The ultraviolet spectra were taken on a Cary 118 spectrophotometer, using ether as a solvent. Mass spectra were recorded on Varian MAT 731 high-resolution mass spectrometer.

Ozonation of Cholestan-3β-ol Acetate (1). A solution of the title compound (5.0 g) in pentane (100 mL) was mixed with chromatographic grade silica gel (400 g). The solvent was evaporated in a rotatory evaporator, the dry powder was ozonated for 2 h at −78 °C, and the reaction mixture was extracted with ethyl acetate (500 mL). Chromatography on silica gel (500 g) using ether–methylene chloride (8:92) gave the starting material (1.3 g) and cholestane-3β,25-diol 3-acetate (**2**)[2b] (0.285 g): mp 126–127 °C; NMR δ 0.67 (s, 3 H, C-18), 0.87 (s, 3 H, C-19), 1.22 (s, 6 H, C-26,27), 2.03 (s, 3 H, OAc); MS *m/e* 446 (M^+). The remaining more polar products were not separated.

Ozonation of Cholestane-3β,5α-diol 3-Acetate (3). The title compound (1.0 g) dissolved in methylene chloride (100 mL) was adsorbed on silica gel (75 g) as described above and ozonated at −78 °C for 3 h. After being warmed to room temperature, the organic material was eluted with methanol (200 mL). The residue, after evaporation of the solvent, was chromatographed on a column of silica gel (100 g) with a mixture of ether–methylene chloride (93:7) to give the starting material (0.14 g) and cholestane-3β,5α,25-triol 3-acetate (**4**)[2b] (0.093 g): mp 180–182 °C; NMR δ 0.67 (s, 3 H, C-18), 0.9 (d, J = 5 Hz, 3 H, C-21), 1.00 (s, 3 H, C-19), 1.20 (s, 6 H, C-26,27), 2.02 (s, 3 H, OAc); MS *m/e* 462 (M^+). The remaining more polar products were not separated.

Ozonation of 5,6-Dibromocholestan-3β-ol Acetate (6). The title compound (2 g) dissolved in methylene chloride (100 mL) was adsorbed on silica gel (100 g) as described above and ozonated at −78 °C for 3 h, and the material was eluted with ethyl acetate (500 mL). The solvent was evaporated, and the residue was dissolved in ether (50 mL), treated with zinc powder (0.5 g) and acetic acid (2 mL), and stirred at room temperature for 3 h. The reaction mixture was treated with ether (200 mL) and water (100 mL) and decanted, and the zinc was washed with ether (50 mL). The ether extracts were washed with water and dilute hydrochloric acid and evaporated to dryness to give an oily residue (1.18 g). Chromatography on silica gel (100 g) using methylene chloride–ether (95:5) gave the starting material (0.38 g) and 25-hydroxycholesterol acetate[7] (**5**; 0.12 g): mp 138–139 °C; NMR δ 0.68 (s, 3 H, C-18), 1.02 (s, 3 H, C-19), 1.20 (s, 3 H, C-26,27), 2.03 (s, 3 H, OAc).

Preparation of 6β,7α-Dibromocholestan-3β-ol Acetate. (a) 7-Oxocholest-5-en-3β-ol Acetate (14).[8] Cholesterol acetate (5 g) dissolved in anhydrous *tert*-butyl alcohol (500 mL) was treated with mercuric dibromide (5 g) and anhydrous sodium acetate (2.5 g). The mixture was irradiated with an external light source (Rayonet) of 254 nm at room temperature in an open quartz vessel for 10 h. The solution was filtered, and the filtrate was diluted with hexane (500 mL), extracted five times with water (100 mL), and then evaporated to dryness. The residue was chromatographed on silica gel (500 g) with hexane–ether (9:1), resulting in 5α,6α-epoxy cholestan-3β-ol acetate (0.3 g). Elution with hexane–ether (4:1) gave the title compound (3 g), mp 156–158 °C, identical with an authentic sample.

(b) Cholest-6-en-3β-ol Acetate (15).[4] Diborane was passed through a solution of the enone (3 g) in diethylene glycol dimethyl ether (60 mL) for an hour at room temperature. The reaction mixture was stirred for 40 min and then treated with acetic anhydride (30 mL) and heated under reflux for 1 h. The solution was concentrated under vacuum, and the residue was extracted with ether and washed with water and a solution of 10% sodium hydroxide. Evaporation led to a residue which was chromatographed on neutral alumina (activity 1) with hexane to give the title compound (2.25 g), mp 100–105 °C, identical with an authentic sample:[4] NMR δ 0.68 (s, 3 H, C-18), 0.90 (s, 3 H, C-19), 2.03 (s, 3 H, OAc), 5.21, 5.61 (AB, J = 10 Hz, 2 H, C-6,7).

(c) 6β,7α-Dibromocholestan-3β-ol Acetate (8). To a cold and stirred solution (−5 °C) of cholest-6-en-3β-ol acetate (1 g) in dry hexane (25 mL) was added iodobenzene dibromide in hexane (prepared by addition of bromine (4.8 g) to a solution of iodobenzene (7 g) in dry hexane (10 mL) at room temperature) dropwise. The light yellow reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel (100 g) with hexane–ether (4:1) to give the title compound (1.2 g): mp 76–77 °C; NMR δ 0.72 (s, 3 H, C-18), 0.86 (d, J = 6 Hz, 6 H, C-26,27), 1.11 (s, 3 H, C-19A), 2.03 (s, 3 H, OAc), 4.55 (m, 2 H, C-6,7); MS *m/e* 588.1989 (M^+); calculated for $C_{29}H_{48}O_2{}^{79}Br_2$, 588.2000.

Ozonation of 6β,7α-Dibromocholestan-3β-ol Acetate (9). The title compound (1 g) was dissolved in hexane (100 mL), adsorbed on silica gel (100 g), and ozonated at −65 °C for 4 h. The excess of ozone was driven off by argon, and the material was eluted with a mixture of ethyl acetate–methanol (4:1). Chromatography on silica gel (100 g) using methylene chloride–ether (4:1) gave the starting material (0.5 g) and 0.16 g of 6β,7α-dibromocholestane-3β,25-diol 3-acetate (**9**): mp 84–85 °C; NMR δ 0.73 (s, 3 H, C-18), 1.12 (s, 3 H, C-19), 1.21 (s 6 H, C-26,27), 2.03 (s, 3 H, OAc), 4.55 (m, 2 H, C-6,7); MS *m/e* 584.1910 ($M^+ - H_2O$); calculated for $C_{29}H_{46}O_2{}^{79}Br_2$, 584.1864. The remaining more polar products were not separated.

25-Hydroxycholesta-5,7-dien-3β-ol Acetate (10). 25-Hydroxy derivative **9** (14 mg) was dissolved in trifluoroacetic anhydride (1 mL) and left at room temperature for 4 h. The solution was evaporated to dryness under vacuum as the residue was dissolved in hexamethylphosphoramide (10 mL) to which triethylmethylammonium dimethyl phosphate (0.5 mg) was added. The reaction mixture was heated at 135 °C for 2 h under nitrogen. Extraction with ether followed by washing with water and drying of the ether extract with $MgSO_4$ resulted in the title compound **10** (5 mg):[9] UV λ_{max} 262, 272, 282, 284 nm. This compound was converted without purification to 25-hydroxyvitamin D_3 by irradiation in ether solution followed by heating for 1 h at 75 °C in isooctane.[10]

Registry No.—**1**, 1255-88-5; **2**, 2550-91-6; **3**, 1256-33-3; **4**, 52092-66-7; **6**, 514-50-1; **8**, 69707-03-5; **9**, 69707-04-6; **10**, 24281-78-5; **14**, 809-51-8; **15**, 987-53-1; 25-hydroxycholesterol acetate, 10525-22-1; cholesterol acetate, 604-35-3; 5α,6α-epoxycholestan-3β-ol acetate, 4092-57-3; 25-hydroxyvitamin D_2, 19356-17-3.

References and Notes

(1) (a) Z. Cohen, E. Keinan, Y. Mazur, and T. H. Varkony, *J. Org. Chem.*, **40**, 2141 (1975); (b) Y. Mazur, Z. Cohen, E. Keinan, and T. H. Varkony, Israel Patent 47 344, 1975; (c) *Org. Synth.*, in press; (d) Z. Cohen, E. Keinan, Y. Mazur, and A. Ullman, *J. Org. Chem.*, **41**, 2651 (1976); (e) H. Klein and A. Steinmetz, *Tetrahedron Lett.*, 4249 (1975); (f) E. Proksch and A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, **15**, 761 (1976); (g) A. L. J. Beckwith, C. L. Bordkin, and T. Duong, *Aust. J. Chem.*, **30**, 2177 (1977); (h) E. Trifilieff, L. Bang, and G. Ourisson, *Tetrahedron Lett.*, 2991 (1977).

(2) (a) A. Rotman and Y. Mazur, *J. Am. Chem. Soc.*, **94**, 6628 (1972); (b) *J. Chem. Soc., Chem. Commun.*, 15 (1974); (c) Y. Mazur, *Pure Appl. Chem.*, **41**, 145 (1975).

(3) E. Keinan and Y. Mazur, *J. Org. Chem.*, **43**, 1020 (1978).

(4) L. Caglioti, G. Cainelli, G. Maina, and A. Salva, *Gaz. Chim. Ital.*, **92**, 309 (1962).

(5) G. Klopman and C. M. Joiner, *J. Am. Chem. Soc.*, **97**, 5287 (1975).

(6) A. Rotman, unpublished results.

(7) W. G. Dauben and M. L. Bradlow, *J. Am. Chem. Soc.*, **72**, 4248 (1950).

(8) N. Friedman, M. Gorodetsky, and Y. Mazur, *Chem. Commun.* 874 (1971); N. Friedman, Ph.D. Thesis, The Weizmann Institute of Science, Israel, 1971.

(9) S. C. Eyley and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 731 (1976).

10. J. A. Campbell, D. H. Squires, and J. J. Babcock, *Steroids*, **13**, 567 (1969).

One-Step Synthesis of Uranediol by Reaction of Dichlorobis(benzonitrile)palladium(II) with 5α-Pregnane-3β,20β-diol

Enrico Mincione,* Giancarlo Ortaggi,* and Antonino Sirna

Centro C.N.R. per la Chimica delle Sostanze Organiche Naturali and centro C.N.R. dei Meccanismi di Reazione, c/o Istituto di Chimica Organica, Università di Roma, 00185 Roma, Italy

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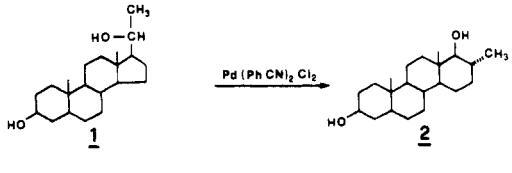
Uranediol (17α-methyl-*D*-homo-5α-androstane-3β,17aβ-diol) is a homosteroid hormone with androgenic and anabolic properties isolated from the urine of pregnant mares.[1] The structure of the compound has been determined[2] and the synthesis accomplished.[3]

During our investigations on the reactions of sterols and epoxysteroids with $Pd(PhCN)_2Cl_2$,[4] we have found that the complex promotes the direct conversion of 5α-pregnane-3β,20β-diol (**1**) into uranediol (**2**). The reaction occurs in ni-



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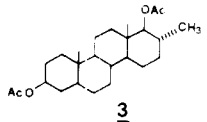
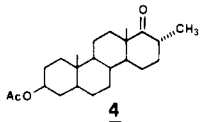
trobenzene at 85 °C (75% yield in 30 min). In toluene as solvent, no reaction occurred at 80 °C. At 100 °C, the formation of a mixture of products was ascertained, but the uranediol yield was only 20%.

The product [mp 209–211 °C (lit.[2] mp 211–213 °C); $[\alpha]_D$ 3.5° ($CHCl_3$) (lit.[5] $[\alpha]_D$ 3.7°)] has been unequivocally identified through its derivatives **3** and **4**. The former [mp 158–160



3



4

°C (lit.[6] mp 160 °C)] shows the same NMR spectrum reported in the literature[6] (see Experimental Section). Compound **4** [mp 169–171 °C (lit.[6] mp 171 °C); $[\alpha]_D$ −36° (lit.[6] $[\alpha]_D$ −38°)] was obtained through the oxidation of **2** with CrO_3, selective reduction with $NaBH_4$ at C-3, and acetylation of the corresponding alcohol.

The improvement of the above synthesis as compared to the previous procedure is relevant. The latter involved the formation of 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate and rearrangement in formic acid at 23 °C to yield uranediol 3-acetate 17a-formate and uranediol.[3,6]

A relevant feature of the reported synthesis is that $Pd(PhCN)_2Cl_2$ reacts more rapidly at the C-20 alcoholic group than at C-3, although the C-3 position has been shown to be chlorinated by the complex.[7] This selectivity, necessary for the successful course of the reaction, is qualitatively shown by the reaction time for the uranediol synthesis (30 min) as compared to the formation time of the 3-chlorocholestanes (180 min).

In contrast, when $Pd(PhCN)_2Cl_2$ was made to react in the same experimental conditions with 5α-pregnane-3β,20α-diol and with its 3-acetate derivative, 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-ol (or its 3-acetate derivative) was isolated in 90% yield, together with a small amount of 5α-pregn-17-en-3β-ol (5%). The difference in the course of the reactions of the two pregnane epimers and the relationship of the products structure to the C-20 configuration of the starting compound is completely similar to the results obtained by Hirschmann et al. in the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate and of its 20-epimer.[8] This analogy suggests that in the *D*-homoannulation promoted by the complex, the preliminary coordination of the C-20 hydroxyl group to Pd(II) occurs with the formation of a complex such as $Pd(PhCN)(ROH)Cl_2$. In the next steps, the complex anion $Pd(PhCN)(OH)Cl_2^-$ probably behaves as a good leaving group, just as the tosylate group in the Hirschmann synthesis does.[6,8]

Experimental Section

Uranediol (2). 5α-Pregnane-3β,20β-diol (**1**, 200 mg) was dissolved in nitrobenzene (5 mL) and $Pd(PhCN)_2Cl_2$ (240 mg) was added. The yellow-brown solution was warmed at 80 °C for 30 min with stirring. After the solution was cooled, diethyl ether was added and then water. The ethereal extracts were evaporated and the residue was chromatographed on a silica gel column by eluting with benzene–ether 7:3. A first band of unidentified products was obtained, then 140 mg of uranediol was recovered. The crystallization from $CHCl_3$–hexane afforded needles: mp 209–211 °C (lit.[2] mp 211–213 °C); $[\alpha]_D$ +3.5 (lit.[5] + $[\alpha]_D$ +3.7).

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.70; H, 11.32. Found: C, 78.75; H, 11.27.

Uranediol Diacetate (3). By acetylation with Ac_2O–piridine, **2** gave the diacetyl derivative **3**: mp 158–160 °C (from MeOH–CH_2Cl_2) (lit.[6] mp 160 °C); $[\alpha]_D$ 28.0° (lit.[6] $[\alpha]_D$ 30°). The NMR spectrum of **3** is as follows: 0.85 (s, 18-H), 0.79 (s, 19-H), 0.75 (d, 17-CH_3), 2.00 and 2.05 (s, 3-OAc, 17a-OAc), 4.33 (d, 17a-H).

Anal. Calcd for $C_{15}H_{40}O_4$: C, 74.20; H, 9.97. Found: C, 74.35; H, 10.02.

Uranol-17a-one Acetate (4). **2** (100 mg) dissolved in acetone (10 mL, distilled on $KMnO_4$) was treated for 2 min with stirring with 0.46 mL of an aqueous solution of H_2CrO_4 (8 N). After 5 min, the excess oxidant was destroyed with methanol. After addition of water and extraction with ether, the ethereal phase was washed with aqueous $NaHCO_3$ and then with water to neutrality. After evaporation of the solvent, the residue was chromatographed on a SiO_2 column by eluting with hexane–ether 4:1; 95 mg of the diketone was obtained. The diketone was selectively reduced with $NaBH_4$ (11 mg) in 14 mL of a mixture of CH_3OH–dioxane (1:1) (room temperature, 15 min). After hydrolysis and extraction with ether, the residue was chromatographed on a SiO_2 column by eluting with benzene–ether (4:1). The reaction product (30 mg) was acetylated by standard procedure to **4**. Crystals (from hexane–ether): mp 169–171 °C (lit.[6] mp 171 °C); $[\alpha]_D$ −36° (in $CHCl_3$) (lit.[6] $[\alpha]_D$ −32°).

17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-ol (5). 5α-Pregnane-3β,20α-diol 3-acetate (100 mg) was dissolved in nitrobenzene (1.5 mL) and $Pd(PhCN)_2Cl_2$ (104 mg) was added. The yellow-brown solution was warmed at 85 °C for 2 h with stirring. After the solution was cooled, diethyl ether was added and then water. The residue from the ethereal extracts was chromatographed on a silica gel column by eluting with ether–hexane (5:1). The first band was the 3-acetate of **5** (25 mg); the second contained *trans*-3β-acetoxy-5α-pregn-17-ene (**6**). After eluting the residue with ether–hexane (3:7), a third yellow band was eluted, which afforded after evaporation a yellow-brown product. It was probably a complex between Pd(II) and the alkene **5** (as 3-acetate), since by treatment with $LiAlH_4$ **5** was quantitatively obtained. **5** was identified by mp [130–133 °C (lit.[8] mp 128.5–131 °C)], the NMR[8] and IR[8] spectra, and the catalytic hydrogenation to 17β-methyl-18-nor-5α,13ξ,14ξ,17α-pregnan-3β-ol [mp 119–121 °C from hexane; lit.[8] mp 122–123.5 °C)]. Crystals of **6** (from methanol) melted at 122–125 °C (lit.[9] mp 120–121.5 °C).

When 5α-pregnane-3β,20α-diol was submitted to the same reaction, the course was just the same. 5α-Pregn-17-en-3β-ol was identified by its mp, 135–136 °C (from methanol) (lit.[9] 136–137 °C).

Acknowledgment. This work is dedicated to Professor L. Panizzi on the occasion of his 70th birthday.

Registry No. —**1**, 516-53-0; **2**, 516-51-8; **3**, 4975-29-5; **4**, 2521-29-1; **5**, 33299-99-9; **5** acetate, 33300-00-4; **6**, 16374-33-7; 5d-pregnane-3β,20d-diol 3-acetate, 33299-98-8; $Pd(PhCN)_2Cl_2$, 14220-64-5.

References and Notes

(1) R. E. Marker, E. Rohrmann, and E. L. Wittle, *J. Am. Chem. Soc.*, **60**, 1561 (1938).
(2) W. Klyne, *Biochem. J.*, **43**, 611 (1948).
(3) H. Hirschmann and J. S. Williams, *J. Biol. Chem.*, **238**, 2305 (1963).
(4) For a survey on the reactions on dichlorobis(benzonitrile)palladium(II), see M. P. Maitlis, "The Organic Chemistry of Palladium", Vol. I and II, Academic Press, New York, 1971.
(5) R. V. Brooks, W. Klyne, E. Miller, and J. Y. F. Paterson, *Biochem. J.*, **51**, 694 (1952).
(6) H. Hirschmann, F. B. Hirschmann, and A. Zola, *J. Org. Chem.*, **31**, 375 (1966).
(7) E. Mincione, G. Ortaggi, and A. Sirna, *Tetrahedron Lett.*, 4575 (1978).
(8) F. B. Hirschamnn, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron*, **27**, 2041 (1971).
(9) H. Reich, M. Sutter, and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

Nitration of 1-R-Pyrroles: Formation of Polynitro-1-R-pyrroles and Orienting Effects in the Reactions of 3-Nitro-1-R-pyrroles

Giancarlo Doddi, Paolo Mencarelli, Arturo Razzini, and Franco Stegel*

Centro di Studio sui Meccanismi di Reazione del Consiglio Nazionale delle Ricerche, c/o Istituto di Chimica Organica, Università di Roma, 00185 Rome, Italy

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Electrophilic substitutions of the pyrroles[1] and five-membered heterocycles as a group[2] have been recently reviewed. We now report briefly two further aspects of the nitration of pyrrole derivatives.

A. Formation of Polynitropyrrole Derivatives. The formation of polyhalogenopyrroles upon electrophilic halogenation is well known[1] and is favored by the fact that the

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