An Efficient Synthesis of 19-Nor-9β,10α Steroids

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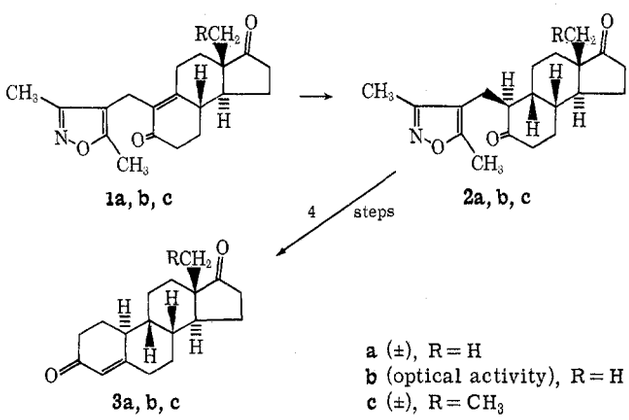
For a number of years, we have been interested in the biological properties of steroids having the abnormal 9β,10α configuration. As a logical extension of this work, we wished to prepare representative 19-nor-9β,-10α steroids. Previous syntheses of these compounds have involved hydrogenation of a de-A-Δ^9-5 ketone over an acidic palladium catalyst followed by closure of ring A,[1b] isomerization of 9α-11-oxoestranes with base followed by Birch reduction,[2] isomerization of a 5α,9α,-10α-11-oxo-19-norandrostane,[3,4] β-face hydrogenation of a $\Delta^{9(11)}$-estrane followed by Birch reduction,[3] hydrogenation of a 5β,10β-$\Delta^{9(11)}$-19-norandrostane followed by aromatization of ring A and Birch reduction,[5]



lithium–ammonia reduction of a Δ^8-estrane,[6] α-face epoxidation of a $\Delta^{9(11)}$-estrane followed by $LiAlH_4$ reduction and Birch reduction,[7] and hydrogenation of a 3-keto-$\Delta^{4,9}$-dienone followed by acid-catalyzed epimerization of C-10.[8] For a variety of reasons (low yield, lack of reduction specificity and/or unavailability of starting materials), these syntheses were not amenable to our purposes. We have, however, devised a stereoselective, high-yield preparation of (±)- and (+)-19-nor-9β,10α-androst-4-ene-3,17-dione (**3a,b**) and (±)-13β-ethyl-9β,10α-gon-4-ene-3,17-dione (**3c**), which were subsequently employed as starting materials for the desired derivatives.[9]

The isoxazole-substituted de-A 9-en-5-ones (**1**) were obtained[10,11] as intermediates in our syntheses of 19-nor steroids. In these syntheses the stereochemistry at C-9 was correctly established by hydrogenation of the enones **1** over palladium on carbon in an ethanol–triethylamine mixture. In order to obtain 19-nor-9β,-10α steroids, it was necessary to effect hydrogenation from the opposite, *i.e.*, β, face. In line with the observations of others,[1b,12] we hoped that a change in pH of the medium would reverse the direction of hydrogenation. In fact, hydrogenation of the enones **1** over palladium on barium sulfate in ethanolic HBr, conditions which were established after considerable experimentation with catalyst, solvent, and acid, gave mixtures containing high ratios (>7:1 by gc) of 9β:9α products. Despite relatively long hydrogenation times, no hydrogenolysis of the isoxazole ring occurred.[13] The 9β-diones **2a,b,c** were isolated by column filtration (to remove minor colored impurities) and crystallization in 75, 71, and 73% yield, respectively.[14] ORD measurements were in agreement with 9β configurations for these compounds;[15] this was confirmed by the obtention of known steroids from these materials.

Conversion of the diones **2** to the desired 19-nor-9β,-10α steroids **3** was carried out by an improved procedure developed earlier by us.[16] Thus, ketalization, hydrogenation in ethanolic NaOH solution, refluxing with aqueous base, and acidic deketalization and ring closure gave products **3a,b,c** in 61, 65, and 58% yield, respectively. These yields are somewhat lower than we have obtained in other similar conversions[10,16] due to the formation of small quantities of isomeric 19-nor-9β-androst-5(10)-ene-3,17-diones in the last step.[8] The completion of the synthesis of steroids **3** demonstrates the usefulness of the enones **1** as intermediates in high-yield syntheses of both 19-nor and 19-nor-9β,10α steroids.

Experimental Section[17]

(+)-19-(3,5-Dimethyl-4-isoxazolyl)-de-*A*-9β-androstane-5,17-dione (2b).—To a solution of 16.37 g (50 mmol) of enone **1b**[11] in 1 l. of absolute ethanol was added 5.0 g of 10% Pd/$BaSO_4$ catalyst (Fluka puriss) and the resulting mixture was stirred at 25° for 15 min. To the flask was added 25 ml (217 mmol) of 47% HBr and the mixture was then hydrogenated at atmospheric pressure and room temperature. After 16.0 hr, the uptake of

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(13) The remarkable effect of pH on the hydrogenolytic lability of isoxazole rings has previously been noted: G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).

(14) A yield of 52% was reported[1b] for a similar hydrogenation.

(15) The products **2** were homogeneous at C-10 (nmr). It is assumed that the side chain, initially α, was isomerized to the stable equatorial (β) position under the reaction conditions.

(16) J. W. Scott, B. L. Banner, and G. Saucy, *J. Org. Chem.*, **37**, 1664 (1972).

(17) Melting points were determined on a Büchi melting point apparatus and are uncorrected. A Varian A-60 spectrometer was used to obtain the nmr spectra; tetramethylsilane was employed as internal standard. Infrared and ultraviolet spectra were recorded on Beckman IR-9 and Cary Model 14M spectrometers, respectively.

H_2 (1170 ml) had ceased. The catalyst was removed by filtration (Filter-Cel) and washed with fresh ethanol. The combined filtrates were cautiously neutralized with saturated $NaHCO_3$ and concentrated at reduced pressure to *ca.* 200 ml. This residue was diluted with benzene, washed with H_2O, and dried (Na_2SO_4). Solvent removal gave a light yellow solid which was filtered through silica gel with 7:3 benzene–ether to give 15.4 g of light tan solid. Crystallization from CH_2Cl_2–ether gave 11.72 g (71.3%) of dione **2b** as fine white needles, sintered at 171°, mp 173–175°. The analytical sample was prepared by a second crystallization from CH_2Cl_2–ether of similarly prepared material: mp 170.5–174°; uv max (C_2H_5OH) 222 nm (ϵ 4750); ir ($CHCl_3$) 1740 (C-17 C=O), 1714 (C-5 C=O), and 1638 cm^{-1} (isoxazole); $[\alpha]^{25}D$ +122.0° (*c* 0.895, $CHCl_3$); mass spectrum (70 eV) *m/e* 329 (M^+) and 110 (base peak); nmr ($CDCl_3$) δ 0.99 (s, 3, C-18 CH_3), 2.20 (s, 3), and 2.37 ppm (s, 3, 2 isoxazole CH_3); ORD (dioxane) $[\alpha]_{230}$ +560°, $[\alpha]_{232}$ ±0°, $[\alpha]_{244}$ −938° (sh), $[\alpha]_{276}$ −2276° (min), $[\alpha]_{295}$ ±0°, and $[\alpha]_{317}$ +2926° (max).

Anal. Calcd for $C_{20}H_{27}O_3N$: C, 72.96; H, 8.26; N, 4.25. Found: C, 72.80; H, 8.40; N, 4.14.

Following similar procedures, we prepared these respective compounds.

(±)-19-(3,5-Dimethyl-4-isoxazolyl)-de-*A*-9β-androstane-5,17-dione (2a).—Very fine white needles were obtained by crystallization from CH_2Cl_2–ether: mp 176–178.5°; nmr, ir, uv, and mass spectrum identical with those of (+) enantiomer **2b**.

Anal. Calcd for $C_{20}H_{27}O_3N$: C, 72.96; H, 8.26; N, 4.25. Found: C, 72.57; H, 8.26; N, 4.13.

(±)-19-(3,5-Dimethyl-4-isoxazolyl)-18-methyl-de-*A*-9β-androstane-5,17-dione (2c).—Fine white needles were obtained by crystallization from CH_2Cl_2–ether: sintered at 159–163°, mp 174–176°; uv max (C_2H_5OH) 221 nm (ϵ 4850); ir ($CHCl_3$) 1730 (C-17 C=O), 1707 (C-5 C=O), and 1634 cm^{-1} (isoxazole); mass spectrum (70 eV) *m/e* 343 (M^+) and 110 (base peak); nmr ($CDCl_3$) δ 0.83 (t, 3, J = 7 Hz, C-18 CH_3), 2.21 (s, 3), and 2.38 ppm (s, 3, 2 isoxazole CH_3).

Anal. Calcd for $C_{21}H_{29}O_3N$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.36; H, 8.52; N, 4.05.

19-Nor-9β,10α-androst-4-ene-3,17-diones (3).—The procedure previously described[10,16] for the conversion of an isoxazole group to the steroid ring A was employed. We obtained the following compounds.

(±)-9β,10α-Estr-4-ene-3,17-dione (3a).—Small white prisms from CH_2Cl_2–ether: mp 149.5–152° and 159–162° (lit.[6] mp 150–151° and 156–157°)[18]; uv max (C_2H_5OH) 241 nm (ϵ 16,800); ir ($CHCl_3$) 1740 (C-17 C=O), 1669 (C-3 C=O), and 1619 cm^{-1} (conjugated C=C); mass spectrum (70 eV) *m/e* 272 (M^+); nmr ($CDCl_3$) δ 0.97 (s, 3, C-18 CH_3) and 5.84 ppm (broad s, 1, C-4 *H*).

(−)-9β,10α-Estr-4-ene-3,17-dione (3b).—Fine white needles from acetone–isopropyl ether: mp 132–135.5° (lit.[19] mp 135°); ir, uv, mass spectrum, and nmr are identical with those of racemic material; $[\alpha]^{25}D$ −23.9° (*c* 1.055, $CHCl_3$).

(±)-13β-Ethyl-9β,10α-gon-4-ene-3,17-dione (3c).—Small colorless prisms from acetone: mp 203.5–207°; uv max (C_2H_5OH) 240 nm (ϵ 17,900); ir ($CHCl_3$) 1730 (C-17 C=O), 1662 (C-3 C=O), and 1615 cm^{-1} (conjugated C=C); mass spectrum (70 eV) *m/e* 286 (M^+) and 110 (base peak); nmr ($CDCl_3$) δ 0.81 (t, 3, J = 7 Hz, C-18 CH_3) and 5.89 ppm (broad s, 1, C-4 *H*).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.64; H, 9.12.

Registry No.—2a, 35085-36-0; 2b, 35085-37-1; 2c, 35085-38-2; 3a, 35085-39-3; 3b, 2645-92-3; 3c, 35085-41-7.

Acknowledgments.—We would like to thank the members of our Physical Chemistry Section for their assistance during the course of this work.

(18) In many preparations this compound exhibited only a single mp of 149.5–152°.

(19) Roussel-Uclaf S.A., French Patent 1,453,221 (1966).

Tautomerism of Acid Derivatives[1a]

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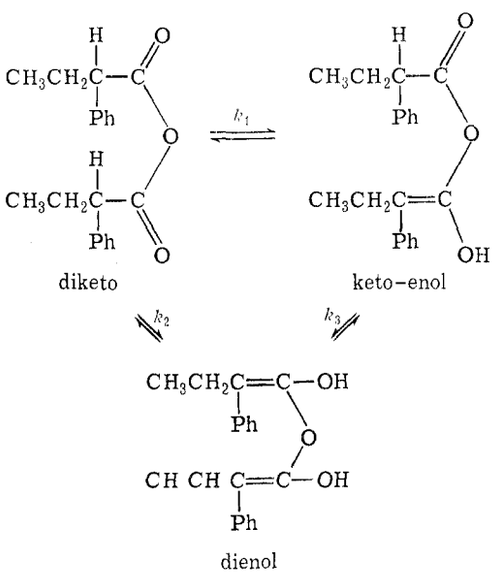
Optically active 2-phenylbutyric acid anhydride has been observed to undergo racemization on vacuum distillation[2,3] and to be thermochromic.[4,5,12] Distillation of the pure 2-phenylbutyric acid anhydride yields a distillate which is bright yellow. After a period of several hours, the yellow color of the distillate disappears. Repeated distillations of a sample of the anhydride give the same result. Nuclear magnetic resonance and infrared spectral studies of the freshly distilled anhydride indicate that diketo, keto-enol, and dienol forms are present.



An equilibrium between diketo and dienol tautomers can be established and maintained in carbon tetrachloride at room temperature. The dienol tautomer is believed to be responsible for the yellow color.

Thermochromism and tautomerism have also been observed during distillations of other acid derivatives

(1) (a) Supported in part by the Committee on Institutional Studies and Research, Murray State University, Murray, Ky. Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Nashville, Tenn., Nov 1971. (b) Abstracted from the M.S. thesis of J. E. Hendon, Murray State University, 1971.

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(5) A variety of organic compounds change color when heated and revert to the original color on cooling. This reversible dependence of color on temperature is known as thermochromism.[6] Thermochromism due to keto–enol equilibria has been observed for chromones, their derivatives, and chromone dimers.[7-9] Thermochromism of bindone has been explained on the basis of keto–enol tautomerism,[10] and the enolization of 1,3-diketo-2-phenyl-5-bromoindan has been used to explain its thermochromism.[11]

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