showed no —C≡N absorption. The crude amine was dissolved in *n*-hexane and HBr gas bubbled into the solution. The yield of the salt was quantitative. Recrystallization from absolute ethanol yielded pure XIV, m.p. 290–292°.

In the synthesis of XV tetrahydrofuran was used as solvent. Due to low solubility, compound VIII was added as a slurry to an excess of $LiAlH_4$ in tetrahydrofuran. The rest of the reaction and work-up was the same as in the synthesis of XIV above. The yield was quantitative for both the free amine and the salt. Pure XV melted at 237–239° when crystallized from absolute ethanol–benzene mixture.

Anal.—Calcd. for $C_{13}H_{19}BrClN$: C, 51.25; H, 6.29; N, 4.60. Found: (XIV) C, 51.46; H, 6.31; N, 4.44. (XV) C, 51.49; H, 6.24; N, 4.45.

Deuteration on C-5 of II, IX–XIII.—Deuterium exchange on C-5 of II was carried out by refluxing 1.5 Gm. of II in 15 ml. of CH_3OD in the presence of 1 Gm. of sodium methoxide. After cooling, 10 ml. of deuterium oxide was added; the resulting suspension was extracted with anhydrous ether and the ether solution dried with Drierite. After removal of the ether, the NMR spectrum of the product indicated that a considerable amount of isomerization of II to I had occurred during the exchange. Deuterated II was obtained by recrystallization from ethanol. Compound II deuterated at C-5 was submitted to the same sequence of reactions as II in order to obtain compounds IX–XIII deuterated at C-5.

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Hypoiodite Oxidation of 3α-Bromo and 3α-Chloro-2β-hydroxy-5α-androstan-17-one

By R. E. COUNSELL and G. W. ADELSTEIN

Hypoiodite oxidation of 3α-bromo and 3α-chloro-2β-hydroxy-5α-androstan-17-one gave the expected 2β,19-oxide along with lesser amounts of 16-iodinated, 19-hydroxylated, and 19-acetoxylated products. The product composition as well as the yield of each product was found to vary considerably even when the reaction was performed under presumably identical conditions. The structures were assigned on the basis of chemical and spectroscopic evidence. The NMR and other spectroscopic properties of the epimeric 16α- and 16β-iodinated derivatives of 3α-bromo-2β,19-oxido-5α-androstan-17-one are discussed.

INTEREST in 19-substituted steroids as potential anabolic agents led to the investigation of the hypoiodite oxidation of 2β-hydroxyandrostanes as a means of introducing functional groups at the C-19 position (1). During the course of these studies it was noted that a number of minor by-products were formed in addition to the expected oxidation product. This report involves a study of this reaction and structural elucidation of the by-products.

DISCUSSION

The conversion of 2β-hydroxysteroids to 19-functionalized products has been accomplished by: (*a*) oxidation with lead tetraacetate alone (2, 3) or in the presence of iodine (hypoiodite) (4) and (*b*) photolysis of nitrite esters (3, 5). In each case, an alkoxy radical (A) is generated which can interact with the proximal angular methyl group. In the hypoiodite reaction, a furan (B) or an iodofuran (C) can form depending on the mechanism of ring closure. (Scheme I).[1] Although compounds of type C have not been isolated, the characterization of the corresponding hydroxy and acetoxy derivatives among the reaction products has suggested the intermediacy of such an iodinated precursor.

In these studies, hypoiodite oxidation of 3α-bromo-2β-hydroxy-5α-androstan-17-one (I) in refluxing carbon tetrachloride afforded a 36% yield of 3α-bromo-2β,19-oxido-5α-androstan-17-one (III) after chromatography.[2] In addition to this expected product, three other crystalline products were isolated. Two of these products preceded the major product on chromatography and were characterized as the 16β- and 16α-iodinated derivatives (IV and V). These epimers were obtained in 1.4 and 1.2% yield, respectively. The third product, obtained in 10% yield, followed the major product on chromatography and was identified as the hemiacetal (VI).

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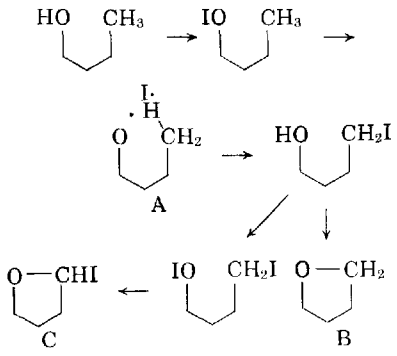
[1] The mechanisms involved in the hypoiodite reaction have been excellently reviewed by Heusler, K., and Kalvoda, J., *Angew. Chem. Intern. Ed.*, **3**, 525(1964).
[2] This product has been isolated in yields as high as 53% under presumably the same conditions (1).



Scheme I

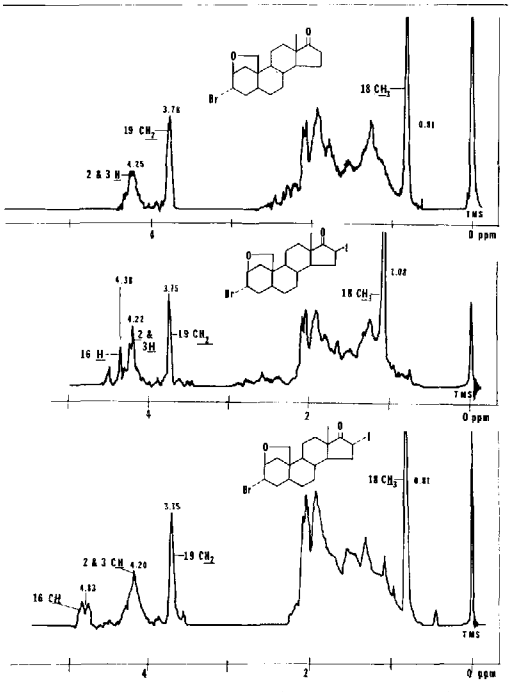


Fig. 1.—NMR spectra of unsubstituted ketone (III) (top) and the epimeric 16β-(IV) (middle), and 16α-iodoketones (V) (bottom).

The hypoiodite oxidation of I was repeated several times under presumably identical conditions using purified reagents and chromatographically pure halohydrins and each time the yield of products and the product composition were found to vary. The 16α-iodo product (V) was isolated in subsequent experiments, but none of the 16β-epimer could be separated. Moreover, in one experiment trituration of the crude reaction product with methanol afforded a high-melting product in 5.5% yield which was subsequently identified as the 19-acetoxy derivative (VII). In this instance none of the corresponding 19-hydroxylated product (VI) could be distinguished after chromatography. In still another experiment, VII was isolated in 5% yield after chromatography of the crude product which would tend to indicate that this ester is not hydrolyzed during chromatography. No explanation can be offered at this time for the variations in product yield and composition.

The structural assignments for the epimeric iodoketones (IV and V) were based on chemical evidence as well as spectral and elemental analysis. The 16α-epimer (V) was synthesized by first converting III to its enol acetate (IX) followed by iodination with iodine and mercuric acetate as described by Mueller and Johns (6). No 16β-isomer (IV) was isolated in this experiment.

The NMR spectra revealed distinct differences between the epimeric iodoketones (see Fig. 1). One epimer displayed a profound downfield shift of 14.5 c.p.s. for the C-18 methyl resonance when compared to the unsubstituted ketone (III). Cross and Beard (7) have noted a similar deshielding of the C-18 methyl protons by 16β-methyl substituted steroids. Moreover, the C-18 methyl resonance is shifted downfield by 19 c.p.s. in 11β-bromo-12-ketosteroids and is essentially unaffected in 11α-bromo-12-ketosteroids (8). On the basis of these findings as well as others indicating that introduction of a new 1:3 nonbonded diaxial interaction with an angular methyl group leads to a noticeable downfield shift in the angular methyl proton frequency (9), the iodine atom in IV was assigned as 16β and that in V is 16α. These assignments also agree with the observed chemical shifts for the 16 proton in each case. The latter appeared as an overlapping doublet at 261 c.p.s. in IV and at 290 c.p.s. in V. Thus, if observations made for steroidal α-haloketones (10) hold for 16-halo-17-ketosteroids, such chemical shifts would indicate that the 16α-hydrogen in IV is pseudoequatorial while the 16β-hydrogen in V is pseudoaxial. A study of the NMR spectra of more readily available 16-iodo-17-ketosteroids is currently in progress.

Although very few studies have been concerned with the ultraviolet absorption of α-iodoketones, Djerassi and co-workers (11) have established that absorption in the 260 mμ region is due to the iodine atom which masks the π-π* absorption band in the 300 mμ region corresponding to the carbonyl

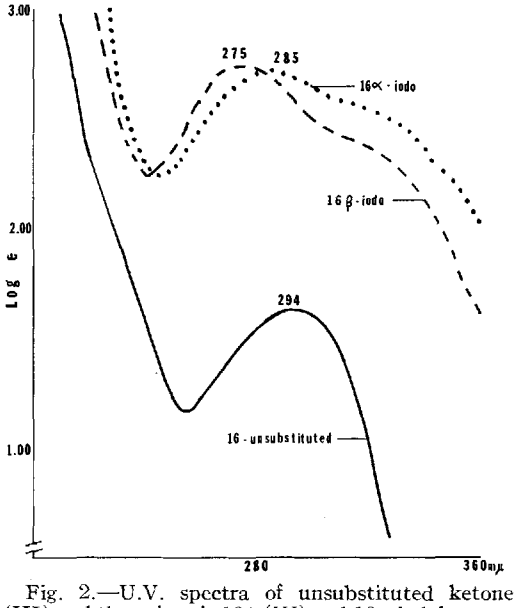
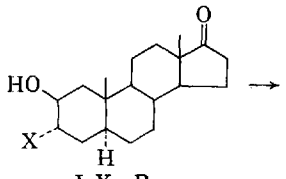
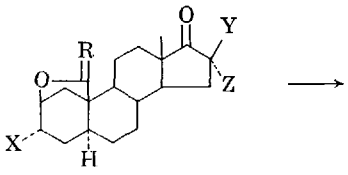


Fig. 2.—U.V. spectra of unsubstituted ketone (III) and the epimeric 16β-(IV) and 16α-iodoketones (V).

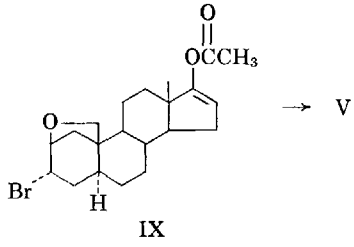


I, X = Br
II, X = Cl



III

III, X = Br, R = H_2, Y = Z = H
IV, X = Br, R = H_2, Y = I, Z = H
V, X = Br, R = H_2, Y = H, Z = I
VI, X = Br, R = H—OH, Y = Z = H
VII, X = Br, R = H—OAc, Y = Z = H
VIII, X = Br, R = O, Y = Z = H
X, X = Cl, R = H_2, Y = Z = H
XI, X = Cl, R = H_2, Y = H, Z = I
XII, X = Cl, R = H—OAc, Y = Z = H



IX

Scheme II

group. They noted, however, that a bathochromic shift of the maximum was apparent for the axially oriented α-iodo-ketosteroids and suggested that this red shift could be used as a spectral criterion for assigning an axial orientation to substituted α-iodocyclohexanones. Ultraviolet analysis of IV and V showed maxima at 275 and 285 mμ, respectively (see Fig. 2). Such results would suggest a pseudoaxial orientation for the iodine atom in V if the above criterion apply. Such an interpretation is contrary to that drawn from the NMR spectra. An attempt to resolve some of these disparities is currently in progress in our laboratories.

In the α-halocyclohexanone series, Jones (12) and Corey (13) were able to distinguish between an axial and equatorial halogen atom by the small or large shift in the carbonyl frequency. In the case reported here, however, no conclusion regarding the conformations of the 16 halogens could be made on the basis of the infrared spectra. Both iodoketones (IV and V) showed carbonyl maxima at 1725 cm.$^{-1}$, the same as for the noniodinated product (III). A similar observation was made by Mueller and Johns in the estrone series (6). These results emphasize the hazards in attempting to translate relationships established in the cyclohexanone series to substituted cyclopentanones.

The structure of VI was readily determined from chemical and spectral evidence. The NMR showed a singlet at 318 c.p.s. which shifted to 390 c.p.s. upon acetylation. This is the expected region for a hemiacetal acetate proton (4, 14) and the downfield shift of 72 c.p.s. corresponds to that observed upon acetylation of secondary alcohols (8). The hemiacetal was readily oxidized with Jones reagent (15) to the corresponding lactone which lacked a proton in the 300–400 c.p.s. region. The configuration of the 19-hydroxyl group remains to be established.

Similar results were obtained upon hypoiodite oxidation of the chlorohydrin (II). The major product was the expected 2β,19-oxide (X) but the corresponding 16α-iodinated (XI) and 19-acetoxylated (XII) derivatives were isolated in low yield by chromatography. Although this reaction has been carried out several times, no 16β-iodinated product has been isolated. (Scheme II.)

EXPERIMENTAL[3]

Hypoiodite Oxidation of 3α-Bromo-2β-hydroxy-5α-androstan-17-one (I).—A mixture of I (21.1 Gm.), lead tetraacetate (78.5 Gm.), and iodine (29.6 Gm.) in carbon tetrachloride (2.15 L.) was stirred under reflux for 8 hr. The reaction mixture was allowed to stand at room temperature for 3 hr. and filtered. The filter cake was washed with methylene chloride until no longer pink. The filtrate was washed with 10% sodium thiosulfate solution (2 × 200 ml.) and water (200 ml.), the layers separated, and the organic phase dried over anhydrous sodium sulfate. Evaporation of the solvent left an orange oil which was dissolved in benzene and adsorbed onto a column of silicic acid (500 Gm.). The column was eluted with benzene, followed by benzene containing increasing concentrations of ethyl acetate. The benzene–ethyl acetate (19:1) eluates afforded two distinct crystalline products. The first product was established to be 3α-bromo-16β-iodo-2β,19-oxido-5α-androstan-17-one (IV, 0.26 Gm.), m.p. 196–198° (from methanol); $\gamma_{max.}$ 1725, 1228, and 1018 cm.$^{-1}$; $\lambda_{max.}$ 275 mμ, log ϵ 2.72; NMR: 63.5 (C-18 methyl), 224 (C-19 proton), 251 (C-2 and C-3 protons, multiplet), and 261 c.p.s. (C-16 proton, overlapping doublet $J_{AX} + J_{BX} = 17$).

Anal.—Calcd. for $C_{19}H_{26}BrIO_2$: C, 46.26; H, 5.31. Found: C, 46.42; H, 5.43.

The other product was characterized as the epimer, 3α-bromo-16α-iodo-2β,19-oxido-5α-androstan-17-one (V, 0.3 Gm.), m.p. 210–212° (from methanol); $\gamma_{max.}$ 1725, 1232, and 645 cm.$^{-1}$; $\lambda_{max.}$ 285 mμ, log ϵ 2.73; NMR: 50 (C-18 methyl), 225 (C-19 proton), 252 (C-2 and C-3 protons, multiplet), and 290 c.p.s. (C-16 proton, overlapping doublet $J_{AX} + J_{BX} = 8$).

Anal.—Calcd. for $C_{19}H_{26}BrIO_2$: C, 46.26; H, 5.31; Br, 16.20; I, 25.73. Found: C, 46.27; H, 5.27; Br, 16.35; I, 25.73.

Further elution with benzene–ethyl acetate (9:1) furnished 3α-bromo-2β,19-oxido-5α-androstan-17-one (III, 7.6 Gm.), m.p. 130–132° (from methanol),

[3] The melting points were taken on a Fisher-Johns apparatus and are corrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Infrared spectra were taken in KBr disks with a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DK2A spectrophotometer in 95% ethanol. The NMR spectra were obtained in $CDCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as the internal standard. The lead tetraacetate used in the experiments was obtained from Arapahoe Chemicals, Inc., and recrystallized from benzene prior to use. The silicic acid used in the column chromatography was Baker and Adamson reagent grade.

undepressed by admixture with an authentic sample (1). Elution with benzene–ethyl acetate (1:1) gave 3α-bromo-19-hydroxy-2β,19-oxido-5α-androstan-17-one (VI, 2.1 Gm.), m.p. 168–170° (from methanol–water); $\gamma_{max.}$ 3440, 1715, and 1012 cm.$^{-1}$; NMR: 52 (C-18 methyl), 249–269 (C-2 and C-3 protons, multiplet), and 318 c.p.s. (C-19 proton).[4]

Anal.—Calcd. for $C_{19}H_{27}BrO_3$: C, 59.53; H, 7.10; Br, 20.85. Found: C, 59.61; H, 7.21; Br, 20.92.

19-Acetoxy-3α-bromo-2β,19-oxido-5α-androstan-17-one (VII).—A solution of VI (10 mg.) in acetic anhydride (0.5 ml.) and pyridine (0.5 ml.) was allowed to stand at room temperature for 23 hr. The solution was added slowly to cold water and the product collected by filtration. Recrystallization from methanol afforded pure VII, m.p. 235–237°; $\gamma_{max.}$ 1725, 1219, 1016, and 1009 cm.$^{-1}$; NMR: 50 (C-18 methyl), 130 (acetate methyl), 259–265 (C-2 and C-3 protons, multiplet), and 390 c.p.s. (C-19 proton).

Anal.—Calcd. for $C_{21}H_{29}BrO_4$: C, 59.30; H, 6.87. Found: C, 59.13; H, 6.86.

3α-Bromo-2β,19-oxido-19-oxo-5α-androstan-17-one (VIII).—The hemiacetal (VI, 14 mg.) was dissolved in acetone (2 ml.) and the solution cooled to 0°. An 8 *N* chromic acid solution (15) (0.1 ml.) was added and the mixture stirred for several minutes. The excess oxidant was decomposed with a few drops of isopropyl alcohol. The solution was diluted with water and the crystalline product collected by filtration. The crude product (12 mg.), m.p. 192–194°, was recrystallized from methanol to afford an analytical sample, m.p. 198–200°; $[\alpha]_D^{25}$ + 92°; $\gamma_{max.}$ 1750, 1725, and 715 cm.$^{-1}$; NMR: 57 (C-18 methyl), 275–287 (C-2 proton multiplet), 257–268 c.p.s. (C-3 proton, multiplet).

Anal.—Calcd. for $C_{19}H_{25}BrO_3$: C, 59.85; H, 6.61. Found: C, 59.88; H, 6.56.

3α-Bromo-2β,19-oxido-5α-androst-16-en-17-ol Acetate (IX).—A solution of III (0.5 Gm.) and *p*-toluene sulfonic acid (75 mg.) in isopropenyl acetate (10 ml.) was slowly distilled for 4 hr. and 5 ml. of distillate collected. Another portion of isopropenyl acetate (10 ml.) was added along with sodium bicarbonate (0.5 Gm.). The solvent was removed by distillation and the remaining traces removed *in vacuo*. The residue was extracted with ether which was subsequently washed with an ice-cold saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the brown residue recrystallized from methanol. This afforded pure IX (0.1 Gm.), m.p. 150–151°.

Anal.—Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14. Found: C, 61.51; H, 7.20.

Iodination of IX.—A solution of IX (55 mg.) and mercuric acetate (9 mg.) in acetic acid (3 ml.) was cooled in an ice bath. A solution of iodine (50 mg.) in acetic acid (3 ml.) was added dropwise with stirring. The iodine was decolorized after adding a few drops, but then the color persisted. The brown solution was poured into water, and the precipitate collected by filtration. The crude product was washed with 10% sodium thiosulfate solution, water, and air dried. Recrystallization from methanol gave V (20 mg.), m.p. 205–207°, undepressed by admixture with the product isolated above.

Hypoiodite Oxidation of 3α-Chloro-2β-hydroxy-5α-androstan-17-one (II).—Oxidation of II (3.3 Gm.) with lead tetraacetate (13.6 Gm.) and iodine (5.2 Gm.) in refluxing carbon tetrachloride (340 ml.) was carried out as described above. The resulting orange oil was adsorbed onto a column of silicic acid (100 Gm.) and eluted with benzene. This was followed by benzene containing increasing concentrations of ethyl acetate. Fractions obtained by elution with benzene–ethyl acetate (19:1) gave 3α-chloro-16α-iodo-2β,19-oxido-5α-androstan-17-one (0.1 Gm.), m.p. 197–200° dec. Recrystallization from methanol afforded pure XI, m.p. 212–214° dec.; $\gamma_{max.}$ 1725, 1235, and 643 cm.$^{-1}$; NMR: 50 (18-methyl), 224 and 227 (C-19 protons, inner peaks of unresolved quartet), 240–265 (C-2 and C-3 protons), and 283–300 c.p.s. (16β-proton).

Anal.—Calcd. for $C_{19}H_{26}ClIO_2$: C, 50.85; H, 5.84. Found: C, 50.97; H, 5.94.

Further elution with benzene–ethyl acetate (9:1) gave a crude crystalline product (1.7 Gm.), m.p. 120–128°. Recrystallization from methanol gave a high-melting compound (0.2 Gm.), m.p. 235–236°. Recrystallization of this product from methanol gave a pure sample characterized as 19-acetoxy-3α-chloro-2β,19-oxido-5α-androstan-17-one (XII), m.p. 243–244°; $\gamma_{max.}$ 1735, 1710, and 1235 cm.$^{-1}$; NMR: 49 (C-18 methyl), 128 (acetate methyl), 252–257 (C-2 and C-3 protons) and 384 c.p.s. (C-19 proton).

Anal.—Calcd. for $C_{21}H_{29}ClO_4$: C, 66.21; H, 7.67. Found: C, 66.00; H, 7.64.

Concentration of the mother liquor afforded a crystalline product (0.4 Gm.) shown to be identical with authentic 3α-chloro-2β,19-oxido-5α-androstan-17-one (X)[5] described previously (1).

[4] In another experiment involving hypoiodite oxidation of 36.3 Gm. of I, trituration of the crude reaction product with methanol afforded a crystalline product (1.7 Gm.) which upon recrystallization from methanol was found to be the hemiacetal acetate (VII), identical with that obtained by acetylation of VI.

[5] In another experiment, oxidation of II (3.7 Gm.) gave X (1.9 Gm.) and XII (0.2 Gm.), but no XI could be isolated.

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