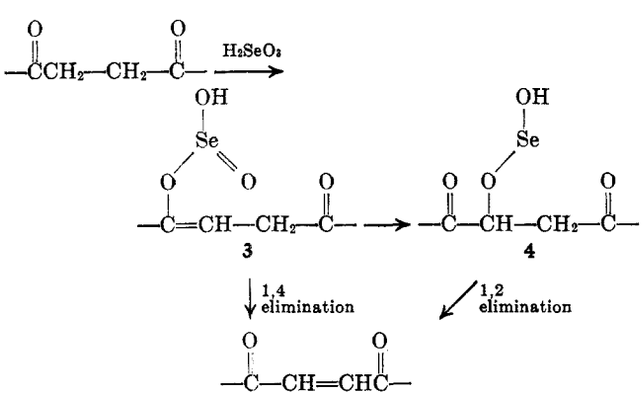


attack of selenious acid on the enol.[27] Banerji, Barton, and Cookson have found that the rate of selenium dioxide dehydrogenation of a number of 1,4 diketones depends on the concentrations of both diketone and selenium dioxide.[20] Schaefer has also found this concentration dependency and proposed a mechanism essentially the same as that proposed for diketone formation but which involves either 1,4 elimination of the enol ester, partial structure 3, or 1,2 elimination of the α-ketoselenium(II) ester, partial structure 4.[28]



Langbein studied the rate of the Δ^1 dehydrogenation of cortisoneacetate by selenium dioxide and obtained a second-order rate constant from a plot which contained the concentrations of ketone and selenium dioxide.[29] He outlined a mechanism similar to the one proposed by Schaefer but which involves direct formation of an α-ketoselenium ester by a process which seems similar to enolization. Hence, the dehydrogenation reaction, like the oxidation reaction, is rate dependent on the concentrations of both reactants; it appears to involve enolization or some process mechanistically similar to enolization, and, in unsymmetrical ketones, to be directed by the direction of enolization.[9] Since enolization of a 5α-3-keto steroid is considered to involve preferential loss of the 2β-axial hydrogen owing to more efficient orbital overlap in the transition state,[24a] the net process in the introduction of a double bond at the 1,2 position by selenium dioxide would be one of diaxial hydrogen loss, thus paralleling the steric course of the enzymatic dehydrogenation.[23] The mechanisms of the enzymatic and selenium dioxide dehydrogenations may be similar; the former has been formulated as 1,4 elimination of an enzyme-bound Δ^2-enol *via* hydride loss at the 1α position.[21,23b]

However, introduction of a double bond at the 4,5 position in a 5α-3-keto steroid does not follow the normal direction of enolization.[30] We believe that this is due to the position of the transition state along the reaction coordinate. The difference in energy between the Δ^2-enol and Δ^3-enol of a 19-methyl-5α-3-keto steroid is considered to be approximately the 2.1 kcal/mole found for the difference in the heats of hydrogenation between cholest-2-ene and cholest-3-ene, the former being more stable.[31] Corey and Sneen concluded that the 3-ene is the less stable of the two because there is a greater 10-methyl-6β-H interaction in it than in the 2-ene.[32] The distance difference was calculated as *ca.* 0.30 A using 10-methyl-octalin as a model. In the acid-catalyzed enolization (or enol ester formation) of a 5α-3-keto steroid, the ground state is the same for either Δ^2- or Δ^3-enol formation; the protonated ketone. As enolization commences, strain introduced in the B ring changes the 10-methyl–6β-H interaction so that it is greater in the incipient Δ^3-enol than in the incipient Δ^2-enol. Finally in the fully formed enols, the difference in strain is the greatest.

In an enolization-dependent reaction where the transition state of the enolization step is close to enol in geometry, almost full advantage is taken of the 2 kcal/mole difference in energy between the Δ^2- and Δ^3-enols, greatly favoring the Δ^2-enol as the kinetic (and thermodynamic) enol. However, in an enolization where the transition state is close to starting ketone or even between ketone and enol in geometry, the energy difference between the transition states for enol formation will be less than 2 kcal/mole, perhaps much less, allowing some Δ^3-enol production as part of the *kinetic* product. Malhotra and Ringold have shown by deuterium incorporation experiments on Δ^4-3-keto steroids that weak acid catalyzed (acetic) enolization heavily favors formation of the less stable $\Delta^{2,4}$-enol as the kinetic product, whereas strong acid (hydrochloric) moderately favors the more stable $\Delta^{3,5}$-enol.[24b] This was explained as little C–H bond stretching in the transition state with acetic acid so that it resembled ketone and considerable C–H bond stretching with hydrochloric acid. Our system contained two acids capable of catalyzing enolization, acetic and selenious acids. The former is weak, $K_t = 1.75 \times 10^{-5}$, while the first ionization constant for selenious acid, $K_t = 2.4 \times 10^{-3}$, definitely indicates that it is not a strong acid, *i.e.*, not completely ionized.[33] Therefore, it is possible that, even if selenious acid catalyzes enolization, the transition state will be enough like starting ketone to give some of the Δ^3-enol as part of the kinetic product of the enolization (enol ester formation) step.

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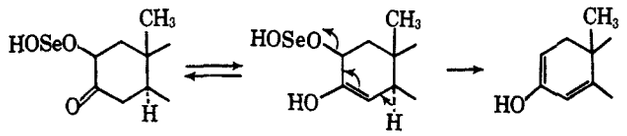
An alternate explanation would be one similar to Kuehne's for Δ^4 formation from the dehydrobromination of a 2-bromo-3-keto compound.[19] The elimination would occur from the Δ^3-enol of the α-ketoselenium(II) ester, partial structure **5**. However this explanation also involves enolization in the unfavorable direction.



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In connection with 1,4 *vs.* 1,2 elimination, the introduction of a Δ^1 bond in a 5α-3-keto steroid by bromination followed by dehydrobromination appears to involve a net *trans*-diaxial loss (1α, 2β) of hydrogen. The bromination reaction occurs with preferential loss of the 2β hydrogen[24a] and the elimination involves favored loss of the 1α hydrogen.[34]

Experimental Section[35]

Oxidation of 5α-Androstane-3,17-dione.—5α-Androstane-3,17-dione (498 mg, 1.74 mmoles), selenium dioxide (201 mg, 1.82 mmoles), *t*-amyl alcohol (25 ml), acetic acid (0.6 ml), and water (1.6 ml) were placed in a three-neck, 100-ml flask fitted with a condenser, the top of which was attached to a silicone oil "bubbler." The system was thoroughly flushed with nitrogen and sealed off so that gas could escape through the bubbler. The mixture was heated at reflux in an oil bath at 110–120° with constant magnetic stirring for 17.5 hr. At the end of this time the reaction solution was yellow and black selenium had deposited at the bottom of the flask. The reaction was terminated by cooling and the solvent was removed at the aspirator. The oily residue was taken up in warm methylene chloride, filtered to remove selenium, washed with water several times, and dried over sodium sulfate. The mixture was filtered to remove drying agent and the organic phase was stripped to yield an oil. The oil was taken up in methylene chloride and centrifuged to remove more selenium and the supernatant liquid was stripped to yield 610 mg of an amber oil.

Chromatography of this oil on six preparative tlc plates by developing twice in 3:7 ethyl acetate–benzene gave seven zones which were located partly by spraying side bands with 2,4-dinitrophenylhydrazine reagent and in part by using 253.7-mμ ultraviolet radiation. The silica gel in each band was removed from the plate and the compound recovered by elution with acetone (see Table I).

TABLE I

Band	R_f	Wt, mg	Product
I	0.8	11	Yellow oil
II	0.66	42	Amber oil
III	0.58	257	Yellow oil
IV	0.42	78	Yellow oil
V	0.35	43	Yellow oil
VI	0.31	73	Yellow oil
VII	0.25 to origin	102	Oil

Rechromatography of band III on four preparative tlc plates by developing twice in 15:85 ethyl acetate–benzene gave four zones which were located and isolated as before (see Table II).

TABLE II

Band	R_f	Wt, mg	Product
IIIA	0.75	5	Yellow oil
IIIB	0.7	82	Yellow oil
IIIC	0.6	25	Yellow oil
IIID	0.55	66	Yellow oil

Thin layer chromatography of bands II and IIIA against 5α-androstane-3,17-dione indicated that they were chiefly this compound. Both bands were combined, developed on a preparative tlc plate, and eluted to give 24 mg of 5α-androstane-3,17-dione, 4.8%. Two more chromatographies on two preparative tlc plates in 2:8 ethyl acetate–benzene gave 14 mg of amber crystals. Recrystallization from acetone–hexane gave 5α-androstane-3,17-dione as tan crystals, mp 129–130.5°. The infrared spectrum of this compound in $CHCl_3$ was identical with that of starting material.

Band IIIB was submitted to rechromatography on a preparative tlc plate in 15:85 ethyl acetate–benzene to give 66 mg of 5α-androst-1-ene-3,17-dione, 13.3%. Recrystallization from acetone–hexane gave 52 mg, mp 141.5–142°. The infrared spectrum in $CHCl_3$ was identical with that of authentic material.

Band IIIC was placed on a column made from 8 g of Fluorosil. Elution with various solvent systems from benzene through ether to methylene chloride gave only 6 mg of yellow oil which was eluted with 2:8 ether–benzene. The infrared spectrum of this material contained strong bands at 1730, 1670, and 1265 cm^{-1}. The compound was not further identified.

Band IIID was placed on a column made from 8 g of silica gel in benzene. The majority of the material was removed in four 15-ml cuts with 1:9 ether–benzene. All of the fractions had identical R_f values on tlc and were combined to give 42 mg of a yellow solid. This was purified on a preparative tlc plate by developing four times in 15:85 ethyl acetate–benzene. The major zone gave 42 mg of a tan solid after elution. Rechromatography on a preparative tlc plate in 4:6 ethyl acetate–benzene gave two zones. The least polar was almost at the solvent front and gave 9 mg of a tan solid after elution. The infrared spectrum of this material was quite simple with a band at 1720 cm^{-1} and a series of three bands at 1270, 1120, and 1060 cm^{-1}. This compound was not further characterized. The second band, R_f 0.5, gave a yellow oil on elution. Its infrared spectrum had intense bands at 1735, 1660, and 1590 cm^{-1} and a complex pattern of bands between 900 and 1300 cm^{-1}. The material was dissolved in ether and shaken with aqueous ammonium polysulfide solution. The ether was dried and stripped to give an oil which was developed on a preparative tlc plate in 4:6 ethyl acetate–benzene. Two zones were obtained, one at the solvent front and the other with R_f 0.55. The latter gave 12 mg of yellow crystals after elution whose infrared spectrum was essentially identical with that of 5α-androst-1-ene-3,17-dione. Elution of the least polar band gave 4 mg of a yellow oil whose infrared spectrum was identical with that of the 9 mg previously isolated from IIID.

Bands IV and V were combined and placed on two preparative tlc plates and developed three times in 15:85 ethyl acetate–benzene. Five zones were located and eluted as described previously (see Table III).

TABLE III

Band	R_f	Wt, mg	Product
IVA	0.55	4	Yellow oil
IVB	0.45	57	Yellow oil
IVC	0.40	9	Yellow oil
IVD	0.38	24	Yellow oil
IVE	0.25	10	Yellow oil

Band IVB was placed on one preparative tlc plate and developed twice in 15:85 ethyl acetate–benzene to give 40 mg, 8.1%, of a yellow oil identified as androst-4-ene-3,17-dione from its R_f value. This material was placed on a column made from 6 g of silica gel in benzene. Elution with 3:7 ether–benzene gave 38 mg of a yellow oil which was decolorized with charcoal and recrystallized from acetone–hexane to give 25 mg of androst-4-ene-3,17-dione, mp 164.5–168°. However, since this material was still colored, it and the oil obtained from the mother liquors were placed on a column made from 8 g of silica gel in benzene. Elution with 2:8 ether–benzene gave 34 mg of material which

(34) F. J. Schmitz and W. S. Johnson, *Tetrahedron Letters*, **No. 15**, 647 (1962).

(35) All melting points are corrected. Infrared spectra were taken on Perkin-Elmer spectrophotometers 137, 337, and 521. Mass spectrograms were obtained on a Consolidated Electrodynamics instrument at the Mass Spectroscopy Laboratory of Stevens Institute of Technology. A "preparative tlc plate" is a thin layer chromatography plate made from silica gel GF_{254} (Stahl) and having the dimensions 8 in. × 8 in. × 1 mm.

had the same R_f value as androst-4-ene-3,17-dione on tlc but also contained a trace of less polar material. All 34 mg was placed on a preparative tlc plate and developed twice in 15:85 ethyl acetate–benzene to give, after elution of the main band, 31 mg of a tan solid. Two recrystallizations from acetone–hexane gave 12 mg of white crystals, mp 171.5–172°. The infrared spectrum in KBr was identical with that of authentic androst-4-ene-3,17-dione. An additional 9 mg of slightly yellow crystals was obtained as a second crop.

Band VI was submitted to rechromatography on one tlc plate in 15:85 ethyl acetate–benzene three times. The main zone was eluted to give 26 mg, 5.3%, of a yellow oil, identified as androsta-1,4-diene-3,17-dione from its R_f value, which was placed on a column made from 8 g of Fluorosil in benzene. Elution with 4:6 ether–benzene gave 14 mg of a yellow solid whose infrared spectrum was almost identical with that of androsta-1,4-diene-3,17-dione. The compound was placed on a preparative tlc plate and developed in 4:6 ethyl acetate–benzene to give, after elution, 11 mg of a slightly yellow solid. Recrystallization from acetone–hexane gave cream-colored crystals, mp 140–141.5°, of androsta-1,4-diene-3,17-dione. The infrared spectrum of this material was essentially identical with that of authentic compound and its melting point was undepressed on admixture with androsta-1,4-diene-3,17-dione.

Oxidation of 1α-Deuterio-5α-androstane-3,17-dione.—1α-Deuterio-5α-androstane-3,17-dione (217 mg, 0.75 mmole) 85.6% deuterium, 96% 1α and 4% 1β,[21] selenium dioxide (87 mg, 0.78 mmole), *t*-amyl alcohol (11 ml), acetic acid (0.26 ml), and water (0.70 ml) were placed in a 50-ml, three-neck flask. The reaction was carried out as described for the nondeuterated compound except that it was run for 19 hr. The work-up was carried out in the same manner as for the nondeuterated compound to give 255 mg of an amber oil. The oil was submitted to chromatography on three preparative tlc plates and developed in 3:7 ethyl acetate–benzene, and the bands were located by ultraviolet and 2,4-dinitrophenylhydrazine. Elution of each band with acetone gave the results shown in Table IV.

TABLE IV

Band	R_f	Wt, mg	Product
I	0.6	34	Yellow oil
II	0.5	75	Yellow oil
III	0.4	49	Yellow oil
IV	0.3	24	Yellow oil
V	0.2	15	Yellow oil
VI	0.95	11	Yellow oil

The material from band I was placed on a preparative tlc plate and developed twice in 15:85 ethyl acetate–benzene. Elution of the major band, R_f 0.5, gave 31 mg of a tan, oily solid identified as starting ketone.

The material from band II was rerun on a preparative tlc plate and developed three times in 1:9 ethyl acetate–benzene. Two major zones were located in addition to a small amount of starting material (see Table V).

All the recovered starting dione was recrystallized from acetone–hexane to give 9 mg of 1α-deuterio-5α-androstane-3,17-dione: mp 130.3–131.8°, $\lambda_{max}^{CHCl_3}$ 2148 cm^{-1} C–D stretching (lit.[23b] $\lambda_{max}^{CHCl_3}$ 2155 cm^{-1}). The melting point was not depressed when the sample was mixed with nondeuterated androstanedione. Mass spectral analysis indicated 86.6% monodeuterated species present. Similar analysis of the starting material gave 85.3%. Work-up of the filtrate from the recrystallization gave an additional 15 mg of yellow-amber crystals.

TABLE V

Band	R_f	Wt, mg	Product
IIA	0.45	18	Yellow oil
IIB	0.3–0.4	31	Yellow oil

Bands IIA and IIB were submitted to chromatography separately on preparative tlc plates in 1:9 ethyl acetate–benzene. Each had two zones at R_f 0.9 and 0.8 which were located by ultraviolet. These were eluted and combined to give 6 and 10 mg, respectively. However, their infrared spectra in dilute solution were identical with and essentially the same as the spectrum of the 9 mg obtained from band IIID in the nondeuterated experiment and which had the three bands at 1270, 1120, and 1060 cm^{-1}. Band IIB had another zone at R_f 0.2 ,15 mg, which had an infrared spectrum in dilute solution essentially the same as the R_f 0.5 material obtained from band IIID in the nondeuterated experiment and which contained the complex pattern of bands between 1300 and 900 cm^{-1}. Band IIA had another zone at R_f 0.25, 12 mg of a yellow oil, which was developed and eluted two separate times on preparative tlc plates in 2:8 ethyl acetate–benzene to yield 10 mg of 5α-androst-1-ene-3,17-dione. One recrystallization from acetone–hexane gave mp 138–140° which was not depressed by admixture with authentic nondeuterated material. Mass spectral analysis indicated 7.0% monodeuterated and 2.2% of a M + 3 species. Assuming that 0.092 atoms of deuterium remain at the C-1 position and using an iterated calculation, the stereoselectivity is 93% removal from the 1α position.

Band III was developed on a preparative tlc plate in 4:6 ethyl acetate–benzene. The zone, R_f 0.5, corresponding to 5α-androst-4-ene-3,17-dione, was eluted to give 30 mg of a yellow oil which was placed on another preparative tlc plate and developed four times in 15:85 ethyl acetate–benzene. The major band was eluted to give 21 mg of tan crystals which was again placed on a preparative tlc plate in 4:6 ethyl acetate–benzene to yield 16 mg of material, R_f 0.5. Recrystallization from acetone–hexane gave 10 mg of 1α-deuterioandrost-4-ene-3,17-dione: mp 171–171.5°, $\lambda_{max}^{CHCl_3}$ 2160 cm^{-1} C–D stretching (lit.[23b] $\lambda_{max}^{CHCl_3}$ 2160 cm^{-1}). The melting point was not depressed by admixture with authentic nondeuterated material. Mass spectral analysis indicated 83.2% monodeuterated and 2.8% dideuterated species.

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