TABLE I
PMR CHEMICAL SHIFTS

Compd	$COCH_3$	$POCH_3$	-CH=NOH	OH
2	3.48	3.55, 3.75	7.71	10.8
3	3.28	3.53, 3.75		11.2
4	3.45	3.68, 3.74		

Compound 2 reacted smoothly with refluxing acetic anhydride in a reaction typical of aldoximes to give the nitrile 3 in 89% yield. Further evidence for the oxime function in 3 was provided by the ^1H nmr, δ 10.8 (s, exchangeable) and 7.71 ppm (s), and by the infrared spectrum, ν 3550 (w) and 3220 cm^{-1} (s, broad).

The oxidation of 2 with cold, dilute, neutral potassium permanganate gave an acidic product, 4, whose elemental analyses were consistent with an empirical formula of $C_{11}H_{15}O_6P$. This was in good agreement with the mass spectrum, which showed a molecular ion at M^+ 274. That carbon was not lost in this reaction and that the product was an acid indicated that the third methoxyl was on the carbon α to the phenyl group. This is also in agreement with the observed singlet for the aldoximino proton of 2 at 7.71 ppm. These data are consistent only with 2-dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde oxime as the structure of 2.

The mechanistic implications of these results currently are being investigated.

Experimental Section[4]

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde Oxime (2).—A solution of 30 g (0.2 mol) of β-nitrostyrene (1) in 300 ml of *tert*-butyl alcohol was placed in a three-neck flask equipped with a condenser, pressure-equalizing dropping funnel, and thermometer and 62 g (0.5 mol) of trimethyl phosphite was run in. An initial cooling of 4° was observed followed by a slow increase in temperature to a maximum of 65–75° usually within 20 min. The reaction was accompanied by a slight darkening and a barely discernible gas evolution at higher temperatures. After 3 hr the solvent was removed by rotary evaporation, the residue was cooled and seeded, and the walls of the vessel were scratched. Slow crystallization from the red oil began immediately. After standing overnight the crystals were filtered, washed twice with 20 ml of toluene, and recrystallized from 1,2-dimethoxymethane to give 16.63 g of white, crystalline 2, mp 134–136°. A second crop from the reaction mixture treated in the same way gave an additional 1.92 g for a total yield of 34%: mass spectrum *m/e* (rel intensity) M^+ 273 (0.5), 243 (18), 164 (100), 132 (83), 105 (37), 77 (42); ^1H nmr ($CDCl_3$) δ 3.47 and 3.48 (pair of singlets, 3, $COCH_3$), 3.55 (d, 3, J_{HP} = 10.6 Hz, $POCH_3$), 3.75 (d, 3, J_{HP} = 10.6 Hz, $POCH_3$),[5] *ca.* 7.40 (m, 5, C_6H_5–), 7.71 ppm (s, 1, -CH=N), 10.8 (s, 1, OH); ^{31}P nmr ($CHCl_3$) δ −20.5 ppm [heptet, J_{HP} = 10.6 Hz, $P(O)(OCH_3)_2$]; ir ($CHCl_3$) 3550 (w) and 3220 (s, br, OH), 1280 (vs, P=O), 1065 cm^{-1} (vs, POC). *Anal.* Calcd for $C_{11}H_{16}NO_5P$: C, 48.35; H, 5.90; N, 5.13; P, 11.33. Found: C, 48.20; H, 5.91; N, 5.15; P, 11.83.

The red oil that remained was not distillable at pressures of 0.25 mm and temperatures of 180–200°.

The reaction also produced an undetermined amount of a colorless gas which was trapped with a Dry Ice–acetone cold finger distillation head placed at the top of the water-jacketed condenser: nmr (CCl_4) δ 3.98 ppm (s, CH_3ONO); ir (CCl_4) 1665 (s) and 1610 cm^{-1} (s, -ONO).

These spectra were identical with those of an authentic sample of methyl nitrite prepared by reaction of methyl iodide with sodium nitrite in dimethylformamide.

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetonitrile (3).—The white solid 2, 5.4 g (0.02 mol), and 20 ml of acetic anhydride were placed in a round-bottom flask with condenser and heated at reflux for 8 hr. The volatile materials were removed at aspirator pressure and the residue was distilled to give 4.54 g (89%) of a water-white liquid, bp 140–144° (0.7 mm). Redistillation gave an analytical sample: bp 133–135° (0.25 mm); ir (CCl_4) 2250 cm^{-1} (vw, C≡N);[6] nmr (CCl_4) δ 3.28 (s, 3, $COCH_3$), 3.53 (d, 3, J_{HP} = 10.5 Hz, $POCH_3$), 3.75 (d, 3, J_{HP} = 10.5 Hz, $POCH_3$),[5] 7.41 ppm (m, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 255 (0.5), 146 (100), 109 (8), 105 (49), 77 (12). *Anal.* Calcd for $C_{11}H_{14}NO_4P$: C, 51.72; H, 5.53. Found: C, 51.59; H, 5.53.

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetic Acid (4).—A solution of 2.73 g (0.01 mol) of 2 in 150 ml of water, which was prepared by warming the water until the solid 2 just dissolved, was added to a solution of 1.58 g of $KMnO_4$ in 150 ml of H_2O in such a way that the temperature did not go above 35°. After 0.5 hr the mixture was filtered and the water was removed under vacuum. The solid–oil mixture that resulted was taken up in $CHCl_3$ and extracted three times with 20 ml of 10% K_2CO_3 solution. The combined water layers were extracted once with 15 ml of $CHCl_3$ and neutralized with excess HCl. The turbid mixture was extracted three times with 20 ml of $CHCl_3$ and the combined organic layers were dried over $MgSO_4$ and evaporated to give 1.44 g of a yellow oil Trituration in benzene gave a white solid which was collected by filtration Recrystallization from toluene gave 0.86 g (31%) of 4 as a white solid: mp 148–150°; mass spectrum *m/e* (rel intensity) 274 (0.5), 230 (18), 215 (15), 165 (61), 121 (94), 105 (100), 77 (61); ir 1750 (s, C=O), 1240 (s, P=O), 1060 cm^{-1} (s, POC); nmr ($CDCl_3$) δ 3.45 (s, 3, $COCH_3$), 3.68 (d, 3, J = 10.5 Hz, $POCH_3$), 3.74 (d, 3, J = 10.5 Hz, $POCH_3$),[5] *ca.* 7.5 (m, 5, C_6H_5), 11.2 ppm (s, 1, CO_2H). *Anal.* Calcd for $C_{11}H_{15}O_6P$: C, 48.18; H, 5.51; P, 11.29. Found: C, 48.31; H, 5.22; P, 11.16.

Acknowledgments.—We acknowledge the support of donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of the State University of New York for their partial support of this research.

Registry No.—1, 102-96-5; 2, 42151-03-1; 3, 42151-04-2; 4, 42151-05-3.

(4) Infrared spectra were determined on a Perkin-Elmer Model 221G spectrophotometer, nmr spectra on a Hitachi Perkin-Elmer R-20B, and mass spectra on a Du Pont Model 21-491 gc–mass spectrometer.

(5) The nonequivalence of methoxyl groups is expected of phosphinyl groups attached to a carbon bearing three different substituents and further supports structures 2, 3, and 4: R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 75; J. H. Boyer and R. Selvarajan, *J. Org. Chem.*, **35**, 1229 (1970).

(6) The nitrile infrared band may disappear altogether when attached to a carbon bearing an oxygen: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, p 266.

Convenient, High Yield Conversion of Androst-5-ene-3β,17β-diol to Dehydroisoandrosterone

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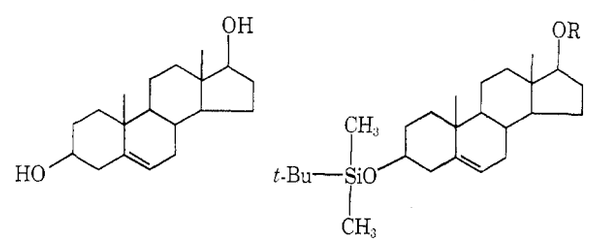
In connection with the investigation of the mechanism of steroid biotransformations we required dehydroisoandrosterone labeled with tritium in specific locations and orientation. To prepare these substrates with adequate specific activities, a convenient and high yield method of converting androst-5-ene-3β,17β-diol which is readily obtainable from androstenedione or testosterone to dehydroisoandrosterone was required. Since direct selective oxidation of the

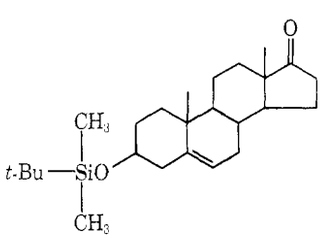
17-hydroxyl function was not promising,[1] selective protection of the 3β-hydroxyl group appeared to offer the best chance of success. Kupfer, *et al.*,[2] have previously used digitonin complexes for the selective protection of the 3β-hydroxyl in 3,17-diols followed by subsequent oxidation. The yields, however, were variable and the method was therefore deemed not suitable for a radiochemical synthesis where high yields were essential. In this communication we wish to report a convenient synthesis of dehydroisoandrosterone from androst-5-ene-3β,17β-diol which proceeds with high yield and is applicable to small-scale radioactive preparations.

Dimethyl-*tert*-butylsilyl chloride has been used as protective group for hydroxyl function by Corey and Venkateswarlu[3] in their prostaglandin syntheses. The principal advantages of this reagent are the lack of a chiral center and the ease of removal under mild conditions. Of particular interest to us was the large bulk of the reagent suggesting that it may lead to selective derivatization in the case of androstenediol (I).

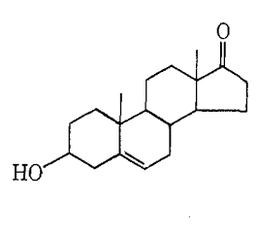


I

IIa, R = H
b, R = $Si(CH_3)_2 \cdot t\text{-}Bu$



III



IV

Reaction of 60 mg of androstenediol (I) with 110 mg of dimethyl-*tert*-butylsilyl chloride in 2 ml of dimethylformamide in the presence of imidazole yielded the desired androst-5-ene-3β,17β-diol 3-dimethyl-*tert*-butylsilyl ether (IIa) in 71% yield. Evidence for the highly selective silylation at C-3 was observed by conversion to dehydroisoandrosterone 3-dimethyl-*tert*-butylsilyl ether (III), identical with that obtained from dehydroisoandrosterone. Although the 3β,17β-disilyl ether (IIb) was formed in 28% yield, only trace material with the expected mobility of the 17β-monosilyl derivative was observed.

Oxidation of IIa with the CrO_3–pyridine complex gave dehydroisoandrosterone 3-dimethyl-*tert*-butylsilyl ether (III) in quantitative yield, while oxidation with the Jones reagent was less successful giving a yield of only 40%.

Cleavage of the 3β-dimethyl-*tert*-butylsilyl group of III was performed in a mixture of AcOH–H_2O–THF or by exposure to tetra-*n*-butylammonium fluoride. Dehydroisoandrosterone (IV) was generated quantitatively in the both instances.

The overall yield of IV from I was at least 64%. When the sequence was repeated starting with 0.6 mg of [4-^{14}C]androst-5-ene-3β,17β-diol the final overall yield of [4-^{14}C]dehydroisoandrosterone was 51%.

(1) M. Gut and M. Uskoković, *J. Org. Chem.*, **24**, 673 (1959).

(2) D. Kupfer, E. Forchielli, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 1257 (1960).

(3) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).

Experimental Section[4]

Androst-5-ene-3β,17β-diol 3-Dimethyl-*tert*-butylsilyl Ether (IIa).—To a solution of androst-5-ene-3β,17β-diol (60 mg) in DMF (2 ml) were added dimethyl-*tert*-butylsilyl chloride (110 mg) and imidazole (140 mg) at 0°. The solution was shaken for 5 min and allowed to stand at room temperature for 20 min. The reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4, and the solvent was evaporated at 40° under reduced pressure. Purification of the crystalline product by preparative tlc using cyclohexane–AcOEt (4:1) as developing solvent gave 59 mg (71%) of IIa: mp 171–172° (from MeOH); R_f 0.41; $[\alpha]^{23}D$ −43.5° ($CHCl_3$); ir (KBr) 3400, 1670, 1260, 1100, 840, 775 cm^{-1}; nmr ($CDCl_3$) δ 0.05 (6 H), 0.75 (3 H), 0.88 (9 H), 1.00 (3 H), 3.2–3.7 (2 H), 5.32 (1 H).

Anal. Calcd for $C_{25}H_{44}O_2Si \cdot {}^1/_2H_2O$: C, 72.58; H, 10.96. Found: C, 72.73; H, 10.75.

Elution of less polar fraction (R_f 0.75) gave 30 mg of androst-5-ene-3β,17β-diol of di(dimethyl-*tert*-butylsilyl) ether (IIb, 28%): mp 113–115° (from ether–MeOH); $[\alpha]^{22}D$ −31.9° ($CHCl_3$); ir (KBr) 1672, 1250, 1110, 840, 775 cm^{-1}; nmr ($CDCl_3$) δ 0.02 (6 H), 0.05 (6 H), 0.72 (3 H), 0.88 (18 H), 1.00 (3 H), 3.2–3.7 (2 H), 5.32 (1 H).

Anal. Calcd for $C_{31}H_{58}O_2Si_2$: C, 71.74; H, 11.27. Found: C 71.94; H, 10.91.

Trace material was observed with a R_f (0.34), which probably was the 17-monosilyl ether. There was insufficient amount for further identification.

3β-Hydroxyandrost-5-en-17-one 3-Dimethyl-*tert*-butylsilyl Ether (III). A. From Dehydroisoandrosterone.—To a solution of dehydroisoandrosterone (200 mg) in DMF (5 ml) were added dimethyl-*tert*-butylsilyl chloride (370 mg) and imidazole (470 mg), and the solution was allowed to stand at room temperature for 1 hr. The reaction mixture was worked up in the usual way to give III (265 mg, 96%): mp 146–147° (from MeOH); $[\alpha]^{23}D$ +7.7° ($CHCl_3$); ir (KBr) 1750, 1670, 1260, 1100, 840, 776 cm^{-1}; nmr ($CDCl_3$) δ 0.05 (6 H), 0.88 (12 H), 1.00 (3 H), 3.2–3.7 (1 H), 5.32 (1 H).

Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.56; H, 10.51. Found: C, 74.67; H, 10.23.

B. From Oxidation of IIa.—A solution of IIa (50 mg) in pyridine (1 ml) and 0.4 ml of CrO_3–pyridine complex (1:10 w/v) was allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with ether and washed with 10% AcOH and 5% $NaHCO_3$ and dried over anhydrous Na_2SO_4. Purification of the crystalline product by preparative tlc using cyclohexane–AcOEt (3:1) as developing solvent gave 46 mg (92%) of III, mp 146–147° (from MeOH). The ir spectrum was identical with that of authentic sample obtained by method A.

Desilylation of III. A. With Acetic Acid.—A solution of 61 mg of III in 5.5 ml of a AcOH–H_2O–THF mixture (3:1:1.5) was allowed to stand at 50° for 4 hr. The reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$ and H_2O and dired over anhydrous Na_2SO_4. Upon usual work-up, the crystalline product was purified by preparative tlc to give 44 mg (100%) of dehydroisoandrosterone (IV), mp 146–147° (from acetone–hexane).

B. With Tetra-*n*-butylammonium Fluoride.—To a sclution of 61 mg of III in 1 ml of THF was added tetra-*n*-butylammonium fluoride (160 mg) and the solution was allowed to stand at room temperature for 3.5 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, and dried over anhydrous Na_2SO_4. After work-up, the crystalline product was purified by preparative tlc to give 44 mg (100%) of dehydroisoandrosterone (IV), mp 141–142° (from acetone–hexane).

(4) Melting points are uncorrected. Ir spectra were measured on a Beckman IR-9 infrared spectrophotometer. Nmr spectra were obtained on a Varian EM-360 nmr spectrometer. Radioactive counting was done on a Nuclear-Chicago Unilux liquid scintillation counter.

Conversion of Androst-5-ene-3β,17β-diol to Dehydroisoandrosterone on a Microgram Scale.—To 612 μg of [4-^{14}C]androst-5-ene-3β,17β-diol (47,000 cpm) was added 0.10 ml of dimethyl-*tert*-butylsilyl chloride solution which was prepared from 60 mg of dimethyl-*tert*-butylsilyl chloride and 70 mg of imidazole in 1.5 ml of DMF under cooling. The mixture was stored at 0° with occasional shaking. After 1 hr the reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4.

The 3-monosilyl ether purified by preparative tlc was oxidized with 0.2 ml of CrO_3–pyridine complex in 0.2 ml of pyridine at room temperature for 16 hr. Following usual work-up the oxidation product was treated without purification with 0.5 ml of a AcOH–H_2O–THF (3:1:1.5) solution at 55° for 3.5 hr. Ethanol was added and the solvent was evaporated under reduced pressure. The residue was submitted to tlc. The thin layer plate was scanned for radioactivity and the dehydroisoandrosterone area eluted was diluted with 20.2 mg of cold material and recrystallized to a constant specific activity of 335 cpm/μ*M* from acetone–hexane. Total counts were 23,800 cpm. This material was acetylated with Ac_2O and pyridine and the dehydroisoandrosterone acetate obtained was recrystallized to a constant specific activity of 334 cpm/μ*M* from aqueous acetone.

Acknowledgment.—This work was supported by Grant CA 07304 from the National Cancer Institute of Health.

Registry No.—I, 521-17-5; IIa, 42151-21-3; IIb, 42151-22-4; III, 42151-23-5; IV, 53-43-0; acetic acid, 64-19-7; tetra-*n*-butylammonium fluoride, 429-41-4; dimethyl-*tert*-butylsilyl chloride, 18162-48-6.

Heterocyclic Derivatives of Cholestane

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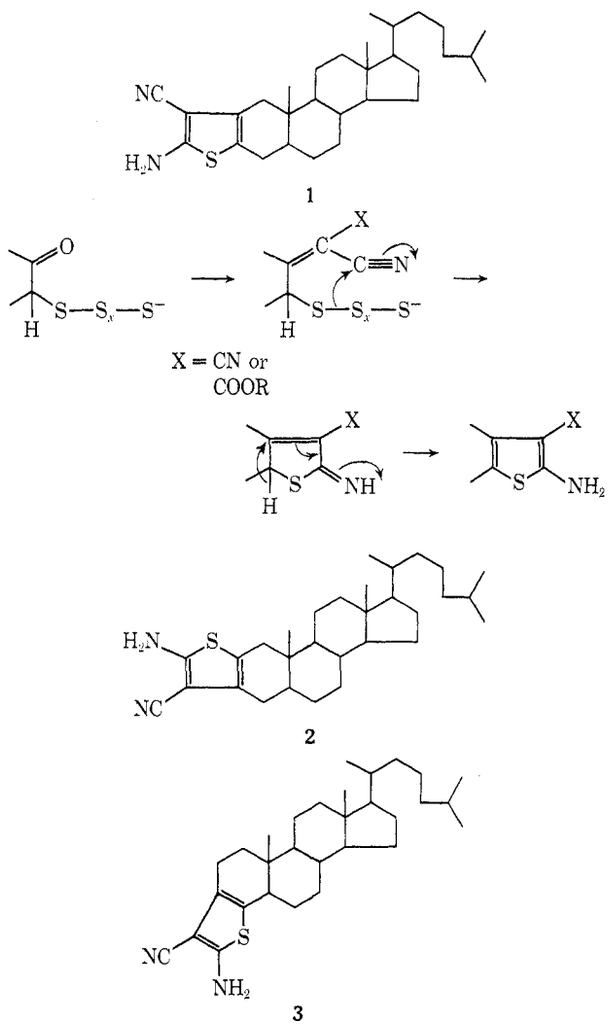
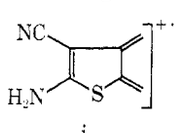
The reaction of cholestanone was reported[1] to give the 2′-aminocholest-2-eno[3,2-*b*]thiophene-4′-carbonitrile (**1**) under Gewalds'[2] conditions using sulfur and malononitrile. However, considering the proposed mechanism[2] (Scheme I) of the reaction, the assigned structure (**1**) seemed improbable. Since the initial step of the reaction requires enolization of the ketone followed by reaction with sulfur at the α position, the reaction product should have structure **2** as 3-keto steroids with 5α configuration are known[3] to enolize from the C_2 position to give the Δ^2 enol. However, the formation of the 4,3-*b* isomer (**3**) as a minor product of the reaction cannot be ruled out in view of the formation[4] of both the positional isomers of the steroidal indole derivatives from cholestanone by the Fischer indole synthesis. An unambiguous synthesis of **2** was achieved from cholestan-3-one-2α-thiol[5] following a known procedure.[6] The thiophene derivative (**2**) thus prepared was identical with the material prepared in our laboratory from cholestanone with sulfur and malononitrile.

Identical mass spectra of the samples of **2** from both

SCHEME I



the procedures indicate that the compound **2** obtained from cholestanone is free from the angular isomer **3**. The mass spectra of the compound **2** shows the peak for the molecular ion (*m/e* 466) besides a peak (*m/e* 150) for the retro-Diels–Alder fragment (i), which is the base



i

peak, with the metastable ion at *m/e* 48.5 (calcd, 48.3). Such a fragmentation is a characteristic mass spectral feature[7] of the steroidal heterocycles in which the heterocyclic ring is fused at the C_2 and C_3 positions of a Δ^2 steroid.

The melting point of the product **2**, prepared by both the procedures, is much higher than that reported[1,8] for the product obtained from cholestanone under Gewald's condition.

Since the preparation of pure alkanone-2-thiols, which are required for the regiospecific synthesis of the cycloalkenothiophene derivatives of type **2**, from the

(1) M. S. Manhas, V. V. Rao, P. A. Seetharaman, D. Succardi, and J. Pazdera, *J. Chem. Soc. C*, 1937 (1969).
(2) K. Gewald, E. Schinke, and H. Bottcher, *Ber.*, **99**, 94 (1966).
(3) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, p 161.
(4) D. J. Harvey and S. T. Reid, *Tetrahedron*, **28**, 2489 (1972).
(5) D. A. Lightner and C. Djerassi, *Steroids*, **2**, 583 (1963).
(6) K. Gewald, *Ber.* **98**, 3571 (1965).
(7) H. E. Audier, J. Bottin, M. Fetizon, and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 4027 (1971); P. Jacquignon, M. Croisy-Delcey, and A. Croisy, *ibid.*, 4251 (1972); D. J. Harvey, W. A. Laurie, and R. I. Reed, *Org. Mass Spectrom.*, **5**, 1183 (1971).
(8) Professor Manhas has kindly informed the author that the actual melting point of **2** is 285° and that the reported melting point, 235°, is a typographical error.