# The Stereochemistry of the Kinetically Controlled Bromination of 19-Methyl-5α-3-keto Steroids

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Recently, the steric course of bromination of 5α-3-keto steroids has been investigated[2] with the finding that under kinetically controlled conditions, where β attack is sterically inhibited by a 19-methyl group, the 2α-bromo 3-ketone is the product by direct attack on the Δ²-enol from the α side. This result was first encountered[3] when conditions (carbon tetrachloride–acetic acid–sodium acetate), which did not epimerize 2β-bromocholestan-3-one, gave the 2α-bromo compound on bromination of Δ²-cholesten-3-ol acetate. Subsequently,[2,4] a number of 19-methyl-5α-Δ²-enol acetates were similarly brominated to give the 2α-bromo 3-ketones directly. In the case of 2-methyl-Δ²-androstene-3,17-diol diacetate, the 2α-bromo 3-ketone which was obtained was actually the thermodynamically less stable epimer.[4]

While the enol acetates could be brominated under the conditions described above, the bromination of the 3-ketones could not be effected and it was found necessary to add trace amounts of hydrogen bromide in acetic acid.[2,4] The monobromo products from reaction of the ketones had the same stereochemistry as those from the enol acetates, namely the 2α-configuration. With 17β-hydroxy-2α-methylandrostan-3-one, kinetic control must have been maintained since the 2α-bromo-2β-methyl 3-ketone which was isolated is the less stable isomer. However, in the case of the ketones which are not methylated at C-2, the 2α-bromo 3-ketone *is* the thermodynamically more stable product and the question may be raised as to whether kinetic control was actually maintained in their bromination or if the 2β-bromo isomer was initially formed and then underwent hydrogen bromide catalyzed inversion.

To determine whether kinetic control was in fact maintained, we have investigated the bromination of 2,2,4,4,16,16-hexadeuterio-5α-androstane-3,17-dione in nondeuterated acetic acid. Since this substrate contains deuterium atoms at the 2α- and 2β-positions, the resultant 2α-bromo 3-ketone will have one atom of deuterium at the C-2 position if the 2α-bromo product is kinetically controlled but will contain no deuterium at C-2 if the 2β-bromo compound is the kinetic product, since in an acidic solvent the deuterium at C-2 must exchange during epimerization.

Although in the previous work, the 3-ketones did not undergo bromination in a carbon tetrachloride–acetic acid–sodium acetate solution,[2] we have found that hexadeuterioandrostanedione did take up bromine, albeit slowly, in an acetic acid–sodium acetate solution. The reaction was allowed to proceed 2–4 days at ambient temperature, terminated before completion by pouring into water, and the 2α-bromo ketone was separated from dibromo ketone and starting material by thin layer chromatography. An n.m.r. analysis of the monobromo product was carried out to determine whether hydrogen was present at the 2β-position since 2β-hydrogen in a 2α-bromo-3-keto steroid appears as a distinct quartet, centered at τ 5.20.[5] In each experiment, the n.m.r. spectrum revealed this quartet. However, the multiplet always integrated for less than one atom; our best results indicated the presence of 42–43% deuterium at the 2β-position.

Our results indicate that the kinetically controlled bromination of 19-methyl-5α-3-keto steroids involves at least a 43% α attack on the Δ²-enol since the 2α-bromo-2β-deuterio 3-ketone we isolated most certainly came from this steric approach. The failure to retain 100% of the deuterium in the 2β-position may be due to one or all of three possibilities: (a) loss of deuterium in the work-up, (b) exchange of deuterium in the monobromo product during the later stages of the reaction by sodium acetate, and (c) some β-bromination followed by epimerization. That a and b are possibilities is indicated by a shoulder at 1418 cm.$^{-1}$ (KBr film) in the infrared spectrum of recovered starting ketone, not present in the starting ketone, which is indicative of some hydrogen incorporation at a $CD_2$ adjacent to a carbonyl. Our results cannot exclude c. However, the possibility that 57% bromination occurred from the β side to give the 2β-bromo-2α-deuterio 3-ketone and that conditions were such that this epimerized without any of the 2α-bromo-2β-deuterio 3-ketone exchanging appears unlikely. If c does occur, the amount of β attack is probably much less than α attack.

## Experimental[6]

**2,2,4,4,16,16-Hexadeuterio-5α-androstane-3,17-dione.**—5α-Androstane-3,17-dione (0.494 g., 1.72 × 10$^{-3}$ mole) and anhydrous diglyme (20 ml.) were placed in a 100-ml. three-neck flask fitted with a condenser, the top of which was connected to a silicone oil bubbler. While nitrogen was passed through the system, potassium (0.500 g., 12.7 × 10$^{-3}$ g.-atom) was added in several pieces, followed by dropwise addition of a solution made from 10 ml. of diglyme and 5 ml. of deuterium oxide (99.8%). When the addition was complete and all the potassium had dissolved, the reaction flask was placed in an oil bath maintained at 90° for 15 hr. The exchange was terminated by cooling the reaction solution to room temperature and pouring it into 100 ml. of chilled 2% hydrochloric acid solution. The precipitated solid was filtered, washed with water until free of acid, and dried in a vacuum desiccator over calcium sulfate. The dried solid was taken up in acetone and filtered, and the acetone was removed to yield 0.400 g. of a yellow solid. All the crude product was placed on a column made from 10 g. of silica gel in benzene. Elution with benzene gave 0.040 g. of an oil and further elution with 9:1 benzene–ether gave 0.359 g. of a slightly colored solid. Rechromatography of the latter on 10 g. of silica gel and elution with 19:1 benzene–ether gave 0.321 g. in eleven 25-ml. fractions. The solid product was recrystallized once from acetone–hexane to give white crystals, m.p. 132–134°. The infrared spectrum in carbon tetrachloride, in addition to

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having bands at 2150–2050 cm.$^{-1}$ due to C–D stretching vibrations, was transparent from 1443 to 1387 cm.$^{-1}$ indicating the absence of a $CH_2$ group adjacent to a carbonyl[7] and revealed a band at 1038 cm.$^{-1}$ which has been assigned to a $CD_2$ scissoring vibration at C-16 in a 17-keto steroid.[8]

*Anal.* Calcd. for $C_{19}H_{22}D_6O_2$: D, 21.43 atom % excess. Found: D, 20.30, 20.40 atom % excess (5.7 atoms D).

**The Bromination of 2,2,4,4,16,16-Hexadeuterio-5α-androstane-3,17-dione.**—2,2,4,4,16,16-Hexadeuterio-5α-androstane-3,17-dione (114.5 mg., 0.389 mmole) containing 5.7 atoms of deuterium and 1.0 ml. of a bromine–sodium acetate–acetic acid solution containing 0.348 mmole of bromine and 0.58 mmole of sodium acetate/ml. of solution, were placed in a 10-ml., round-bottom stoppered flask and stirred magnetically at ambient temperature for 84 hr. The reaction was terminated with some bromine still present by pouring it into 35 ml. of chilled saturated sodium chloride solution. The orange precipitate was collected by filtration, washed with 2% sodium bicarbonate solution and then water, and air dried on the filter for 2 hr. until the orange color disappeared. The filter cake was dissolved in acetone, the solution was filtered to remove sodium chloride, and the solvent was removed at the aspirator to give 130 mg. of a tan solid. Thin layer chromatography of this product was carried out on two 1-mm.-thick silica gel plates in a 30% ethyl acetate–benzene solvent system. Development of side bands with 2,4-dinitrophenylhydrazine reagent indicated the presence of three zones: dibromoandrostane-3,17-dione, 2α-bromoandrostane-3,-17-dione, and unreacted starting ketone. The monobromo zone was separated from the plates and the compound eluted from the silica gel with acetone. Removal of the solvent gave 36.7 mg. of deuterated 2α-bromoandrostane-3,17-dione, 25.4% yield. One recrystallization from acetone–hexane yielded 31 mg. of white crystals: m.p. 192–195°; $\lambda_{max}^{KBr}$ 1736, 1712, 1433, and 1379 cm.$^{-1}$. Authentic nondeuterated 2α-bromoandrostane-3,17-dione had m.p. 204.5–206°; $\lambda_{max}^{KBr}$ 1733, 1712, 1433, 1403, and 1376 cm.$^{-1}$. The n.m.r. spectra of both the deuterated and nondeuterated compounds, taken at the same concentration, revealed a quartet centered at $\tau$ 5.23 due to the 2β-proton ($J_{1\beta,2\beta}$ = 6.5 c.p.s. and $J_{1\alpha,2\beta}$ = 13.5 c.p.s.). Comparison of the areas under these quartets indicated that, in the deuterated compound, the quartet represented 0.58 atom of hydrogen or 42% deuterium in the 2β position.

In another experiment, terminated after 46 hr., where the work-up excluded the bicarbonate wash and air drying period, the monobromo product was obtained in 14% yield. The n.m.r. analysis indicated 43% deuterium in the 2β position.

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## The Addition of Silicon Hydrides to Olefinic Double Bonds. XI. Exchange of Methyl and Trimethylsiloxy Groups in Bistrimethylsiloxymethylsilane

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During the addition of bistrimethylsiloxymethylsilane to hexene-2 in the presence of chloroplatinic acid a methyl–trimethylsiloxy exchange in bistrimethylsiloxymethylsilane occurred so that the products formed included those expected from pentamethyldisiloxane

$$2(Me_3SiO)_2SiMeH \longrightarrow Me_3SiOSiMe_2H + (Me_3SiO)_3SiH$$

and tristrimethylsiloxysilane. No example has been observed previously of such a reaction under the mild conditions of these experiments.

A study of the addition of bis(trimethylsiloxy)methylsilane [I, $(Me_3SiO)_2SiMeH$], to hexene-2 in the presence of chloroplatinic acid revealed a most unexpected side reaction. An exchange of methyl and trimethylsiloxy groups occurred in a way never before observed under such mild conditions (<138°).

Up to this time the rupture of silicon–alkylcarbon bonds has been observed to occur only under vigorous conditions. For example, Eaborn[1] discusses the redistribution of chloromethylsilanes at temperatures between 250 and 400° under pressure, preferably in the presence of aluminum chloride.

Ryan[2] has reported the redistribution of alkylalkoxysilanes at temperatures in the range of 250° in the presence of catalytic amounts of a strong base. It was therefore surprising to find that methyl–silicon bonds had been broken when the temperature was less than 140° and the mole ratio of chloroplatinic acid to bistrimethylsiloxymethylsilane was $5 \times 10^{-5}$.

The addition of bistrimethylsiloxymethylsilane to hexene-2 in the presence of chloroplatinic acid yielded the expected product, bistrimethylsiloxymethylhexylsilane, eq. 1. Tristrimethylsiloxysilane, hexylpenta-

$$\underset{\text{I}}{(Me_3SiO)_2SiMeH} + \text{hexene-2} \longrightarrow \underset{\text{II}}{(Me_3SiO)_2SiMeHex} \quad (1)$$

methyldisiloxane, and 3,5-bistrimethylsiloxyoctamethyltetrasiloxane $[(Me_3SiO)_2SiMeOSiMe(OSiMe_3)_2]$ were also formed as by-products of the reaction.

The only plausible explanation for the existence of the first two by-products requires an intermolecular methyl–trimethylsiloxy exchange according to eq. 2. Tris-

$$2(Me_3SiO)_2SiMeH \xrightarrow[\text{hexene-2}]{Pt} Me_3SiOSiMe_2H + (Me_3SiO)_3SiH$$
$$\downarrow \text{hexene}$$
$$Me_3SiOSiMe_2Hex \quad (2)$$

trimethylsiloxysilane does not add to hexene-2 under the conditions of the experiment. The third by-product, $[(Me_3SiO)_2SiMe]_2O$, is the oxidation product of I.

The experiment was repeated twice to check the reproducibility of the reaction. In all cases the results were identical.

The purity and identity of each reagent were carefully checked. The unexpected products cannot be ascribed to impurities in the reagents.

At the present time little is known of the scope of the rearrangement reaction or the specific conditions which will permit its occurrence.

The use of cyclohexene instead of hexene-2 under the same conditions apparently leads to comparable results as followed by vapor phase chromatography. However, no similar rearrangements could be detected with hexene-1 and bistrimethylsiloxymethylsilane, nor with pentamethyldisiloxane and either hexene-1 or hexene-2.

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