characteritic of acetyl groups, and a one-proton absorption at δ 3.28 ppm for the OH proton, which was consistent with the expected α-acetoxy methyl ketone **20**.

In a 25-ml three-neck flask equipped with a Dewar condenser and mechanical stirrer was collected 10 ml of liquid ammonia (freshly distilled from dissolved sodium), and a solution of 0.090 g of **20** in 5 ml of anhydrous dioxane was added. To this solution was added 0.065 g of freshly cut calcium. After stirring for 1 hr, the blue solution was filtered into a flask containing about 0.1 g of solid ammonium chloride and swirled until the blue color disappeared. The solvent was removed *in vacuo*, and the residue was dissolved in ether and water. The ether layer was separated, dried (Na_2SO_4), and concentrated to give 0.0561 g of a light yellow oil which was dissolved in 5 ml of acetone and titrated with Jones reagent[21] until the color of the reagent persisted. One drop of isopropyl alcohol was added, and the reaction mixture was filtered. Removal of the solvent *in vacuo* left a yellow oil (0.050 g) which was chromatographed on 5 g of silica gel. Elution with 40% ether in hexane gave 0.015 g of *dl*-oplopanone (**4**): mp 101.5–102°; nmr ($CDCl_3$) δ 0.69 and 0.89 (pair of d's, J = 6 Hz, 6 H, CH_3CHCH_3), 1.19 (s, 3 H, CH_3), and 2.18 ppm (s, 3 H, Ac); ir (CCl_4) 3583 (OH), 1711 (C=O), 1466, 1385, 1370, and 1359 cm^{-1}.

The synthetic material exhibited nmr, ir, and glc properties identical with those of authentic oplopanone.[6,22]

Registry No.—**1b**, 35049-20-8; **2b** (X = Ac), 35049-21-9; **4**, 35049-27-5; **5**, 35049-26-4; **6**, 35049-23-1; **7**, 35106-10-6; **8**, 41263-23-4; **9**, 35049-22-0; **12**, 35049-25-3; **13**, 41263-25-6; 2α-**14**, 35049-37-7; 2β-**14**, 35049-36-6; **15**, 41263-27-8; **16**, 41263-28-9; **17**, 41263-29-0; **18**, 41263-30-3; **19**, 35049-28-6; **20**, 35049-29-7; 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone, 41263-33-6; 2-methylcyclopentanone, 1120-72-5; 1,4-dimethoxy-2-butanone, 25680-86-8; 2-methyl-5-isopropylcyclopentanone, 6784-18-5; 7α-acetoxy-2α-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-36-9; 7α-acetoxy-2β-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-37-0; 2α,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41312-35-0; 2β,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-38-1.

The Synthesis of 7α-Trifluoromethyltestosterone Acetate[1]

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Attempted hydrolysis of 7α-cyanotestosterone acetate *via* an imino ether has given the novel bicyclic ring system of 5α-amino-7α-carboxy-17β-hydroxyandrostan-3-one lactam. Decomposition of the *N*-nitroso derivative of the lactam with hydroxide, ethoxide, and *tert*-butoxide has given 7-carboxyandrostanes with a varying amount of substitution at the 5 position. Reaction of 7α-carboxytestosterone acetate with sulfur tetrafluoride under mild conditions has given 7α-trifluoromethyltestosterone acetate.

The increased anabolic and androgenic activity associated with incorporation of certain 7α substituents into steroidal androgens, particularly the high activity of the 7α-methyl derivatives,[2] has led us to attempt the synthesis of 7α-trifluoromethyltestosterone acetate (**2e**). The trifluoromethyl group is about the same size as a methyl group[3] and would be expected to be compatible with biological activity. The metabolic stability as well as the high electron-withdrawing feature of this group gave us reason to anticipate that some unique change in biological activity might result with its incorporation into androgenic steroids.[4]

The most direct method of introduction of substituents into the 7α position of steroids is the conjugate addition of appropriate nucleophiles to the 3-keto-$\Delta^{4,6}$ system.[2d,5] Since the trifluoromethyl anion, because of its instability and difficulty of preparation,[6] would not be suitable for the direct preparation of the 7α-trifluoromethyl group, we sought to derive the desired compound from a 7α-cyano steroid obtained by conjugate addition of cyanide to the dienone system. The hydrolysis of the nitrile to a carboxyl function followed by its reaction with sulfur tetrafluoride appeared to be a suitable means of obtaining our objective.

Reaction of the dienone **1** with a mixture of excess anhydrous hydrogen cyanide and triethylaluminum[7] in tetrahydrofuran afforded a good yield of 7α-cyanotestosterone acetate (**2a**). This method of preparation of **2a** is vastly superior to that reported[8] in that it gives a much higher yield of cleaner product. No products of diaddition were encountered as is found when excess aqueous cyanide is condensed with dienones.[8] There was also no indication of the presence of the epimeric 7β-cyano compound showing that the reaction was also highly stereospecific.

It was hoped that the cyano group of **2a** could be converted to a carbomethoxy function by hydrolysis of its corresponding imino ether hydrochloride. However, when a solution of **2a** in methanol was treated with hydrogen chloride, a product hydrochloride having only weak absorption in the carbonyl region of its ir spectrum was obtained. Aqueous hydrolysis of this material afforded, in addition to traces of the ester **2b**, a material containing ir absorption at 5.88 and 5.94 μm and no uv absorption characteristic of an α,β-unsaturated ketone. The product, $C_{20}H_{29}NO_3$, is the steroidal

(1) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, ORGN 125.

(2) (a) J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1970, p 61; (b) A. Segaloff, *Steroids*, **1**, 299 (1963); (c) J. A. Campbell, S. C. Lyster, G. W. Buncan, and J. C. Babcock, *ibid.*, **1**, 317 (1963); (d) G. C. Buzby, Jr., C. R. Walk, and H. Smith, *J. Med. Chem.*, **9**, 782 (1966).

(3) W. A. Sheppard and C. L. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1969, p 433.

(4) The introduction of a trifluoromethyl group into hormonal steroids at the 3, 4, 6, 9, 16, and 20 positions has been reported, respectively: (a) A. F. Pascual and M. Wolff, *J. Med. Chem.*, **14**, 164 (1971); (b) ref 1; (c) W. Godfredsen and S. Vangedal, *Acta Chem. Scand.*, **15**, 1786 (1961); (d) J. H. Fried, U. S. Patent 3,409,610 (1968) [*Chem. Abstr.*, **70**, 58144 (1968)]; (e) A. Bowers and J. Edwards, U. S. Patent 3,151,132 (1964) [*Chem. Abstr.*, **62**, 618 (1964)]; (f) S. Nakaniski, K. Morita, and E. V. Jensen, *J. Amer. Chem. Soc.*, **81**, 5260 (1959).

(5) J. A. Campbell and J. C. Babcock, *J. Amer. Chem. Soc.*, **81**, 4069 (1959); H. Kaneko, K. Nakamura, Y. Yamato and M. Kurokawa, *Chem. Pharm. Bull.*, **17**, 11 (1969).

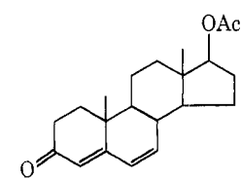
(6) J. Villiéras, *Bull. Soc. Chim. Fr.*, 1520 (1967).

(7) (a) H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 1866 (1966); (b) W. Nagata, M. Yoshioka and M. Murakami, *J. Amer. Chem. Soc.*, **94**, 4654 (1972). The latter reference reports the successful preparation of 7α-cyanotestosterone utilizing Et_2AlCN. Contrary to their results we have found that the combination reagent ($AlEt_3$–HCN) works equally well in introducing a 7α-cyano group into these compounds.

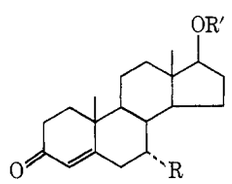
(8) R. G. Christiansen and W. S. Johnson, *Steroids*, **1**, 620 (1963).

lactam **4a** and the intermediate hydrochloride is probably that of the imino ether **3**. While somewhat frustrating in the attainment of our synthetic objective, the ease of formation of this material serves to verify the assignment of the 7α configuration to the original cyano group. A 7β-cyano group being equatorial would be expected to form such a lactam across the face of the steroid only with considerable distortion.

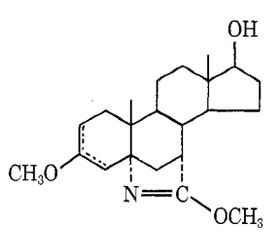
After several unsuccessful attempts at strong base or acid hydrolysis of **4a** the base-catalyzed decomposition of the *N*-nitroso derivative **4b** was attempted. This material was prepared by reaction of **4a** with nitrosyl chloride in acetic anhydride. Because the carbon atom at position 5 is fully substituted, decomposition of **4b** cannot be expected to form a diazo function at that position. Thus, a carbonium-ion-like transition state would be expected to form which could be neutralized by loss of a 4 proton to give the desired Δ^4-3-keto steroid. Treatment of **4b** with ethanolic potassium hydroxide gave an acidic steroid, $C_{22}H_{34}O_5$, containing a saturated carbonyl group. This material is most likely the 5-ethoxy compound **5a**. When the decomposition was



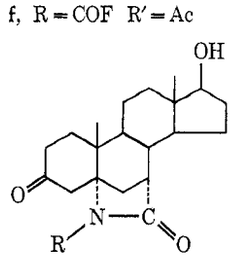
1



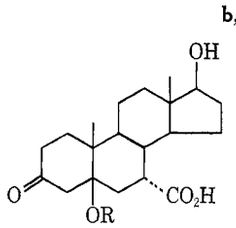
2a, R = CN R′ = Ac
b, R = CO_2CH_3 R′ = H
c, R = CO_2H R′ = H
d, R = CO_2H R′ = Ac
e, R = CF_3 R′ = Ac
f, R = COF R′ = Ac



3



4a, R = H
b, R = NO



5a, R = Et
b, R = H

carried out in the less nucleophilic system of potassium hydroxide in aqueous glyme, two acidic products were obtained in approximately equal amounts. One of these was the desired product **2c** as evidenced by its ir, uv, and mass spectra. The other product, which contained a saturated carbonyl group and had a M^+ of 350 in its mass spectrum, is presumably the 5-hydroxy compound **5b**. Both **5a** and **5b** resisted conversion to **2c** on treatment with aqueous base. The ethoxy group in **5a** and of the hydroxyl group in **5b** are probably β oriented as a result of back-side displacement of the diazonium-like intermediate. The resistance of these groups to elimination also affords an argument for the assignment of β sterochemistry as removal of the 4α proton, necessary for trans elimination, would be difficult both sterically and by charge repulsion with the diaxially oriented 7α-carboxylate group. Finally, when **4b** was treated with the poorly nucleophilic but highly basic potassium *tert*-butoxide in *tert*-butyl alcohol, the desired acid **2c** was the major product isolated.

Although other workers have shown that carboxylates and the intermediate acyl fluorides are more reactive toward sulfur tetrafluoride than unsaturated ketones and esters,[9] we were concerned that the hindered nature of the 7α-carboxyl function in **2d** might render it less reactive and thus upset the desired selectivity of the reaction. It was pleasing to find that reaction of **2d** with an excess of sulfur tetrafluoride–hydrogen fluoride in methylene chloride solution at room temperature for 40 hr resulted in the desired conversion to **2e**, albeit in low yield. If the reaction were interrupted after a shorter period of time the presence of the intermediate acyl fluoride **2f** could be detected by its ir absorption at 5.43 μm.

When tested subcutaneously in a standard assay in rats,[10] the trifluoromethyl testosterone acetate **2e** exhibited ~0.1 the androgenicity and 0.3 the anabolic activity of testosterone acetate.

Experimental Section[11]

7α-Cyanotestosterone Acetate (2a).—A solution of 0.355 g of hydrogen cyanide (freshly distilled) in 4 ml of anhydrous tetrahydrofuran was added under nitrogen with stirring to a cold (0°) solution of 2.00 g of triethylaluminum in 4 ml of tetrahydrofuran. After stirring at 0° for 10 min this solution was added dropwise at 0° to a solution of 880 mg of Δ^6-testosterone acetate in 6 ml of tetrahydrofuran. After 2 hr at 0° the reaction mixture was poured on a mixture of 100 g of ice and 100 ml of 10% sodium hydroxide solution. After brief mixing the product was isolated by chloroform extraction. The organic layer was washed with water until the washings were neutral and then dried and concentrated to a noncrystalline residue. This material was eluted through 100 g of a 6:5 mixture of Stahl silica gel G[12]–diatomaceous earth with 5–10% ether in benzene. Early fractions contained 278 mg of starting dienone **1**. The crystalline product **2a** eluted separately and amounted to 515 mg. Recrystallization from aqueous methanol gave 306 mg of needles: mp 204–207°; $[\alpha]_D$ (dioxane) +73°; uv max (CH_3OH) 237 nm (ϵ 1.6 × 10^4); nmr τ 4.14 (wide s, 4-CH), 7.96 (s, CH_3CO), 8.78 (s, 19-CH_3), 9.13 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.03; H, 8.16; N, 3.79.

5α-Amino-7α-carboxy-17β-hydroxyandrostan-3-one Lactam (4a).—A solution of 500 mg of the cyano compound **2a** in 10 ml of anhydrous methanol was saturated with hydrogen chloride at 0° and was allowed to stand at 0–5° for 24 hr. The solution was then purged with dry nitrogen until the effluent gas indicated

(9) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962).

(10) Hershberger test [L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953)] performed in these laboratories by Dr. D. J. Patanelli.

(11) Melting points were determined on a Kofler hot stage and are uncorrected. Ir spectra are in accord with the assigned structures and were taken either as Nujol mulls or as chloroform solutions. Nmr spectra were determined in deuteriochloroform solutions with a Varian Associates Model A-60A spectrometer unless otherwise noted. Rotational data were obtained on 1% solutions. Mass spectra were run on either a CEC Model 21-110 or an LKB Type 9000 spectrometer by the direct probe technique. The purity of isolated material was checked by thin layer chromatography (tlc) on silica gel coated glass plates.

(12) E. Merck, A. G. Darmstad, Germany. Distributed by Brinkmann Instrument Co., Catiague Road, Westbury, N. Y. 11590.

only traces of hydrogen chloride vapors. The remaining solution was concentrated under reduced pressure to a crystalline, hygroscopic solid which had weak, but sharp ir absorption at 5.91, 6.02 and 6.20 μm. This solid, after dissolving in 50 ml of water, gave a precipitate (369 mg) which was removed by filtration and was rinsed with water. After washing with ether material, **4a** of mp 310–315° was obtained: ir 5.89, and 5.94 μm; *m/e* 331 (M^+), 316, 313, 303, 288, 274, 96 (base).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.60; H, 8.66; N, 4.27.

This material (**4a**) was acetylated with 1:1 pyridine–acetic anhydride at room temperature for 16 hr. The product acetate was isolated by quenching with water, filtering, and recrystallization from ethyl acetate. This material had mp 310–314°; $[\alpha]_D$ ($CHCl_3$) −43°; no uv max; nmr τ (T-60) 3.44 (br, NH), 5.40 (m, CHO), 7.96 (s, CH_3CO), 8.76 (s, 19-CH_3), and 9.15 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.52; H, 8.47; N, 3.73.

7α-Carbomethoxytestosterone (2b).—When the cyano compound **2a** (1.0 g) was allowed to react in methanolic hydrogen chloride as described above, but with the methanol being only partially removed in the work-up and quenching being carried out with aqueous sodium bicarbonate, the resulting crude product (613 mg) contained two components in roughly equal amounts. The more polar component, lactam **4a**, separated selectively from ethyl acetate. Concentration of the mother liquor gave crystalline material (**2b**) which after recrystallization from methanol amounted to 249 mg and had mp 221–223°; $[\alpha]_D$ ($CHCl_3$) +43.7° (lit.[8] mp 222–224°, $[\alpha]_D$ +46.8° for **2b**).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.71; H, 8.63.

Preparation of the *N*-Nitroso Derivative 4b.—A solution of 0.8 *N* nitrosyl chloride in acetic anhydride was added dropwise at 0° to a solution of 100 mg of the lactam **4a** in a mixture of 3 ml acetic acid, 0.6 ml acetic anhydride, and 2 ml of pyridine. Addition was stopped when the combined solution gave a persistent positive starch iodide test. The solution stood at 0° for 3 hr. It was poured into water and the product *N*-nitroso compound **4b** was worked up in chloroform. The material was usually used immediately in this form but crystalline **4b** could be obtained after treatment with ether: mp 235–255° with decomposition; ir 5.65 and 5.82 μm.

Decomposition of the *N*-Nitroso Derivative 4b with Ethanolic Potassium Hydroxide. 7α-Carboxy-5β-ethoxy-17β-hydroxyandrostan-3-one (5a).—A solution of the nitroso compound **4b** (prepared from 100 mg of lactam **4a**) in 10% ethanolic potassium hydroxide stood at 0° for 18 hr. The solution was concentrated at room temperature. The residue was treated with water and washed with ethyl acetate. The aqueous layer was acidified with 10% hydrochloric acid and the product was worked up in ethyl acetate to give 103 mg of crude product. Two crystallizations from aqueous methanol gave 54 mg of **5a**: mp 166–168°; ir (mull) 5.79 and 5.89 μm; nmr (DMSO-d_6) 5.98 (q, J = 7 Hz), 8.87 (t, J = 7 Hz), 9.02 (s, 19-CH_3), 9.36 (s, 18-CH_3); CD (dioxane) $[\Theta]_{345}$ +594, $[\Theta]_{319}$ 0, $[\Theta]_{306}$ −171, $[\Theta]_{280}$ +125, and $[\Theta]_{253}$ 0; *m/e* 378 (M^+), 360, 333, 332, 305, 287 (base), and 231.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.52; H, 9.19.

Decomposition of the *N*-Nitroso Derivative 4b with Aqueous Potassium Hydroxide.—A solution of the nitroso compound **4b** (from 100 mg of the lactam **4a**) in 5 ml of dimethoxyethane was treated with excess 10% aqueous potassium hydroxide. After 60 min the reaction was diluted with water and extracted with ethyl acetate to remove any nonacidic impurities. The aqueous layer was acidified and the product extracted into ethyl acetate. Work-up afforded a mixture consisting of two components (tlc eluted with 3% formic acid in ether). These components were separated by preparative tlc in the same system to give about an equal quantity of each. The more mobile component had mp 225–230° and *m/e* 332 (M^+) and was identified as 7-carboxytestosterone **2c** described below. The less mobile component assigned the 5β-hydroxy-7-carboxyandrostanone structure (**5b**) had mp 222–224°, *m/e* 350 (M^+) and no α,β-unsaturated carbonyl chromophore in its ir spectrum.

7α-Carboxytestosterone (2c).—To a solution of the *N*-nitroso compound **4b** (from 350 mg of lactam **4a**) in 5 ml of anhydrous *tert*-butyl alcohol was added 5 ml of a 10% solution of potassium *tert*-butylate in *tert*-butyl alcohol under nitrogen. After 10 min the mixture was added to excess dilute hydrochloric acid solution. The crude product was extracted with ethyl acetate. After washing with water the organic layer was extracted with dilute potassium hydroxide. The alkaline layer was washed with ethyl acetate and then was acidified. The product was extracted and worked up in ethyl acetate to give 309 mg of product, **2c**, mp 226–230°, with decomposition. Material recrystallized from ethyl acetate had mp 230° with decomposition; *m/e* 332 (M^+, base), 317, 314, 304, 289, 124.

This material was acetylated by heating a 5% solution in 1:1 pyridine:acetic anhydride for 15 min on a steam bath. The solution was concentrated at room temperature under reduced pressure and the residue was triturated with water. The separated solid was crystallized from ethyl acetate to give **2d**: mp 304° dec; $[\alpha]_D$ (DMSO) +25°; uv max (MeOH) 243 nm (ε 1.55 × 10^4); nmr (DMSO-d_6) 4.43 (br s, 4-CH), 5.48 (m, CHOAc), 8.02 (s, CH_3CO), 8.82 (s, 19-CH_3), 9.20 (s, 18-CH_3).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.27; H, 7.94.

7α-Trifluoromethyltestosterone Acetate (2e).—A solution of 420 mg of the carboxy steroid **2d** in 8 ml of methylene chloride was treated successively with 18.4 g of sulfur tetrafluoride and 0.3 ml of water to form endogenous hydrogen fluoride. The reaction was kept in a sealed vessel at 20° for 40 hr. After the reaction was vented the resulting solution–suspension was poured onto 5% sodium bicarbonate solution. The product mixture was diluted with methylene chloride. After washing with water and drying ($CaSO_4$) the solution was concentrated. The residue was eluted through a mixture of 80 g of Stahl silica gel H[12] and 80 g of diatomaceous earth with 2% ether in benzene using a fraction collector. The crystalline product (143 mg) was separated twice from heptane to give 60 mg of **2e**: mp 153.5–155°; $[\alpha]_D$ ($CHCl_3$) +13°; uv max (MeOH) 238 nm (ε 1.6 × 10^4); nmr (HR-100) τ 4.26 (br s, 4-CH), 5.40 (m, CHOAc), 7.99 (s, CH_3CO), 8.77 (s, 19-CH_3), 9.17 (s, 18-CH_3); *m/e* 398 (M^+, base), 356, 296 and 124.

Anal. Calcd for $C_{22}H_{29}F_3O_3$: C, 66.33; H, 7.28; F, 14.32. Found: C, 65.95; H, 7.29; F, 14.52.

Registry No.—**1**, 2352-19-4; **2a**, 41498-96-8; **2b**, 3461-03-8; **2c**, 41498-98-0; **2d**, 41498-99-1; **2e**, 41499-00-7; **4a**, 41499-01-8; **4a** acetate, 41499-02-9; **4b**, 41499-03-0; **5a**, 41499-04-1; **5b**, 41499-05-2; hydrogen cyanide, 74-90-8.