Preparation of 19-Hydroxy-$\Delta^{4,7}$- and 8,19-Oxido-$\Delta^{4,6}$-3-Keto Steroids

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The deconjugation of 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** and of 10-methyl-$\Delta^{4,6}$-3 ketone **3** to $\Delta^{4,7}$-3 ketones **7**, **8**, and **9** by treatment with sodium methoxide in dimethyl sulfoxide and subsequent treatment of the basic mixture with aqueous hydrochloric acid is described. Under the same conditions 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** gave an unstable product which was considered to be the free enol **16** and which on treatment with pyridine gave 8,19-oxide **11**. Oxidation of 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8** with ferric chloride also led to 8,19-oxide formation yielding compounds **10** and **11**, respectively. The effect of methanol on the deconjugation of $\Delta^{4,6}$-3 ketone **3** and its 19-hydroxy analog **1** was studied, and it was found that increasing amounts of methanol in the basic reaction mixture inhibit the deconjugation of the former ketone more than that of the latter. It was concluded that during the base treatment the 19-hydroxy group, in its anionic form, assists in the conversion of **1** to the intermediate enol anion **4** by abstracting the proton from the 8β position. The preparation of 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** from 6,19-oxide **12** is described.

Recently in these laboratories[1b] the deconjugation of estra-4,6-diene-3,17-dione and 6-dehydrotestosterone to the corresponding $\Delta^{4,7}$-3 ketones has been accomplished. The deconjugations were affected by deprotonation of the $\Delta^{4,6}$-3 ketones with base in dimethyl sulfoxide and subsequent protonation of the thus formed 3,5,7-trien-3-ol anions by treatment with acid. It appeared interesting to attempt the deconjugation of $\Delta^{4,6}$-3 ketones carrying substituents which may be expected to exert a pronounced effect on the deconjugation itself as well as on the reactivity of the products formed. Accordingly, as a first venture into this rather large field of study, 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** and 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** (Scheme I) were subjected to deconjugation conditions.

Treatment of $\Delta^{4,6}$-3 ketones **1** and **2** with sodium methoxide in dimethyl sulfoxide and subsequent treatment with excess aqueous hydrochloric acid yielded precipitates consisting essentially of $\Delta^{4,7}$-3 ketones **7** and **8**, respectively. A similar treatment afforded 10-methyl-$\Delta^{4,7}$-3 ketone **9** from $\Delta^{4,6}$-3 ketone **3**, though as a more impure material, from which the pure product could only be isolated by chromatography. By contrast, 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** did not give the corresponding $\Delta^{4,7}$-3 ketone **18** under the above deconjugation conditions but a precipitate which had uv max 305 (sh) and 318 and 333 mμ (sh). After being allowed to stand at room temperature for several hours, the precipitate changed into a material having uv max 255 (major peak) and 298 mμ (minor peak). The uv spectrum thus indicates that the freshly filtered precipitate is 4-chloro-3,5,7-trien-3-ol (**16**), which then on standing converts mainly into 4-chloro-$\Delta^{4,7}$-3-keto steroid **18**.[2] Attempts failed to isolate the latter compound in the pure form.

Attempted acetylation of 3,19-diol **16** with acetic anhydride and pyridine gave 8,19-oxido-$\Delta^{4,6}$-3 ketone **11** and it was also found that this conversion proceeds in pyridine alone. Possibly the free enol **16** yields first the unstable $\Delta^{5,7}$-3 ketone **17** in which the 4-chlorine atom is in an allylic position to the double bond in position 5. Intramolecular substitution with rearrangement[3] would then be expected to lead to a facile expulsion of the chlorine atom by the 19-hydroxy group yielding 8,19-oxide **11** and pyridinium hydrochloride.

Oxidation of 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8** with anhydrous ferric chloride in methanol–tetrahydrofuran (1:1) also led to 8,19-oxide formation yielding **10** or **11**, respectively. An 8,19-oxide, which in subsequent reactions gave 8,19-oxidoprogesterone, has previously been obtained as a by-product on treatment of 3β,5,-14,19-tetrahydroxy-5β,14β-etianic acid with ethanolic hydrogen chloride.[4]

The apparently rather ready interaction of the 19-hydroxy group with the 8-carbon atom in the formation of 8,19-oxides **10** and **11** is paralleled by the interaction of the 19-hydroxy group with the 2-carbon atom in the conversion of 2α-halo-19-acetoxy-$\Delta^{4,6}$-3 ketones to the corresponding 2,19-oxido-$\Delta^{4,6}$-3 ketones under hydrolysis conditions.[5] An interaction of the 19-alkoxy group with the acidic hydrogen atoms in the 2β and 8β position during the base treatment in the deconjugation of the 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** may then also be expected. That this is so has been indicated by comparative studies on the effect of methanol in the basic mixture on the deconjugation of 19-hydroxy-$\Delta^{4,6}$-3 ketone **1** and its 10-methyl analog **3** to the corresponding $\Delta^{4,7}$-3-ones **7** and **9**, respectively. In the blank reaction the solvent employed consisted of equal volumes of dimethyl sulfoxide and tetrahydrofuran. The latter solvent was then replaced by increasing amounts of methanol in subsequent reactions. Because of the presence of methanol and tetrahydrofuran as cosolvents, the comparative reactions could be carried out at the convenient temperature of 2° (melting point of dimethyl sulfoxide 18°).

The experimental results indicate that increasing proportions of methanol in the cosolvent mixture inhibit the deconjugation. Such an inhibition can be ascribed to a decrease of the basicity of the methoxide anion due to hydrogen bonding[6] with the protic methanol. The experiments indicate in particular that the deconjugation of $\Delta^{4,6}$-3-one **3** is considerably more inhibited by the presence of methanol than the deconjugation of the analogous 19-alcohol **1**. Thus, for example, when the cosolvent mixture contained 60% of methanol, inhibition of the deconjugation of **3** was found to be virtually complete while the deconjugation

(1) (a) Bio-Research Laboratories, Pte. Claire, Quebec, Canada. (b) D. S. Irvine and G. Kruger, *J. Org. Chem.*, **35**, 2418 (1970).

(2) H. Mori, *Chem. Pharm. Bull.*, **10**, 429 (1962), and references therein; 4-chlorotestosterone acetate also has uv max 255 mμ.

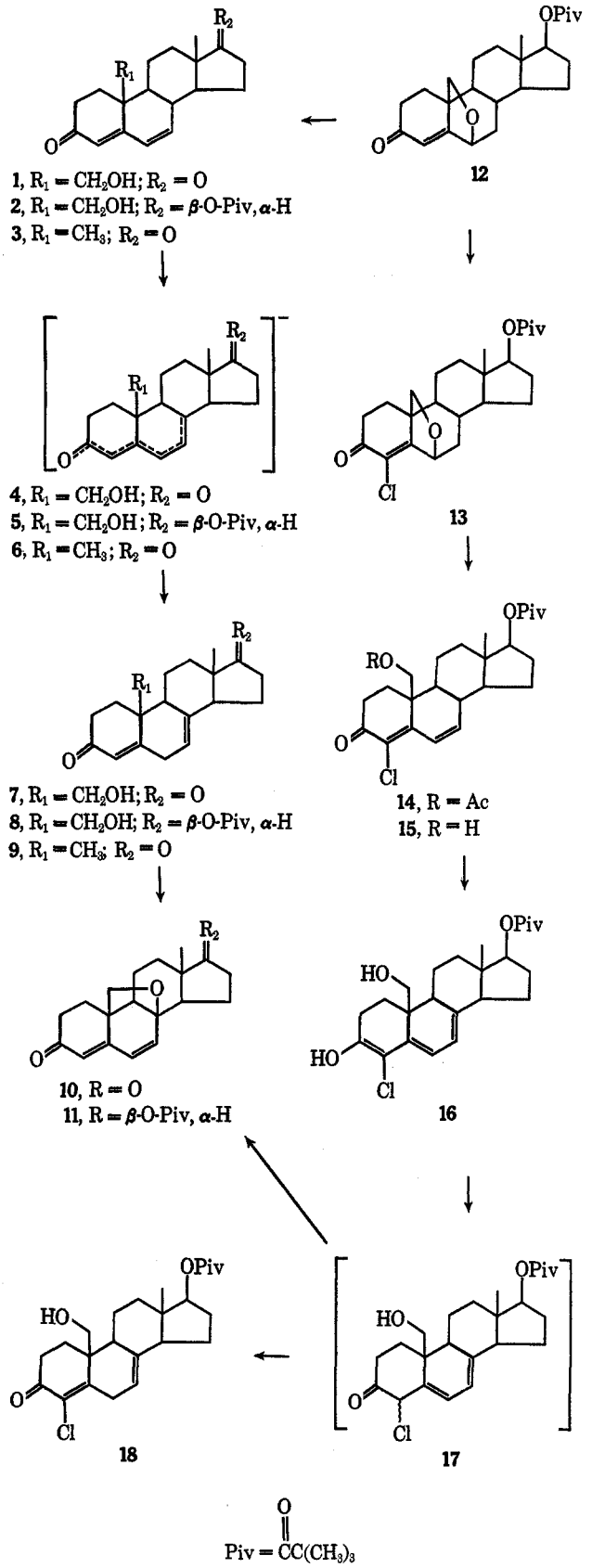
(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, pp 589, 596.

(4) K. Otto and M. Ehrenstein, *J. Org. Chem.*, **26**, 2871 (1961).

(5) G. Kruger and A. Verwijs, *ibid.*, **35**, 2415 (1970).

(6) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163, 175 (1962), and references therein.

SCHEME I



of **1** was only moderately inhibited and 4,7-diene **7** was still the major product (see Experimental Section). The difference in degree of inhibition by methanol may be rationalized by the assumption that the 19-alkoxide anion of **1**, which can be expected to form even in the presence of relatively large amounts of methanol, accepts the proton from the 8β position by intramolecular abstraction. Alternately the 19-alkoxide anion may first remove the more acidic[7] 2β proton to yield the corresponding 2,4,6-trien-3-ol anion. Subsequent successive intramolecular migration of the 19-hydroxy proton to the anionic 3-oxygen atom of the latter and of the 8β proton to the 19-oxygen atom could then yield the thermodynamically[8] more stable 3,5,7-trien-3-ol anion **4**. In the 10-methyl-$\Delta^{4,6}$-3-one **3**[8] no such intramolecular proton abstraction or transport is possible and thus considerably more basic conditions are required for its conversion to the 3,5,7-trien-3-ol anion **6**.

The preparation of the 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** commenced with the 6,19-oxido-Δ^{4}-3 ketone **12**.[5] Treatment with sulfuryl chloride and collidine in carbon tetrachloride at elevated temperature gave the 4-chloro derivative **13**. Previously steroidal Δ^{4}-3 ketones have been converted in good yield to the 4-chloro analogs with sulfuryl chloride in pyridine at or below room temperature.[2] The 6,19-oxide **12**, however, gave largely starting material under these conditions even when the reaction temperature was increased to 70°. As previously noticed[2] part of the sulfuryl chloride is consumed in side reactions, and it thus appeared that these side reactions became the predominant reaction. It was assumed that it was the pyridine present in the reaction which was responsible for the consumption of the sulfuryl chloride and for this reason the less reactive collidine was used. Very little reaction took place when, in an effort to obtain 19-acetate **14**, 4-chloro-6,19-oxide **13** was treated with acetic anhydride and *p*-toluenesulfonic acid under conditions which readily brought about the conversion of **12** to **2**; when, however, the amount of *p*-toluenesulfonic acid was increased tenfold the reaction was complete within 10–15 min. Possibly the chlorine atom, by its strong negative inductive effect, makes a neighboring-group participation of the 4,5 double bond during the expulsion of the ethereal oxygen atom at position 6 more difficult. Base-catalyzed hydrolysis of the 19-acetate **14** finally gave the 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15**.

The structure of the novel compounds prepared has been supported by their ir, uv, and nmr spectra. Of interest are the signals given by the protons at position 6 and 7 in $\Delta^{4,6}$-3 ketones **2**, **10**, **11**, and **15**. Both protons appear as a singlet in $\Delta^{4,6}$-3 ketone **2**, but as a pair of doublets in 8,19-oxido-$\Delta^{4,6}$-3 ketones **10** and **11**, while the 4-chloro-$\Delta^{4,6}$-3-one **15** reveals the 2 protons as a pair of quartets (ABX system, with H_X being bonded to C-8). Apparently the neighboring oxygen or chlorine atoms in **10**, **11**, and **15** bring about an unequal deshielding of the 2 protons and thus a greater downfield shift for one proton signal than for the other. Both inductive and tautomeric electron displacements may play a role and for this reason it may be difficult to decide as to which of the two protons suffered the greater downfield shift. Also of interest is a comparison of the 19-methylene signals given by the deuteriochloroform solutions of the 19-hydroxy-$\Delta^{4,6}$-3 ketone **2** and of the 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8**. The $\Delta^{4,6}$-3

(7) S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 1997 (1964).

(8) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

ketone shows the methylene protons as a singlet at 3.87 ppm, which, depending on the noise level of the nmr spectrometer, may be accompanied by two barely observable satellites at J = 11 Hz, while the $\Delta^{4,7}$-3 ketones show these protons as pairs of doublets at 3.83–3.84 ppm, with J = 11 Hz and $\delta_A - \delta_B$ = 0.32 ppm. The rather large $\delta_A - \delta_B$ value of the $\Delta^{4,7}$-3 ketones may be taken as an indication of a more restricted rotation of their 19-hydroxy groups.[9,10] Recent, more detailed nmr studies on 19-hydroxy-Δ^4-3-keto steroids have established values of $\delta_A - \delta_B$ = 0.06 ppm for chloroform solutions and of $\delta_A - \delta_B$ = 0.09–0.15 ppm for pyridine solutions.[10] By comparison, the 8,19-oxido-$\Delta^{4,6}$-3 ketones **10** and 11 show their 19-methylene protons as pairs of doublets centered at 4.06 ppm with J = 9 Hz and $\delta_A - \delta_B$ = 0.25 ppm.

Experimental Section[11]

17β-Pivaloxy-19-hydroxyandrosta-4,6-dien-3-one (2).—A mixture of 10 g of 6,19-oxide 12,[5] 30 ml of acetic anhydride, and 0.1 g of *p*-toluenesulfonic acid was treated at 100° for 40 min whereupon 50 ml of water was added at a slow rate. Extraction with methylene chloride, drying, and evaporation yielded the crude 19-acetate of **2** as a resin. The resin was dissolved in 10 ml of methanol and left to stand at room temperature with 0.05 g of sodium methoxide for 4 hr, whereupon 0.1 ml of glacial acetic acid was added. Evaporation and recrystallization from methanol yielded the analytical sample: mp 191–192°; ir ($CHCl_3$) 3640, 3460 (OH), 1715 (pivalate), 1650 ($\Delta^{4,6}$-3 ketone), 1615 and 1585 cm^{-1} (>C=C<); uv max (EtOH) 283 mμ (ε 26,600); nmr 6.15 (s, 2, C-6, C-7), 5.79 (s, 1, C-4), 4.6 (m, 1, C-17), and 3.86 ppm (s, 2, C-19).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.37; H, 8.92.

19-Hydroxyandrosta-4,7-diene-3,17-dione (7).—To a solution of 1 g of 1[12] in 10 ml of dimethyl sulfoxide was added 2.0 g of sodium methoxide in one portion. The mixture was stirred briefly under nitrogen and then poured into 60 ml of ice-cold 2 *N* hydrochloric acid with stirring. The precipitate was filtered and washed with water. Digestion with acetone and ethyl acetate yielded 0.70 g of crude **7**, uv max (EtOH) 239 mμ (ε 14,700). Recrystallization from methanol yielded the pure product: mp 222–223° (lit.[13] mp 212–214°); uv max (EtOH) 239 mμ (ε 16,400); nmr 5.96 (d, 1, J = 2 Hz, C-4), 5.45 (m, 1, C-7), and 3.84 ppm (d of d, 2, J = 11 Hz, $\delta_A - \delta_B$ = 0.32 ppm,[14] C-19).

17β-Pivaloxy-19-hydroxyandrosta-4,7-dien-3-one (8) was prepared from **2** as above yielding 70% of crude material. Recrystallization from methanol gave the analytical sample: mp 193–194°; uv max (EtOH) 238 mμ (ε 16,300); ir ($CHCl_3$) 3640 (OH), 1715 (pivalate), 1650 (Δ^4-3 ketone), 1615 and 1585 cm^{-1} (>C=C<); nmr 5.95 (d, 1, J = 2 Hz, C-4), 5.3 (m, 1, C-7), and 3.83 ppm (d of d, 2, J = 11 Hz, $\delta_A - \delta_B$ = 0.32 ppm, C-19).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.82; H, 8.65.

8,19-Oxidoandrosta-4,6-diene-3,17-dione (10).—To 5 g of **7** dissolved in 250 ml of tetrahydrofuran–methanol (1:1) was added 20 g of anhydrous $FeCl_3$. The solution was stirred under nitrogen for 20 min whereupon 250 ml of ethyl acetate and 750 ml of water were added. The ethyl acetate phase was washed with water, dried with sodium sulfate, and concentrated to a thick paste. Filtration yielded 1.67 g of yellow crystals which showed a single spot on thin layer chromatography. Recrystallization from ethyl acetate yielded 0.8 g of the analytical sample: mp 224–226°; uv max (EtOH) 289 mμ (ε 24,400); ir ($CHCl_3$) 1740 (17 ketone), 1655 (conjd ketone), 1619 and 1581 cm^{-1} (>C=C<); nmr 6.40 (d of d, 2, J = 9 Hz, $\delta_A - \delta_B$ = 0.28 ppm, C-6, C-7), 5.74 (s, 1, C-4), 4.06 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.25 ppm, C-19), and 1.12 ppm (s, 3, C-18, 8β-O).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.43; H, 7.15.

8,19-Oxido-17β-pivaloxyandrosta-4,6-dien-3-one (11).—To 0.8 g of **8** dissolved in 20 ml of tetrahydrofuran was added a freshly prepared solution of 2.4 g of anhydrous $FeCl_3$ in 20 ml of methanol. After 5 min of stirring the mixture was poured into 400 ml of 2 *N* aqueous hydrochloric acid. Extraction with benzene, evaporation, and recrystallization of the residue from methanol yielded 0.116 g of the analytical sample: mp 195.5–196°; uv max (EtOH) 290 mμ (ε 26,880); ir ($CHCl_3$) 1720 (pivalate), 1660 (conjd ketone), and 1615 cm^{-1} (>C=C<); nmr 6.33 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.27 ppm, C-6, C-7), 5.72 (s, 1, C-4), 4.06 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.25 ppm, C-19), and 1.05 ppm (s, 3, C-18, 8β-O).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.27.

4-Chloro-6,19-oxido-17β-pivaloxyandrost-4-en-3-one (13).—To a solution of 8 g of 12,[5] warmed at 50°, in 16 ml of carbon tetrachloride and 8 ml of *sym*-collidine was added over 4 min and with stirring a solution of 16 ml of redistilled sulfuryl chloride in 32 ml of carbon tetrachloride. Stirring was continued for another 8 min whereupon the mixture was poured into 48 ml of methylene chloride and 48 ml of 2 *N* aqueous hydrochloric acid. The organic phase was extracted four times with aqueous hydrochloric acid and then with water. Concentration to a thick paste and filtration yielded 3.8 g of off-white crystals. Recrystallization from methanol yielded the analytical sample: mp 212–214°; uv max (EtOH) 252 mμ (ε 13,450); ir ($CHCl_3$) 1720 (pivalate), 1690 and 1660 cm^{-1} (Δ^4-3 ketone); nmr 3.92 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.64 ppm, C-19), and 0.90 ppm (s, 3, C-18).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.54; H, 7.89; Cl, 8.42. Found: C, 68.74; H, 7.98; Cl, 8.68.

4-Chloro-17β-pivaloxy-19-hydroxyandrosta-4,6-dien-3-one (15).—A solution of 3 g of **13** and 3 g of paratoluenesulfonic acid in 15 ml of acetic anhydride was left to stand at 100° under nitrogen for 10 min whereupon it was poured into 150 ml of water and stirred for 1 hr. The aqueous phase was decanted from the viscous resin, the resin was dissolved in benzene, and the solution was stirred under nitrogen with 1 vol of 50% aqueous potassium hydroxide for 4 hr in an effort to destroy residual amounts of acetic anhydride. The benzene phase was dried with sodium sulfate and evaporated at reduced pressure. The residue, consisting largely of 19-acetate **14**, was dissolved in 30 ml of methanol and left to stand with 0.3 ml of 50% aqueous potassium hydroxide under nitrogen for 1 hr whereupon 0.3 ml of glacial acetic acid was added and the mixture was concentrated to a thick paste. Filtration gave 1.3 g of off-white crystals which after one recrystallization from methanol gave 1.0 g of **15**, mp 220–228°. The analytical sample had mp 232–233°; uv max (EtOH) 298 mμ (ε 26,700); ir ($CHCl_3$) 3640, 3500 (OH), 1720 (pivalate), 1675 (conjd ketone), and 1615 cm^{-1} (>C=C<); nmr 6.53 (d of q, 2, J_{AB} = 10, J_{AX} = 2, J_{BX} = 1.5 Hz, $\delta_A - \delta_B$ = 0.53 ppm, C-6, C-7), and 3.85 ppm (s, 2, C-19).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.54; H, 7.89; Cl, 8.42. Found: C, 68.22; H, 7.93; Cl, 8.47.

Preparation of Enol 16 and Its Conversion to 8,19-Oxide 11.—The conditions above used for the deconjugation of 4,6-diene **1** to **7** gave, when applied to 500 mg of 4-chloro-4,6-diene **15**, an acidic aqueous suspension, which after filtration and brief drying at high vacuum at room temperature for 20 min yielded enol **16** having uv max (MeOH) 305 (sh), 318 (major peak), and 333 mμ (sh). On standing of 10 mg of the enol under nitrogen for 10 hr a product was obtained having uv max (MeOH) 255 (major peak), 285 (sh), 298 (minor peak), 318 (sh), and 333 mμ (sh). The remainder of the freshly prepared enol **16** was left to stand in 15 ml of pyridine under nitrogen at room temperature for 10 hr. Dilution with water, extraction with benzene, and chromatographic separation of the benzene solution on silica gel gave, after elution with benzene–ethyl acetate (10:1), evaporation, and digestion of the residue with methanol, 90 mg of 8,19-oxide **11**, mp 186–188°, the infrared spectrum of which was identical with that of the product prepared by oxidation of **8** with ferric

(9) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 90–93.

(10) T. Takahashi, *Agr. Biol. Chem. (Tokyo)*, **27**, 633 (1963); *Tetrahedron Lett.*, No. 11, 565 (1964).

(11) Melting points were determined with a Thomas-Hoover apparatus and are corrected. Infrared spectra were determined with a Perkin-Elmer spectrophotometer, Model 21; nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane.

(12) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962).

(13) J. F. Bagli, P. R. Morand, K. Wiesner, and R. Gaudry, *Tetrahedron Lett.*, No. 8, 387 (1964).

(14) Reference 9, p 43.

chloride. Recrystallization from methanol gave the pure sample, mp 195–196°.

Treatment of the free enol **16** with pyridine–acetic anhydride (3:1) instead of pyridine alone gave an essentially identical crude product as evidenced by its ultraviolet spectrum and by thin layer chromatography. Isolation of pure 8,19-oxide **11** was accomplished by chromatography and recrystallization, while identity was established by comparison of infrared spectra.

Deconjugation of 1 and 3 in the Presence of Methanol.—A mixture of 4 g of sodium methoxide, 10 ml of dimethyl sulfoxide, and 10 ml of cosolvent, consisting of varying amounts of methanol and tetrahydrofuran, was stirred in an ice bath and in an atmosphere of prepurified nitrogen until it had cooled down to a temperature of 2–3°. A solution of 1.66 mmol of **1** (500 mg) or of **3** (473 mg) in a mixture of 10 ml of dimethyl sulfoxide and 10 ml of cosolvent was cooled to 2° and then added to the basic reaction mixture in one portion. The temperature of the stirred mixture was maintained at 2–3° for 5 min whereupon 100 ml of benzene and a freshly prepared mixture of 20 ml of concentrated hydrochloric acid and 40 g of ice was added in quick succession. The mixture was stirred for 45 min in a water bath having a temperature of 20°; 10 ml of ethyl acetate and 140 ml of water were then added. The organic phase was extracted five times with 50 ml of water, dried with sodium sulfate, and evaporated at reduced pressure. The residue, which had been freed from all traces of benzene at high vacuum, was dissolved in methanol and its uv spectrum was recorded with a Unicam Sp 800 spectrophotometer. The percentage of $\Delta^{4,7}$-3 ketone in the mixture of $\Delta^{4,7}$- and $\Delta^{4,6}$-3 ketones was then calculated by the equation, % $\Delta^{4,7}$-3 ketone = 100 × wt of $\Delta^{4,7}$-3 ketone/wt of $\Delta^{4,7}$-3 ketone + wt of $\Delta^{4,6}$-3 ketone = $100(A_1\epsilon_1 - 100A_2\epsilon_2)/(A_2\epsilon_3 - A_1\epsilon_1 - A_2\epsilon_2)$, where A_1 = log I_0/I of reaction mixture at 239 mμ, A_2 = fog I_0/I of reaction mixture at 284 mμ, ϵ_1 = 26,500 (284 mμ) for **1** and 28,400 (284 mμ) for **3**, ϵ_2 = 3220 (238 mμ) for **1** and 3745 (238 mμ) for **3**, and ϵ_3 = 16,400 (238 mμ) for **7** and 15,600 (238 mμ) for **9**. The ε value of $\Delta^{4,7}$-3 ketones **7** or **9** at 285 mμ was only 469 or 440, respectively, and was neglected. In the case of 19-hydroxy-4,6-diene **1**, individual runs with cosolvent mixtures containing 0, 20, 40, 60, 80, or 100% of methanol gave products with 86, 86, 80, 73, 33, and 16% $\Delta^{4,7}$-3-one **7**, respectively. In the case of the 10-methyl analog **3**, runs with cosolvent mixtures containing 0, 20, 40, or 60% methanol gave products with 52, 53, 40, and 1% $\Delta^{4,7}$-3-one **9**, respectively.

When the base treatment in the individual runs was prolonged from 5 to 10 min and also when the isomeric mixtures of 4,6-dienes and 4,7-dienes, *i.e.*, of **1** and **7** or of **3** and **9**, was isolated first by thick layer chromatography on silica gel and was then subjected to uv analysis, essentially the same dependencies of the percentage of $\Delta^{4,7}$-3 ketones **3** and **9** on the percentage of methanol in the respective cosolvent mixtures was observed. When the base treatment was further prolonged, by-products were formed in increasing amounts. No formation of $\Delta^{4,7}$-3 ketones could be observed when the base treatment was carried out in 40 ml of methanol instead of the mixture of cosolvent and dimethyl sulfoxide, and starting materials **1** or **3** were recovered largely unchanged.

Androsta-4,7-diene-3,17-dione (9).—When 473 mg of **3** was treated under the conditions outlined above, except that the cosolvent was replaced by dimethyl sulfoxide, a crude product was obtained which, as calculated from its uv spectrum, contained 89% **9**. Chromatography on silica gel yielded a semicrystalline material on elution with benzene–acetone (20:1) which after recrystallization from methanol gave product **9**: mp 129–142°; uv max (EtOH) 238 mμ (ε 15,600); ir ($CHCl_3$) 1736 (17 ketone), 1670 (Δ^4-3 ketone), and 1632 cm^{-1} (>C=C<) nmr 5.82 (s, 1, C-4) and 5.37 ppm (m, 1, C-7).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.44; H, 8.37.

Registry No.—**2**, 29172-45-0; **7**, 2863-83-4; **8**, 29172-47-2; **9**, 4675-73-4; **10**, 29172-49-4; **11**, 29172-50-7; **13**, 29172-51-8; **15**, 29172-52-9; **16**, 29172-53-0.

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Relative Nucleophilicities of Carbanions Derived from α-Substituted Phenylacetonitriles[1]

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The relative nucleophilicities of carbanions derived from α-substituted phenylacetonitriles toward various alkylating agents have been determined in liquid ammonia solution. The nucleophilicities toward methyl iodide are in the order indicated for sodio derivatives of phenylacetonitrile with the following α substituents: ethyl ~ *n*-butyl > methyl > isopropyl > benzyl > hydrogen > 3-pentyl ≫ phenyl. Other data are presented with isopropyl bromide or *n*-butyl halide as alkylating agent and with potassium or lithium as cation. The results are discussed in terms of inductive and steric effects.

The literature contains many examples of the alkylation of phenylacetonitrile with alkyl halides.[3] Of the many bases and solvents employed, the procedure with sodium amide and liquid ammonia is particularly convenient and efficient but gives a product contaminated with the dialkylation product and unreacted phenylacetonitrile.[4]

Mono- and dialkylation occurs as depicted in Scheme I. Studies of the factors in this reaction which would be important in synthesis have been carried out in this laboratory[5] and elsewhere.[6] We now report a quantitative study of the nucleophilicities in liquid ammonia

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