A Salamander Alkaloid Synthesis

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Lithium–ethylamine reduction of 17β-acetoxy-1α-hydroxy-2a-aza-*A*-homo-5β-androstan-3-one, obtained by a Schmidt reaction on 17β-acetoxy-1α-hydroxy-5β-androstan-3-one, yielded an alkaloid isolated from *Cryptobranchus maximus* Stanley and provided access to other salamander alkaloids.

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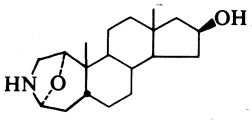
La réaction de Schmidt sur l'acétoxy-17β hydroxy-1α androstane-5β one-3 conduit à l'acétoxy-17β hydroxy-1α aza-2a *A*-homo-androstane-5β one-3 qui par réduction avec du lithium en présence d'éthylamine conduit à un alkaloide isolé du *Crystobranchus maximus* Stanley; cette méthode permet aussi d'obtenir d'autres alkaloides de la Salamandre.

Apart from toxicities, to which they presumably owe their role as predator-repellants, the salamander alkaloids possess some interesting and potentially useful physiological properties; thus samandarine (**1**) has been reported to be a potent local anesthetic (1). As supplies of the alkaloids from natural sources are limited and difficult to obtain their synthesis therefore has some practical importance.



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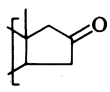

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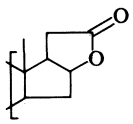

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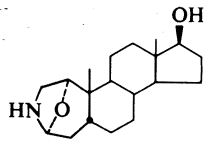
The characteristic skeleton of the alkaloids is that of a 2a-aza-*A*-homo-5β-steroid and, as exemplified by samandarine, samandarone (**2**), and samandaridine (**3**), there is usually a 1α,3α-oxide bridge and further oxygenation at C-16. The visualization of the alkaloids as steroid metabolites has some experimental substantiation in the observation that cholesterol can function as their precursor (2). Intrigued by this transformation we decided to construct our synthetic approach to the alkaloids by attempting to mimic reactions which might occur *in vivo*.

The formation of **2** from a simple sterol can be considered as involving two operations: the synthesis of a 16-oxoandrostane (3); and formation of the expanded and oxygen-bridged ring *A*. We concentrate our discussion here on the second of these operations, selecting as our target the alkaloid **4** isolated from *Cryptobranchus maximus* Stanley (4).

The most obvious routes for construction of the desired *A*-ring system proceed either by way of 2,3-seco intermediates, involving **5** or its equivalent, or else employ ring expansion followed by bridging *e.g.* **7** → **8** → **10** → **4**. Both the first two successful syntheses of salamander alkaloids (5, 6) employed seco steroid routes.



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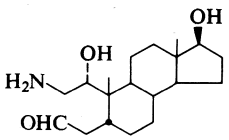

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We preferred the alternative approach, and planned our synthesis as shown in Scheme 1.

Experiments by Pelc and Hodková (7) have revealed that hydrogenation of 1α,2α-epoxy-3-oxoandrosta-4,6-dienes, prepared by alkaline hydrogen peroxide epoxidation (8*a*) of the corresponding 1,4,6-trien-3-one (8*b*) yielded 1α-hydroxy-3-oxo-5β-androstanes. Application of their procedure to **6** gave reasonable yields of the desired 1α-hydroxy compound **7**. The stereochemistry at C-5 was established unequivocally by the following methods: the half-band width of the C-19 protons was within the range suggested for 5β-steroids (9); the mass-spectral cleavage of combined C-3 and C-4 units (42

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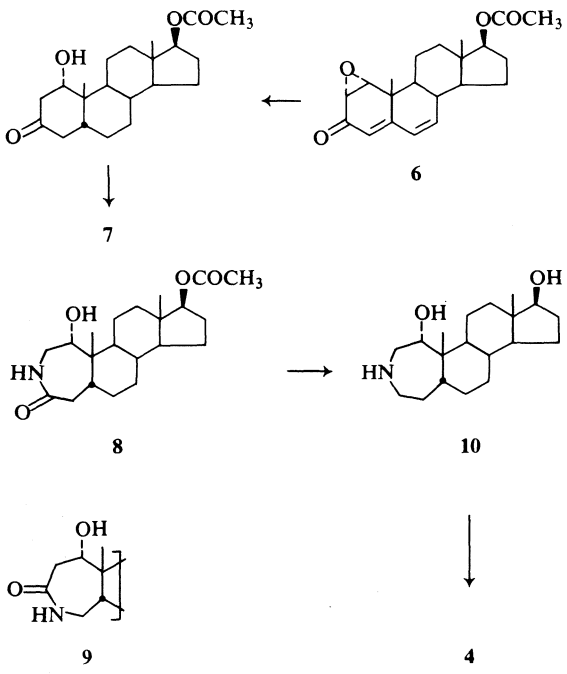


SCHEME 1

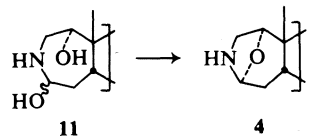
a.m.u.) from the molecular ion or the dehydrated molecular ion was weak, in accordance with the findings of Egger (10); and finally, a weakly negative Cotton effect was observed, analogous to 5β-cholestanone (11).

Our original plan was to prepare the mixed *E*- and *Z*-oximes of 17β-acetoxy-1α-hydroxy-5β-androstan-3-one (**7**), separate them (12) and identify them by p.m.r. (13). Stereospecific Beckmann rearrangement (14) of the *Z*-oxime should then afford the lactam **8** with the correct skeleton and functionalization for conversion to **4**. An attractive feature of this approach is that the "wrong" *E*-oxime might be isomerized to provide more of the "right" *Z*-oxime. In the event, preliminary experiments with 1α-hydroxy-5β-cholestan-3-one persuaded us that it would probably be less time consuming to convert **7** to a mixture of **8** and **9** by a Schmidt reaction, and then to separate the mixed lactams, and this we did. The conversion of **7** to **8** and **9** was good. Separation of the mixed lactams ultimately proved to be the most difficult step in the entire synthesis and was achieved by careful preparative thin-layer chromatography.

The assignment of structures **8** and **9** to the two lactams was made on the basis of spectroscopic evidence, including the relatively facile formation of an αβ-unsaturated lactam when (**9**), was heated briefly with acetic anhydride in the presence of pyridine. Final proof of the correctness of the assignments was provided by the successful conversion of the lactam **8** to the *Cryptobranchus* alkaloid.

Lithium aluminum hydride reduction of **8** gave satisfactory yields of 1α,17β-dihydroxy-2α-aza-*A*-homo-5β-androstane (**10**) but partial back-oxidation with a variety of agents including silver(II) picolinate (15), gave complex mixtures in which, however, the presence of **4** was evidenced by g.l.c.–m.s.

Another approach to the ring-*A* transformation involves a direct partial reduction of the lactam to the intermediate iminol **11** which should spontaneously cyclize to the more stable oxazolidine structure.



Benkeser *et al.* (16) have shown that such a partial reduction can be accomplished electrolytically. Using an analogous, but technically simpler approach, dissolving lithium in a solution of **8** in ethyl amine containing 2-methyl-2-propanol, we were indeed able to convert lactam **8** to the *Cryptobranchus* alkaloid in a reasonable yield.

Since **4** has been converted into **1** (*5a*), and this into **2** and **3** (*1*), in a formal sense our synthesis also provides access to these other salamander alkaloids.

Experimental

Melting points were uncorrected. Thin-layer chromatography was carried out on silica gel G plates. Proton magnetic resonance spectra were measured on a Varian A60 or HA100 spectrometer. Mass spectra were recorded on AEI-MS9 and Varian-M-18-CH5 spectrometers and g.l.c.–m.s. were carried out on a Varian CH7 spectrometer coupled with a Varian G2700 gas chromatograph fitted with a 6 ft column containing 3% OV1 on Chromosorb Q (oven 210°; He 50 ml/min). Optical rotary dispersion and c.d. curves were determined on a Durrum-Jasco ORD-UV/5 spectropolarimeter with 20 c.d. modification, at 31°, in chloroform–ethanol. The estimated $[\alpha]_D$ error was ±2°.

Preparation of 17β-Acetoxy-1,4,6-androstatrien-3-one

17β-Acetoxyandrostan-1,4-dien-3-one (18.246 g; 55.6 mmol) (Sigma Chemical Co.) was dissolved in distilled, anhydrous, oxygen-free (scrubbed with nitrogen) carbon tetrachloride (200 ml). To this solution was added *N*-bromosuccinimide (10.00 g; 56.2 mmol) and benzoyl

peroxide (0.63 g) and the mixture was refluxed in the dark for 5 h, with continuous stirring, in a slow current of nitrogen with rigorous exclusion of moisture. The resulting red-brown suspension was allowed to cool to room temperature in the dark under a nitrogen atmosphere. It was then filtered and the solid which had separated was collected and washed well with carbon tetrachloride. The filtrate and washings were combined, and evaporated to dryness at room temperature under reduced pressure.

The product, a red-brown gum (31 g) was dissolved in anhydrous, freshly distilled dimethylformamide (300 ml) containing suspended powdered calcium carbonate (10 g), and the reaction mixture was stirred and refluxed, under an atmosphere of nitrogen, for 1 h. It was then cooled, acidified with 2 *N* hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium bicarbonate solution, and water, dried ($MgSO_4$), filtered, and finally evaporated to dryness under reduced pressure. The residual red-brown gum (20 g) was chromatographed on a column of Florisil from which ether–benzene (1:8) eluted 17β-acetoxy-1,4,6-androstatrien-3-one as a yellow solid (16.7 g, 92.5%). This substance, which was more than 90% pure on t.l.c. (R_f 0.19; EtOAc–C_6H_6, 1:2), was recrystallized from aqueous ethanol and then carbon tetrachloride – hexane to yield yellowish prisms, m.p. 151–152° (lit. (8*b*) m.p. 151–153°); t.l.c. homogeneous (R_f 0.32; Et_2O–C_6H_6, 1:2); ν_{max} (KBr) 3030, 1735, 1650, 1610, and 1580 cm^{-1}; λ_{max} 220 (ε 18 120), 258.5 (ε 11 100), and 305 nm (ε 16 160) [*cf.* lit. (17) 222 (11 100), 257 (9500), and 299 nm (12 800)]; δ 0.88 (S)(3H), 1.18 (S) (*ca.* 3H), 1.97 (S) (*ca.* 3H), 4.37–4.75 (m) (1H), 5.70–6.37 (m) (4H), and 6.94 p.p.m. (d; J = 10 Hz) (1 H).

The Epoxidation of 17β-Acetoxy-1,4,6-androstatrien-3-one: Preparation of 1α,2α-Epoxy-17β-acetoxy-4,6-androstadien-3-one (6)

The trienone (16.8 g; 51 mmol) was dissolved in a 2:1 mixture of methanol–dichloromethane (660 ml). After the addition of 10% aqueous sodium hydroxide (11 ml), the mixture was kept at room temperature for ¾ h and 30% hydrogen peroxide (66 ml) was then added, after which the reaction mixture was kept at 0° for 12 h. At the end of this time the solvents were removed under reduced pressure, at room temperature, with the simultaneous addition of small amounts (*ca.* 10 ml) of water until the total volume was about 100 ml. The solid (11 g) which separated was collected and washed with water until the washings were neutral. The mother liquors were diluted with more water and extracted with ethyl acetate. The organic extracts were combined, washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure to yield a gum (1.18 g).

The solid and gum products were combined and acetylated with acetic anhydride (30 ml) and pyridine (15 ml), at room temperature, overnight. The reaction mixture was then diluted with ice water and extracted with chloroform. The combined chloroform extracts were washed successively with 2 *N* sulfuric acid, water, saturated aqueous sodium bicarbonate, water, and then dried ($MgSO_4$), filtered, and evaporated to dryness.

The crude product from the acetylation was purified by p.l.c. (Et_2O–C_6H_6, 1:2) with low loadings, giving three components: R_f 0.17 (0.8 g), 0.28 (0.15 g), and 0.41 (11 g; 62%).

The component with R_f 0.41, 1α,2α-epoxy-17β-acetoxy-4,6-androstadien-3-one (**6**) was recrystallized from acetone–hexane to yield colourless needles m.p. 187–203°, not raised by further recrystallization, (*cf.* lit. (8*a*) 205–206°); ν_{max} ($CHCl_3$) 1735, 1675, 1630, 1595, and 1260 cm^{-1} (lit. 1725, 1665, 1620, 1590, and 1250 cm^{-1}); λ_{max} 293 nm (ε 35 870) (lit. (8*a*) 292 nm (34 300)); δ 0.94 (S) (3H); 1.21 (S) (*ca.* 3H), 2.05 (S) (*ca.* 3H), 3.41 (q; J = 2 and 4 Hz) (1 H), 3.57 (d; J = 4 Hz) (1 H), 4.63 (m) (1 H), 5.61 (d; J = 2 Hz) (1 H), and 6.04 p.p.m.(m) (2 H), (*cf.* lit.(7) δ 0.92 (S), 1.19 (S), 2.04 (S), 3.41 (q; J = 2.4 Hz), 3.54 (d; J = 4 Hz), 4.62 (b), 5.62 (d; J = 2 Hz), and 6.05 p.p.m. (m)); *m/e* 342 ($M^{+\bullet}$) (30), 300 (40), 282 (30), and 43 a.m.u. (100).

The component with R_f 0.28, 1ξ,2ξ-6ξ,7ξ-diepoxy-17β-acetoxy-4-androsten-3-one, was recrystallized from acetone–hexane as yellow rods m.p. 230–250°, unchanged by further recrystallization; g.l.c. showed it to be almost pure (R_T 23.2 min; 90% of total area); ν_{max} ($CHCl_3$) 1735, 1685, and 1635 cm^{-1}; λ_{max} 243 nm (ε 11 250); δ 0.92 (S) (3H), 1.19 (S) (*ca.* 3H), 2.08 (S) (*ca.* 3H), 3.28–3.99 (m) (*ca.* 4H), 4.54–4.90 (m) (1 H), and 6.12 (S) (1H); *m/e* 358 ($M^{+\bullet}$) (12), 342 (3), 326 (30), 316 (8), 300 (10), 284 (40), and 43 a.m.u. (100).

The component with R_f 0.17, 1α-methoxy-17β-acetoxy-4,6-androstadien-3-one was recrystallized repeatedly from acetone–hexane to give colorless rods, m.p. 202.5–207.5°; $[\alpha]_D$ +159; ν_{max} ($CHCl_3$) 1735, 1670, 1630, and 1600 cm^{-1}; λ_{max} 290 nm (ε 16 900); δ 0.90 (S) (3H), 1.14 (S) (*ca.* 3H), 2.06 (S) (*ca.* 3H), 2.64 (q; J = 3 and 17 Hz) (1 H), 2.84 (q; J = 3 and 17 Hz) (1 H), 3.31 (S) (3 H), 3.63 (t; J = 3 Hz) (1 H) 4.67 (t; J = 7 Hz) (1 H), 5.74 (S) (1 H), and 6.12 p.p.m. (S) (2 H); *m/e* 358.2135 ($M^{+\bullet}$ Calcd. for $C_{22}H_{30}O_4$: 358.2144) (10), 326 (30), 298 (5), 284 (60), 266 (10), 251 (10), and 28 a.m.u. (100).

The Hydrogenation of 1α,2α-Epoxy-17β-acetoxy-4,6-androstadien-3-one: Preparation of 17β-Acetoxy-1α-hydroxy-5β-androstan-3-one (7)

Various solvent systems were investigated for the room-temperature, atmospheric-pressure hydrogenation of **6**, over 5% palladium on calcium carbonate. The most satisfactory conditions which we discovered used 2-propanol as solvent and a typical experiment is described below.

A solution of the epoxide **6** (0.393 g; 1.15 mmol) in 2-propanol (40 ml) was added to a mixture of prereduced 5% palladium on calcium carbonate (0.200 g) and 2-propanol (10 ml). The hydrogenation was carried out at room temperature and atmospheric pressure. The uptake of hydrogen gas was constant at 85.2 ml (*cf.* calculated hydrogen uptake 95.4 ml) after 42 min.

The reaction mixture was filtered through Celite and then evaporated to dryness at room temperature under reduced pressure. The colorless gum (0.442 g) so obtained was separated by p.l.c. with low loadings (Et_2O–C_6H_6 1:2; developed twice), whereby one major fraction (R_f 0.34), and three minor fractions (R_f values 0.13, 0.60, and 0.75) were isolated.

The major fraction, corresponding to 17β-acetoxy-1α-hydroxy-5β-androstan-3-one (**7**), (0.198 g; 49% yield) was recrystallized from acetone–hexane as colorless rods, m.p. 185–188°, ν_{max} ($CHCl_3$) 3520, 1735, and 1700 cm^{-1}; $[\alpha]_D \approx 0$; $[\theta]_{294}$ −522; δ 0.92 (S) (3 H), 1.22 (S) (*ca.* 3H), 2.04 (S) (*ca.* 3H), 3.64 (t; J = 8 Hz) (1 H), and 4.45–4.83

p.p.m. (m) (1 H); the difference in the half band-widths of the C-19 methyl and TMS absorptions = 0.1 Hz (15% w/v steroid in $CDCl_3$; 2% TMS) (*cf.* ≤ 0.36 Hz for 5β-steroids (9)); *m/e* 348 ($M^{+\bullet}$) (8), 330 (6), 262 (40), 202 (40), and 28 a.m.u. (100).

The Schmidt Reaction of 17β-Acetoxy-1α-hydroxy-5β-androstan-3-one (7)

A solution of 17β-acetoxy-1α-hydroxy-5β-androstan-3-one (2 g; 5.75 mmol) in anhydrous chloroform (300 ml) was treated with a freshly prepared and standardized 0.89 *M* solution of hydrazoic acid in chloroform (7.1 ml; 6.32 mmol). The mixture was cooled in an ice bath under anhydrous conditions, and to it was added, dropwise, concentrated sulfuric acid (2 ml) at such a rate that the temperature of the mixture was maintained below 5°. The reaction mixture was stirred throughout the addition, and was stirred for a further 20 min at 0° after the addition had been completed. Excess ice water was then added and the mixture was left in the refrigerator overnight.

The reaction mixture was brought to p*H ca.* 6 with 2 *N* sodium hydroxide, and then extracted exhaustively with chloroform. The combined chloroform extracts were washed with saturated aqueous sodium bicarbonate and then water, dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The greenish foam (2.22 g) thus isolated was separated by p.l.c. ($MeOH–CHCl_3–Et_2O$ 1:3:3) into three components; R_f 0.41 (0.101 g; u.v. active), R_f 0.24 (0.377 g; barely visible on the p.l.c. plates under u.v. light), and R_f 0.20 (0.793 g; barely visible on the p.l.c. plates under u.v. light). The last two components had to be eluted with 20% methanol–chloroform as neither was soluble in pure chloroform; they were purified by crystallization.

The major component, R_f 0.20, 17β-acetoxy-1α-hydroxy-2a-aza-*A*-homo-5β-androstan-3-one (**8**) (38% yield), separated from acetone as a gel, but this gradually turned into colorless plates when air dried, m.p. 223–228.5°; $[\alpha]_D$ +128; ν_{max} (KBr) 3400, 1735, and 1630 cm^{-1}; λ_{max} (CE) 210 nm (ε 15 130), $\delta^{CF_3CO_2D}$ 0.97 (S) (3 H), 1.24 (S) (*ca.* 3H), 2.20 (S) (*ca.* 3H), 2.78–3.00 (m) (2 H), 4.76 (t; *J* = 8 Hz) (1 H), and 4.94 p.p.m. (q; *J* = 3 and 10 Hz) (1 H); *m/e* 363.2426 ($M^{+\bullet}$, Calcd. for $C_{21}H_{33}NO_4$: 336.2410) (12), 348 (1), 346 (1), 334 (20), 320 (2), 304 (3), 303 (3), 291 (6), 273 (10), 262 (8), 260 (10), 243 (10), and 30 a.m.u. (100); microanalysis: Calcd.: *N*, 3.85. Found: *N*, 3.62.

The pure 2a-aza-lactam (0.050 g) was acetylated by allowing it to stand overnight, at room temperature, in a mixture of pyridine (5 ml) and acetic anhydride (10 ml). The solution so obtained was diluted with ice water and then extracted repeatedly with chloroform. The chloroform extracts were combined, washed successively with saturated aqueous sodium bicarbonate solution and water, then dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The colorless crystalline residue (0.048 g) of 1α,17β-diacetoxy-2a-aza-*A*-homo-5β-androstan-3-one was recrystallized once from acetone–hexane and obtained as colorless needles, m.p. 222–224.5°; $[\alpha]_D$ −64; ν_{max} 3460, 3100, 1735, and 1680 cm^{-1}; δ 0.79 (S) (3 H), 1.12 (S) (*ca.* 3H), 1.98 (S) and 2.03 (S) (*ca.* 6H), 2.55 (d; *J* = 9 Hz) (2 H), 2.98 (heptet; *J* = 3.5, 10.5, and 14 Hz) (1 H), 3.99 (octet; *J* = 2, 8, and 14 Hz) (1 H), 4.30 (q; *J* = 2 and 10.5 Hz) (1 H), and 4.56 p.p.m. (q; *J* = 7 and 9 Hz) (1 H); *m/e* 405.2532 ($M^{+\bullet}$ Calcd. for $C_{23}H_{35}NO_5$: 405.2515) (20), 346 (10), 333 (35), 291 (40), 286 (15), and 273 a.m.u. (90), and 43 a.m.u. (100).

The other major product of the Schmidt reaction, R_f 0.24, 17β-acetoxy-1α-hydroxy-3a-aza-*A*-homo-5β-androstan-3-one (**9**) (18% yield), crystallized from methanol–chloroform as colorless microcrystals, m.p. 322–325° (dec.); $[\alpha]_D$ −16; ν_{max} (KBr) 3455, 3235, 3090, 1735, and 1675 cm^{-1}; λ_{max} (CE) 209 nm (ε 13 360); $\delta^{CF_3CO_2D}$ 0.96 (S) (3 H), 1.13 (S) (*ca.* 3H), 2.17 (S) (*ca.* 3 H), 3.00–3.40 (m) (3 H), 4.05–4.47 (m) (2 H), and 4.55–4.85 p.p.m. (m) (1 H); *m/e* 363.2426 ($M^{+\bullet}$, Calcd. for $C_{21}H_{33}NO_4$: 363.2410) (20), 345 (5), 335 (25), 320 (15), 303 (8), 290 (8), 276 (20), 216 (60), and 101 a.m.u. (100).

Lactam **9** (0.05 g) was allowed to stand overnight at room temperature, in a mixture of pyridine (51 ml) and acetic anhydride (10 ml). This lactam, however, did not dissolve. The mixture was therefore refluxed for 10 min, cooled, and the homogeneous solution so obtained diluted with ice water. The mixture was extracted well with chloroform and the chloroform extracts were combined, washed successively with 2 *N* sulfuric acid, water, saturated aqueous sodium bicarbonate, and water, then dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. A slightly yellowish gum (0.053 g), a mixture of 1α,17β-dihydroxy-3a-aza-*A*-homo-5β-androstan-3-one triacetate and 17β-hydroxy-3a-aza-*A*-homo-5β-androst-1-en-3-one diacetate obtained, which could not be induced to crystallize. The gum had ν_{max} (film) 1735, 1695, 1675, and 1630 cm^{-1}; λ_{max} 225 nm (ε 5875); δ 0.81 (S) (3 H), 1.04 (S) and 1.12 (S) (*ca.* 3 H), 2.03 (S) (*ca.* 4 H), 2.45 (S) and 2.52 (S) (*ca.* 3H), 3.13–3.71 (m) (1.5–2 H), 4.10–4.93 (m) (2.5–3 H), 5.85 (d; *J* = 13 Hz) (0.5 H), and 6.28 p.p.m. (d; *J* = 13 Hz) (*ca.* 0.5 H).

The minor product apparently 17β-acetoxy-3a-aza-*A*-homo-5β-androst-1-en-3-one, R_f 0.41 (5.5% yield), was repeatedly recrystallized from acetone–hexane from which it separated as light yellow rods, m.p. 323–333°; g.l.c. (C) suggested that it was more than 90% pure, R_T 25.2 min; ν_{max} (KBr) 3030, 1735, 1675, and 1630 cm^{-1}; δ 0.82 (S) (3 H), 1.14 (S) (*ca.* 3H), 2.03 (S) (*ca.* 3H), 3.49–3.82 (m) (2 H), 4.60 (t; *J* = 7 Hz) (1 H), 5.73 (d; *J* = 13 Hz) (1 H), 6.20 (d; *J* = 13 Hz) (1 H), and 6.80–7.04 p.p.m. (m) (1 H); *m/e* 345.2318 ($M^{+\bullet}$, Calcd. for $C_{21}H_{31}NO_3$: 345.2304) (50), 330 (40), 316 (15), 302 (10), 285 (8), 270 (15), and 43 a.m.u (100).

The Reduction of 17β-Acetoxy-1α-hydroxy-2a-aza-A-homo-5β-androstan-3-one 17-Acetate (8)

The reduction with lithium aluminum hydride could not be carried out in ether because the compound was insufficiently soluble.

The lactam (0.119 g; 0.33 mmol) was added to a suspension of lithium aluminum hydride (0.6; 15.2 mmol) in freshly double-distilled tetrahydrofuran (100 ml) and the mixture was refluxed for 29 h. Ice was added slowly to the cold, well-stirred reaction mixture until the evolution of gas became mild; then water was added until the solids turned almost completely white. The mixture was filtered and the filter cake washed well with chloroform. The mother liquor and the washings were combined, dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The colorless solid, **10**, so obtained (0.096 g; 80.3%) m.p. 235–240° and 250–260° (dec.), was sublimed (193°; 0.003 mm Hg), giving almost quantitative

amounts of colorless microcrystals, m.p. 247.5–248.5°; ν_{max} (KBr) 3370–3400, 3320 cm^{-1}; *m/e* 307.2499 ($M^{+\bullet}$, Calcd. for $C_{19}H_{33}NO_2$: 307.2511) 292 (10), 278 (45), 274 (10), 234 (5), and 44 a.m.u. (100).

A solution of the amine **10** (0.082 g; 0.267 mmol) in anhydrous, freshly distilled dimethyl sulfoxide (30 ml) was stirred with argentic picolinate (0.188 g; 0.534 mmol) at room temperature for 45 min after which time the color had turned from red to colorless. The mixture was filtered and then diluted with water (70 ml), followed by the addition of concentrated ammonia until the p*H* became 11 to 11.5 (indicator paper). The brown solution was exhaustively extracted with ether; and the extracts were combined, washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness under water-pump vacuum, and finally under high vacuum, overnight at room temperature.

The crude product so obtained (0.058 g) was compared with a genuine sample of **4** by both t.l.c. and g.l.c. The t.l.c. suggested that the reaction product was a mixture of seven components, three of them major R_f 0.00, 0.16, and 0.25; two medium, R_f 0.36 and 0.50, and two minor R_f 0.10 and 0.60. The spot at R_f 0.25 was coincident, and cochromatographed with **4**. Gas–liquid chromatography analysis revealed only four components but the second of these cochromatographed with **4**, and upon g.l.c.–m.s. the fragmentation pattern of this component was identical to that of the *Cryptobranchus* alkaloid: *m/e* 305 (7) (M^+), 287 (4), 277 (8), 262 (4), 260 (5), 246 (8), 218 (5), 201 (5), 187 (7), 176 (4), and 85 a.m.u. (100). An attempt was made to isolate this component by preparative t.l.c. ($MeOH–CHCl_3–Et_2O$ 1:3:3; detected by iodine vapor) but we were unable to recover the compounds from the silica gel, even when 50% methanol–chloroform was used as eluant.

Preparation of the Cryptobranchus Alkaloid by a Modified Birch Reduction of ***8***

Anhydrous ethylamine (Eastman; *ca.* 7 ml) was distilled into a cold mixture of 17β-acetoxy-1α-hydroxy-5β-androstan-3-one (14 mg; 38.6 μmol) and 2-methylpropan-2-ol (MCB; 0.5 ml) under anhydrous conditions. The reaction mixture was allowed to warm up to the room temperature and small pieces of freshly-cut lithium metal were added in two portions of *ca.* 50 mg ½ h apart. The reaction mixture was allowed to stir vigorously at room temperature. After a total reaction time of 1½ h, the light blue suspension was treated with dropwise addition of saturated aqueous ammonium chloride until excess lithium was destroyed. After removal of most of the ethylamine on a rotary evaporator, the mixture was diluted with water and then extracted extensively with ether. The combined ether extract was washed with water, then extracted with dilute hydrochloric acid. The combined acid extracts were washed with ether, cooled, and finally basified with solid sodium hydroxide. The colorless solid which separated was extracted with ether. The combined ether extracts were washed with water, dried, and evaporated to dryness, giving a colorless gum (6.4 mg) which was crystallized from acetone–hexane as colorless needles (5.8 mg; 49.3%); m.p. 186–188°; m.p. of supplied sample[2] 186–188°; mixed m.p. 186–188° (lit.(*5a*) m.p. 191–193°). Gas-liquid chromatography (3% OV 1, 6 ft; 230°; 60 ml/min) revealed a single component which cochromatographed with a genuine sample; t.l.c. (methanol–chloroform–ether 1:3:3) also showed identical mobility and the i.r. (in KBr) was superimposable upon that of the authentic alkaloid.

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[2]Kindly supplied by Dr. S. Hara.