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Conversion of Dehydroabietonitrile into a *C*-Aryl-18-norsteroid. Formation of the D Ring

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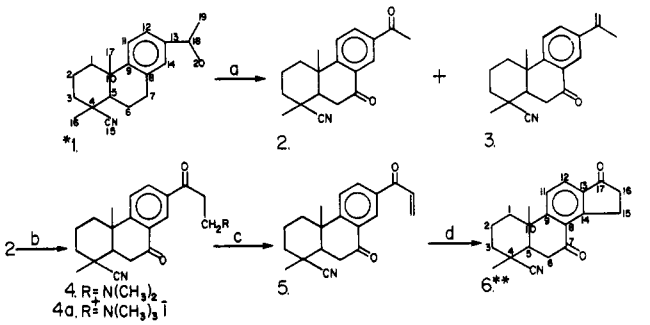
The conversion of dehydroabietonitrile (1) to a 17-keto steroid is reported.[1] The pathway described represents a new route for the conversion of the 13-isopropyl group of a dehydrophenanthrene to the D ring of the steroid skeleton.

The synthesis of the steroid skeleton from resin acids or their derivatives has been the goal of numerous research groups for the last several decades. In recent years *C*-aryl-18-norsteroids have been reported totally synthesized[2] or prepared from podocarpic[3-5] or dehydroabietic[6] resin acids and by conversion of naturally occurring steroids to the *C*-benzenoid system.[7,8] These methods usually suffered either from use of multiplestep sequences that resulted in poor yields or from ambiguous cyclization reactions that required laborious chromatographic separation procedures. This paper describes a synthesis of a 17-keto-*C*-aryl-18-norsteroid from an inexpensive starting material, utilizing simple separation procedures that result in a single product in 12% overall yield. Dehydroabietonitrile (1) with its aromatic ring C and C_{13} isopropyl side chain provided a starting material that is easily obtainable or prepared from resin acids present in pine oleoresin.[9]

Results and Discussion

To reach our goal of an efficient steroid synthesis from 1, several previously reported methods were utilized. These included our modification of an oxidation procedure reported by Sanderson[10] and modified by Tahara[5] followed by a vinyl phenyl ketone cyclization procedure as described by Bruce and Co-workers.[11] Thus oxidation of 1 by CrO_3 in acetic acid acetic anhydride[10] followed by pyrolysis[5] at 210 °C[5] yielded the diketone 2 (43% yield) and the 7-oxo-13-isopropenyl derivative 3 (26% yield) as a mixture. Isolation of 2 was simplified by its insolubility in ether, thus eliminating time-consuming and yield-reducing chromatographic separation procedures. Mannich reaction of 2 with formaldehyde and dimethylamine hydrochloride yielded the corresponding Mannich base (4) in 80% yield. Structure confirmation of this compound was obtained from its ^1H NMR spectrum. The structure of 4 is supported by its NMR, which has a 6 H singlet at δ 2.25 (Me_2N) and does not show the acetyl methyl peak that appears in the spectrum of 2. Conversion of the base (4) to the quaternary salt (4a) was accomplished in 68% yield. In addition to this, there was some elimination of the amine, resulting in the formation of the vinyl phenyl ketone 5 in 11% yield. Heating the methiodide salt 4 in ether yielded additional vinyl phenyl ketone 5 and unreacted 4a. However, heating 4a in acetone–water or methanol–water



(a) CrO_3, HOAC, AC_2O. (b) CH_2O, HCl·$N(CH_3)_2$, HCl. (c) CH_3I. (d) $AlCl_3$, NaCl.

*Numbered as a resin acid.
**Numbered as a steroid

(1) Partial support from a Faculty Research Grant from the University of Alabama in Birmingham, Birmingham, AL.
(2) Chattergee, A.; Hazra, B. G. *J. Chem. Soc. D* **1970**, 618.
(3) Davis, B. R.; Watkins, W. B. *Tetrahedron Lett.* **1982**, *23*, 2165.
(4) Davis, B. R.; Watkins, W. B. *Aust. J. Chem.* **1968**, *21*, 1611.
(5) Wheeler, D. M. S.; Whitt, P. R. *J. Org. Chem.* **1972**, *37*, 4211.
(6) Tahara, A.; Shimagaki, M.; Marigaya, Y.; Onada, M. *Chem. Lett.* **1974**, *651*.
(7) Hammer, C. F.; Savage, D. S.; Thompson, J. B.; Stevenson, R. *Tetrahedron Lett.* **1964**, 929.
(8) Levy, D.; Stevenson, R. *Tetrahedron Lett.* **1966**, 3063.
(9) Bardyshev, I. I.; Paderin, V. Y. *Chem. Abstr.* **1972**, *76*, 4027*f*.
(10) Sanderson, T. F. U.S. Patent 2750367.
(11) Bruce, D. B.; Sorrie, A. J. S.; Thompson, R. H. *J. Chem. Soc.* **1953**, 2403.

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yielded a mixture of vinyl phenyl ketone **5** and the diketone **2**. The ^1H NMR spectrum of **5** confirmed the proposed structure as evidenced by the absence of the 6 H singlet at δ 2.25 and the formation of an ABX pattern typical of a terminal vinyl group. Cyclization to form ring D was carried out by using **5** in a melt of sodium and aluminum chloride.[11] The *C*-aryl-18-norsteroid **6** was obtained in 70% yield as the sole product of this cyclization reaction. That cyclization occurred as indicated can be seen on examination of the ^1H NMR data of both **5** and **6**. Thus the proton at C_{11} of **5** is seen as a doublet due to coupling with the ortho proton at C_{12} ($J_{11,12}$ = 9 Hz). The C_{11} proton shows no discernable coupling with the C_{14} proton. For the C_{12} proton there is a coupling interaction with the ortho proton at C_{11} ($J_{11,12}$ = 9 Hz) and also with the meta proton at C_{14} ($J_{12,14}$ = 2.5 Hz). The proton at C_{14} shows a 2.5-Hz coupling with the C_{12} proton but no coupling with the proton at C_{11}. Hence, for this spectrum of **5**, one observes a doublet for the C_{11} proton, a doublet of doublets for the C_{12} proton, and a doublet for the C_{14} proton. For the cyclized product **6**, there are only two sets of aromatic protons (AB type); each has a coupling constant of 9.0 hZ and results in a doublet. The disappearance of the C_{14} proton on cyclization coincides with the collapse of the proton doublet of doublets at C_{12} into a doublet. This indicates that the C_{12} proton is now a doublet coupling only with the C_{11} proton. Had cyclization occurred at C_{12} rather than at C_{14}, one would have seen singlet ^1H NMR peaks for the C_{11} and C_{14} protons since they are para to each other. Hence, cyclization has occurred exclusively at C_{14}.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. The ^1H NMR spectra were determined on a Varian EM-390 spectrometer. Chemical shifts are expressed in parts per million downfield from added tetramethylsilane. Significant ^1H NMR data are reported in the following order: chemical shift in Hz, multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet), number of protons, and the carbon containing these protons. Mass spectra were obtained with a Hewlett-Packard 5985A spectrometer. Major mass spectrum ions are reported as m/z (intensity expressed as percent of total ion current). Elemental analyses were performed by Gailbraith Labs., Knoxville, TN. Dehydroabietonitrile was obtained from Hercules Powder Corp. and was used after being recrystallized twice from ethanol. Unless otherwise noted, reagents were used as received from commercial suppliers.

Oxidation of Dehydroabietonitrile. Formation of 2. Dehydroabietonitrile **1** (74.4 g, 0.265 mol) was dissolved in 700 mL of acetic acid and 400 mL of acetic anhydride. To the resulting solution was added chromium trioxide (122.6 g, 1.33 mol) over a period of 8 h at room temperature. After the addition was completed the reaction mixture was poured onto a solution of 300 mL of ice water and 133 g of sodium acetate and stirred for 2 h. The solid left after decantation of the liquid layer was triturated with Et_2O and washed with H_2O. The material insoluble in both Et_2O and H_2O was collected by filtration. This solid material was recrystallized from EtOH and identified as the diketone **2**: mp 170–171 °C; yield 28.3 g; IR (Kbr disk) 2220 cm^{-1} (CN), 1700 (C=O); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, C_{10} CH_3), 1.45 (s, 3 H, C_4 CH_3), 2.6 (s, 3 H, C_{13} acetyl CH_3), 7.39 (d, 1 H, C_{11} ($J_{11,12}$ = 9.0 Hz)), 8.03 (dd, 1 H, C_{12}($J_{11,12}$ = 9.0 Hz)), 8.42 (d, 1 H, C_{14} ($J_{12,14}$ = 2.5 Hz)); mass spectrum, m/z 295 (55), 280 (100), 278 (4). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75. Found: C, 77.48; H, 7.33; N, 4.69.

Formation of 3. The ether layer, obtained from the above procedure, was dried ($MgSO_4$) and rotary evaporated, and the residue (57.4 g) was heated under reduced pressure (0.2 mm) at 200–210 °C for 45 min. After being cooled, the mixture was again stirred with ether to obtain an additional 5.5 g of the sparingly soluble diketone **2** for a total yield of 43%. The ether was then evaporated, and the residue was repeatedly taken up in ether. On final evaporation of the solvent at reduced pressure there was obtained 20.2 g (26%) of the 7-oxo-13-isopropenyl derivative (**3**): mp 130–131 °C; IR (KBr disk) 2220 cm^{-1} (Cn), 1680 (C=O), 1620 (C=C); ^1H NMR $CDCl_3$) δ 1.2 (s, 3 H, C_{10} CH_3), 1.4 s, 3 H, C_4 CH_3), 2.1 (s, 3 H isopropenyl CH_3), 5.05 (s, 1 H, vinyl proton), 5.35 (s, 1 H, vinyl proton), 7.22 (d C_{11} ($J_{11,12}$ = 9.0 Hz)), 7.57 (dd, 1 H, C_{12} ($J_{11,12}$ = 9.0, $J_{12,14}$ = 2.5 Hz)), 8.0 (d, 1 H, C_{14} ($J_{12,14}$ = 2.5 Hz). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.91; H, 7.85; N, 4.78. Found: C, 81.87; H, 7.80; N, 4.73.

Mannich Reaction of the Diketone 2. To a 250 mL round-bottom flask, fitted with a reflux condenser, were added **2** (11.8 g, 0.04 mol), 40% formaldehyde solution (4.8 mL, 0.17 mol) dimethylamine hydrochloride (4.8 g, 0.06 mol), and a few drops of concentrated HCl. The reaction mixture was refluxed for 12 h. Upon cooling, the hydrochloride product and the unreacted diketone **2** precipitated and were filtered. The filtrate was evaporated, and the combined precipitates were washed with acetone to remove the unreacted diketone **2**. The hydrochloride product obtained (12.5 g, 80% yield) was dissolved in ice-bath-cooled 10% sodium hydroxide solution and extracted with Et_2O to obtain the Mannich base **4** (10.56 g, 75% yield), which was structurally confirmed by its ^1H NMR spectrum ($CDCl_3$): 1.27 (s, 3 H, C_{10} CH_3), 1.49 (s, 3 H, C_4 CH_3), 2.25 (s, 6 H, *N*-dimethyl), 7.35 d, 1 H, C_{11} ($J_{11,12}$ = 9.0 Hz)), 8.04 (dd, 1 H, C_{12} ($J_{11,12}$ = 9.0, $J_{12,14}$ = 2.5 Hz)), 8.43 (d, 1 H, C_{14} ($J_{12,14}$ = 2.5 Hz)). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 75.12; H, 7.87; N, 7.90.

Preparation of 5 from the Quaternary Methiodide Salt 4a. The Mannich base **4** (10.5 g, 0.20 mol) obtained above was stirred in Et_2O with excess methyl iodide at room temperature. After 12 h the precipitated solid was collected by vacuum filtration to yield methiodide salt **4**, 10.0 g, 67.5%). Evaporation of the filtrate on a rotary evaporator yielded 1.0 g (11%) of a solid identified as the vinyl phenyl ketone **5**: mp 126–127 °C[11] dec; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, C_{10} CH_3), 1.48 (s, 3 H, C_4 CH_3), 5.86 (dd, 1 H, $^1H_{20b}$ ($J_{19,20}$ = 10.5, $J_{20a,20b}$ = 2 Hz)), 6.34 (dd, 1 H, $H_{20a'}$ ($J_{19,20}$ = 16.5, $J_{20a,20b}$ = 2 Hz)), 7.13 (q, 1 H, $H_{19'}$ ($J_{19,20a}$ = 16.5, $J_{19,20b}$ = 10.5 Hz)), 7.4 (d, 1 H, $C_{11'}$ ($J_{11,12}$ = 10.5 Hz)), 8.05 (dd, 1 H, C_{12} ($J_{11,12}$ = 9.0, $J_{12,14}$ = 2.5 Hz)), 8.45 (d, 1 H, C_{14} ($J_{12,14}$ = 0.5 Hz).

Elimination Reactions of 4a To Form 5. The methiodide product (**4**) was heated under ether reflux for 12 h. After filtration of the unchanged methidide, the ether was evaporated to yield 0.62 g (10%) of the vinyl phenyl ketone **5**. Alternatively, methiodide (5.0 g) and salt **4a** were dissolved in a mixture of acetone (75 mL) and water (25 mL) and refluxed for 3 h. After cooling, water was added, and the resulting aqueous solution was extracted with ether. Removal of the ether solvent in vacuo after drying over anhydrous magnesium sulfate yielded a residue (1.09 g) that was shown to be a mixture of the vinyl phenyl ketone **5** and the diketone **2** in 22.5% and 12% yield as determined by the ^1H NMR spectra of this material. (See reported ^1H NMR data above.)

Cyclization of 5 to the 17-Keto-*C*-aryl-18-norsteroid System. A mixture of anhydrous aluminum chloride (5.0 g) and sodium chloride (1.0 g) was melted in a 50-mL beaker by heating over a Bunsen flame. To this melt was added with stirring at 140 °C 1.0 g (0.003 mol) of **5**. The temperature was raised rapidly to 180 °C and kept at 180–200 °C for 2 min. The mixture was then cooled and decomposed with a solution of ice–water and dilute HCl, followed by extraction with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated on a rotary evaporator. To the residue were added a few drops of Et_2O, and the resulting mixture was filtered to yield the cyclized product (0.70 g, 69.5% yield of **6**, mp 258–259 °C). Analysis by TLC showed this to be a single product whose ^1H NMR data indicates cyclization exclusively at C_{14}: ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H, C_{10} CH_3), 1.49 (s, 3 H, C_4 CH_3), 7.4 (d, 1 H, $C_{11'}$ ($J_{11,12}$ = 9.0 Hz)), 7.85 (d, 1 H, C_{12} ($J_{11,12}$ = 9.0 Hz)), IR (KBR disk) 2220 cm^{-1} (CN), 1720 (C_{17}=O), 1690 (C_7=O); mass spectrum, m/z 307 (100), 292 (27). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.30; H, 6.72; N, 4.49.

Registry No. **1**, 31148-95-5; **2**, 85850-58-4; **3**, 85850-59-5; **4**, 85864-52-4; **4**·HCl, 85850-60-8; **4a**, 85850-61-9; **5**, 85850-62-0; **6**, 85850-63-1.