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Simple Method for the Reductive Dehalogenation of 9α-Bromo Steroids

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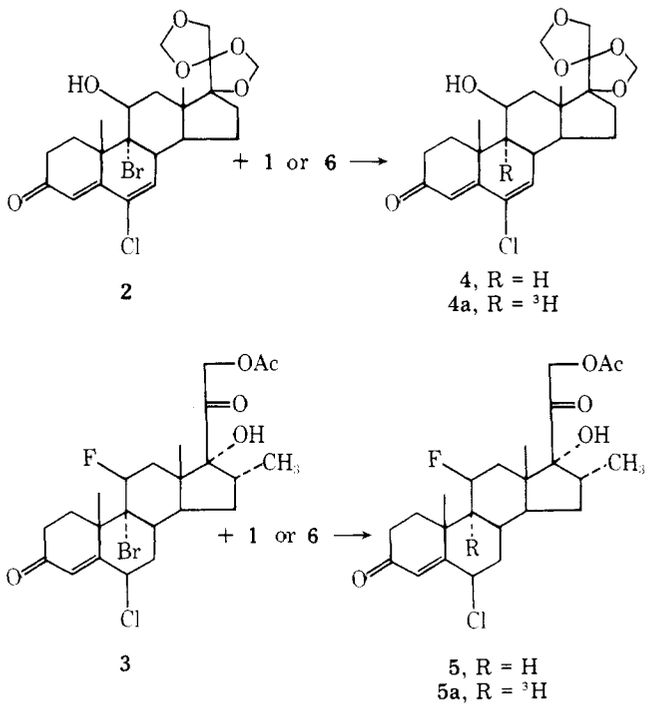
Received April 24, 1978

The 11β-hydroxy group is an important structural feature which contributes to the high biological activity of corticosteroids. It is reasonable to suppose, therefore, that other substituents at C-11 might lead to new, highly active compounds. A convenient route to such compounds would be by reductive dehalogenation of an 11β-substituted 9α-bromo steroid. This type of precursor is readily available from various $\Delta^{9(11)}$ steroids.[1-3] A survey of the literature shows, however, that only one reagent, chromous acetate in the presence of butanethiol (or other hydrogen atom transfer agent),[4] has been found to effect the desired reduction. Other reducing agents are either unreactive or cause elimination to the $\Delta^{9(11)}$ compound. The $Cr^{II}(OAc)_2$/BuSH procedure, however, is cumbersome and operationally difficult to implement. We wish, therefore, to describe a new and efficient method for the reductive dehalogenation of 9α-bromo steroids using *n*-Bu_3SnH (**1**).

The use of *n*-Bu_3SnH as a selective reducing agent toward halogen is well known and has been reviewed by Kuivila,[5,6] yet there have been no attempts to reduce 9α-bromo steroids[9] with this reagent. We felt that **1** would effect the desired debromination for two reasons. First of all, as in the case of $Cr^{II}(OAc)_2$/*n*-BuSH, reductions involving **1** are believed to proceed by a free-radical process. Furthermore, bromohydrins and certain vicinal dihalides undergo reduction rather than elimination,[7] which is the case with other reducing agents.

The bromohydrin **2** and the 9α-bromo-11β-fluoro steroid **3** were chosen as model compounds and our process is outlined in Scheme I. In each case the 9α-bromo steroid was stirred in THF solution either at room temperature or at reflux with a small excess of *n*-Bu_3SnH (in some cases a trace of azobis(isobutyrylnitrile) was added to initiate the reaction). The reaction mixture was examined by TLC until no further change in composition was observed. Aqueous workup followed by chromatographic purification or crystallization afforded the reduced products **4** and **5** in yields of 63 and 64%, respectively. There was no trace of the $\Delta^{9(11)}$ elimination product.

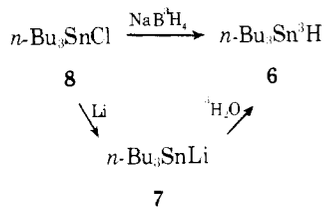
Scheme I



2 4, R = H; 4a, R = ^3H

3 5, R = H; 5a, R = ^3H

Scheme II



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The NMR and mass spectra of the products were consistent with their proposed structures. The NMR spectra of **4** and **5** were easily distinguishable from their respective starting materials **2** and **3** by a clear upfield shift in the 19-CH_3 resonance [30 Hz for **4** and 17 Hz for **5**] of the former.

The method described above was extended to the synthesis of 9α-tritiated steroids with the preparation of *n*-Bu_3Sn^3H (**6**). Neither **6** nor 9α-^3H steroids have been previously reported.

Two methods were used to prepare **6** (Scheme II). In method a, *n*-Bu_3SnLi[8] (**7**) was quenched with freshly prepared ^3H_2O. In method b, **6** was generated by reduction of *n*-Bu_3SnCl (**8**) with NaB^3H_4. In each case **6** was reacted, without isolation, with either **2** or **3** (Scheme I). The 9α-tritiated products, **4a** and **5a,** respectively, were isolated from the reaction mixture by extraction and purified by TLC. Both labeled products were identified by comparing their radiochromatography scans against the authentic standards, **4** and **5**, which were prepared as described above. Method b is clearly preferred over method a for the generation of **6**. It is operationally much simpler to carry out, results in cleaner reaction mixtures, and affords higher yields.

We are currently investigating the scope of the selective debromination reaction described here toward the preparation of other 11β-substituted steroids. In addition, our preparation of *n*-Bu_3Sn^3H now offers the possibility of synthesizing a variety of specifically labeled compounds, many of which would be quite difficult to prepare by other methods.

0022-3263/79/1944-0151$01.00/0

Experimental Section

Radiochromatography scans were obtained using a Packard Model 7201 radiochromatogram scanner. Radioassays were obtained using a Packard Tri-Carb Model 574 liquid scintillation counter. Corrections for quenching were made by the channels ratio method. NaB^3H_4 and tritium gas were purchased from Amersham Corporation and Oak Ridge National Laboratories, respectively. NMR spectra were recorded on a Varian HA-100 spectrometer in $CDCl_3$ or Me_2SO-d_6 as noted and chemical shifts are reported in ppm (δ) from Me_4Si. Mass spectra were recorded on a Varian-MAT CH-4 spectrometer. NMR and mass spectra refer to nonradioactive reference standards.

6-Chloro-9α-bromo-11β,17α,21-trihydroxypregna-4,6-diene-3,20-dione BMD (BMD=bis(methylenedioxy) protecting group) (2). 2 was prepared in 97% yield from the corresponding $\Delta^{9(11)}$ compound by the method of Fried and Sabo.[1] Addition of water to the reaction mixture gave a white precipitate which was filtered and dried. This material was homogeneous by TLC (SiO_2; hexane–acetone, 2:1): NMR (Me_2SO) δ 1.10 (3 H, s, 18-CH_3), 1.60 (3 H, s, 19-CH_3), 4.37 (1 H, m, 11 α-H), 6.23 (1 H, d, J = 2 Hz, 7-H).

Tri-*n*-butyltin Tritide (6). Method a. Tritiated water (20 Ci; 30 Ci/matm; 0.3 mmol) was prepared on a vacuum line by the reaction of $^3H_2$ (20 Ci; 30 Ci/matm) with Pt_2O (100 mg). The ^3H_2O was distilled (on the vacuum line) from the reaction vessel into a 10-mL side-arm flask containing a rubber septum in the side arm. Freshly prepared Bu_3SnLi[8] (0.2 mmol) in THF was injected into the flask containing ^3H_2O. A precipitate of LiO^3H formed instantaneously, indicating that the reaction was complete.

Method b. A solution of *n*-Bu_3SnCl (85 mg; 0.26 mmol) in EtOH (1 mL) was added to NaB^3H_4 (9.8 mg; 0.26 mmol; 75.6 mCi; 293 mCi/mmol). The suspension was stirred at room temperature for 30 min until the NaB^3H_4 had completely reacted (disappearance of purple color) and a white precipitate (NaCl) had formed.

6-Chloro-11β,17α,21-trihydroxypregna-4,6-diene-3,20-dione BMD (4). To a solution of **2** (300 mg; 0.58 mmol) in THF (5 mL) was added *n*-Bu_3SnH (203 mg; 0.7 mmol). The reaction was stirred at room temperature for 18 h and then partitioned between brine and methyl ethyl ketone. The organic phase was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The residue was crystallized from methyl ethyl ketone to yield the product (160 mg, 63%) as off-white crystals. This material was chromatographically homogeneous (SiO_2; hexane–acetone, 4:1, run three times): NMR (Me_2SO-d_6) δ 1.08 (3 H, s, 18-CH_3), 1.30 (3 H, s, 19-CH_3), 4.15 (1 H, m, 11α-H), 6.43 (d, 1 H, J = 2 Hz, 7-H); mass spectrum *m/e* 420–422 (M^+).

6-Chloro-11β,17α,21-trihydroxy[9α-^{3}H]pregna-4,6-diene-3,20-dione BMD (4a). A solution of **2** (78 mg; 0.15 mmol) in THF (2 mL) was injected into a flask containing **6** [prepared by method a]. The reaction was stirred at room temperature for 18 h and labile tritiated materials were removed by distilling to dryness from EtOH two times on the vacuum line. The residue was partitioned between methyl ethyl ketone and water. The organic phase (1180 mCi) was dried over Na_2SO_4 and taken to dryness at reduced pressure. Chromatographic purification (2000 μm SiO_2 plates; hexane–acetone, 4:1, run three times) afforded pure **4a** (142 mCi). The radiochromatogram of this material was superimposable with standard **4**.

9α-Bromo-11β-fluoro-16α-methyl-17α,21-dihydroxypregn-4-ene-3,20-dione 21-Acetate (3). This substance was prepared from the corresponding $\Delta^{9(11)}$ compound by the method of Bowers[4] in 67% yield: mp 177 °C dec; NMR ($CDCl_3$) δ 0.9 (3 H, d, J = 2 Hz, 18-CH_3), 0.93 (3 H, d, J = 7 Hz, 16-CH_3), 1.6 (3 H, d, J = 4 Hz, 19-CH_3), 5.25 (d, J = 47 Hz, 11α-H); mass spectrum *m/e* 498–500 (M^+), 397–399, 317, 297.

11β-Fluoro-16α-methyl-17α,21-dihydroxypregn-4-ene-3,20-dione 21-Acetate (5). To a solution of **3** (600 mg; 1.05 mmol) in THF (25 mL) containing a trace of azobis(isobutyrylnitrile) was added *n*-Bu_3SnH (305 mg; 1.05 mmol). The reaction was heated at reflux for 30 min [TLC (toluene–EtOAc, 4:1) showed no starting material remaining] and partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. Crystallization from CH_2Cl_2/CH_3OH afforded 325 mg (64%) of pure **5**: mp 279–279.5 °C; NMR ($CDCl_3$) δ 0.9 (3 H, d, J = 7 Hz, 16-CH_3), 0.95 (3 H, d, J = 2 Hz, 18-CH_3), 1.35 (3 H, d, J = 4 Hz, 19-CH_3), 3.07 (1 H, d, J = 47 Hz, 11α-H); mass spectrum *m/e* 420 (M^+), 319, 299.

9α-^{3}H-11β-Fluoro-16α-methyl-17α,21-dihydroxypregn-4-ene-3,20-dione 21-Acetate (5a). To **6** [prepared by method *b*] was added a solution of **3** (150 mg; 0.3 mmol) in EtOH (1 mL). The reaction was stirred at reflux for 30 min (radiochromatogram showed no further increase in size of product peak) and partitioned between EtOAc and water. The organic phase was taken to dryness at reduced pressure. Chromatographic purification (toluene–EtOAc, 4:1) of the residue afforded pure **5a** (11.3 mCi) in 60% yield: UV (MeOH) 242 nm (ϵ 16 700); specific activity 71.4 mCi/mmol (theory 73.3 mCi/mmol).

Registry No.—**1**, 688-73-3; **2**, 68238-03-9; **3**, 68225-92-3; **4**, 68213-12-7; **4a**, 68213-13-8; **5**, 68213-14-9; **5a**, 68213-15-0; **6**, 68213-16-1; **7**, 4226-01-1; **8**, 1461-22-9; 6-chloro-17α,21-dihydroxypregna-4,6,9(11)-triene-3,20-dione BMD, 68213-17-2; 16α-methyl-17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate, 34542-56-0; NaB^3H_4, 35576-64-8.

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Reduction of Substituted Decalones. Stereochemical Reversal in the Lithium–Ammonia Reduction of Ketones

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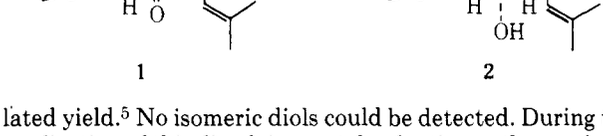
Received May 30, 1978

Several reports have appeared in the literature over the years describing "anomalous" dissolving metal (lithium–ammonia) reductions of cyclic ketones.[2] Past observations coupled with the recent report by Huffman and Copley describing the reduction (lithium–ammonia) of 24-nor-5β-cholan-12-one and 23,24-dinor-5β-cholan-12-one in the presence of a proton source (methanol)[3,4] prompt us to record our observations concerning the reduction of substituted decalones.

In conjunction with our efforts directed toward the total synthesis of cytotoxic sesquiterpene lactones, we had observed the smooth reduction (lithium–ammonium chloride–ammonia) of epoxy ketone **1** to the equatorial diol **2** in ca. 80% isolated yield.[5] No isomeric diols could be detected. During the application of this dissolving metal reduction to the synthesis of temisin,[6] we observed that reduction (lithium–ammonia) of epoxy ketone **3** under rigorously anhydrous conditions followed by quenching with solid ammonium chloride gave (78%) a mixture of the C-6 (steroid numbering) equatorial diol **4** and the C-6 axial diol **5** in a ratio of 1.8:1 (see Table I). Furthermore, if the strictly anhydrous conditions were not adhered to, the major product of the reaction was the C-6 axial diol **5**. For example, dissolving metal reduction of **3** in the presence of ammonium chloride gave as the major product



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