Bromination with Cupric Bromide. II.[1,2] Bromination in the Presence of an Olefinic Bond

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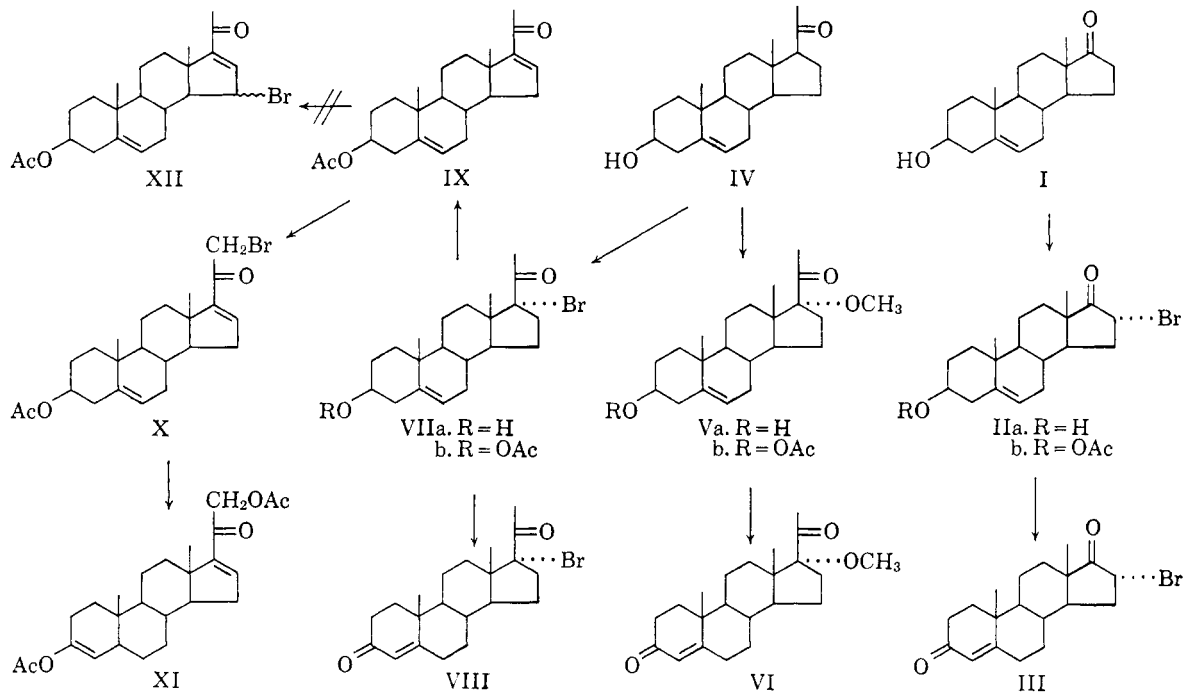
Further information on the utility of cupric bromide as a brominating agent is presented. It is shown that steroidal ketones can be brominated in the presence of an isolated double bond without this bond being affected. A novel method for the formations of the hitherto unreported 17α-methoxypregnanes and 21-bromo-Δ[16]-20 ketones is also presented.

In a continuing investigation of the utility of the bromination of steroidal ketones with cupric bromide, we have found that bromination can be effected without affecting the integrity of the olefinic bond at C-5,[3,4] that C-20 ketones can be brominated to give 17α-bromo-20-ketones, and further, that Δ[16]-20-ketones yield the previously unreported 21-bromo-Δ[16]-20-ketones. When the bromination of the saturated 20-ketone is run in methanol solvent, it was found that displacement of the initially formed 17α-bromine occurs to yield the hitherto unknown 17α-methoxypregnane.



That the C-5 olefin remained intact was shown first by the bromination of 3β-hydroxyandrost-5-en-17-one (I), yielding 3β-hydroxy-16α-bromoandrost-5-en-17-one (IIa), which on Oppenauer oxidation afforded 16α-bromoandrost-4-en-3,17-dione (III). All these compounds are known. The properties of those described in this publication compare favorably with the properties given in the literature, and further, they all give satisfactory analyses. These bromination reactions were run in methanol solution, which has been shown[5] to give methoxylation when the newly introduced bromine is in a favorable position, *i.e.*, C-6. This methoxylation has been shown not to occur for 16α-bromo-17-ketones.[2] In all probability, this is due to the necessity for further flattening of the five-membered D-ring, which already contains one trigonal carbon, during the transition state of the substitution reaction, which flattening would involve imparting greater strain to the ring. It has been postulated that the difficulty in the synthesis of Δ[15]-17-ketones is due also to the necessary flattening of the D-ring by olefin for-

(1) This work was supported by a grant from G. D. Searle and Co., Chicago, Ill.

(2) Part I, E. R. Glazier, *J. Org. Chem.*, **27**, 2937 (1962).

(3) R. P. Arganbright and W. F. Yates, *ibid.*, **27**, 1205 (1962), have reported the chlorination of olefins with cupric chloride, but at high temperatures, *ca.* 300°.

(4) K. B. Doifode, *ibid.*, **27**, 2665 (1962), has reported the bromination of an olefinic bond with cupric bromide in dioxane. In this case, the olefin is not an isolated bond as is the steroidal C-5 olefin. The brominating agent was postulated to be dioxane dibromide, a known bromination agent, formed by prior reaction between cupric bromide and dioxane.

(5) P. B. Sollman and R. M. Dodson, *ibid.*, **26**, 4180 (1961).

mation which must impart greater strain to the ring.[6]

When cupric bromide bromination of 3β-hydroxypregn-5-en-20-one was attempted, using methanol as solvent, it was found that the product isolated contained no bromine (Va). Formation of crude 3β-hydroxy-17α-bromopregn-5-en-20-one (VIIa) was achieved by cupric bromide bromination using tetrahydrofuran as the solvent. This crude α-bromo ketone could be easily transformed into the 3β-acetate (VIIb), into the known 17α-bromoprogesterone (VIII) by Oppenauer oxidation, or into 3β-acetoxypregn-5,16-dien-20-one (IX) by reaction with lithium carbonate–lithium chloride–dimethylformamide reagent and subsequent acetylation. Refluxing crude 3β-hydroxy-17α-bromopregn-5-en-20-one (VIIa) in methanol solution with a small amount of added hydrobromic acid afforded compound Va, indicating that the complete reaction with cupric bromide in methanol probably passes through the 17α-bromo-20-ketone. The n.m.r. spectrum of Vb, the 3-acetate, showed a sharp peak for three protons at τ 6.908 indicative of an —OCH_3 group. This new compound has been formulated as 3β-acetoxy-17α-methoxypregn-5-en-20-one. The methoxylation is considered to have occurred by an acid-catalyzed nucleophilic substitution by methoxyl ion at C-17. Oppenauer oxidation of Va afforded a good yield of 17α-methoxyprogsterone as indicated by the infrared spectrum of the product which contained the bands typical for a Δ^4-3-ketone-20-ketone system. Both of these new methoxy steroids gave correct elementary analyses.[7]

Reaction of 3β-acetoxypregn-5,16-dien-20-one (IX) with cupric bromide in tetrahydrofuran was carried out with the thought of producing results analogous to those obtained by Sollman and Dodson,[5] that is, introduction of a bromine at C-15 to yield XII. The product, however, was shown to be the 21-bromo derivative X by elemental analysis and n.m.r. spectroscopy. The expected quadruplet in the n.m.r. spectrum for the C-15 proton in XII was absent. Instead, a sharp singlet at τ 5.850 and representing the two protons of a CH_2X grouping at C-21 appeared. The singlet for the C-21 methyl was absent in the spectrum. The 21-bromo-Δ^{16}-20-ketone was transformed,[8] *via* the 21-iodide to the known 3β,21-diacetoxypregn-5,16-dien-20-one (XI). The bromination reaction is thought to proceed *via* the Δ^{20}-enol. Enolization toward C-17 probably is not favored for this would involve forming an olefinic bond in a five-membered ring which contains a trigonal carbon. As mentioned above, this would necessitate flattening the ring and greatly increasing its steric strain.[6]

Experimental[9]

3β-Hydroxy-16α-bromoandrost-5-en-17-one (IIa).—A solution of 3β-hydroxyandrost-5-en-17-one (1.65 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) in 200 ml. of methanol was refluxed for 24 hr. The light yellow solution was poured into water and the resulting mixture extracted with chloroform. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to yield a clear brown glass. The glass was chromatographed on silica gel and afforded, upon elution with 25 and 50% ether in benzene, a semicrystalline mixture. This crude product was recrystallized four times from methanol to yield 0.89 g. (45%) of white needles, m.p. 175–176°; $[\alpha]^{25}D$ −24° (*c*, 2.51) [reported values[10]: m.p.177–178°; $[\alpha]^{20}D$ −23° (*c*, (*c*, 2.94)].

Anal. Calcd. for $C_{19}H_{27}BrO_2$: C, 62.12; H, 7.41; Br, 21.76. Found: C, 62.14, 62.04; H, 7.31, 7.22; Br, 20.92, 21.05.

3β-Acetoxy-16α-bromoandrost-5-en-17-one (IIb).—3β-Hydroxy-16α-bromoandrost-5-en-17-one (480 mg.) was acetylated in the usual manner with pyridine and acetic anhydride. The mixture, on dilution with water, yielded a white solid. After drying, this solid was recrystallized three times from methanol to afford 240 mg. of white needles, m.p. 173–175°; $[\alpha]^{25}D$ −25° (*c*, 1.95) [reported values[10]: m.p. 181–183°; $[\alpha]^{20}D$ −24° (*c*, 3.37)].

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.72, 61.80; H, 7.07, 7.21; Br, 20.33, 20.06.

16α-Bromoandrost-4-ene-3,17-dione (III).—Approximately 70 ml. of solvent was distilled from a mixture of 800 mg. of IIa, 20 ml. of cyclohexanone, and 140 ml. of toluene. Aluminum isopropoxide (500 mg.) in 40 ml. of dry toluene was added and the reaction mixture was refluxed. During a period of 75 min., 40 ml. of distillate was collected. The residue was cooled, diluted with ether, extracted with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water. The ether solution was then steam distilled. The residue from this distillation was extracted with chloroform. After drying, the organic extracts were evaporated *in vacuo* to a yellow glass, which was then chromatographed on silica gel. Elution with 30% ether in benzene yielded a colorless glass, which, after three crystallizations from ethyl acetate–heptane, afforded 300 mg. white prisms, m.p. 172–174°; $[\alpha]^{25}D$ +113° (*c*, 1.70) [reported values[10]: m.p. 173–175°; $[\alpha]^{20}D$ +114° (*c*, 1.97)]. The infrared spectrum had bands at 1750, 1665, and 1645 $cm.^{-1}$.

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90; Br, 21.88. Found: C, 62.33, 62.19; H, 6.77, 6.99; Br, 21.90, 21.86.

3β-Hydroxy-17α-methoxypregn-5-en-20-one (Va).—(A). A mixture of 3β-hydroxypregn-5-en-20-one (6.32 g., 0.02 mole) and cupric bromide (8.96 g., 0.04 mole) in 300 ml. of methanol was refluxed overnight. The work-up was iden-

(6) J. Fajkos, *Collection Czech. Chem. Commun.*, **23**, 1559 (1958).

(7) After completion of this work, it was found that 17α-methoxyprogesterone had been unambiguously prepared by R. Beyler and F. Hoffman of the Merck, Sharp and Dohme Research Laboratories, Rahway, N. J., by the methylation of the 17α-hydroxy steroid with silver oxide and methyl iodide. A comparison of samples showed them to be identical. We wish to thank Dr. Glen Arth for a sample of the Merck compound and information of these unpublished results.

(8) *Cf.* the method of: G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

(9) Melting points were taken on a Kofler block and are uncorrected. Infrared spectra were obtained on a Perkin–Elmer Infracord 137 in chloroform solution. Optical rotations were also measured in chloroform solution. The silica gel used for chromatography was grade 923 obtained from Davison Chemical Corp., Baltimore, Md. Elemental analyses were performed by Weiler and Strauss, Oxford, England. N.m.r. spectra were run by Mr. T. Wittstruck of these laboratories on a Varian Associates high resolution spectrometer, Model 4302, operating at a frequency of 60 Mc. Spectra were obtained in deuteriochloroform using tetramethylsilane as an internal standard.

(10) J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 766 (1959).

tical to that in the preparation of IIa to yield a yellow semicrystalline mixture. This mixture on chromatography on silica gel and elution with 10–25% ether in benzene yielded yellow crystals, which after two crystallizations from methanol afforded 2.27 g. (33%) of colorless plates, m.p. 206–210°; $[\alpha]^{25}D$ 3.8° (*c*, 2.08). The infrared spectrum had a single carbonyl band at 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.90; H, 9.36. Found: C, 76.21, 75.91; H, 9.96, 9.68.

(B). 3β-Hydroxypregn-5-en-20-one (1.58 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) in 100 ml. of tetrahydrofuran was refluxed for 2 hr. This mixture was worked up in the usual fashion to yield a yellow glass which was dissolved in 50 ml. of methanol containing 1 ml. of 48% hydrobromic acid. After being refluxed for 5 hr., the reaction was again worked up and the residue put on silica gel. Elution with 25–50% ether in benzene yielded a crude white solid, which, after extensive recrystallization from methanol, afforded 100 mg. of white plates, m.p. 204–208°, identical in all respects to Va obtained above.

3β-Acetoxy-17α-methoxypregn-5-en-20-one (Vb).—3β-Hydroxy-17α-methoxypregn-5-en-20-one (220 mg.) was acetylated in the usual fashion with pyridine and acetic anhydride. From methanol, there were obtained white crystals, m.p. 174–176° $[\alpha]^{25}D$ −4.6° (*c*, 1.60). The infrared spectrum had carbonyl peaks at 1700 and 1723 cm.$^{-1}$. The n.m.r. spectrum had peaks at τ equal 4.608 (couplet), 5.416 (multiplet), 6.908, 7.828, 7.978, 8.791, and 9.300, which are attributed to the following protons successively: C-6 proton, C-3α proton, methoxy protons, C-21 methyl, acetate methyl, C-19 methyl, and C-18 methyl.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.17, 74.13; H, 8.95, 8.99.

17α-Methoxypregn-4-ene-3,20-dione (VI).—From mixture of 500 mg. of Va, 5 ml. of cyclohexanone, and 50 ml. of toluene was distilled approximately 25 ml. of solvent. Aluminum isoproxide (100 mg.) was added in 20 ml. of dry toluene over 15 min. to the refluxing solution. After being refluxed a further 45 min., the reaction mixture was hydrolyzed with a concentrated aqueous solution of Rochelle salts. The resulting mixture, after steam distillation, cooling in the refrigerator, and filtration, yielded a white solid. Crystallization twice from methanol afforded 350 mg. of flat plates, m.p. 205–208°; $[\alpha]^{25}D$ 163° (*c*, 2.05). The infrared spectrum had bands at 1700, 1680, and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.63. Found: C, 76.33, 76.52; H, 9.08, 9.21.

A mixture melting point of the above and an authentic sample[7] showed no depression. The infrared spectra were identical.

3β-Hydroxy-17α-bromopregn-5-en-20-one (VIIa).—A solution of 3β-hydroxypregn-5-en-20-one (3.16 g., 0.01 mole) and cupric bromide (4.48 g., 0.02 mole) in 150 ml. of tetrahydrofuran was refluxed for 1 hr. The light yellow solution was worked up in the usual fashion to yield a yellow glass which was then chromatographed on silica gel. A semicrystalline material, *ca.* 3 g., was eluted with 25% ether in benzene, but this material, even after extensive crystallization from benzene and benzene–heptane, could not be purified.

17α-Bromopregn-4-ene-3,20-dione (VIII).—The crude VIIa (2 g.) was treated under the same Oppenauer oxidation conditions used in the preparation of III. After work-up, the crude material was put on silica gel, from which, a yellow glass was eluted with 25% ether in benzene. After extensive crystallization from methanol, white needles, (95 mg.) were obtained with m.p. 159–161°; $[\alpha]^{25}D$ 23° (*c*, 2.03) [reported values[11]: m.p. 162–163°; $[\alpha]^{24}D$ 20° (*c*, 0.949)].

Anal. Calcd. for $C_{21}H_{33}BrO_3$: C, 64.12; H, 7.43; Br, 20.32. Found: C, 63.81, 64.05; H, 7.36, 7.17; Br, 22.25, 21.93.

3β-Acetoxy-17α-bromopregn-5-en-20-one (VIIb).—A solution of 3β-hydroxypregn-5-en-20-one (1.58 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) in 100 ml. of tetrahydrofuran was refluxed for 2 hr. The usual work-up gave a yellow glass. The crude product was acetylated with pyridine and acetic anhydride. The crude acetate was chromatographed on silica gel. Elution with 15% ether in benzene yielded a white solid which, after extensive crystallization from methanol, afforded 120 mg. of white plates, m.p. 142–144°; $[\alpha]^{25}D$ −108° (*c*, 2.44) (reported value[11]: m.p. 146–147°).

Anal. Calcd. for $C_{23}H_{33}BrO_3$: C, 63.15; H, 7.61; Br, 18.27. Found: C, 63.62, 63.75; H, 7.49, 7.76; Br, 21.65, 22.03.

3β-Acetoxypregn-5,16-dien-20-one (IX).—A solution of 3β-hydroxypregn-5-en-20-one (3.16 g., 0.01 mole) and cupric bromide (4.46 g., 0.02 mole) in 200 ml. tetrahydrofuran was refluxed for 2 hr. The usual work-up afforded a yellow glass, which was dissolved in 100 ml. of dimethylformamide containing 5 g. of lithium carbonate and 5 g. of lithium chloride. The mixture was heated at *ca.* 110° overnight, then cooled and poured into water. The solid residue obtained was collected by filtration, washed with water, and dried *in vacuo*. The crude dry product was then acetylated with pyridine–acetic anhydride, worked up in the usual manner, and the crude acetate chromatographed on alumina. Elution with 5% ether in benzene yielded white crystals, which, after crystallization from methanol, afforded 800 mg. of white needles, m.p. 171–173°, and identical in every respect to an authentic sample of 3β-acetoxypregn-5,16-dien-20-one.

3β-Acetoxy-21-bromopregn-5,16-dien-20-one (X).—A solution of 3β-acetoxypregn-5,16-dien-20-one (1.42 g., 0.004 mole) and cupric bromide (1.79 g., 0.008 mole) in 100 ml. of tetrahydrofuran was refluxed for 2 hr. The usual work-up yielded a yellow solid, which was chromatographed on silica gel. Elution with 10% ether in benzene afforded yellow crystals, which, after crystallization from methanol yielded 500 mg. of white crystals, m.p. 169–171°; $[\alpha]^{25}D$ −48° (*c*, 2.20). The n.m.r. spectrum had peaks at τ equal 3.167 (multiplet), 4.610 (multiplet), 5.380 (multiplet), 5.850 (singlet), 7.992 (singlet), 8.959 (singlet), and 9.080 (singlet). These are attributed to the following protons, successively: C-16 proton, C-6, 3α, C-21, 3-acetate methyl, C-19 methyl, and C-18 methyl.

Anal. Calcd. for $C_{23}H_{31}BrO_3$: C, 63.44; H, 7.18; Br, 18.35. Found: C, 63.24, 63.12; H, 6.90, 6.92; Br, 16.78, 17.00.

3β,21-Diacetoxypregn-5,16-dien-20-one (XI).—A solution of the 21-bromo-20-ketone X (1 g.) and sodium iodide (1 g.) in 40 ml. acetone was refluxed for 20 min. The hot solution was filtered and the filtrate added to a mixture of 5 g. of potassium bicarbonate and 4 ml. of acetic acid. This mixture was then refluxed overnight, cooled, and poured into a large excess of water. The resulting white precipitate was collected by filtration, dried *in vacuo*, and finally recrystallized twice from methanol to afford 490 mg. of white crystals, m.p. 153–155°; $[\alpha]^{25}D$ −39.5° (*c*, 2.10) (reported values[12]: m.p. 156–157°; $[\alpha]^{24}D$ −33.5°). The infrared spectrum had carbonyl bands at 1730, 1720, and 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.31, 72.27; H, 8.35, 8.39.

(11) Ch. R. Engel and H. Jahnke, *Can. J. Biochem. Physiol.*, **35**, 1047 (1957).

(12) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **76**, 1722 (1954).