its infrared absorption spectrum no evidence was found for the presence of the trimethylsilyl group, and the spectrum resembled in every way that of aniline. This was confirmed by forming derivatives of III with phenyl isocyanate and 2,4-dinitrochlorobenzene. It thus appears that the Beckmann rearrangement of 4-trimethylsilylacetophenone oxime occurs in good yield; however, conditions for the preparation of 4-trimethylsilylaniline from this Beckmann product have not been found.

## EXPERIMENTAL

*Beckmann rearrangements of* I. A solution of I (20.7 g., 0.1 mole) in anhydrous diethyl ether (500 ml.) was treated with thionyl chloride (12 g., 0.1 mole). After the initially exothermic reaction had moderated, the mixture was heated at reflux for 0.5 hr. Water (500 ml.) was then added to decompose unreacted thionyl chloride. Excess powdered sodium bicarbonate was then cautiously added to the stirred mixture, the ether layer separated, washed three times with water, then dried over anhydrous sodium sulfate. On distilling off the ether a yellow crystalline solid remained, yield 18 g. (87%). After two treatments with charcoal, and a further recrystallization from alcohol, colorless flat crystalline plates were obtained of m.p. 171°,[8] in good agreement with the literature[5] value of 169–170°.

*Anal.* Calcd. for $C_{11}H_{17}NOSi$: N, 6.76; Si, 13.55. Found: N, 6.64; Si, 13.29.

Employing the same experimental conditions with phosphorus pentachloride (21 g., 0.1 mole) the yield of II was 18 g. With concentrated sulfuric acid (10 g., 0.1 mole) the yield of II was 15 g. (72.5%).

*Infrared absorption spectrum of* II. The spectrum was determined using a Perkin-Elmer Model 112 spectrophotometer with sodium bromide optics. Prominent bands included those assigned to NH stretching at 3257; aliphatic CH stretch at 2927; amide C:O at 1666; aromatic C:C at 1506 and 1592; NH bend at 1537; parasubstitution at 823; and three strong bands due to the trimethylsilyl group at 1248, 838, and 759 cm.$^{-1}$ [9,10]

*Attempted alkaline hydrolysis of* II. One-gram samples of II were dissolved in 20–30 ml. of 40% potassium hydroxide in dilute (1:1) alcohol. On heating at reflux for 30 min., cooling, and making slightly acid, II was quantitatively recovered, m.p. 170–171°. Similar results were obtained using 70% potassium hydroxide in dilute alcohol.

*Acid hydrolysis of* II. On heating II (10 g.) under reflux with excess dilute (1:10) sulfuric acid for 15 min. the solution turned dark brown. Heating was continued for a further 15 min. to ensure complete reaction. Excess 10% sodium hydroxide solution was then added to liberate the free base. The crude amine (approx. 7 g.) was extracted with ether, the extracts washed with water, dried, and the ether removed. Fractional distillation yielded 3.5 g. of a colorless oil, b.p. 100–120°/12–15 mm. The oil was redistilled and the fraction of b.p. 112–115°/12–15 mm. collected. Yield, 2.0 g.

*Identification of hydrolysis product.* The infrared absorption spectrum of the colorless oil obtained by acidic hydrolysis of II was identical with that of an authentic specimen of freshly distilled aniline.

Phenyl isocyanate reacted with the oil to give 1,3-diphenylurea, m.p. 238°; and 2,4-dinitrochlorobenzene reacted to give 2,4-dinitrodiphenylamine, m.p. 156°. Both these data are identical with those for the corresponding aniline derivatives.

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[8] All melting points are uncorrected.

[9] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1954, pp. 274–81.

[10] E. G. Rochow, D. T. Hurd, and R. N. Lewis, *The Chemistry of Organometallic Compounds*, John Wiley & Sons, Inc., New York, 1957, pp. 146–7.

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# 16-Hydroxylated Steroids. IX.[1] Synthesis of 12α-Bromo-16α-hydroxycortisone 21-Acetate and 16,21-Diacetate

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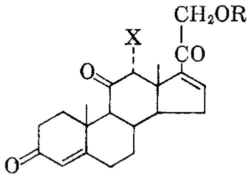
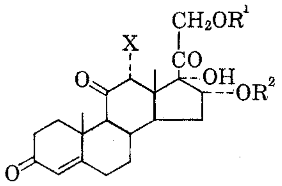
Recently described work from this Laboratory on 16α-hydroxycorticoids[2] has now been extended to include those containing a 12α-halogen group.[3] The present note describes the synthesis of 12α-bromo-16α-hydroxycortisone (12α-bromo-16α,17α-21-trihydroxy-4-pregnene-3,11,20-trione) in the form of its 21-acetate IIa and 16,21-diacetate IIb.



Ia. R = Ac; X = Br
Ib. R = Ac; X = H
Ic. R = X = H



IIa. $R^1$ = Ac; $R^2$ = H; X = Br
IIb. $R^1$ = $R^2$ = Ac; X = Br
IIc. $R^1$ = $R^2$ = Ac; X = H

Hydroxylation of 21-acetoxy-12α-bromo-4,16-pregnadiene-3,11,20-trione (Ia)[4] with potassium permanganate in aqueous acetone[5a,b] gave a mixture of products[6] from which the desired 21-acetoxy-12α-

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[1] Paper VIII, S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, 429 (1959).

[2] (a) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956); (b) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, and W. S. Allen, *J. Am. Chem. Soc.*, **79**, 4555 (1957); and (c) S. Bernstein, *Rec. Prog. Hormone Res.*, **14**, 1 (1958).

[3] (a) D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Am. Chem. Soc.*, **78**, 2912 (1956); (b) J. E. Herz, J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **78**, 2017 (1956); and (c) J. Fried, J. E. Herz, E. F. Sabo, and M. H. Morrison, *Chem. and Ind.* (*London*), 1232 (1956).

[4] W. F. McGuckin and H. L. Mason, *J. Am. Chem. Soc.*, **77**, 1822 (1955).

[5] (a) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4373 (1955); (b) B. Ellis, F. Hartley, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 4383 (1955).

[6] The reaction mixture was shown by paper-strip chromatographic analysis to contain at least five products. No attempt was made to isolate and identify the byproducts.

bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) was obtained by direct crystallization. Acetylation gave the solvated 16α,21-diacetate IIb in an 8% over-all yield from Ia. The same final product IIb was obtained in 10% yield when the hydroxylation was carried out with osmic acid in benzene.[7,8] These yields are to be compared with a 28% yield obtained by hydroxylation of the parent nonhalogenated compound 21-acetoxy-4,16-pregnadiene-3,11,20-trione (Ib) with permanganate,[5b] and with a 50% yield by hydroxylation of Ic with osmic acid.[7]

The lower yields observed in the preparation of the 12α-bromo-16α,17α-diols may, in part, be ascribed to steric hindrance. Examination of a molecular model of Ia shows the axial 12α-bromine atom to be in close proximity to the rear side of the C16,17-double bond. Consequently, the bromine atom may inhibit the formation of a large osmate or permanganate complex on the rear side of the D-ring.

The assigned structure of IIb was confirmed by the reductive removal of the bromine atom with zinc in acetic acid[9] to afford in good yield the known 16α,21-diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione (IIc).[5b,7]

## EXPERIMENTAL[10]

*21-Acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione* (IIa). To a solution of 926 mg. of 21-acetoxy-12α-bromo-4,16-pregnadiene-3,11,20-trione (Ia) in 40 ml. of acetone at 0° was added 320 mg. of potassium permanganate dissolved in 25 ml. of 85% aqueous acetone. The mixture was stirred at 0° for 7 min. when a solution of cold saturated sodium bisulfite was added. The resulting inorganic precipitate was separated by filtration. The filtrate was concentrated and 440 mg. of white solid, m.p. 200–205°, was collected. Paper strip chromatographic analysis revealed the presence in appreciable amount of five Blue Tetrazolium reducing products.

Crystallization of this mixture from acetone–petroleum ether gave 88 mg. of crude product, m.p. 250° (dec.). Two further crystallizations from acetone gave 20 mg. of pure IIa, m.p. 263° (dec.), $[\alpha]^{25}_{D}$ +39° (*c*, 0.28, pyridine); $\nu_{max}$ 3400, 1738, 1714, 1664, 1662, and 1236 cm.$^{-1}$

*Anal.* Calcd. for $C_{23}H_{29}O_7Br$ (497.38): C, 55.54; H, 5.88; Br, 16.07. Found: C, 55.85; H, 5.95; Br, 16.21.

In another run with 1.4 g. of Ia in 60 ml. of acetone, 480 mg. of potassium permanganate in 50 ml. of 85% acetone, and 0.35 ml. of acetic acid there was obtained 180 mg. (12% yield) of IIa, m.p .261° (dec.); $\lambda^{methanol}_{max}$ 237 mμ (ε 16,400).

*16α,21-Diacetoxy-12α-bromo-17α-hydroxy-4-pregnene-3,11,20-trione* (IIb). (a) To a solution of 155 mg. of 21-acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) in 6 ml. of pyridine was added 0.6 ml. of acetic anhydride. After standing at room temperature for 20 hr. the mixture was poured into ice water and filtered to afford 135 mg. of a white powder, m.p. 219–221° (dec.). Crystallization from acetone–petroleum ether gave 105 mg. of IIb, m.p. 228–229°. Further crystallization did not change the melting point; $\nu_{max}$ 3430, 1740, 1718, 1760, 1622, and 1238 cm.$^{-1}$

*Anal.* Calcd. for $C_{25}H_{31}O_8Br$ (539.42): C, 55.66; H, 5.79; Br, 14.82. Found: C, 56.46; H, 5.97; Br, 14.55.

(b) A solution of 575 mg. of osmic acid in 10 ml. of benzene was added to a solution of 926 mg. of the diene Ia in 25 ml. of benzene containing 0.4 ml. of pyridine. The mixture was stirred at room temperature for 7 hr. when a solution of 3.8 g. of sodium sulfite and 3.8 g. of potassium bicarbonate in 40 ml. of water and 25 ml. of methanol was added. After being stirred at room temperature overnight the mixture was filtered, and the residue was washed thoroughly with ethyl acetate. The combined filtrates were washed, dried, and filtered. Evaporation gave an intractable oil which on acetylation resisted crystallization.

The crude diacetate was subjected to partition chromatography on 150 g. of Celite[11] with a ternary system consisting of 10 parts petroleum ether (b.p. 90–100°), 3 parts dichloromethane, and one part ethylene glycol. The second hold-back volume (240 ml.) upon concentration gave 83 mg. of crystals, m.p. 225–227° (dec.). Three crystallizations from acetone–petroleum ether gave 50 mg. of pure IIb, m.p. 228–229° (dec.), $\lambda^{ethanol}_{max}$ 237 mμ (ε 13,700); $[\alpha]^{24}_{D}$ +26° (*c*, 0.99, chloroform). Infrared spectral analysis showed this product to be identical with that obtained from the potassium permanganate hydroxylation.

*16α,21-Diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione* (IIc). A mixture of 60 mg. of zinc dust and 54 mg. of the 12α-bromo-diacetate IIb in 5 ml. of glacial acetic acid was stirred at 15–20° for 20 min. It was then filtered and the separated solid was washed with several portions of ethanol. The combined filtrates were evaporated (bath temperature <40°), and the residue was extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate and saturated saline solution. The dried extract was filtered and evaporated. A single crystallization of the crude product from acetone–petroleum ether gave 36 mg. of IIc, m.p. 233–234°. The product exhibited a negative Beilstein test for halogen, and its infrared spectrum was identical with that of an authentic sample.[5b,7]

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[7] W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

[8] Here also the reaction mixture was complex and no attempt was made to isolate and identify the by-products.

[9] V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

[10] Melting points are uncorrected. The petroleum ether used had a b.p. 60–70°, unless otherwise specified. The infrared absorption spectra were determined in a potassium bromide disk.

[11] The adsorbent was specially treated Celite "545" which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and was washed with water, followed by alcohol and/or acetone. Finally, it was dried at 100°. Celite is the trade-mark of Johns-Manville Co. for diatomaceous silica products.

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## 4-(3-Pyridyl)-4-ketobutyric Acid

Harvey N. Wingfield, Jr.

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A synthesis of 4-3-pyridyl-4-ketobutyric acid which would give increased yields was desired, as this compound is an intermediate in the synthesis of