hr. The work-up was identical to that in 1-A. The crude product, after two recrystallizations from chloroform–heptane, yielded 2.22 g. (59%) of IIIa as white needles, m.p. 161.5–163°. A mixture melting point with bromo ketone from 1-A showed no depression, and the infrared spectra were identical.

C. 3β,17-Diacetoxy-5α-androst-16-ene (II)[10] (1.87 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 300 ml. of methanol. The solution was refluxed for 24 hr. After a similar work-up as in 1-A, white crystals were obtained which, after two recrystallizations from acetone–heptane, yielded 1.12 g. (60%) of IIIa as white needles, m.p. 156–157.5°; $[\alpha]^{27}D$ +60° (*c* 2.00). A mixture melting point with material from 1-A showed no depression, and the infrared spectra were identical.

D. 3β-Acetoxy-16α-bromo-5α-androstan-17-one (IIIb, see below) (600 mg.) was dissolved in a mixture of 10 ml. of 48% hydrobromic acid, 10 ml. of chloroform, and 40 ml. of methanol and the solution was stirred at room temperature overnight. After evaporation to one-half volume *in vacuo* at room temperature, the residue was poured into water and the resulting mixture was cooled in a refrigerator. The white crystals which had formed were separated by filtration, washed well with water, and dried *in vacuo* at 60°. After two recrystallizations from chloroform–heptane, there was obtained 540 mg. of IIIa as white needles, m.p. 158.5–159.5°; $[\alpha]^{26}D$ +50° (*c* 2.26). A mixture melting point with material from 1-A showed no depression, and the infrared spectra were identical.

2. **3β-Acetoxy-16α-bromo-5α-androstan-17-one (IIIb).**—A. 3β,17-Diacetoxy-5α-androst-16-ene (II) (1.87 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 300 ml. of methanol. Pyridine (850 mg.) was added, causing an immediate heavy green precipitate. The mixture was refluxed for 24 hr. at which time the solution had become light green and a black precipitate had formed. After filtration, the solution was evaporated to a paste, which was taken up in chloroform and water and shaken. The organic layer was separated and the aqueous solution was extracted twice more with chloroform. After being combined and dried, the organic extract was evaporated *in vacuo* to a mixture of green glass and crystals. This residue was chromatographed on 100 g. of silica gel. Elution with 5% ether in benzene yielded a white solid from which, after two recrystallizations from chloroform–heptane, there was obtained 834 mg. (44%) of IIIb as white plates, m.p. 166–167°; $[\alpha]^{27}D$ +41° (*c* 2.69) [reported values[9]: m.p. 171–172°; $[\alpha]^{20}D$ +38° (*c* 2.14)]. The infrared spectrum had bands at 1750, 1725, and 1250 (br.) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 61.41, 61.43; H, 7.62, 7.70; Br, 19.44, 19.18.

B. 3β-Hydroxy-16α-bromo-5α-androstan-17-one (IIIa) (510 mg.) was dissolved in 15 ml. of pyridine and 5 ml. of acetic anhydride. After standing at room temperature for 24 hr., the solution was poured into a large volume of water. The resulting white solid was collected by filtration, dried, and recrystallized twice from methanol to yield IIIb (266 mg.) as white plates, m.p. 164–165°; $[\alpha]^{25}D$ +42° (*c* 2.47). A mixture melting point with the 3β-acetoxy bromo ketone from 2-A showed no depression, and the infrared spectra were identical.

3. **Attempted Preparation of 3β-Hydroxy-16,16-dibromo-5α-androstan-17-one.**—3β-Hydroxy-5α-androstan-17-one (1.45 g., 0.005 mole) and cupric bromide (4.48 g., 0.02 mole) were dissolved in 200 ml. of methanol and refluxed for 24 hr. The usual work-up afforded white crystals which were chromatographed on 70 g. of silica gel. Only one compound was eluted, with 25% ether in benzene. After recrystallization twice from acetone–heptane, 1.20 g. of white needles was obtained, m.p. 160–161°; $[\alpha]^{25}D$ +60° (*c* 2.80). A mixture melting point with (IIIa) prepared above showed no depression and the infrared spectra were identical.

(10) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2941 (1954).

Chromic Acid Oxidation of Organoboranes. A Convenient Route to 6-Keto Steroids

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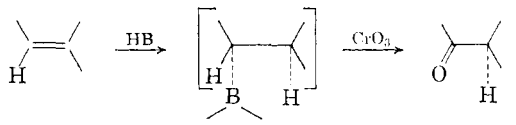
A conventional route to 6-keto steroids from Δ^5-compounds is *via* nitration with fuming nitric acid.[1] The reagents involved and the critical nature of the reaction[2] make this method unsuitable for large scale work. A recent report by Brown and Garg[3] of a one-step procedure for converting olefins to ketones, and the fact[4] that diborane reduces



esters comparatively slowly, prompted us to investigate the scope of this method to obtain 6-keto steroids, from their 3β-acetoxy C-5 unsaturated progenitors.

Using a modified hydroboration procedure, 3β,20β-diacetoxypregn-5-ene (I) was converted into monoketone (III, 48%)[5] and diketone (IV, 14%). The structure of ketone III was confirmed by its independent[6] synthesis from I, *via* nitration by concentrated nitric acid and sodium nitrite, followed by treatment with zinc and acetic acid. The structure of diketone IV was established by its conversion to 20β-acetoxy-5α-pregnane (VII).

3β-Acetoxy-17α-methyl-17β-carbomethoxyandrost-5-ene (II) on treatment with diborane, followed by oxidation with chromium trioxide, gave monoketone (V, 34%)[5] and diketone (VI, 14%). The structure of compounds V and VI are supported by their elemental analysis and their infrared spectra. When a tenfold excess of reagents was used either in the ether–diglyme medium or in dry tetrahydrofuran, excessive destruction of acetate groups was observed. From two such experiments with diacetate (I), 5α-pregnan-3,6,20-trione was isolated in

(1) (a) A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3802 (1959). (b) C. E. Anagnostopoulos and L. F. Fieser, *ibid.*, **76**, 532 (1954).

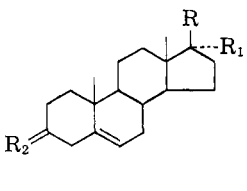
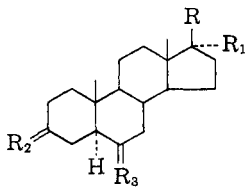
(2) See footnote 12 and 24 in ref. 1a.

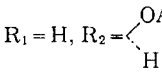
(3) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).

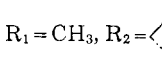
(4) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

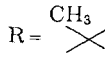
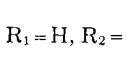
(5) Yields are based on recovered starting material.

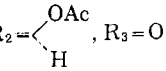
(6) Recently a synthesis of ketone III was independently reported by D. H. R. Barton *et al.*, *J. Am. Chem. Soc.*, **83**, 4076 (1961).

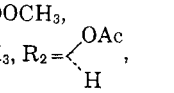
I. R = -CH(OAc)CH$_3$, R_1 = H, R_2 = 

II. R = -COOCH$_3$, R_1 = CH$_3$, R_2 = 

VIII. R =  , R_1 = H, R_2 = 

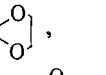
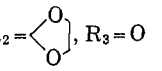
III. R = -CH(OAc)CH$_3$, R_1 = H, R_2 =  , R_3 = O

IV. R = -CH(OAc)CH$_3$, R_1 = H, R_2 = R_3 = O

V. R = -COOCH$_3$, R_1 = CH$_3$, R_2 =  , R_3 = O

VI. R = -COOCH$_3$, R_1 = CH$_3$, R_2 = R_3 = O

VII. R = -CH(OAc)CH$_3$, R_1 = H, R_2 = R_3 = H$_2$

IX. R =  , R_1 = H, R_2 =  , R_3 = O

15% and 31% yield, respectively. In contrast, when use of diglyme was avoided by adding boron trifluoride in dry ether to a suspension of sodium borohydride in a dry ethereal solution of steroid, the reaction was completely inhibited. That the reduction rather than fortuitous hydrolysis is involved in the conversion of the C-3 and C-20 acetates to hydroxyl group was demonstrated by following experiment. An excess of externally generated diborane was passed through a dry ethereal solution of diacetate (I) for two hours. An infrared spectrum of the crude product, which resulted from oxidation, showed essentially complete absence of bands due to acetate grouping.

It has been reported[7] that for compounds possessing an ethylene-dioxy grouping, *in situ*, generation of diborane can not be used for Brown hydration. Also the yields[8] in general are much lower when diborane is generated externally rather than *in situ*. We have successfully applied *in situ* generation of diborane for hydrobroration of diketal VIII to yield ketone IX in an over-all yield of 37%.

Experimental[9]

Hydroboration-Oxidation.—To a solution of steroid (5.0 mmoles) and boron trifluoride etherate (7.5 mmoles) in dry ether was added a saturated solution of sodium borohydride (3.7 mmoles) in dry diglyme under nitrogen atmosphere. After stirring at room temperature for 2 hr., an oxidation mixture of sodium dichromate (7.38 mmoles) and sulfuric acid (29.5 mmoles) made up to 9 ml. with water was added. After stirring for 2 more hours, the organic layer was separated, the aqueous layer extracted with ether, the organic liquor was worked up as usual, and the products separated by chromatography.

Two grams of **3β,20β-diacetoxypregn-5-ene (I)** when treated as above yielded 1.96 g. of crude product. Elution from a column of Florisil with benzene gave 0.8 g. of starting material, confirmed by its m.p., mixed m.p., and infrared spectrum. Elution with solvents of increasing polarity up to ether–benzene (1:9) gave a solid which after one crystallization from acetone–hexane yielded 0.586 g. of monoketone (III), m.p. 175–177°. Two more crystallizations yielded an analytical sample, m.p. 182–183° [α]D—13°; ν 1725 (ester carbonyl), 1710 (C_6-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.90; H, 9.04.

Further elution with ether–benzene (1:1) followed by ether afforded 0.16 g. of IV, m.p. 198–200°. Crystallization from acetone–hexane gave an analytical specimen, m.p. 203–204°, [α]D + 14°, ν 1725–1705 (ester and ketone carbonyl stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.82; H, 9.08.

Two grams of **3β-acetoxy-17α-methyl-17β-carbomethoxyandrost-5-ene (II)**, when treated as described above, yielded from a chromatogram on elution with benzene 0.62 g. of unchanged starting material. Elution with solvents of increasing polarity (ether–benzene 1:9) yielded a solid which after one crystallization from acetone–hexane gave 0.484 g. of ketone (V), m.p. 142–144°. Several crystallizations afforded an analytical sample, m.p. 155–156°, [α]D −36.7°; ν 1725–1710 (ester carbonyl, C_6-ketone stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.15; H, 8.90.

Elution with ether–benzene (1:1) followed by ether afforded a solid which on crystallization from acetone–hexane gave VI (0.17 g.) m.p. 185–188°. Further crystallizations gave an analytical sample, m.p. 189–190°, [α]D −17.6°; ν 1720–1705 (ester and ketone carbonyl stretching) cm.$^{-1}$.

Anal. Calcd. $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; Found: C, 73.35; H, 8.89.

Hydroboration of I (4 g.) using a tenfold excess of boron trifluoride and sodium borohydride each in dry tetrahydrofuran gave after oxidation **5α-pregnane-3,6,20-trione** (1.04 g.) m.p. 226–230°, [α]D + 59°; reported[10] m.p. 232–233°; [α]D +61°.

20β-Acetoxy-5α-pregnane (VII).—A solution of diketone (IV, 0.7 g.) in diethylene glycol (25 ml.) and hydrazine hydrate (85%, 0.8 ml.) was refluxed for 0.5 hr., cooled, and sodium hydroxide (0.5 g.) in a few drops of water was added. The solution was refluxed for half an hour more and the temperature was raised to 200° and maintained for 2 hr. The solution was cooled, diluted with water, and extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed. The residue (0.55 g.) was acetylated in pyridine (3 ml.) and acetic anhydride (2 ml.) in the usual manner to yield crude acetate (0.58 g.). Crystallizations from aqueous ethanol gave 0.2 g. of VII, m.p. 154–156°, [α]D +34°; reported[11a] m.p. 156–158°; [α]D +34°. An infrared spectrum was identical to that reported.[11b]

3,20-Diethylenedioxy-5α-pregnan-6-one (IX).—To a suspension of sodium borohydride (0.35 g.) in a solution of

(7) M. Nussim and F. Sondheimer, *Chem. Ind.* (London), 400 (1960).

(8) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

(9) All m.p.'s are uncorrected. Infrared spectra are recorded in chloroform using Perkin-Elmer Model 21 spectrophotometer. Rotations are recorded in chloroform. We wish to thank Dr. G. Papineau-Couture and his associates for microanalysis, rotations, and infrared spectra.

(10) C. P. Balant and M. E. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952)

(11) (a) H. Hirshmann, J. B. Hirschmann, and M. A. Daus, *J. Biol. Chem.*, **178**, 751 (1949). (b) G. Roberts, B. S. Gallagher, and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publishers, New York, 1958, Vol. II, # 351.

diketal (VIII, 1.62 g.) in dry tetrahydrofuran (40 ml.) was added boron trifluoride etherate (0.89 g.) in dry tetrahydrofuran (8.0 ml.) over 1 hr. under nitrogen. The reaction mixture was stirred for 2 more hours. Excess hydride was destroyed with acetone (2 ml.) and the mixture filtered. To the filtrate was added 1% ethanolic sodium hydroxide (10 ml.) and 30% hydrogen peroxide (0.7 g.), and the mixture heated on steam bath for 0.5 hr., cooled, diluted with water, and extracted with ether. The ether extracts were washed, dried, and the solvent removed to yield a colorless sirup. This was taken up in dry pyridine (10 ml.) and added to a freshly prepared complex of chromium trioxide (1.5 g.) and pyridine (15 ml.). The mixture was stirred overnight, filtered, and the residue washed with ether. The filtrate was diluted with water and extracted with ether. The ether extract was washed, dried, and the solvent removed. The residue was taken up in methanol (15 ml.) containing sodium (0.1 g.) and heated for 15 min. Concentration of the solution and subsequent cooling gave 0.52 g. of ketone (IX), m.p. 163–166°, and a second crop 0.09 g., m.p. 150–158°. Recrystallization gave an analytical sample m.p. 173–175°, $[\alpha]_D$ −11.8°, ν 1705 (C_6-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}O_5$: C, 71.74; H, 9.15. Found: C, 71.57; H, 9.06.

Reaction of Some Indole Ketones with Iodine and Pyridine

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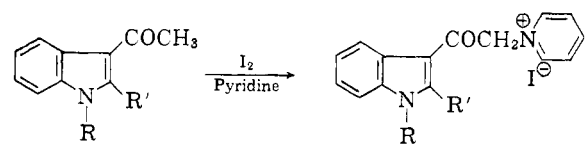
The reaction of iodine and tertiary organic bases with an arylmethyl ketone[2] forming an *N*-(2-aryl-2-oxoethyl) quaternary salt of the base has been applied to heterocyclic ketones such as the 2-, 3-, and 4-pyridylmethyl ketones,[3a] 2-thienylmethyl ketone,[3b] and to several heterocyclic compounds where reaction occurs with a methyl group activated by being in the α- or γ-position to the heteroatom.[2-4] This reaction offers a convenient method of converting such a methyl group into an aldehyde group.[4]

One of us recently[5] utilized the reaction of 3-acetylindole with isoquinoline in a synthesis of hexadehydroyohimbane, and in this communication we wish to report some observations on the condensation of some other ketones of the indole series with pyridine and the usefulness of this reaction as a means of obtaining the corresponding carboxylic acids by the alkaline hydrolysis of these salts.[6] This latter reaction verifies the structures assigned to the quaternary salts. Those acids that are unsubstituted in the 2-position are especially readily available by this method. 3-Acetylindole, 1-methyl-3-acetylindole, and 2-methyl-3-acetylindole all reacted readily with iodine and pyridine forming the corresponding 1-(2-3′-indolyl-2-oxoethyl)pyridinium salts (I) in excellent yield. These salts were previously only available in poor yield by reaction of an indolylmagnesium iodide with a haloacetyl halide and treatment of the resulting ω-halogeno ketone with pyridine.[7] The exchange of the iodide anion for picrate or perchlorate anion was readily effected by treating an aqueous solution of the iodide with an aqueous solution of the appropriate acid. Ketones such as 4-indol-3-yl-2-butanone and 4-(1-methylindol-3-yl)-2-butanone which contain an aliphatic-type carbonyl group also underwent reaction but to a lesser degree. As acetone gives a dipyridinium salt,[3a] these ketones might be expected to react in a similar fashion. However, only a monopyridinium salt (II) was obtained and reaction occurred at the terminal methyl group as evidenced by the formation of the corresponding indole-3-propionic acids on alkaline hydrolysis. Variation of reaction solvent, temperature, or time failed to raise the yield of the pyridinium salt above 40%. Pyridinium hydroiodide (40% yield) was always isolated from this reaction; its identity was established by analytical and spectral data and by hydrolysis to pyridine. An equivalent quantity of unchanged ketone was usually recovered and accounted for the poor yield of the quaternary salt.



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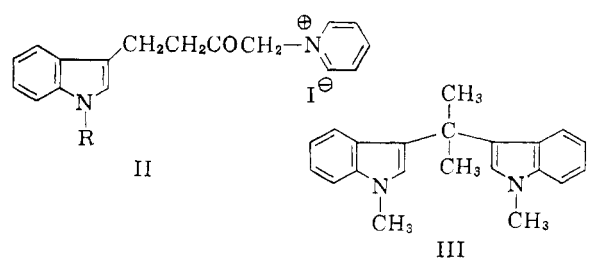

II III

The hydrolysis of the pyridinium salts was readily effected by gently heating on a water bath with dilute alkali solution. Several incidental methods used for the preparation of acids for comparison purposes are described in the Experimental.

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(2) L. C. King, *J. Am. Chem. Soc.*, **66**, 894 (1944); L. C. King and M. McWhirter, *ibid.*, **68**, 717 (1946); J. L. Hartwell and S. R. L. Kornberg, *ibid.*, **68**, 868, 1131 (1946).

(3) (a) F. Kröhnke and K. F. Gross, *Chem. Ber.*, **92**, 22 (1959); (b) L. C. King, M. McWhirter, and R. L. Rowland, *J. Am. Chem. Soc.*, **70**, 240 (1948).

(4) J. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956); W. Reid and H. Bender, *Chem. Ber.*, **89**, 1893 (1956); W. Reid and R. M. Gross, *ibid.*, **90**, 2646 (1957).

(5) D. R. Liljegren and K. T. Potts, *Proc. Chem. Soc.*, 340 (1960).

(6) F. Kröhnke, *Ber.*, **66**, 604 (1933).

(7) G. Sanna, *Gazz. Chim. Ital.*, **59**, 838 (1929); Q. Mingoia, *ibid.*, **61**, 646 (1931).