needles: mp 166–167 °C; IR ($CHBr_3$) 1250 cm^{-1} (N^+–O^-); ^1H NMR ($CDCl_3$) δ 5.8 (s, 2 H), 6.8 (d, 1 H, J = 2 Hz), 7.2–7.4 (m, 5 H), 8.1 (m, 1 H), 8.2 (s, 1 H), 8.5 (dd, 1 H, J = 6, J = 1 Hz); m/e 225 (M^+).

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.1; H, 4.9; N, 18.9.

The *N*-oxide **29** gave the corresponding 3-methylperchlorate **30** by methylation and conversion to the perchlorate, which crystallized as flakes (from EtOH): mp 212–214 °C.

***N*-(1-Oxido-2-pyridylmethyl)triethylammonium Chloride (26).** Et_3N (0.500 g) and the 1-oxide **25** (0.360 g) were heated under reflux in MeCN (40 mL) for 24 h. MeCN was evaporated 80 °C (15 mmHg) and the residue was washed with hot Et_2O (2 × 20 mL) leaving the chloride **27** (0.590 g, 96%), which separated from EtOH–Et_2O as prisms: mp 194–196 °C; IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H NMR [$(CD_3)_2SO$] δ 1.1 (t, 9 H, J = 8 Hz), 3.2 (q, 9 H, J = 8 Hz), 4.6 (s, 2 H), 7.2–7.6 (m, 2 H), 7.8 (dd, 1 H, J = 8 Hz, J = 1 Hz), 8.3 (dd, 1 H, J = 6, J = 1 Hz).

The salt was characterized as the dipicrate, which crystallized from EtOH as yellow needles: mp 120.5–122 °C.

Anal. Calcd for $C_{12}H_{22}N_2O\cdot[(NO_2)_3C_6H_2O]_2$: C, 43.3; H, 3.9; N, 16.8. Found: C, 43.4; H, 4.0; N, 16.8.

1-Benzyl-3-methylbenzimidazolium Bromide. 1-Methylbenzimidazole (1.32 g) and benzyl bromide (1.71 g) were stirred in EtOAc (20 mL) for 24 h. The precipitated bromide (1.70 g, 56%) crystallized from EtOH–Et_2O as prisms: mp 78–80 °C; ^1H NMR [$(CD_3)_2SO$] δ 4.1 (s, 3 H), 5.8 (s, 2 H), 7.3–8.1 (m, 9 H), 10.3 (s, 1 H). The salt was characterized as the perchlorate rods (from EtOH): mp 146–147.5 °C; IR ($CHBr_3$) 1650 (C=N), 1080 cm^{-1} (ClO).

Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.8; H, 4.7; N, 8.7. Found: C, 55.9; H, 4.9; N, 8.3.

2-Benzylisoquinolinium Bromide. Isoquinoline (1.29 g) and benzyl bromide (1.71 g) were heated under reflux in MeCN (25 mL) for 3 h. Solvent was removed at 80 °C (15 mm), and the residual bromide (2.83 g, 94%) crystallized from EtOH–Et_2O as needles: mp 108–110 °C (lit.[25] mp 110–111.5 °C); ^1H NMR [$(CD_3)_2SO$] δ 6.1 (s, 2 H), 7.3–7.8 (m, 5 H), 7.9–8.4 (m, 4 H), 8.6 (d, 1 H), 9.0 (d, 1 H), 10.7 (s, 1 H, finely split, J = 1 Hz).

The corresponding perchlorate crystallized from EtOH as prisms: mp 170–172 °C (lit.[25] mp 167–168 °C).

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Registry No.—**12,** 13198-73-7; **13** (R = NHPh), 66809-32-3; **13** [R = $N(CH_2)_5$], 66809-33-4; **14,** 66809-34-5; **15,** 66809-35-6; **16,** 66809-36-7; **17,** 66809-37-8; **18,** 45939-70-6; **19** (X = OTs), 66809-39-0; **19** (X = Cl), 66809-40-3; **20,** 66809-41-4; **21,** 66809-42-5; **22,** 66809-43-6; **23,** 66809-45-8; **24,** 66809-46-9; **25,** 31640-94-5; **26,** 31640-96-7; **26** dipicrate, 66809-49-2; **27,** 66809-50-5; **27** dipicrate, 66809-53-8; **28,** 66809-54-9; **29,** 66809-55-0; **30,** 66809-56-1; **30** perchlorate, 66809-58-3; aniline, 62-53-3; piperidine, 110-89-4; pyrazole, 288-13-1; imidazole, 288-32-4; *N*-methylimidazole, 616-47-7; pyridine 1-oxide, 694-59-7; 2-chloro-4,6-dimethylpyrimidine, 4472-44-0; benzimidazole, 51-17-2; isoquinoline, 119-65-3; 1-methylbenzimidazole, 1632-83-3; 2-(1-oxido-2-pyridylmethyl)isoquinolinium chloride, 66809-59-4; 2-(1-oxido-2-pyridylmethyl)isoquinolinium perchlorate, 66809-61-8; 1-benzyl-3-methylbenzimidazolium bromide, 66809-62-9; 1-benzyl-3-methylbenzimidazolium perchlorate, 66809-77-6; benzyl bromide, 100-39-0; 2-benzylisoquinolinium bromide, 23277-04-5; pyridine, 110-86-1.

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D-Homoandrostanes. 3. Incubation of Some *D*-Homo-5α-androstanes with *Aspergillus ochraceus*[1a]

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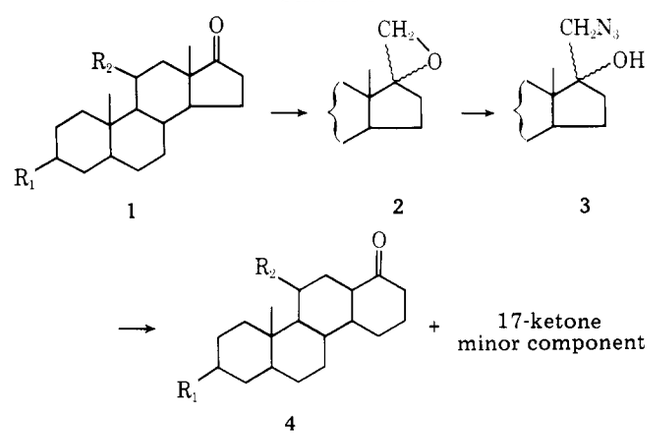
In preparing *D*-homo-5α-androstanes[2] our intention was to determine the effect of increase in terminal ring size on the course of microbiological hydroxylation as compared with that of normal steroids. For part of these studies we chose the microorganism *Aspergillus ochraceus,* which has been extensively documented[3] as an 11α-hydroxylator of steroids with very occasional transformations at C(1),[4] C(6),[5] and C(7).[5] Work with cell-free cultures of this microorganism has demonstrated[6] that two independently acting hydroxylase enzymes are responsible for the 11α- and 6β-hydroxylations.

Table I presents the times of incubation, the amount of starting material recovered, and the observed modifications of the steroid substrates, which have, with certain exceptions, been synthesized previously.[2]

3α-Hydroxy-*D*-homo-5α-andostan-17α-one[7] was prepared according to the established route (Scheme I, **1a** → **4a**). The two, 3,11-dioxygenated steroids were prepared from the

Scheme I



a, R_1 = α-OH, R_2 = H_2; b, R_1 = β-OH; R_2 = α-OH

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Table I

substrate	registry no.	incubation, days	starting material recovered, %	reaction and % conversion[a]	registry no.
3-ketone	39851-65-5	4	>90	none observed	
Δ^4-3-ketone	51057-29-5	4	8	11α,6β-diOH, 14; 11α,6β-diOH → 11α-OH,6-C=O, 19	62193-74-2
3,6-diketone	61231-98-9	4.5	50	11α-OH, 29	62193-61-7
3,7-diketone	61232-04-0	6	24	11α-OH, 20	62193-62-8
3,11-diketone	62193-54-8	4	10	none observed	
11α-hydroxy-3-ketone	62193-43-5	4	85	none observed	
3,17a-diketone	61231-79-6	4	0	11α-OH, 73	66966-81-2
3,17-diketone	20377-71-3	4.5	24	11α-OH, 79	62193-63-9
2,17a-diketone	61231-93-4	6	61	11α-OH, 65	66966-82-3
3β-hydroxy-17a-ketone	26729-16-8	5	38	11α-OH, 46; 11α-OH, 3β-OH → 11α-OH,3-C=O, 41	66966-83-4
3α-hydroxy-17a-ketone	62193-42-4	5	33	11α-OH, 48	62193-71-9
Δ^5-3β-hydroxy-17a-ketone	3278-99-7	5	43	11α-OH, 35	56103-43-6

[a] Conversion is calculated after subtracting starting material, assuming remainder is all converted steroid.

product of the ring expansion of 3β,11α-dihydroxy-5α-androstan-17-one[5] (**1b**) by reduction to the diol and appropriate oxidation. The procedure involved in determining the site of hydroxylation depends a great deal on spectroscopic examination of the modified steroid and its oxidation products, and is best illustrated for 3β-hydroxy-*D*-homo-5α-androstan-17a-one. The microbially transformed steroid was shown to be a dihydroxylated ketone both by elemental analysis and by the appearance of an additional one-proton signal at τ 6.00 in the NMR. Calculation of the expected chemical shift positions of the C(18) and C(19) methyl groups in $CDCl_3$ using values obtained by Zürcher[8] for the different possible positions of the introduced hydroxyl group, and in the derived triketone by oxidation for the "new" carbonyl group, and comparison with the observed values, gives the site and orientation of microbial attack as C(11α). This method depends on the additivity of shifts due to different structural features in one solvent and is augmented by calculations on shifts caused by change of solvent from $CDCl_3$ to benzene[9] for the triketone.

In order to apply the above method, various *D*-homoandrostanes were prepared and their methyl chemical shifts were measured in $CDCl_3$ solution.[10] This permitted us to determine the substituents effects. For keto steroids the information was extended to measurement of solvent shift values for the different carbonyl groups. The structure of the product **4b** was obtained by incubating 3β-hydroxy-5α-androstan-17-one with *Aspergillus ochraceus*[5] and subjecting the incubation product to the ring expansion procedure (**1b** → **4b**). In addition both materials gave the known 3,11,17a-trione[11] on oxidation.

The products of the other incubations were identified by simple chemical conversion and application of the spectroscopic method as outlined above, as mono-11α-hydroxylated steroids, in keeping with the known behavior of the microorganism. For the 3,11-diketone, hydroxylation is effectively blocked by the 11-keto group, while the lack of 6β-hydroxylation in the 3-keto-11α-hydroxy steroid is surprising as this molecule might have been expected to induce the responsible hydroxylase,[6] which is clearly functioning for the Δ^4-3-ketone. Here a second product owing to isomerization of the 6β-hydroxy-4-en-3-one system to the 3,6-dione was isolated. Such isomerization has been observed under acidic[5] and basic[12] conditions.

As a general observation, the ring D homologation leads to a lower conversion compared with those of the normal series analogues. Such effects might be tentatively attributed to the combined effects of differences in solubility as well as molecular geometry and flexibility.

Experimental Section

General directions have been described previously.[2]

3α-Hydroxy-*D*-homo-5α-androstan-17a-one (4a) and 3β,11α-Dihydroxy-*D*-homo-5α-androstan-17a-one (4b). Sodium hydride (50% in oil, 2 g) was washed with dry benzene and added in portions to a stirred suspension of 12 g of trimethyloxosulfonium iodide in 40 mL of dimethylformamide under nitrogen. After evolution of hydrogen, 3 g of 3α-hydroxy-5α-androstan-17-one (**1a**) was added and stirring continued until TLC analysis by green spot formation in iodine vapor and lack of carbonyl absorption in the IR indicated completion of the reaction. Addition of water and extraction with ethyl acetate gave a quantitative yield of spirooxiranes **2a:** IR 3610, 3430, 1023, 850 cm^{-1}; NMR τ 9.18 (CH_3-19 and CH_3-18 of 17 α-oxirane), 9.11 (CH_3-18 of 17β-oxirane), 7.39 and 7.07 (2d, J = 5 Hz, H-20), 5.90 (m, $W_{1/2}$ = 8 Hz, H-3).

In a similar manner **1b**[13] (3 g from an incubation as described in the third experiment) was converted to spirooxirane mixture **2b:** IR 3600, 3400, 1030 cm^{-1}; NMR τ 9.13 (CH_3-18 of 17α-oxirane), 9.08 (CH_3-18 of 17β-oxirane), 9.03 (CH_3-19), 7.40 (m, oxirane protons), 4.60–4.00 (m, H-3 and H-11).

The spirooxiranes **2a** (3g) in 100 mL of dimethylformamide were heated at reflux temperature with 2 g of sodium azide and 2 g of boric acid for 3 h. Dilution with water and extraction with ethyl acetate gave a 98% yield of hydroxy azides **3a.** The dihydroxy azide **3b** was prepared in a similar manner. Both had the characteristic azide absorption at 2100 cm^{-1} in the IR.

The crude epimeric hydroxy azides **3a** were dissolved in 25 mL of acetone and acidified to pH 1–2 with concentrated hydrochloric acid and treated with 2 g of zinc powder added in small portions. After hydrogen evolution had ceased the remaining zinc was filtered out and washed with acetone. The combined filtrates were diluted with 120 mL of water and extracted with ether to remove neutral components. The stirred aqueous layer, cooled to below 5 °C, was treated with 3 g of sodium nitrite during 30 min. After 4 h at this temperature extraction with ethyl acetate gave a mixture of 1 g of 17a- and 17-ketones as an oil, from which was isolated only 0.8 g of 3α-hydroxy-*D*-homo-5α-androstan-17a-one by PLC, as plates from ethyl acetate: mp 205–208 °C (lit.[7] 203–205 °C); IR 3600, 3440, 1700 cm^{-1}; NMR τ 9.21 (CH_3-19), 8.88 (CH_3-18), 6.00 (m, $W_{1/2}$ = 8 Hz, H-3).

Likewise with similar quantities **3b** was converted to 3.8 g of an oily mixture of **4b,** which was chromatographed on 300 g of silica gel. Chloroform–methanol (9:1) produced crude 17a-ketone, which on repeated recrystallization from ethyl acetate gave 3β,11α-dihydroxy-*D*-homo-5α-androstan-17a-one (**4b**) as needles: mp 233–235 °C; IR 3600, 3440, 1700 cm^{-1}; NMR τ 9.04 (CH_3-19), 8.87 (CH_3-18), 6.33 (m, $W_{1/2}$ = 22 Hz, H-3), 6.00 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1. Found: C, 75.3; H, 9.9.

***D*-Homo-5α-androstane-3,11-dione and 11α-Hydroxy-*D*-homo-5α-androstan-3-one.** A standard Huang-Minlon reduction of 1.2 g of **4b** gave 1.1 g of a yellow oil, homogeneous by TLC. A small portion, purified by PLC, gave *D*-homo-5α-androstane-3β,11α-diol as plates from hexane: mp 85–87 °C; IR 3600, 3420 cm^{-1}; NMR τ 9.17 (CH_3-18), 9.07 (CH_3-19), 6.34 (m, H-3) overlapped with 6.13 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.2. Found: C, 78.1; H, 11.0.

The crude diol (700 mg) was refluxed for 45 h with 10 g of silver carbonate on Celite[14] in 25 mL of benzene and sufficient chloroform to achieve steroid dissolution, the reaction being monitored by TLC. Filtration of insoluble material which was washed with ethyl acetate and evaporated gave an oil which was purified by PLC to give 660 mg of the title hydroxy ketone as needles from acetone: mp 134 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.13 (CH_3-19), 8.87 (CH_3-18), 6.07 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.1; H, 10.6.

The crude diol (300 mg) dissolved in acetone was treated with Jones reagent. Extraction gave 280 mg of the dione as a colorless chromatographically homogeneous oil, which defied attempts at recrystallization: IR 1700 cm^{-1}; NMR τ 9.19 (CH_3-18), 8.78 (CH_3-19); M^+ *m/e* 302. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.3; H, 10.1.

Similar treatment of the hydroxy ketone (500 mg) gave the dione (45 mg) having identical chromatographic behavior and NMR spectrum to that above.

Incubation of the Different Substrates with *Aspergillus ochraceus* Wilhelm (CBS 132.52).[15] General Procedure. A nutrient medium prepared from 2 g of malt extract, 2 g of beef extract, 2 g of yeast, 5 g of glucose, and 5 mL of cornsteep liquor dissolved in 1 L of distilled water and with pH adjusted to 5.5 with dilute hydrochloric acid was introduced into 1-L conical flasks in portions of 200 mL. After sterilization in an autoclave each flask was inoculated with 7 mL of a suspension of spores of the microorganism[13] prepared from slopes containing 2% nutrient agar and 3% malt extract under aseptic conditions, plugged with cotton wool, and agitated at room temperature (~25 °C) for 2 days. A solution of the steroid substrate in dimethyl sulfoxide was added under sterile conditions (80 mg of substrate in 12 mL of solvent per flask) and the flasks were shaken for the specified time. The contents of the flasks were combined and filtered through cotton wool. The mycelium was extracted with acetone in a Soxhlet and the aqueous portion after addition of sodium chloride was continuously extracted with ethyl acetate. The combined extracts were evaporated, leaving crude steroid mixtures.

The following substrates were subjected to this procedure.

***D*-Homoandrost-4-en-3-one** (380 mg) gave 240 mg of crude mixture. PLC separation yielded 30 mg of starting material, 55 mg of 6β,11α-dihydroxy-*D*-homoandrost-4-en-3-one recrystallized from ethyl acetate [mp 178–180 °C; IR 3600, 3440, 1670 cm^{-1}; NMR τ 9.08 (CH_3-18), 8.50 (CH_3-19), 6.00 (sx, *J* = 10, 10, 5 Hz, H-11), 5.60 (t, *J* = 3, 3 Hz, H-6), 4.20 (H-4); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.0; H, 9.6], and 74 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,6-dione as needles from ethyl acetate [mp 189–192 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.14 (CH_3-18), 8.94 (CH_3-19), 6.00 (m, $W_{1/2}$ = 20 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.4; H, 9.8.].

Oxidation of a small portion of the hydroxy dione with Jones reagent gave *D*-homo-5α-androstane-3,6,11-trione, which was recrystallized from ethyl acetate: mp 188–191 °C: IR 1710 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.84 (CH_3-19); M^+ *m/e* 316. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.9; H, 8.9.

***D*-Homo-5α-androstane-3,6-dione** (100 mg) gave 70 mg of crude material. PLC separation gave 50 mg of starting material and 15 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,6-dione. Both the hydroxy dione and the oxidation product were identical with those obtained in the preceding experiment.

***D*-Homo-5α-androstane-3,7-dione** (200 mg) gave 186 mg of crude material. Separation by PLC gave 48 mg of starting material and 32 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,7-dione as needles from acetone–hexane: mp 233–236 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.12 (CH_3-18), 8.60 (CH_3-19), 5.86 (m, $W_{1/2}$ = 19 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.4; H, 9.7.

Oxidation of 45 mg of the hydroxy dione with Jones reagent gave 40 mg of *D*-homo-5α-androstane-3,7,11-trione as a colorless oil which could not be crystallized: IR 1700 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.52 (CH_3-19). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.5; H, 8.8.

***D*-Homo-5α-androstane-3,17a-dione** (240 mg) gave a solid residue which was purified by PLC to give 185 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17a-dione recrystallized from ethyl acetate as needles: mp 202–207 °C; IR 3600, 1705 cm^{-1}; NMR τ 8.84 (CH_3-19 and CH_3-18), 6.07 (sx, *J* = 10, 10, 5 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.3; H, 9.5.

Oxidation of 40 mg of the hydroxy dione with Jones reagent yielded 35 mg of *D*-homo-5α-androstane-3,11,17a-trione, which was recrystallized from acetone–hexane: mp 230–233 °C (lit.[11] 226–228 °C); IR 1705 cm^{-1}; NMR τ 8.92 (CH_3-18), 8.73 (CH_3-19); M^+ *m/e* 316.

Standard Huang-Minlon reduction of 74 mg of hydroxy dione gave 60 mg of *D*-homo-5α-androstan-11α-ol from methanol: mp 121–124 °C; IR 3640 cm^{-1}; NMR τ 9.17 (CH_3-18), 9.06 (CH_3-19), 6.10 (sx, *J* = 10, 10, 5 Hz, H-11); M^+ *m/e* 290. Anal. Calcd for $C_{20}H_{34}O$: C, 87.5; H, 12.5. Found: C, 87.4; H, 12.8.

***D*-Homo-5α-androstane-3,17-dione** (85 mg) gave 80 mg of a pale yellow oil. Separation by PLC gave 10 mg of starting material and 54 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17-dione as needles from acetone: mp 207–210 °C; IR 3590, 1705 cm^{-1}; NMR τ 9.16 (CH_3-19), 8.85 (CH_3-18), 6.07 (sx, *J* = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.3; H, 9.7.

Oxidation of 35 mg of this hydroxy dione gave *D*-homo-5α-androstane-3,11,17-trione as a white solid, which was recrystallized from ethyl acetate: mp 229–231 °C; IR 1695 cm^{-1}; NMR τ 9.21 (CH_3-18), 8.74 (CH_3-19). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.1; H, 9.0.

A small portion of the hydroxy dione was acetylated with acetic anhydride–pyridine, forming 11α-acetoxy-*D*-homo-5α-androstane-3,17-dione as plates from ethyl acetate–acetone: mp 212–214 °C; IR 1705, 1250 cm^{-1}; NMR τ 9.10 (CH_3-18), 8.90 (CH_3-19), 8.00 ($OCOCH_3$), 4.87 (m, $W_{1/2}$ = 24 Hz, H-11). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.3; H, 9.0. Found: C, 73.1; H, 8.9.

***D*-Homo-5α-androstane-2,17a-dione** (300 mg) gave after purification by PLC 184 mg of starting material and 80 mg of 11α-hydroxy-*D*-homo-5α-androstane-2,17a-dione, which was recrystallized from acetone-hexane: mp 191–193 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.12 (CH_3-19), 8.90 (CH_3-18), 6.13 (sx, *J* = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.2.

Oxidation of a small portion of the hydroxy dione gave *D*-homo-5α-androstane-2,11,17a-trione as a colorless oil: IR 1700 cm^{-1}; NMR τ 9.01 (CH_3-19), 8.98 (CH_3-18). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.7; H, 8.8.

3β-Hydroxy-*D*-homo-5α-androstan-17a-one (280 mg) gave 270 mg of crude material. Separation by PLC gave 105 mg of starting material, 75 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17a-dione identical with that obtained previously, and 85 mg of 3β,11α-dihydroxy-*D*-homo-5α-androstan-17a-one identical with that obtained by ring expansion of 3β,11α-dihydroxy-5α-androstan-17-one.

3α-Hydroxy-*D*-homo-5α-androstan-17a-one (75 mg) gave 65 mg of a crude mixture. Separation by PLC gave 50 mg of starting material and 25 mg of 3α,11α-dihydroxy-*D*-homo-5α-androstan-17a-one, which recrystallized from ethyl acetate as needles: mp 203–205 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.08 (CH_3-18), 8.91 (CH_3-19), 6.30 (m, $W_{1/2}$ = 20 Hz, H-11), 6.00 (m, $W_{1/2}$ = 8 Hz, H-3); M^+ *m/e* 320. Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1. Found: C, 74.7; H, 10.1.

A small portion of this dihydroxy ketone was oxidized in the usual manner, giving *D*-homo-5α-androstan-3,11,17a-trione identical with that described previously.

3β-Hydroxy-*D*-homoandrost-5-en-17a-one (235 mg) gave 200 mg of crude material. Separation by PLC gave 100 mg of starting material and 50 mg of 3β,11α-dihydroxy-*D*-homoandrost-5-en-17a-one as needles from ethyl acetate: mp 162–164 °C; IR 3600, 1700 cm^{-1}; NMR τ 8.83 (CH_3-18), 8.80 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 6.00 (m, $W_{1/2}$ = 22 Hz, H-11), 4.60 (q, *J* = 6, 2 Hz, H-6); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.4.

The product from several microbiological experiments (200 mg) was dissolved in 30 mL of diethylene glycol and the solution was refluxed for 1 h with 2 mL of hydrazine hydrate, before raising the temperature to 195 °C. After cooling the solution, 1 g of potassium hydroxide was added and the solution was heated for 3 h at 195 °C. After cooling and addition of water, the solution was acidified with concentrated hydrochloric acid, and extraction with benzene gave a spongy solid which was recrystallized from ethyl acetate to give 185 mg of *D*-homoandrost-5-ene-3β,11α-diol as needles: mp 84–86 °C; IR 3600 cm^{-1}; NMR τ 9.16 (CH_3-18), 8.86 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 6.00 (sx, *J* = 10, 10, 5 Hz, H-11), 4.60 (q, *J* = 6, 2 Hz, H-6). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.0; H, 10.5.

This diol (160 mg) was dissolved in acetone and treated with Jones reagent for 10 min. Dilution with water followed by ether extraction gave 120 mg of a yellow oil which was separated by PLC into 30 mg of *D*-homoandrost-4-ene-3,11-dione, which was recrystallized from ethyl acetate [mp 168–170 °C; IR 1700, 1670 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.56 (CH_3-19), 4.30 (H-4). Anal. Calcd for $C_{20}H_{28}O_2$: C, 80.0; H, 9.4. Found: C, 79.7; H, 9.3], and 20 mg of 3β-hydroxy-*D*-homoandrost-5-en-11-one as needles from ethyl acetate [mp 183–185 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.21 (CH_3-18), 8.78 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 4.60 (m, $W_{1/2}$ = 8 Hz, H-6). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.5; H, 9.9.].

The remaining three substrates were subjected to this incubation procedure on a similar scale to the other experiments described above. No hydroxylated products were detected and only starting material (see Table I) was recovered.

Registry No.—**1a**, 53-41-8; **1b**, 481-29-8; **2a**, 67010-38-2; **2b**, 67010-39-3; **3a**, 66966-84-5; **3b**, 52401-33-9; *D*-homo-5α-androstane-3β,11α-diol, 62193-45-7; *D*-homo-5α-androstane-3,7,11-trione, 62193-82-2; *D*-homo-5α-androstane-3,11,17a-trione, 66966-85-6; *D*-homo-5α-androstan-11α-ol, 35649-44-6; *D*-homo-5α-androstane-3,11,17-trione, 62193-85-5; 11α-acetoxy-*D*-homo-5α-androstane-3,17-dione, 62193-69-5; *D*-homo-5α-androstane-2,11,17a-trione, 66966-86-7; *D*-homoandrost-5-ene-3β,11α-diol, 62193-46-8; *D*-homoandrost-4-ene-3,11-dione, 62193-55-9; 3β-hydroxy-D-homoandrost-5-en-11-one, 62193-41-3; trimethyloxosulfonium iodide, 1774-47-6; sodium azide, 26628-22-8; acetic anhydride, 108-24-7.

References and Notes

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Trianions from α-Hydroxy Carboxylic Acids

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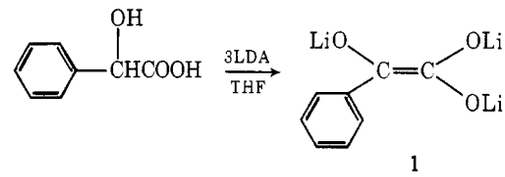
Polymetalated organic compounds are of both practical interest as synthetic reagents and of theoretical interest as models for charge distribution and stabilization.[1-3] The recent development and use of hindered amide bases has made many diverse types of mono- and dianions available by simple deprotonation reactions.[4-6] In this note, we wish to report the first preparation of a trianion from a substituted α-hydroxy acid (eq 1). The limitations of this procedure for forming such

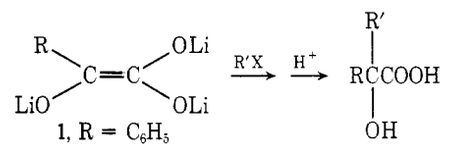


(1)

1

enetriolates have been evaluated and possible synthetic applications of these reactive intermediates have been explored. In addition, we have qualitatively compared the kinetic acidity of dilithio mandelic acid with other weak acids in an attempt to estimate the effect of an adjacent negatively charged electronegative atom on the acidity of a proton attached to the carbon.

Enetriolates like 1 are ambident nucleophiles which could react with electrophiles at either a nucleophilic carbon or oxygen. Based on the known reactions of alkoxyenediolates, geminal enediolates, or enamidolates,[4] alkylation at carbon to give a substituted α-hydroxy acid was expected. This was shown to be the case (see Table I) for enetriolate 1. However, alkylation of 1 or other enetriolates (eq 2) gives only modest



(2)

1, R = C_6H_5
2, R = CH_3
3, R = H

yields of product α-hydroxy acids and would not be synthetically useful when compared to existing procedures. Apparently deprotonation of alkyl halides by the enetriolates results in elimination reactions which compete with the desired substitution reaction. Efforts to increase the yield of desired alkylation product by addition of hexamethylphosphoramide (HMPA) failed, although a higher yield was obtained when an alkyl chloride was used instead of an alkyl bromide or iodide. Deprotonation of mandelic acid with *n*-BuLi (6 eq) and potassium *tert*-butoxide (3 eq) in pentane for 24 h at 25 °C followed by methylation with methyl iodide also failed to yield an alkylated product.[7]

Attempts to generate enetriolates **2** and **3** by deprotonation of glycolic and lactic acid were less successful as is noted in Table I. This failure could be ascribed to the expected de-

Table I. Products Formed in Reactions of Enetriolates with Various Electrophiles

α-hydroxy acid precursor	registry no.	electrophile	product	registry no.	% yield[a] product	% yield[a] (precursor)
mandelic acid	90-64-2	*n*-C_4H_9Cl	$C_6H_5C(n\text{-}C_4H_9)OHCO_2H$	4445-12-9	55	(8)
		n-C_4H_9Br			37	(56)
		n-C_4H_9Br[b]			18	(81)
		n-C_4H_9I			13	(71)
		c-$C_6H_{11}I$	none		0	
		D_2O	$C_6H_5CDOHCO_2H$	67315-76-8	58[c]	
		CH_3I	$C_6H_5C(CH_3)OHCO_2H$	515-30-0	40[d]	(60)
glycolic acid	79-14-1	*n*-$C_{10}H_{21}Br$	$(n\text{-}C_{10}H_{21})CHOHCO_2H$	2984-55-6	10[e]	
		n-$C_{10}H_{21}I$	*f*			
		CH_3I	$(CH_3)_2COHCO_2H$	594-61-6	~10[g]	
lactic acid	50-21-5	CH_3I	$(CH_3)_2COHCO_2H$		<10	

[a] Yields determined by GC after esterification (see text). [b] HMPA was added before the butyl bromide. [c] The crude acid before esterification was 41% d_1 by NMR. [d] The atrolactic acid yield was determined by NMR of the crude reaction mixture. [e] This is an isolated yield. [f] While no alkylation product was isolated, significant amounts of $C_{20}H_{42}$ from reductive dimerization of the *n*-$C_{10}H_{21}I$ were formed. [g] In addition, a trace of lactic acid was formed.

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