general methods employed are illustrated for symmetrically or unsymmetrically substituted carbinolamines by the following 2 examples.

1,1-Di-(4-fluorophenyl)-3-dimethylaminopropan-1-ol.—A soln of 29.0 g (0.2 mole) of ethyl β-dimethylaminopropionate in 50 ml of anhyd Et_2O was added gradually with stirring to a cooled (0°) Et_2O soln of a Grignard reagent prepd from 105 g (0.6 mole) of p-BrC_6H_4F and 14.6 g (0.6 mole) of Mg. After stirring in the cold for 1 hr and then refluxing for 2 hr, the cooled mixture was decompd with 200 ml of a 10% w/v soln of NH_4Cl. Basification with NH_4OH and extraction with $CHCl_3$ (3 × 250 ml) afforded a $CHCl_3$ soln which on drying and evapn gave 58.0 g of a crude oil. This crude product was dehydrated without further purification.

3-Dimethylamino-1-(4-fluorophenyl)-1-phenylpropan-1-ol.—β-Dimethylaminopropiophenone·HCl (21.4 g, 0.1 mole) was added portionwise to a cooled (0°), stirred Et_2O soln of the Grignard reagent prepared from 35 g (0.2 mole) of p-BrC_6H_4F and 4.8 g (0.2 mole) of Mg. After stirring in the cold for 1 hr and then refluxing for 2 hr, the cooled mixture was decompd and worked up as above. The crude colorless solid (11 g) was dehydrated without further purification.

1,1-Di-(4-fluorophenyl)-3-dimethylaminoprop-1-ene (25).—A soln of 41.0 g (0.14 mole) of the carbinolamine in 250 ml of AcOH and 80 ml of concd HCl was refluxed for 30 min. The soln was concd under reduced pressure, dild with H_2O, and basified with NH_4OH. The base was extracted Et_2O, and Et_2O soln was dried and evapd. Distn under reduced pressure gave 20.5 g of an oil. The base was converted into its hydrochloride in anhyd Et_2O. Crystn of the hydrochloride from EtOAc–EtOH gave an anal. sample, mp 211–213°.

1,1-Di-(4-fluorophenyl)-3-dimethylaminopropane (53).—A soln of 5 g of the olefin·HCl in 20 ml of EtOH was hydrogenated at atm temp and pressure using 2.5 g of 5% Pd–C. After 1 mole of H_2 had been absorbed, the catalyst was filtered, the soln was concd, and the product was pptd with Et_2O. Filtration give 3.0 g of material. Crystn from EtOAc–EtOH gave an anal. sample, mp 188–189°.

1,1-Diphenylprop-1-enylamine (1).—Diethyl phosphonoacetate (106 g) was added dropwise to a stirred suspension of NaH (15 g) in dry dimethoxyethane (500 ml) at 0°. The mixture was stirred for 1 hr after the evoln of H_2 ceased, and a soln of benzophenone (91 g) in dimethoxyethane (100 ml) was then added dropwise. The mixture was stirred at 20° for 2 hr, then poured into H_2O (2000 ml), and extracted (Et_2O). Evapn and distn of the extract gave β,β-diphenylacrylonitrile (63 g, mp 48–49°). This (60 g) was added dropwise to a stirred soln of LAH (20 g) in dry Et_2O (500 ml) at −20°. The mixture was stirred for 2 hr at −20° and for 15 min at 0°. Excess LAH was destroyed by addn of H_2O, and the organic phase was sepd, dried ($MgSO_4$), and evapd. 1,1-Diphenylprop-1-enylamine (1) was isolated from the residual oil as its hydrochloride (58 g, mp 206–208°) by addn of ethereal HCl. The hydrochloride, recrystd from EtOH–Et_2O, had mp 214–216°.

Notes

Synthesis of 3-Trifluoromethyl Steroids[1a]

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The function of the carbonyl moiety of C-3 of steroid hormones in eliciting the biological response has been the subject of intensive study in this laboratory. Among C-2 and/or C-3 substituted steroids prepared to test the possibility that π bonding,[2] high electron density, or H bonding[2] might be important in terms of steroid–receptor interaction have been steroidal cyclopropanes[2] and nitro derivatives.[3] In the present study, the preparation of steroidal C-3 substituted CF_3 derivatives was undertaken, inasmuch as CF_3 represents a center which is both electron rich and capable of H bonding.

The introduction of a CF_3 group by photochemical addition of CF_3I across a double bond has been applied to 3β-ethoxy-17β-hydroxypregna-3,5-dien-20-one acetate[4] but such reactions with unconjugated olefinic steroids have not been reported. In the present study, several methods were tried in preparing the 3-CF_3 steroids. Attempted conversion of a 3-CO_2H substituent into a 3-CF_3 group by reaction with SF_4[4] failed. Likewise, reaction of a 3-keto steroid, dihydrotestosterone acetate, with F_3CMgI[5] yielded only starting material. Finally, employing a modified method of Godfredsen and Vangedal,[6] the 3-CF_3 steroid derivative was obtained.

A solution of 5α-pregn-3-en-20-one (**1**) in CCl_4, CF_3I, and a small amount of pyridine was irradiated with uv light for 8 hr under N_2. Only one product, 3α-trifluoromethyl-4β-iodo-5α-pregn-20-one (**2**), was isolated from the reaction mixture although 8 isomeric adducts (4 cis and 4 trans) could be formed from this reaction. The stereochemistry of **2** was established from further reactions as shown in Scheme I and from the nmr spectra of the adduct and its derivatives.

The C-19 Me peak of **2** was shifted 0.36 ppm downfield compared with **1** and upon hydrogenolysis of the iodo group with LAH, the C-19 Me resonance shifted 0.33 ppm upfield. As it is well known that electronegative groups produce a deshielding effect (0.25 ppm) on the C-19 Me group when they are in a 1:3 diaxial

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(2) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

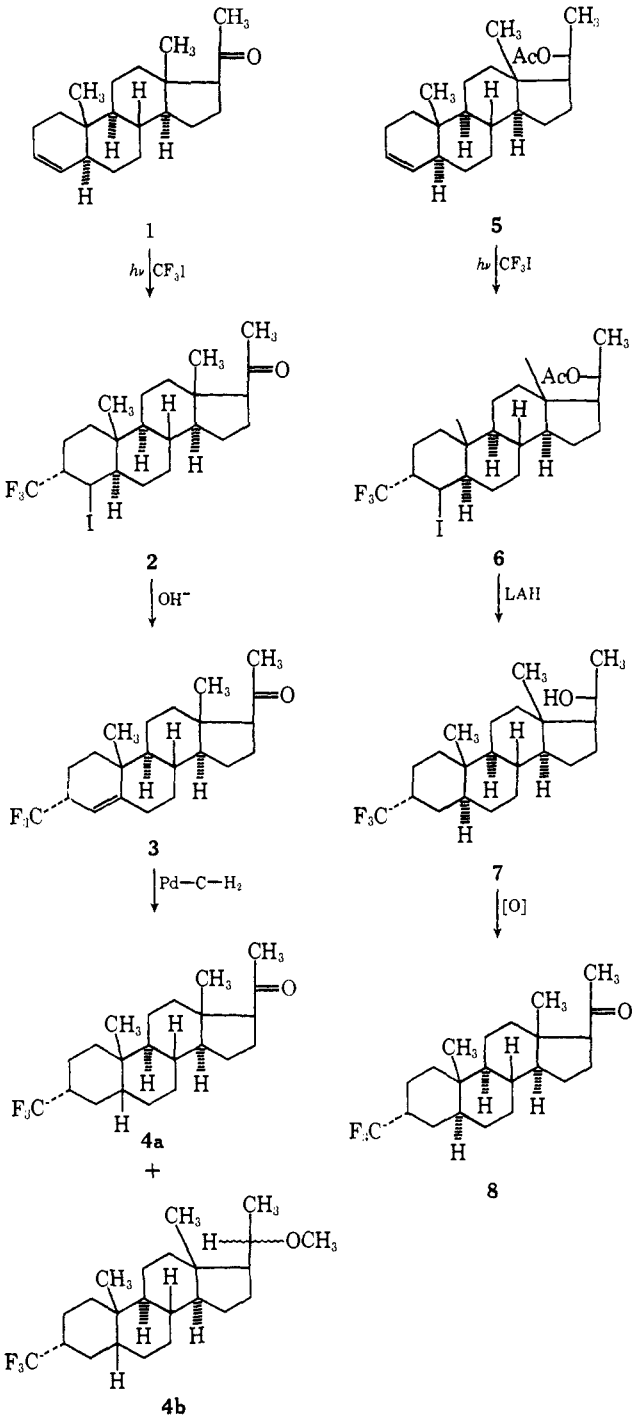
(3) M. E. Wolff and R. C. Boguslaski, *ibid.*, **11**, 285 (1968).

(4) (a) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960). (b) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962).

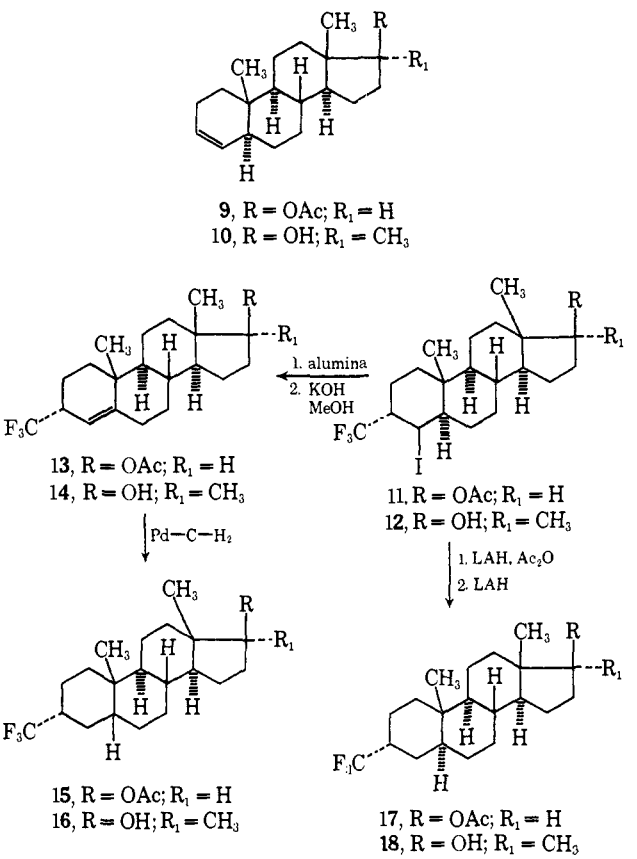
(5) (a) R. N. Haszeldine, *J. Chem. Soc.*, 1273 (1954). (b) E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Org. Chem.*, **28**, 1131 (1963).

(6) W. Godfredsen and S. Vangedal, *Acta Chim. Scand.*, **15**, 1768 (1961).

SCHEME I



SCHEME II



relationship with the C-19 Me and a small deshielding effect (0.0–0.3 ppm) when they are in the equatorial or α-axial position,[7] the iodo group in **2** must be 4β, and the product is either the trans adduct **2** or the corresponding cis isomer, 3β-trifluoromethyl-4β-iodo-5α-pregnan-20-one.

Dehydrogenation of the last compound with base *via* a trans elimination mechanism should give a Δ^3-olefin considering that the 3 proton geminal to 3-CF_3 is more acidic than the 5 proton. On the other hand, a similar treatment of **2** should give a Δ^4-olefin since only the 5 proton is on a trans-diaxial relationship with the iodo group. Upon refluxing the adduct in methanolic KOH,[8] olefin **3** was obtained as indicated in the nmr by the presence of a doublet (J = 4 Hz) centered at 5.2 ppm. The large downfield shift (0.23 ppm) of the C-19 Me peak of **3** compared with that of **1** strongly suggested a Δ^4-olefin.[9] Moreover, the ^{19}F nmr spectrum[10] showed a doublet (J = 10 Hz) centered at 603 Hz on the high-field side of external $C_6H_5CF_3$ reference. This indicates the splitting of the F atoms by the 3-H and therefore, confirms the assignment of the double bond to the 4 position.

Catalytic hydrogenation of **3** in MeOH with Pd–C gave a mixture of 3α-trifluoromethyl-5β-pregnan-20-one (**4a**) and 3α-trifluoromethyl-5β-pregnan-20-methyl ether (**4b**).[11] The 5β configuration of **4a** and **4b** is evident from the nmr spectra. In both compounds, the C-19 Me peak is shifted 0.15 ppm downfield compared to the 5α isomer. This large difference of the 19-Me of 5α- and 5β-steroids is well established.[7] The 5α isomer, 3α-trifluoromethyl-5α-pregnan-20-one (**8**), was prepared by hydrogenolysis of 3α-trifluoromethyl-4β-iodo-5α-pregnan-20β-ol acetate (**6**) with LAH followed by CrO_3 oxidation of the resulting 20β-hydroxy derivative **7**.

The absence of any 5α isomer from the catalytic hydrogenation reaction mixture indirectly confirms the

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 13–41.

(8) The same product was obtained by passage of the solution through neutral alumina (grade I).

(9) A double bond at the 4 position is known to shift the 19-angular methyl peak downfield by 0.25 ppm.[7]

(10) The ^{19}F nmr spectrum was obtained by Dr. William Budde at Midwest Research Institute, Kansas City, Mo.

(11) The reduction of ketones to Me ethers under similar conditions has been reported by S. Nishimura, T. Itaya, and M. Shiota, *Chem. Commun.*, 422 (1967).

α orientation of the 3-CF_3. Catalytic hydrogenation of Δ^4-steroids in a neutral solvent is known to give a mixture of 5α and 5β isomers with the 5β isomer predominating.[12] Introduction of a bulky group at the 3β-equatorial position increases steric hindrance on the β side. Thus, hydrogenation of 3β-methoxy-4-cholestene occurs mostly from the α side to give 60% of the 5α isomer.[13] Conversely, a 3α-axial substituent such as CF_3 should increase steric hindrance on the α side and give the 5β isomer.

From this evidence, the addition product of CF_3I and 5α-pregn-3-en-20-one is 3α-trifluoromethyl-4β-iodo-5α-pregnan-20-one (**2**).

A similar sequence of reactions was carried out in the androstane series as shown in Scheme II.

Biological Testing.[14]—Compounds **2**, **3**, and **8** were tested for progestational activity in a Clauberg-type test[15] at a level of 3.0 mg/rabbit and were inactive at this level. Compounds **11**, **12**, **13**, **14**, **15**, and **16** were tested for myotrophic androgenic activity[16] at levels of 3.0 mg/rat and were inactive at this level. It was concluded that a trifluoromethyl cannot assume the role of the 3-oxo group in progesterone and testosterone.

Experimental Section[17]

Photolytic Additions of Trifluoroiodomethane to Δ^3-Steroid Olefins.—A soln of 1 g of the steroid olefin in 150 ml of CCl_4 and 2 ml of pyridine was placed in a vessel equipped with a Dry Ice condenser, a water-cooled lamp well, and a gas inlet tube at the bottom. Enough Hg was added to cover the bottom of the vessel. The soln was chilled in an ice–salt bath and treated with an excess (20–30 g) of CF_3I. The system was irradiated with uv light for 8 hr while N_2 was bubbled slowly through the soln. The uv light was generated by a 200-W, high-pressure mercury lamp and contained in a water-cooled quartz immersion well equipped with a borosilicate filter. The irradiation was interrupted every 2 hr to clean the lamp well. At the end of the reaction, the Dry Ice condenser was removed to allow the excess reagent to evap. The yellow soln was washed with H_2O, dried (Na_2SO_4), and evapd to yield an oil which slowly crystd upon cooling. The product was recrystd several times from MeOH.

3α-Trifluoromethyl-4β-iodo-5α-pregnan-20-one (2).—5α-Pregn-3-en-20-one (1)[18] (1 g) was allowed to react with excess CF_3I under the conditions described above. The product was worked up in the usual manner. Recrystn from MeOH afforded 0.66 g (40%) of **2**, mp 145–150°. Further recrystns from MeOH gave the anal. sample: mp 156–158°; $[\alpha]^{22}D$ + 58° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.61 (m, 4α-H), 2.1 (s, 21-H_3), 1.14 (s, 19-H), and 0.6 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{32}F_3IO$) C, H, I.

3α-Trifluoromethylpregn-4-en-20-one (3).—Compd **2** (250 mg) was dissolved in Et_2O, adsorbed onto neutral Al_2O_3, and left standing for 2 days. After elution with Et_2O and recrystn from aq MeOH, there was obtained 45 mg of **3**, mp 140–143°. Further recrystn from the same solvent system gave the anal. sample: mp 143–145°; $[\alpha]^{22}D$ + 154° (*c* 0.5, $CHCl_3$); nmr ($CDCl_3$) δ 5.28 (m, 4-H), 2.1 (s, 21-H_3), 1.01 (s, 19-H_3), and 0.65 ppm (s, 18-H_3); ^{19}F nmr ($CHCl_3$) 603 Hz on the high-field side of external $PhCF_3$ (d, J = 10 Hz, 3-CF_3). *Anal.* ($C_{22}H_{31}F_3O$) C, H.

3α-Trifluoromethyl-5β-pregnan-20-one (4a).—To a soln of 100 mg of **3** in 50 ml of MeOH was added 300 mg of Pd-C. The mixture was hydrogenated at 0.2 kg/cm^2 for 2 hr. After an addl 100 mg of catalyst was added hydrogenation was contd for another 2 hr to complete the reaction. After filtration and evapn of the solvent, a mixture (2 spots on tlc) was obtained. It was sepd by preparative tlc using pet ether–Et_2O (9:1) solvent system. The lower band yielded 11.6 mg of **4a**: mp 104–105°; $[\alpha]^{22}D$ +88° (*c* 0.5, $CHCl_3$); nmr ($CDCl_3$) δ 2.1 (s, 21-H_3), 0.96 (s, 19-H_3), and 0.6 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O$) C, H.

The upper band was recrystd from aq MeOH and afforded 17.6 mg of 3α-trifluoromethyl-20ξ-methoxy-5β-pregnane (**4b**), mp 164–168°. Further recrystn from aq MeOH gave the anal. sample: mp 167–168°; $[\alpha]^{22}D$ +12° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 3.24 (s, 20-OCH_3), 1.05 (d, J = 6 Hz, 21-H_3), 0.96 (s, 19-H_3), and 0.67 ppm (s, 18-H_3). *Anal.* ($C_{23}H_{37}F_3O$) C, H.

3α-Trifluoromethyl-4β-iodo-5α-pregnan-20β-ol Acetate (6).—20β-Hydroxy-5α-pregn-3-ene acetate (5)[18] (780 mg) was allowed to react with excess CF_3I under the same conditions described in the general procedure. The mixture was worked up in the usual manner. The crude product was recrystd twice from MeOH to yield 300 mg (42%) of **6**: mp 171–172°; $[\alpha]^{22}D$ +11° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.82 (m, 20α-H), 4.65 (m, 4α-H), 2.01 (s, 20α-H), 4.65 (m, 4α-H), 2.01 (s, 20α-OAc), 1.15 (d, J = 6 Hz, 21-H_3), 1.15 (s, 19-H_3), and 0.63 ppm (s, 18-H_3). *Anal.* ($C_{24}H_{36}F_3IO$) C, H, I.

3α-Trifluoromethyl-5α-pregnan-20β-ol (7).—A soln of 250 mg of **6** in 50 ml of anhyd Et_2O was treated with 500 mg of LAH and stirred for 1 day at room temp. After destroying excess LAH with EtOAc, the mixture was treated with a satd soln of Na-K tartarate. The Et_2O layer was sepd and the aq layer was extracted twice with Et_2O. The combined ethereal extract was washed with H_2O, dried (Na_2SO_4), and evapd. The product was purified by preparative tlc and recrystd from aq Me_2CO to give 101 mg of **7**, mp 167–169°. Further recrystn afforded the anal. sample: mp 167–169°; $[\alpha]^{22}D$ +8° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 3.75 (m, 20α-H), 1.14 (d, J = 6 Hz, 21-H_3), 0.82 (s, 19-H_3), and 0.75 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{35}F_3O$) C, H.

3α-Trifluoromethyl-5α-pregnan-20-one (8).—A soln of 8 *N* CrO_3 reagent was added dropwise at room temp to a stirred soln of 70 mg of **7** in 20 ml of Me_2CO until the orange color of the reagent persisted. 2-PrOH was added to destroy the excess reagent. After concg the mixture under reduced pressure, H_2O was added. The ppt was filtered and washed with H_2O. Recrystn from aq MeOH afforded 65 mg of **8**, mp 143–144°. Further recrystn afforded the anal. sample: mp 144–145°; $[\alpha]^{22}D$ +33° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 2.12 (s, 21-H_3), 0.81 (s, 19-H_3), and 0.62 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O$) C, H.

3α-Trifluoromethyl-4β-iodo-5α-androst-17β-ol Acetate (11).—Compd **9**[19] (1.25 g) was allowed to react with excess CF_3I under the conditions described in the general procedure. The product was isolated in the usual manner and recrystd from MeOH to yield 0.6 g of **11**, mp 154–158°. The anal. sample had mp 160–162°; $[\alpha]^{22}D$ + 1° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 2, 4α-H and 17α-H), 1.16 (s, 17-OAc), 1.16 (s, 19-H_3), and 0.78 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{32}F_3IO_2$) C, H, I.

3α-Trifluoromethylandrost-4-en-17β-ol Acetate (13).—Compd 11 (400 mg) was dissolved in 20 ml of Et_2O and adsorbed onto 30 g of neutral Al_2O_3 (grade I). After it was left standing for 6 hr, the column was eluted with Et_2O. Evapn of the solvent gave 300 mg of cryst solid which was recrystd from aq MeOH to afford 148 mg of **13**, mp 87–90°. Further recrystn afforded the anal. sample: mp 93–95°; $[\alpha]^{22}D$ +88° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.28 (m, 4-H), 4.6 (m, 17α-H), 2.03 (s, 17-OAc), 1.03(s, 19-H_3), and 0.82 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{31}F_3O_2$) C, H.

3α-Trifluoromethyl-5β-androstan-17β-ol Acetate (15).—To a soln of 96 mg of **13** in 100 ml of MeOH was added 300 mg of Pd-C. The mixture was hydrogenated at 0.2 kg/cm^2 for 3 hr. After filtration and evapn of the solvent, a solid residue was obtd.

(12) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, pp 271–273.

(13) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(14) Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis.

(15) T. Miyake, *Methods Hormone Res.*, **2**, 135 (1962).

(16) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175 (1953).

(17) Melting points were taken with a Thomas-Hoover apparatus equipped with a corrected thermometer. Ir spectra were obtained with a Perkin-Elmer 337 instrument. Microanalyses were carried out by the Microanalytical Lab., Chemistry Department, University of California, Berkeley, Calif. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Nmr spectra were obtained from samples in $CDCl_3$ on Varian A-60 A and Jeolco JNM 4H-100 instruments, respectively (TMS). The ^{19}F nmr spectrum was obtained from a sample in $CHCl_3$ on a Varian HA-100 instrument using $PhCF_3$ as external standard by Dr. William Budde at Midwest Research Institute, Kansas City, Mo.

(18) P. Longevialle and R. Goutarel, *Bull. Soc. Chim. Fr.*, **11**, 3225 (1965).

(19) A. Bowers, A. Cross, J. Edwards, H. Carpio, M. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

The desired product was purified by preparative tlc and recrystd from MeOH to afford 45 mg of **15**, mp 117–118°. Further recrystn gave the anal. sample: mp 117–118°; $[\alpha]^{22}D$ +9° (c, 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 17α-H), 2.03 (s, 17-OAc), 0.97 (s, 19-H_3), and 0.78 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O_2$) C, H.

3α-Trifluoromethyl-5α-androstan-17β-ol Acetate (17).—A soln of 200 mg of **11** in 50 ml of anhyd Et_2O was treated with 1 g of LAH and stirred for 1 day at room temp. After destroying the excess hydride by careful addition of EtOAc, the mixture was treated with a satd soln of Na-K tartarate. The Et_2O layer was sepd and the aq layer was extracted with Et_2O. The combined Et_2O extract was washed with H_2O, dried (Na_2SO_4), and evapd to give a gummy residue. The crude product (1 spot on tlc), 3α-trifluoromethyl-5α-androstan-17β-ol, was dissolved in 10 ml of pyridine and 2 ml of Ac_2O and left standing for 18 hr at room temp. The mixture was dild with H_2O and was extracted with Et_2O. The ethereal extract was washed with 5% HCl and H_2O, dried (Na_2SO_4), and evapd. The product was isolated by preparative tlc and recrystd from aq MeOH to give 50 mg of **17**, mp 99–100°. Further recrystn afforded the anal. sample: mp 100–101°; $[\alpha]^{22}D$ +7° (*c*, 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 17α-H), 2.03 (s, 17-OAc), 0.82 (s, 19-H_3), and 0.78 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O_2$) C, H.

17α-Methyl-5α-androst-3-en-17β-ol (10).—To a soln of 1.1 g of 5α-androst-3-en-17-one[20] in 100 ml of Et_2O–THF (4:1) was added 25 ml of 3 *M* MeMgBr in Et_2O. The reaction mixture was refluxed overnight, poured into ice, and acidified with 10% HCl. The Et_2O layer was sepd and the aq layer was extracted with Et_2O. The combined extracts were washed with 5% Na_2CO_3 and H_2O, dried (Na_2SO_4), and evapd to give a gummy residue. The crude product was dissolved in C_6H_6 and adsorbed onto 50 g of neutral alumina. The column was eluted with C_6H_6–Et_2O (1:1 and 1:4). Recrystn from aq MeOH afforded 0.6 g of **10**, mp 140–141° (lit.[21] mp 139.5–140°) from a similar method).

3α-Trifluoromethyl-4β-iodo-17α-methyl-5α-androstan-17β-ol (12).—A quantity of 800 mg of **10** was allowed to react with excess CF_3I under the conditions described above. The product was isolated in the usual manner and recrystd from MeOH to afford 440 mg of **12**, mp 104–115°. Several recrystns from MeOH gave the anal. sample: mp 117–120°; $[\alpha]^{22}D$ −7° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 4α-H), 1.20 (s, 17-CH_3), 1.17 (s, 19-H_3), and 0.83 ppm, (s, 18-H_3). *Anal.* ($C_{21}H_{32}F_3IO$) C, H, I.

3α-Trifluoromethyl-17α-methylandrost-4-en-17β-ol (14).—A quantity of 366 mg of **12** was dissolved in 50 ml of 10% H_2O in MeOH containing 2 g of KOH. The mixture was refluxed for 2 hr. After cooling, H_2O was added to ppt the product. This was collected, washed with H_2O, and dried under vacuum. Recrystn from hexane afforded 124 mg of **14**, mp 149–151°. Further recrystn from hexane afforded the anal. sample: mp 149–150°; $[\alpha]^{22}D$ +77° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.28 (m, 4-H, 1.20 (s, 17-CH_3), 1.03 (s, 19-H_3), and 0.88 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{31}F_3O$) C, H.

3α-Trifluoromethyl-17α-methyl-5β-androstan-17β-ol (16).—To a soln of 100 mg of **14** in 75 ml of MeOH was added 300 mg of Pd–C. The mixture was hydrogenated at 0.2 kg/cm² for 4.5 hr. It was filtered and the filtrate was evapd to yield a solid residue. The residue was recrystd from hexane twice to afford 38.6 mg of **16**, mp 189–190°. Further recrystn from hexane afforded the anal. sample: mp 189–190°; $[\alpha]^{22}D$ −4° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.22 (s, 17-CH_3), 0.98 (s, 19-H_3), and 0.83 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{33}F_3O$) C, H.

3α-Trifluoromethyl-17α-methyl-5α-androstan-17β-ol (18).—A soln of 100 mg of **12** in 30 ml of anhyd Et_2O was treated with 400 mg of LAH and stirred overnight at room temp. After destroying the excess hydride with EtOAc, the mixture was treated with a satd soln of Na–K tartarate. The Et_2O layer was sepd, and the aq layer was extracted twice with Et_2O. The combined extracts were washed with H_2O, dried (Na_2SO_4), and evapd. The product was isolated by preparative tlc and recrystd from aq MeOH to give 31 mg of **18**, mp 131–134°. Further recrystn from MeOH gave the anal. sample: mp 134°; $[\alpha]^{22}D$ +2° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.21 (s, 17-CH_3). 0.85 (s, 19-H_3), and 0.82 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{33}F_3O$) C, H.

(20) 5α-Androst-3-en-17-one was obtd from 5α-androst-3-en-17β-ol acetate (**9**) by hydrolysis of the 17-AcO group with 2% MeOH–KOH followed by CO_3 oxidn of the corresponding 17-OH group.

(21) P. D. Klimstra, U. S. Patent 3,166,578 (1965); *Chem. Abstr.*, **62**, 9207*c* (1965).

Studies on the 4-Hydroxycoumarins. Synthesis of the Metabolites and Some Other Derivatives of Warfarin[1]

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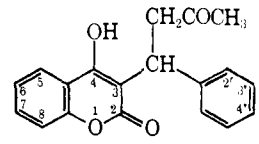
Studies on the metabolism of warfarin [3-(α-acetonylbenzyl)-4-hydroxycoumarin] (I) in the rat have been described elsewhere.[2] The high physiological activity



I

of the anticoagulant precludes the isolation of excreted metabolic products in quantities large enough for classical chemical identification. Therefore, metabolic fate studies on warfarin were conducted using [4-^{14}C]warfarin sodium. The excreted radioactive metabolites from rats treated with the labeled compound were compared with known compounds, using chromatographic and isotope dilution techniques. This paper describes the syntheses of 5 compounds shown to be metabolites of warfarin, namely, 6-, 7-, 8-, and 4′-hydroxywarfarin and 2,3-dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-*c*]-[1]benzopyran. The syntheses of several hydroxylated warfarin derivatives which were not metabolites are also described.

Chemistry.—Warfarin may be synthesized by the Michael addition of 4-hydroxycoumarin to benzalacetone under a wide range of acidic or basic conditions.[3] The 4-hydroxycoumarin used in this reaction can be easily prepared by the method of Dickenson,[4] using *o*-hydroxyacetophenone and diethyl carbonate. However, this method did not prove successful for the synthesis of any of the desired dihydroxycoumarins from appropriate dihydroxyacetophenones, possibly due to the extreme insolubility of the disodium salts in the reaction solvent, benzene. Blocking the nonortho OH group by formation of a benzyl ether provided an intermediate which would undergo the desired reaction with $(EtO)_2CO$.

Therefore 6-, 7-, and 8-hydroxywarfarin were synthesized as shown in Scheme I.

The synthesis of 5-hydroxywarfarin, which could not be achieved by Scheme I, proceeded by the route shown in Scheme II.

It was found later that this method of synthesis also gave 6-, 7-, and 8-hydroxywarfarin in considerably bet-

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(2) W. M. Barker, M. A. Hermodson, and K. P. Link, *J. Pharm. Exp. Ther.*, **171**, 307 (1970).

(3) C. Schroeder, Ph.D. Thesis, University of Wisconsin, Madison, Wis. (1955).

(4) H. G. Dickenson (to Ward, Blenkinsop and Co., Ltd.), cyclic lactones, U. S. Patent 2,449,162, Sept 14, 1948 [*Chem. Abstr.*, **43**, 694 (1949)].