Nor Steroids. IX. Synthesis of *A*-Norandrostanes *via* the Dieckmann Cyclization[1,2]

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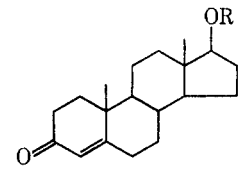
The Dieckmann cyclization of dimethyl 2,3-*seco*-5α-androstan-17β-ol-2,3-dioate 17-propionate (**4b**) to 3α-carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**5**), followed by methylation at C-3 and subsequent hydrolysis and decarboxylation to give 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**), is described. Improved procedures for the reduction of testosterone esters to the 5α-3-keto compound and oxidation of this to the 2,3-*seco* acid are also reported.

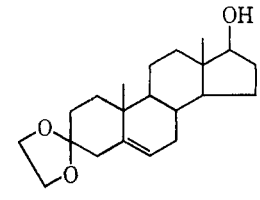
Of the various methods available for the preparation of A-nor steroids, Fuchs and Loewenthal[4] reported that the Dieckmann cyclization of the 2,3-seco dimethyl ester of cholestanedioic acid proceeded in good yield to the A-nor β-keto ester.[5] If the β-keto ester could be alkylated at the active methylene group in good yield, hydrolysis and decarboxylation of the product would provide a good route to A ring alkylated A-nor ketones, which are often difficult to prepare from the A-nor ketones.[6] This paper reports the successful application of this method to the synthesis of 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**).

For the cyclization step, the dimethyl ester of a 2,3-*seco*-5α-androstan-17β-ol-2,3-dioic acid derivative was required, and was obtained by oxidation and subsequent esterification of a 5α-androstan-17β-ol-3-one derivative. The most readily available starting material for this sequence was testosterone (**1**, R = Me or Et) in the form of the 17-acetate or -propionate. However, catalytic hydrogenation of these compounds with palladium–charcoal gave mixtures of the 5α- and 5β-androstanes, a result also obtained by Shoppee and Krueger.[7] Reduction with palladium on calcium carbonate[8] also gave substantial amounts of the 5β isomer. Reduction of 3,3-ethylenedioxyandrost-5-en-17β-ol (**2**) with a palladium–charcoal catalyst gave a 44% yield of the α isomer by simple crystallization.[9] Reduction with lithium–ammonia[10] proved to be a superior method for obtaining the desired α isomer, **3**, in yields of 81–88%, from testosterone acetate or propionate. Some 3β-hydroxy compound was also formed, but was not separated, since it was reoxidized to the ketone in the subsequent step.

The oxidation of 5α-androstan-17β-ol-3-one 17-hexahydrobenzoate with chromium trioxide in acetic acid at 55–65° was reported by Rull and Ourisson[11] to proceed in about 75% yield. These conditions gave low yields (~25%) when applied to the 17-acetate or -propionate, but when the temperature was raised to 70–80°, yields of 75% of the seco acid 17-propionate **4a** were obtained. The seco acid was then esterified with diazomethane to give the dimethyl ester **4b** in 90% yield.



1a, R = H
b, R = –COMe
c, R = –COEt



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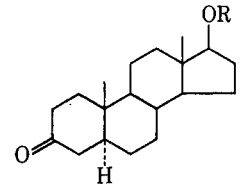
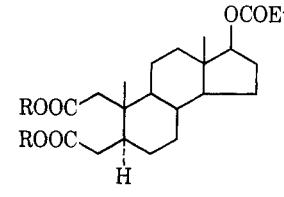
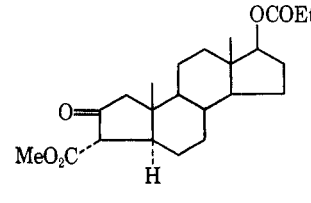


3a, R = –H
b, R = –COMe
c, R = –COEt



4a, R = –H
b, R = –Me



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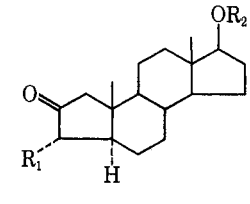

6a, R_1 = –H; R_2 = H
b, R_1 = –Me; R_2 = –COEt

The Dieckmann cyclization was first carried out using potassium *tert*-butoxide in benzene and gave 3α-carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**5**) in only 20% yield. However, when the cyclization was carried out in (5:1) benzene–dimethyl sulfoxide[12] the yield of β-keto ester was increased to 62%. That the β-keto ester was the 2-one and not the 3-one was shown by hydrolysis to the β-keto acid and decarboxylation to give the known *A*-nor-5α-androstan-17β-ol-2-one (**6a**)[5a,13] in 95% yield. The 3α configuration was assigned to the carbomethoxy group in **5** on the basis of the C-19 methyl resonance at δ 1.17 in the nmr spectrum. This corresponds to a value of δ 1.23 for the C-19 methyl resonance in the A-nor ketone **6a**. If the

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(1) For the previous paper in the series, see H. R. Nace and E. M. Holt, *J. Org. Chem.*, **34**, 2692 (1969).

(2) Supported in part by the USPHS under Grant AM 05249-02.

(3) Abstracted from the Ph.D. Thesis of J. L. P., Brown University, 1967; University Fellow, 1962–1963.

(4) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(5) Two more examples have been reported since completion of this work. See (a) S. Hara, *J. Pharm. Soc. Jap.*, **88**, 1227 (1968); (b) K. Oka and S. Hara, *Chem. Commun.*, 368 (1969).

(6) D. H. Nelander, Ph.D. Thesis, Brown University, 1963.

(7) C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 3641 (1961); see also A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.*, **68**, 2097 (1935).

(8) R. Mozingo, *Org. Syn.*, **26**, 77 (1946).

(9) After completion of this work a similar reduction was reported by J. Pospisek, Z. Vesely, and J. Trojanek, *Collect. Czech. Chem. Commun.*, **34**, 3632 (1969).

(10) E. E. van Tamelen and W. C. Proost, Jr., *J. Amer. Chem. Soc.*, **76**, 3632 (1954); F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959).

(11) T. Rull and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1573 (1958).

(12) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895 (1960).

(13) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *ibid.*, **59**, 1363 (1937).

carbomethoxy group were β, it would be expected to exert a much larger deshielding effect on the C-19 methyl, resulting in a larger downfield shift. This assignment is opposite to that of Fuchs and Loewenthal[4] for the analogous product in the cholestane series. Their assignment was based on a series of chemical transformations and assumptions of reactivity based on stereochemical considerations. However, unpublished results obtained in this laboratory,[14] based mainly on nmr studies, indicate that the carbomethoxy group in their compound is also α, and their assignment is incorrect. Stereochemical considerations also suggest that the α configuration is more stable, avoiding 1,3-diaxial interactions with the 19-methyl group.

The β-keto ester was alkylated by treatment with sodium hydride and methyl iodide and the alkylated product (not isolated) was hydrolyzed and decarboxylated to give 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**) in 55% yield. The α assignment of the methyl group is tentative and is based on the fact that the α configuration is sterically favored over the β configuration and is accessible through the enolic intermediate formed in the decarboxylation step.

Experimental Section[15]

Catalytic Reduction of the Dioxolate Derivative 2.—Testosterone (2.0 g, 0.694 mmol), 2-methyl-2-ethyl-1,3-dioxolane (20.8 g, 0.18 mol), and *p*-toluenesulfonic acid (60 mg) were heated at reflux temperature, and methyl ethyl ketone was removed by means of a Dean–Stark trap. After 5 hr, 16 ml of distillate had been collected and no further production occurred. The reaction mixture was taken up in benzene and washed with 5% $NaHCO_3$ and water. The solution was dried (Na_2SO_4), the solvent was removed, and recrystallization gave 1.35 g (58%) of 3,3-ethylenedioxyandrost-5-en-17β-ol (**2**), mp 180–184° (lit.[16] 183–184°). There was no carbonyl absorption in the infrared spectrum.

The product, 498 mg, dissolved in 150 ml of ethanol and was hydrogenated using 5% Pd–C catalyst at ambient conditions. Hydrogen (1 equiv) was absorbed, and no further uptake occurred. After removal of the catalyst and the solvent, the crude product was hydrolyzed by boiling under reflux with 50 ml of acetone for 12 hr. Addition of 500 ml of water precipitated the product, which was recrystallized from heptane–ethyl acetate to give 5α-androstan-17β-ol-3-one (**3a**): 245 mg (44%); mp 176.5–179°; $[\alpha]D$ +34° (*c* 1.0, EtOH); ir (KBr) 1710 cm^{-1}; R_f^{BE} 0.37 (silica) (lit.[17] mp 181°, $[\alpha]D$ +32°).

Reduction of Testosterone Acetate to 5α-Androstan-17β-ol-3-one 17-Acetate (3b).—To a solution of 10.0 g (29.6 mmol) of testosterone acetate (**1b**) in 250 ml of anhydrous ether was added 500 ml of liquid ammonia, and then 2.1 g (0.303 g-atom) of lithium was added in small pieces. After the addition was complete, ammonium chloride was added slowly until the solution was white and pasty. Water (150 ml) was added slowly until the inorganic salts had dissolved and the solution was allowed to stand overnight while the ammonia evaporated. The residue was extracted with ether and with methylene chloride, and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was crystallized from ethyl acetate–heptane and gave 8.50 g (86%) of 5α-androstan-17β-ol-3-one 17-acetate (**3b**), mp 154–156° (lit.[18] mp 158.5–159.5°).

Reduction of Testosterone Propionate.—To a solution of 800 mg (0.116 g-atom) of lithium in 750 ml of liquid ammonia was added over a period of 20 min a solution of 6.98 g (21.1 mmol) of testosterone propionate (**1c**) in 60 ml of dioxane and 50 ml of ether. A small amount of lithium was added to restore the deep blue color of the solution and then after 20 min it was worked up as above to give 6.16 g (84%) of 5α-androstan-17β-ol-3-one 17-propionate (**3c**), mp 119.5–120.5° (lit.[18] mp 121–121.7°).

2,3-*seco*-5α-Androstan-17β-ol-2,3-dioic Acid 17-Propionate (4a).—To a solution of 571 mg (1.65 mmol) of **3c** in 30 ml of glacial acetic acid at 65° was added dropwise with stirring, a suspension of 579 mg (5.79 mmol) of chromium trioxide in 40 ml of glacial acetic acid, and the temperature was kept at 65–70° during the addition. After the addition the temperature was kept at 75–80° for 8 hr, then the solution was cooled to 55° and 100 ml of water was added. The resulting mixture was then heated on a steam bath under an air stream with periodic addition of water until the odor of acetic acid was no longer distinguishable and then extracted (fifteen 100-ml portions) with ether, and the ether extracts were combined, reduced in volume, and extracted with three 10-ml portions of 5% Na_2CO_3 solution. The basic extract was acidified with hydrochloric acid and extracted exhaustively with ether. The ether extract was dried (Na_2SO_4) and the ether was evaporated. The residue was recrystallized from ethanol to give 490 mg (75%) of the seco acid **4a**: mp 223–225°; $[\alpha]D$ +30° (*c* 1.0, $CHCl_3$); ir (KBr) 5.76, 5.80 μ; R_f^{BE} 0.05.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 66.98; H, 8.69. Found: C, 66.90; H, 8.90.

Dimethyl 2,3-*seco*-5α-Androstan-17β-ol-2,3-dioate 17-Propionate (4b).—A solution of diazomethane in 60 ml of ether, prepared from 3.0 g of *N*-nitroso-*N*-methylurea,[19] was dried over solid KOH for 1 hr at 0° and then added to an ice-cold solution of 520 mg (1.32 mmol) of the seco acid **4a** in 250 ml of ether. The solution was cooled in an ice bath for 2 hr and allowed to come to room temperature, the solvent and excess diazomethane were removed under reduced pressure, and the residue was recrystallized from ethanol to give 500 mg (90%) of the dimethyl ester **4b**: mp 72.5–74°; ir (KBr) 5.77 μ; $[\alpha]$ +43.0° (589), +30.7° (578), +28.5° (436), +83.8° (365 mμ) (*c* 0.10, EtOH); nmr δ 0.89 (C-18 CH_3), 1.12 (C-19 CH_3), 3.70 (center of quadruplet, $-CH_2-$ of side chain), and 3.70 (s, 6, ester CH_3); tlc R_f^{BE} 0.64. A trace of seco acid was observed at R_f 0.04. The ester was not further purified but was used directly in the following transformation.

3α-Carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-Propionate (5). A. By Cyclization in Benzene.—In a drybox operation, 240 mg (2.14 mmol) of potassium *tert*-butoxide was added to a solution of 500 mg (1.18 mmol) of the seco ester **4b** in 40 ml of anhydrous benzene (further dried over $MgSO_4$) and the resulting mixture was boiled under reflux ($CaCl_2$ tube) for 14 hr. The mixture was then cooled, 25 ml of dilute HCl was added, the aqueous layer was removed, and the benzene layer was washed with water, dilute $KHCO_3$ solution, and water, and dried (Na_2SO_4), and the solvent removed to give an oily residue which could not be crystallized. Tlc (alumina) analysis with benzene indicated the presence of two major components, starting material, R_f 0.85 (yellow spot with 2,4-DNP), and the desired product, R_f 0.15 (orange spot with 2,4-DNP). Column chromatography on silica and elution with benzene gave starting material: mp and mmp (with an authentic sample) 72–73°; R_f 0.85 (silica); ir spectra superimposable. Elution with ether–methanol gave the product **5**: 90 mg (20%); R_f 0.18 (benzene); ir ($CHCl_3$) 5.74, 5.80, 6.10 μ; mp 113.5–115°, after recrystallization from methanol; $[\alpha]$ +89.0° (589), +48.2° (578), +51.3° (546), +85.5° (436 mμ) (*c* 0.10, EtOH); purple color with ferric chloride; nmr δ 0.96 (C-18 CH_3), 1.07 (t, side chain CH_3), 1.17 (C-19 CH_3), 3.70 (q, side chain $-CH_2-$, and s, ester CH_3).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.48; H, 8.65.

B. By Cyclization in Benzene–Dimethyl Sulfoxide.—To a solution of 600 mg (1.42 mmol) of the seco diester in 95 ml of anhydrous benzene and 20 ml of freshly distilled dimethyl sulfoxide

(14) A. H. Smith, Ph.D. Thesis, Brown University, 1968.

(15) Melting points were determined with a Hershberg apparatus and Anshutz thermometers and are corrected. Microanalyses by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology. Ir spectra were determined with a Perkin-Elmer Infracord or Model 237 spectrometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Nmr spectra were determined with a Varian HR-60 spectrometer in deuteriochloroform solution using TMS as an internal standard. Column chromatography was done with Baker chromatographic grade silica gel or Merck chromatographic grade alumina. Tlc was carried out with silica gel or alumina and the plates were developed with a solution of 2,4-dinitrophenylhydrazine in phosphoric acid and ethanol.

(16) "Elsevier's Encyclopedia of Organic Chemistry," Vol. 14, E. Radt, Ed., Elsevier, New York, N. Y., 1940, p 141.

(17) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 519.

(18) Reference 16, p 2597s.

(19) A. H. Blatt, *Org. Syn.*, **2**, 165 (1943).

was added 282 mg (2.52 mmol) of potassium *tert*-butoxide in a drybox operation, and the resulting mixture was boiled under reflux with a Dean–Stark trap for 16 hr, during which time 20 ml of solvent was removed from the trap. Then the reaction mixture was cooled and extracted with 100 ml of dilute HCl and this extract was extracted extensively with ether ("acid extract"). The reaction mixture was next extracted with 10% $KHCO_3$ solution, and this extract was neutralized with hydrochloric acid and extracted extensively with ether ("basic extract"). The mother liquor (now DMSO-free) and the two extracts were dried separately (Na_2SO_4); the solvent was removed under reduced pressure.

The mother liquor gave, after recrystallization from methanol, 30.6 mg of starting material, mmp 72–76°, infrared spectra and R_f identical.

The basic extract yielded, after recrystallization from methanol, 278 mg of β-keto ester **5**: mp 98–101°; $[\alpha]D$ +80.5° (*c* 0.1, EtOH); ir (KBr) 5.73, 5.77, 6.05 μ; R_f^{BE} 0.05 (silica). The acid fraction yielded in the same manner 65 mg of β-keto ester (total yield, 62%).

***A*-Nor-5α-androstan-17β-ol-2-one (6a).**—To a solution of 30 mg (0.077 mmol) of the β-keto ester **5** in 50 ml of a saturated solution of Na_2CO_3 in methanol was added 10 ml of water and the solution was stirred for 15 hr, then acidified with dilute HCl, and extracted with three 100-ml portions of ether. The extract was dried (Na_2SO_4) and the solvent was removed to give an oily residue. Tlc on silica with (1:1) ether–benzene gave R_f 0.87 (product) and 0.12 (starting material). Column chromatography on silica and elution with (1:1) benzene–ether gave 20 mg (95%) of *A*-nor-5α-androstan-17β-ol-2-one (**6a**): mp 195–197° (lit.[13] mp 197°); ir (KBr) 5.78, 5.83 μ; nmr δ 0.96 (18-CH_3) and 1.23 (19-CH_3).

3α-Methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-Propionate (6b).—To a solution of 62 mg (0.159 mmol) of the β-keto ester **5** in the minimum amount of anhydrous benzene was added 5.0 mg (0.20 mmol) (Nujol dispersion) of sodium hydride and the mixture was stirred 2 hr at room temperature until hydrogen evolution ceased. Then 312 mg (2.2 mmol) of methyl iodide was added and the solution was stirred at room temperature for 9 hr and at 40° for 5 hr. Then 1 ml of methanol was added slowly followed by 5 mg of *p*-toluenesulfonic acid in 10 ml of acetic acid and 5 ml of water, and the resulting mixture was stirred at 60° for 9 hr. After cooling, the aqueous layer was removed and extracted with ether, and the extract was added to the organic layer. This solution was then evaporated under reduced pressure, the residue was taken up in ether, and this solution was washed with saturated Na_2CO_3 solution and with water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was recrystallized from methanol and gave 30.5 mg (55%) in two crops: mp 169.5–171°; ir (KBr) 5.78 and 5.82 μ; $[\alpha]D$ +38.8° (*c* 0.01, EtOH); nmr δ 0.76 (C-3 CH_3), 0.87 (C-18 CH_3), and 1.13 (C-19 CH_3); R_f 0.76 (ether–methanol).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.88; H, 9.64.

Registry No.—**3a**, 521-18-6; **4a**, 26686-22-6; **4b**, 26686-23-7; **5**, 26731-53-3; **6a**, 1032-10-6; **6b**, 26686-25-9.

Steroidal Adducts. III.[1,2] Novel Dehydrogenations of Steroids *via* Ene Adducts with Tetracyanoethylene

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Tetracyanoethylene reacts with the steroidal ring-B dienes, ergosteryl acetate and 9(11)-dehydroergosteryl acetate, to give principally products of ene reactions. A by-product of both reactions is assigned the cycloadduct structure **7**, chiefly from spectral data, including nmr solvent shifts, and is shown to arise from dehydrogenation reactions involving ene adducts. Other reactions between tetracyanoethylene and unsaturated steroids are also discussed.

Tetracyanoethylene reacts rapidly with most cisoid 1,3-dienes to give Diels–Alder adducts.[5] With dienes which cannot assume a cisoid configuration, cyclobutane derivatives are formed[6,7] by 2 + 2 addition to one of the double bonds. In a preliminary communication,[2] we reported the first instances of Alder ene reactions[8–10] between tetracyanoethylene and dienes, and recently some complementary results have been described by others.[11] We now amplify the preliminary report and describe some further reactions of tetracyanoethylene with unsaturated steroids.

Tetracyanoethylene reacts rapidly with ergosteryl acetate **1** in benzene solution to give, after an initial olive-green coloration due to a charge-transfer complex,[12] a 1:1 adduct, mp 135°, in 65% yield, as previously reported.[2] The ene adduct structure **2** was assigned to this compound, chiefly on the basis of uv and nmr data,[13–16] and by analogy with the structures of the three adducts (**3–5**) formed between ergosteryl acetate and acrylonitrile.[13]

The reactions of the adduct **2** are dominated by the lability of the tetracyanoethyl group. The compound is fairly stable in dry, nonprotic, neutral solvents, but loses hydrogen cyanide very readily in moist air, or with basic or protic solvents, apparently giving polymeric products. When **2** was warmed with excess dry ammonia in chloroform, a compound was obtained, which analyzed correctly for the loss of hydrogen

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(2) Preliminary communication: A. M. Lautzenheiser and P. W. Le Quesne, *Tetrahedron Lett.*, **3**, 207 (1969).

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(6) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **79**, 5316 (1957).

(7) J. K. Williams, *ibid.*, **81**, 4013 (1959).

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(14) A. van der Gen, J. Lakeman, U. K. Pandit, and H. O. Huisman, *ibid.*, **21**, 3641 (1965).

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