Unsymmetric Cleavage of C_2—C_3 in 5β-Steroids

JOSEPH KENNETH PAISLEY, RONALD B. WARNEBOLDT, AND LARRY WEILER[1]

Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia

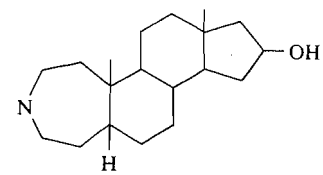
Received September 20, 1973

A method to achieve the unsymmetric cleavage of C-2 and C-3 in 3-keto-5β-steroids is developed. This involves a *cine* substitution of 4-bromoketone to produce the 2-acetoxyketone. Possible mechanisms for this transformation are discussed and the route proceeding through the oxyallyl intermediate is considered most plausible. The 2-acetoxyketone is converted into the hydroxyoxime which undergoes a Beckmann fragmentation to yield the 2,3-seco-steroid. These products are useful intermediates for the synthesis of the salamander alkaloids.

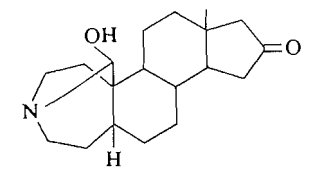
On a développé une méthode pour couper préférentiellement entre les positions 2,3 les céto-3 stéroides-5β. Ceci implique une *ciné* substitution de la bromo-4 cétone pour obtenir l'acétoxy-2 cétone. Les mécanismes possibles pour cette transformation sont discutés et l'on considère que la route passant par un intermédiaire oxyallyle est la plus probable. L'acétoxy-2 cétone est transformé en hydroxyoxime qui subie un réarrangement de Beckmann pour fournir le stéroide coupé entre les positions 2,3. Ces produits sont des intermédiaires utiles pour la synthèse des alkaloides de la salamande. [Traduit par le journal]

Can. J. Chem., **52**, 810 (1974)

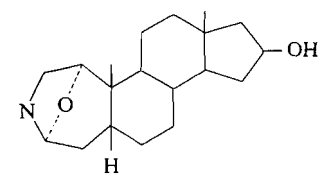
The European salamanders, *Salamandra maculosa taeniata* and *Salamandra maculosa maculosa*, produce a group of toxic defensive principles in their skin glands which have become known as the salamander alkaloids (1). These steroidal alkaloids have attracted attention because of their unusual structural, toxicological, and pharmacological properties. The toxicology and pharmacology studies of the major components of the salamander toxins have shown that these compounds have a dramatic effect on the central nervous system (2). These alkaloids also have unusual structures. They are the only known naturally occurring steroidal alkaloids in which the nitrogen forms an integral part of the steroidal ring system. There are three basic patterns found in the salamander alkaloids which are exemplified by samanine (**1**), cycloneosamandione (**2**), and samandarine (**3**). All of the alkaloids have a nitrogen atom inserted between carbons 2 and 3 of steroidal ring A and a 5β-hydrogen.



1



2



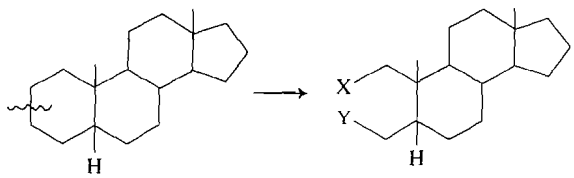
3

Because of these unusual and interesting properties we initiated a program to synthesize these alkaloids and structural variations and modifications of them. In 1967, Hara and Oka (3) reported the first synthesis of one of the salamander alkaloids, namely samandarine (**3**). Although the length of their synthetic sequence should not detract from its elegance and beauty, it does not appear to be a practical solution to our aims. During the course of our work two other syntheses of samandarine (**3**) have appeared (4,5). The work of Shimizu (4) is similar to our own in concept and execution and the synthesis of Benn and Shaw (5) is patterned more on the proposed biosynthesis of **3**. Cycloneosamandione (**2**) has been synthesized by Habermehl and Haaf (6) and there have been several

[1]Author to whom correspondence should be addressed.

syntheses of samanine (**1**) and related systems (7–9).

The key point in all of these methods is the cleavage of the bond between carbons 2 and 3 in a suitably substituted steroid (Scheme 1) to generate an unsymmetric compound of type **4**.

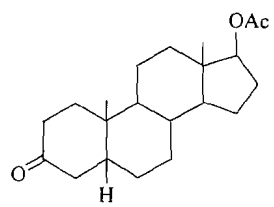


4

SCHEME 1

With the exception of the method of Shimizu (4) and our own (*vide infra* and ref. 10) the previous routes to effect this cleavage (Scheme 1) were either lengthy or nonstereospecific. Here we report our detailed results on this cleavage (10) and the chemistry of some of these derivatives.

The starting material for all our work is 17β-acetoxy-5β-androstan-3-one (**5**) which is readily available from testosterone (11).



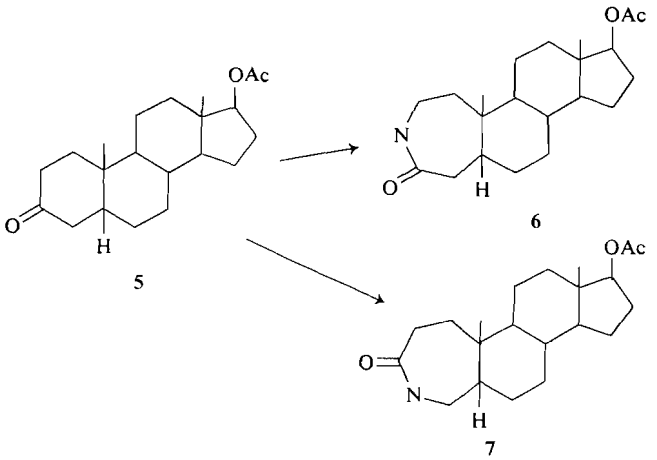
5

There are several oxidative methods available to cleave the carbon–carbon bond adjacent to a ketone. Beckmann rearrangement of the oximes from **5** gave a mixture of the two lactams **6** and **7** in a ratio of *ca.* 1:1 (Scheme 2) (7,12). The difficulty in separation of the isomeric lactams precluded using this method for the synthesis of large quantities of **6** (8,13). The *syn* and *anti* oximes of **5** have been separated and the individual oximes undergo a stereospecific Beckmann rearrangement to **6** or **7** (14). Here also the delicate chromatographic separation and ready equilibration of the two oximes was not compatible with our desired large scale reactions.

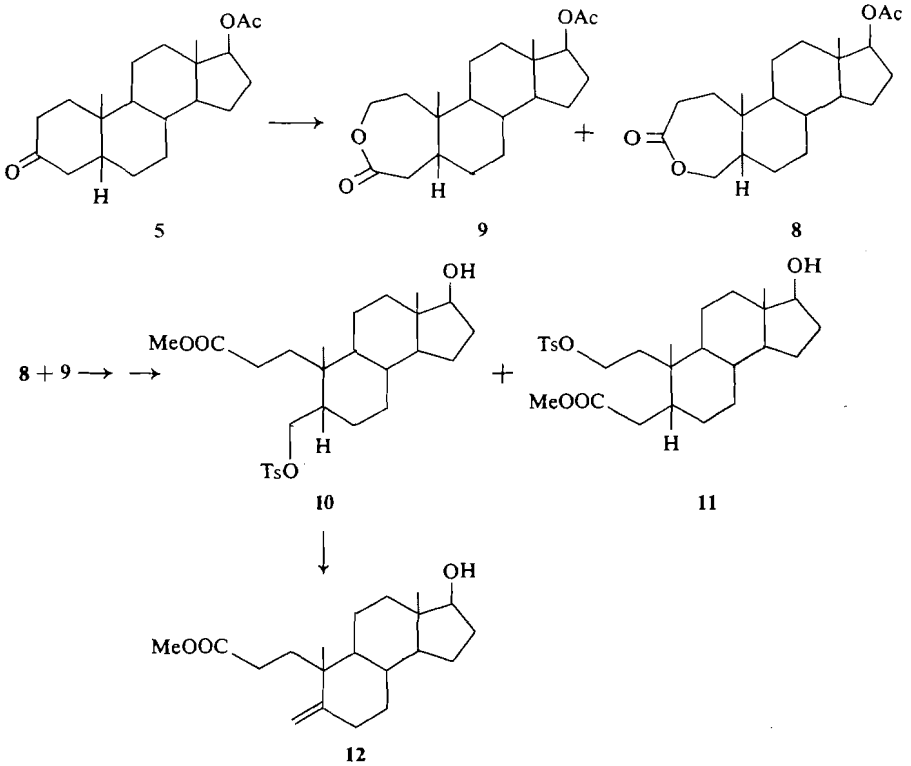
Originally it was reported that the Baeyer–Villiger oxidation of 3-oxo-5β-steroids gave a single lactone, namely, the 3-oxa-4-oxo-A-homo compound (15). However, later re-examination of this reaction showed that, in fact, the Baeyer–Villiger product was a mixture of the two possible lactones (16). We have found that action of *m*-chloroperbenzoic acid on **5** gave a 4:1 mixture of lactones **8** and **9** in 85% yield (Scheme 3). The two lactones could be separated by v.p.c. and their structures were proven as follows. The mixture of lactones was hydrolyzed, esterified, and tosylated to give a mixture of **10** and **11**. Treatment of **10** and **11** gave only the olefin **12** in 32% which indicates that the major lactone in the mixture has structure **8**. This was collaborated by synthesizing the known lactams **6** and **7** (14). These lactams were converted into the *N*-nitrosolactams (17) and pyrolysis of these *N*-nitrosolactams (18) gave the lactones **9** and **8**, respectively (19).

With this experience and the results reported above we felt that it would be essential to introduce a substituent at C-2 of **5** in order that the C_2—C_3 bond cleavage process would be favored. However, this approach is not totally free of obstacles since it is well known that most reactions of 3-keto-5β-steroids involve preferential enolization towards carbon 4 (11,20) and then reaction of this enol (or enolate) to generate mainly, if not exclusively, the C-4 substituted product (11,20,21). One exception to this is the formation of the 2-hydroxymethylene derivative of **5** (21*f*). Formylation is an equilibrium reaction and the 2-hydroxymethylene is more stable than the 4-hydroxymethylene because of the $A_{1,3}$ strain (22) in the latter isomer. This led us to the consideration of two possibilities, either we could obtain a 2-substituted derivative of **5** via a rearrangement of the 4-substituted derivative (Scheme 4) or we could trap an intermediate of type **15** preferentially at C-2 (*vide infra*) (Scheme 5). In the first possibility the reaction would be driven by the relief of the additional *gauche* interaction present in **13** but not in **14**. The work of Warnhoff and co-workers (23) on the rearrangement of α-acetoxyketones (Scheme 6) was a particularly relevant example of the anticipated rearrangement shown in Scheme 4. Although this specific example (Scheme 6) required rather high temperatures other similar rearrangements have been found to occur at lower temperatures (24).

Satoh and co-workers (25*a* and *b*) and Warnhoff and Wang (25*c*) have found that refluxing 4β-bromo-5β-cholestan-3-one in acetic acid containing sodium acetate yields 2β-acetoxy-5β-cholestan-3-one in good yield (Scheme 7).



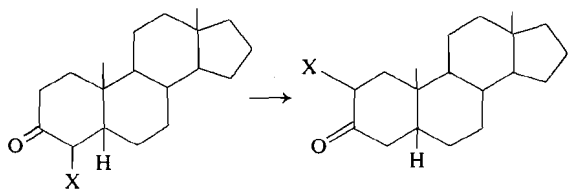
SCHEME 2. Beckmann rearrangement of a 5β-androstan-3-one.



SCHEME 3. Baeyer–Villiger oxidation of a 5β-androstan-3-one.

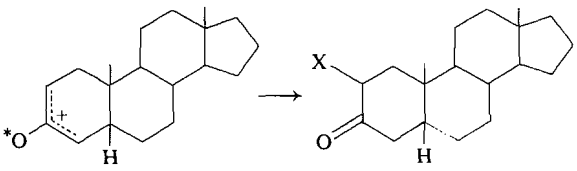
It was not clear how this transformation occurred (*vide infra*) but it did appear to meet our objectives of introducing a substituent at C-2 in a 5β-steroid. Treatment of bromoketone **16** (26) under the same conditions as in Scheme 7 (25) gave 2β,17β-diacetoxy-5β-androstan-3-one (**17**) in *ca.* 70% yield. Either pure bromoketone **16** or the crude mixture of bromoketones from the bromination of **5** could be used with essentially the same overall results. Bromination of **5** gives a 4:1 mixture of two bromoketones, by v.p.c., and the major product is **16** and the minor product probably is 2β-bromoketone.

The structure **17** for the acetoxyketone derived



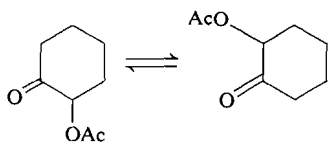
13 14

SCHEME 4



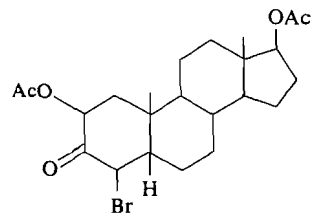
15 14

SCHEME 5



SCHEME 6

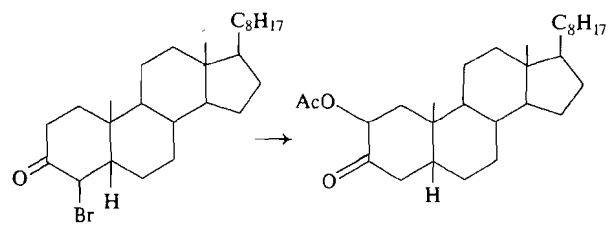
from **16** followed from its analytical and spectral properties. In particular the n.m.r. spectrum of the acetoxyketone had a double doublet (J = 6 and 14 Hz) at δ 5.15 which is assigned to the 2α-hydrogen, a broad triplet (J = 13 Hz) at δ 2.81 assigned to the 4α-hydrogen, and a double doublet (J = 5 and 13 Hz) at *ca.* δ 2.2 assigned to the 4β-hydrogen. Zinc – acetic acid reduction of the acetoxyketone gave **5** which indicates that no acyloxy–ketone exchange had occurred (23,25*c*). Also, bromination of the acetoxyketone gave a monobrominated derivative which had an n.m.r. spectrum consistent only with structure **18**. The salient features in the n.m.r. spectrum of



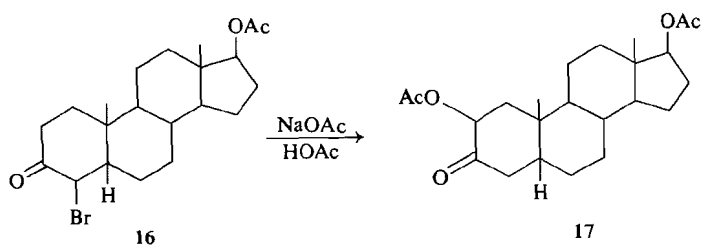
18

18 are a doublet (J = 13 Hz) at δ 4.98 assigned to the 4α-hydrogen and a double doublet (J = 5 and 13 Hz) at δ 5.21 assigned to the 2α-hydrogen. All of these physical and chemical properties are consistent only with structure **17** for the acetoxyketone; also this product is not unexpected in view of the previous *cine* substitution reactions of bromoketones (25,26).

The mechanism of this transformation has been the subject of several reports in recent years. There are several possible mechanisms for the reactions in Schemes 7 and 8. One possibility would involve direct displacement of the bromine at C-4 of **16** to give a 4-acetoxy compound which could rearrange to the 2-acetoxy isomer (Schemes 4 and 6). This possibility was



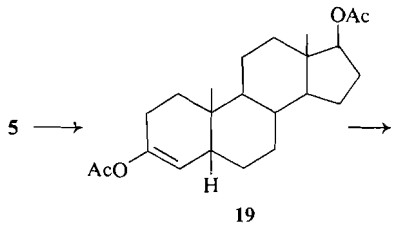
SCHEME 7



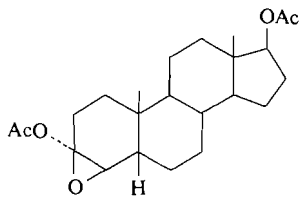
16 **17**

SCHEME 8

tested as follows. Ketone **5** was converted into the enol acetate **19** using the procedure of Liston (11). Compound **19** was contaminated with *ca.*



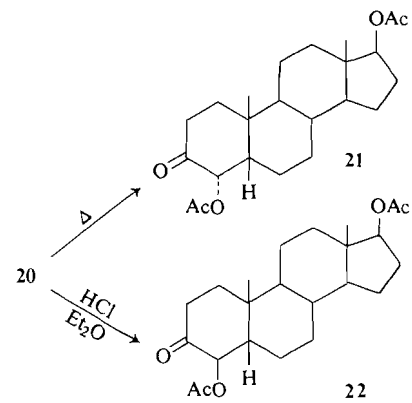
19



20

3% of the isomeric enol acetate but this did not interfere with the subsequent reactions. Enol acetate **19** was epoxidized with *m*-chloroperbenzoic acid – sodium bicarbonate (27) to give the β-epoxide **20** in over 80% yield. The configuration of the epoxidation product **20** was assigned as follows. The β-face of **19** appears to be the sterically more accessible direction for peracid attack (28). The n.m.r. spectrum of **20** has a singlet at δ 3.07 which is assigned to the C-4 hydrogen. Examination of the Dreiding model of **20** indicates that the dihedral angle between the hydrogens on C-4 and C-5 is *ca.* 100° and the dihedral angle between the hydrogens on C-4 and C-5 in the isomeric α-epoxide is *ca.* 50°. In an extensive study of steroidal epoxides and episulfides it was found that the coupling constant of these hydrogens on C-4 and C-5 could approach zero only for dihedral angles of 70–100° while a coupling constant of at least 2 Hz is expected for a dihedral angle of 50° (29). Furthermore, the chemical shift of the C-19 methyl hydrogens in **20** is δ 0.87 which agrees well with that of the C-19 hydrogens of 3β-4β-oxido-5β-cholestane at δ 0.87 (30).

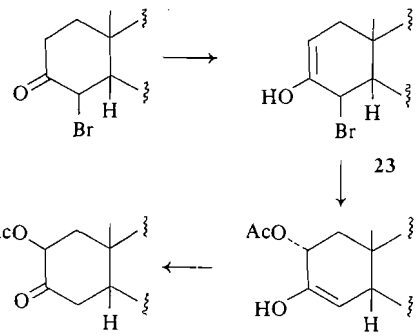
Pyrolysis of **20** at 160° for 5 min gave 4α,17β-diacetoxy-5β-androstan-3-one (**21**) in good yield. The salient feature of the n.m.r. spectrum of **21** which suggested its structure was a one proton doublet (J = 8 Hz) at δ 5.41. This is assigned to the 4β-hydrogen of **21** which is probably in a boat conformation due to the severe interaction



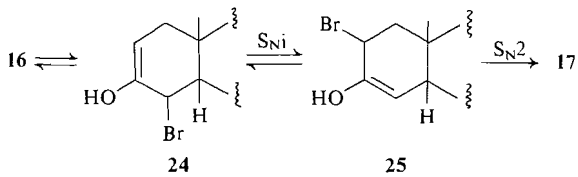
of the 4α-acetoxy group with C-7 and C-9 in the chair conformation. The 4β-isomer **22** was obtained by treating **20** with HCl in ether, and the n.m.r. spectrum of **22** has a one proton doublet (J = 12 Hz) at δ 5.52 which is assigned to the 4α-hydrogen. These epoxide rearrangements parallel those of 2α,3α-oxido-3β-acetoxycholestane (31). When the 4β-acetoxy isomer **22** was subjected to refluxing acetic acid containing sodium acetate, that is, the conditions for reaction in Scheme 8, the starting material was recovered unchanged. Also, the 4α-isomer **21** was cleanly converted into the 4β-isomer **22** on refluxing in acetic acid – sodium acetate. In neither case could any of the 2β-isomer **17** be detected. These experiments indicate that **21** and **22** are not intermediates in the *cine* substitution (Scheme 8). In fact, **21** or **22** did not rearrange to the 2-acetoxy compound even on thermolysis at 160°.

Satoh and Takahashi have detected an intermediate in this reaction in the cholestane system (Scheme 7) and they have suggested that this intermediate is the 2α-acetoxy isomer (32). The above results corroborate this suggestion. Satoh and Takahashi suggest that this involves a *trans* S_N2' displacement on the enol **23** as shown in Scheme 9 (32). Most S_N2' reactions involve a *cis* relation between the entering nucleophile and the leaving group. Also it would appear that the α-face of enol **23** would be more sterically shielded than the β-face, although Satoh and Takahashi suggest that ring B of **23** may be in a boat conformation.

We also considered the possibility of a S_Ni rearrangement of the enol **24** to **25** followed by a S_N2 reaction as shown in Scheme 10. However, Liston has found that the bromoketone **16**

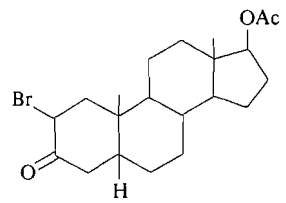


SCHEME 9. Proposed mechanism for *cine* substitution.



SCHEME 10. S_Ni and S_N2 routes for *cine* substitution.

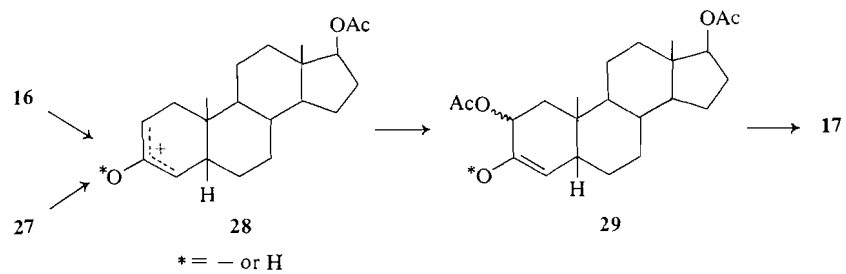
and the 2β-bromo isomer **27** are not interchanged or equilibrated even in HBr—HOAc (11). This would suggest that the S_Ni rearrangement of **24** to **25** is not occurring under our reaction conditions. We have synthesized the 2β-bromo isomer **27** following the method



developed by Hanson and Organ (33), which involved bromination of the enolate of the 2-hydroxymethylene derivative of **5** and in this way the bromine was directed exclusively to the 2 position. Bromoketone **27** was converted to **17** in refluxing acetic acid – sodium acetate at a similar rate for reaction of **16** (Scheme 8). Detailed rate studies were not performed and only the appearance of product **17** was monitored but these results would suggest that **16** and **27** were going to a common intermediate which reacts with acetate in the slow step to give eventually **17**. This possibility is shown in Scheme 11. It is not clear if the intermediate **28** is the zwitterion or the protonated oxyallyl system. A similar mechanism has been previously proposed in the reaction of steroidal bromoenones (34), and more recently in the reaction of α,α'-dibromoketones with acetate in the presence of diiron nonacarbonyl (35) and for the reaction of a range of steroidal bromoketones with sodium acetate (25*c*).

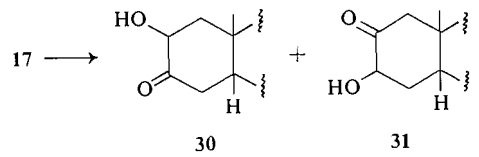
If **28** is an intermediate in this reaction, then the presence of the three contiguous sp^2 carbons in ring A will substantially flatten this ring. Examination of molecular models of this system show that α-attack at C-4 is severely hindered by the C-7 methylene group, β-attack at C-4 introduces torsional strain as the nucleophile enters eclipsed to the C-5 hydrogen, β-attack at C-2 also introduces torsional strain, and attack at the α-face of C-2 is not as sterically or torsionally hindered as the other sites. Thus it is reasonable to expect that the 2α-isomer could result from reaction of **28** and it is subsequently isomerized to the 2β-isomer **17** under the reaction conditions.

Having introduced a substituent at C-2 of **5** we now examined methods to unsymmetrically cleave the C_2—C_3 bond. Mild basic hydrolysis of **17** gave a mixture of the two hydroxyketones **30** and **31** in *ca.* a 1:1 ratio, which precluded using oxidative cleavage of the hydroxyketone **30**. However, treatment of **17** with hydroxylamine in refluxing methanol gave the hydroxyoxime **32** in good yield. The molecular formula of this compound was established by mass

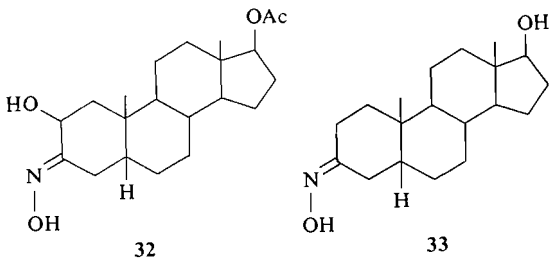


* = – or H

SCHEME 11. Proposed mechanism for *cine* substitution.

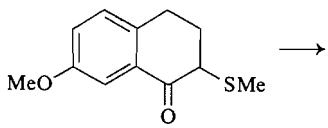


30 31

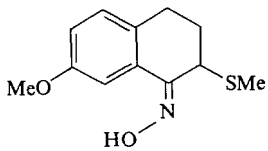


32 33

spectroscopy and analysis. The n.m.r. spectrum confirmed that the ring A acetate had been hydrolyzed and that the hydroxyl group was retained at C-2. A double doublet (J = 5 and 13 Hz) at δ 4.20 was assigned to the 2α-hydrogen and a second double doublet (J = 4 and 14 Hz) at δ 2.79 was assigned to the 4β-hydrogen. Oka and Hara (14*a*) have shown that the equatorial hydrogen *syn* to the OH of a number of steroidal oximes is deshielded and found at lower field than the methylene envelope. For example, the 4β-hydrogen in **33** is a double doublet (J = 5 and 15 Hz) at δ 2.93 (14*a*). The 4β-hydrogen of the isomeric oxime remains engulfed in the methylene envelope and the 2β-hydrogen is a double triplet ($J \simeq$ 4.5 and 14 Hz) at δ 3.08. This would suggest that our oxime has the stereochemistry shown in **32**. Since the acetoxy group at C-17 remained it would appear that the hydrolysis of the C-2 acetate is facilitated by the neighboring oximino group. It is also interesting to note that Autrey and Scullard found that oximation of ketone **34** gave the *anti*-oxime **35** which would appear to be more sterically crowded isomer (36).

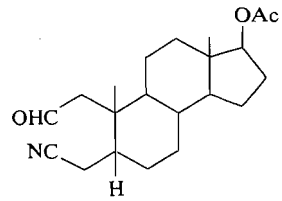


34



35

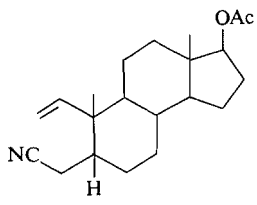
Beckmann fragmentation (37) of oxime **33** to give the cyanoaldehyde **36** was effected in low yield with tosyl chloride and pyridine, or better with thionyl chloride at −20° followed by treatment with 3 *N* potassium hydroxide (38). The n.m.r. spectrum of **36** has a double doublet



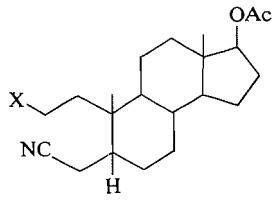
36

($J \simeq$ 1 and 3 Hz) at δ 9.85 due to the aldehyde proton, which is coupled to the two adjacent diastereotopic protons (39). An INDOR n.m.r. experiment was performed on this compound by monitoring the aldehyde peaks while sweeping a perturbing radio-frequency field through the steroidal methylene envelope. A pair of double doublets were found at δ 2.07 (J = 4.0 and 14.5 Hz) and δ 2.52 (J = 1.4 and 14.5 Hz) (40). This indicated that the OHC—CH_2 group was isolated by a quaternary carbon and was compatible only with structure **36** for the product from the Beckmann fragmentation. In this way we had achieved the desired cleavage of ring A in **5**.

The cyanoaldehyde **36** was the key intermediate in our synthesis of the salamander alkaloids. This compound can be converted into the samine family (**1**) by reduction of the aldehyde and nitrile of **36**, and cyclization (41). This material can also be converted to the olefin **37** which has been converted to samandarine (**3**) (4) and thus this would constitute a formal synthesis of the samandarine family. Several attempts to convert the alcohol **38**, readily

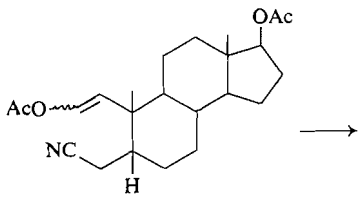


37

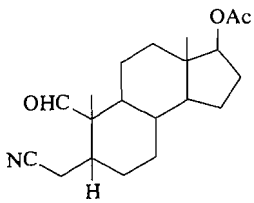


38

available from the sodium borohydride reduction of **36**, into **37** were unsuccessful (19). However, the aldehyde of **36** could be converted into the corresponding enol acetates **39**. The



39



40

n.m.r. spectrum of the mixture of enol acetates suggested that the *cis* and *trans* isomers of **39** were present in *ca.* 1:1 ratio. Ozonolysis of **39** with a reductive work-up gave the cyanoaldehyde **40** in good yield and this compound was converted into **37** by Wittig reaction and subsequent reacylation of the C-17 hydroxyl. A more detailed discussion of the chemistry of intermediates **36–40** is anticipated at a later date.

Experimental

Melting points, which were determined on a Kofler hot stage, and boiling points are uncorrected. Optical rotations were recorded at the sodium D line using a Perkin-Elmer Model 141 Automatic Polarimeter. Ultraviolet spectra were measured in methanol solution on a Unicam model SP800 or Cary Model 14 spectrophotometer. The i.r. spectra were recorded on a Perkin-Elmer model 700 spectrophotometer and were calibrated using the 1601 cm^{-1} band of polystyrene. The ^1H n.m.r. spectra were recorded in deuteriochloroform solution on either a Varian T-60 or Varian HA-100 spectrometer. Line positions are given in the δ scale, with tetramethylsilane as internal standard; the multiplicity, coupling constant, integrated peak areas, and proton assignments are indicated in parentheses. The mass spectra were obtained using an Atlas CH-4 mass spectrometer and high resolution determinations were performed on an AEI MS-9 mass spectrometer. Microanalyses were performed by Mr. Peter Borda, University of British Columbia. The v.p.c. analyses were performed with a Varian Aerograph 90-P-3 using column *A*, 8 ft × ¼ in. column of 5% fluoro silicone (QF-1) on 60–80 mesh Diaport "S"; column *B*, 5 ft × ¼ in. column of 3% SE 30 on Chromosorb W; and column *C*, 5 ft × ¼ in. column of 10% carbowax on 60–80 mesh Chromosorb W; or with a Perkin-Elmer Model 900 using column *D*, 6 ft × ⅛ in. column of 8% SE 30 on 80–100 mesh Chromosorb W. The specific column used, along with the column temperature and carrier gas (helium) flow-rate (in ml/min) are indicated in parentheses. Silica gel GF-254 and a Woelm neutral alumina were used for t.l.c. Silica gel PF-254 and aluminum oxide F-254 were used for preparative-layer chromatography. Silica gel, Woelm alumina, and Fluorisil (100–200 mesh) were used for column chromatography.

17β-Acetoxy-5β-androstan-3-one (5) (11)

The hydrogenation of testosterone (5.0 g, 0.017 mol) was carried out by employing the procedure of Liston (11) to yield 4.98 g of a crystalline product, m.p. 123–127°. To a solution of this material (4.98 g) in dry pyridine (20 ml) was added acetic anhydride (5 ml). The solution was stirred at room temperature for 16 h, then diluted with water (200 ml), and shaken for 15 min. The precipitate was collected, washed with 1 *N* hydrochloric acid (100 ml) and with water (100 ml), and air dried. Vapor phase chromatographic analysis (column *A*, 225°, 60 ml/min) of the crude product indicated 75% of 17β-acetoxy-5β-androstan-3-one (**5**) and 25% of 17β-acetoxy-5α-androstan-3-one (retention times 7.5 and 8.6 min, respectively). Recrystallization from ether afforded 2.19 g (38%) of 17β-acetoxy-5β-androstan-3-one (**5**), m.p. 142–144°, $[\alpha]_D^{25}$ +43° (c, 1 MeOH) (lit. (42) m.p. 140–142°, $[\alpha]_D^{25}$ +45.2°); i.r. ($CHCl_3$), 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.78 (singlet, 3H, C-18 CH_3), 1.03 (singlet, 3H, C-19 CH_3), 2.03 (singlet, 3H, acetate), 4.63 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$); mass spectrum *m/e* (relative intensity), 332(49), 272(85), 257(32), 230(16), 214(12), 160(20), 148(35), 42(100).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.86; H, 9.52.

Baeyer–Villiger Oxidation of 5

To a solution of 17β-acetoxy-5β-androstan-3-one (**5**, 200 mg, 0.60 mmol) in chloroform (15 ml) was added *meta*-chloroperbenzoic acid (155 mg, 0.90 mmol). The reaction mixture was stirred in the dark at room temperature for 2 days. The solution was then poured into saturated sodium bicarbonate solution (30 ml) and extracted with chloroform (40 ml). The chloroform solution was washed with water (2 × 10 ml) and saturated sodium chloride solution (2 × 10 ml), dried over sodium sulfate, and filtered. The solvent was removed by evaporation under reduced pressure to afford 180 mg (85%) of a mixture of compounds **8** and **9** as a crystalline solid, m.p. 118–125°. Thin-layer chromatographic analysis of this product on silica gel with ethyl acetate as the eluant indicated the presence of two compounds, R_f 0.58 and R_f 0.61. Vapor phase chromatographic analysis (column *B*, 300°, 60 ml/min) of the crude product showed two peaks (retention times 18 and 31 min) in *ca.* a 1:4 ratio. An analytical specimen was obtained by three recrystallizations from methanol, m.p. 207–208°; i.r. ($CHCl_3$), 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.80 (singlet, 3H, C-18 CH_3), 1.03 (singlet, 3H, C-19 CH_3), 2.00 (singlet, 3H, acetate), 3.8–4.8 (multiplet, 3H, C-17 $H\alpha$ and C-2 H_2 **9**, C-4a H_2 **8**); mass spectrum *m/e* (relative intensity), 348(15), 288(25), 260(9), 94(100).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.30; H, 9.25. Found: C, 72.02; H, 9.48.

Hydrolysis and Esterification of 8 and 9

A solution of compounds **8** and **9** (100 mg, 0.258 mmol), obtained above, in 5% methanolic sodium hydroxide (30 ml) was heated to reflux. After 2 h of refluxing, the reaction mixture was cooled and the solvent

removed under reduced pressure. The residue was dissolved in water (30 ml) and carefully acidified with dilute acetic acid, and extracted with chloroform (2 × 30 ml). The combined chloroform extracts were washed with saturated sodium chloride (2 × 10 ml), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to yield 100 mg of a crystalline solid, m.p. 185–189°. To a solution of this material (100 mg, 0.30 mmol) in methanol (30 ml) was added a solution of diazomethane in ether (0.35 mmol). After stirring the reaction mixture at room temperature for 5 min the solvent was removed under reduced pressure to yield 66 mg (75%) of a mixture of hydroxy methyl esters as an oil. Attempts to induce crystallization failed. The t.l.c. of this material on silica gel with ethyl acetate as the solvent system showed one broad spot, R_f 0.80; i.r. ($CHCl_3$), 3600, 3450, 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.73 (singlet, 3H, C-18 CH_3), 0.98 and 1.07 (singlets, 3H, C-19 CH_3), *ca.* 3.65 (multiplet, 3H, C-2 H_2 and C-17 $H\alpha$), 3.68 (singlet, 3H, methyl ester group); mass spectrum *m/e* (relative intensity), 338(8), 320(11), 306(76), 274(100), 263(65), 233(84).

Mol. wt. Calcd. for $C_{20}H_{34}O_4$: 338.2456. Found: 338.2442.

*Preparation of a Mixture of Methyl 17β-Hydroxy-2-tosyloxy-2,3-seco-5β-androstan-3-oate (**11**) and Methyl 17β-Hydroxy-2-tosyloxy-2,3-seco-5β-androstan-3-oate (**10**)*

To a pyridine solution of hydroxy esters from the previous experiment (30 mg, 0.088 mmol) was added *p*-toluenesulfonyl chloride (17.1 mg, 0.089 mmol). The reaction mixture was allowed to stand at 20° for 2 days. The pyridine was removed under reduced pressure and the resulting residue dissolved in ethyl ether (40 ml). The ethereal solution was washed with 1 *N* hydrochloric acid (4 × 10 ml), 1 *N* sodium hydroxide (4 × 10 ml), and saturated sodium chloride solution (2 × 10 ml), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to yield 39.3 mg (88%) of a mixture of the tosyloxy methyl esters **10** and **11** as a clear oil. Attempts to induce crystallization failed. The t.l.c. of this material on silica gel with various solvent systems showed one broad spot; i.r. ($CHCl_3$), 3600, 3400, 1720, 1600, 1190 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.71 and 0.73 (singlets, 3H, C-18 CH_3), 0.93 and 0.95 (singlets, 3H, C-19 CH_3), 2.45 (singlet, 3H, tosyl CH_3), 3.33 (singlet, 3H, methyl ester CH_3), *ca.* 3.6 (multiplet, 1H, C-17 $H\alpha$), 4.10 (multiplet, 2H, C-2 H_2 **11** and C-4 H_2 **10**), 7.32 and 7.80 (doublets, J = 9 Hz, 4H, tosylate group); mass spectrum *m/e* (relative intensity), 492(1), 474(1), 460(1), 305(3), 304(4), 288(3), 287(4), 234(12), 233(30), 215(30), 187(20), 91(100).

*Methyl 17β-Hydroxy-3,4-seco-androst-4-en-3oate (**12**)*

A mixture of compounds **10** and **11** (160 mg, 0.32 mmol) from the previous experiment was added to collidine (10 ml). The reaction mixture was refluxed for 4 h under an atmosphere of nitrogen. The solvent was removed by evaporation under reduced pressure to afford a brown oil which was dissolved in ethyl ether (35 ml). The ether solution was washed with saturated sodium bicarbonate (2 × 10 ml) and sodium chloride (2 × 10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to yield a brown oil which was chromatographed on a 20 × 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of benzene and ethyl acetate (1:1, v/v) as the eluant. After elution, the band lying in the region R_f 0.55–0.60 was removed and extracted with ethyl acetate (50 ml). The solvent was removed under reduced pressure to afford 35.5 mg (extrapolated yield, 32%) of methyl 17β-hydroxy-3,4-seco-5-androst-4-en-3-oate (**12**) as a clear oil. Attempts to induce crystallization failed; i.r. ($CHCl_3$), 3600, 3450, 1720, 1630, 900 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.93 (singlet, 3H, C-18 CH_3), 1.03 (singlet, 3H, C-19 CH_3), *ca.* 3.5 (multiplet, 1H, C-17 $H\alpha$), 3.63 (singlet, 3H, ester group), 4.65 (doublet, 2H, C-4 H_2, J = 4 Hz); mass spectrum *m/e* (relative intensity), 320(5), 234(6), 233(25), 215(12), 205(6), 187(9), 160(10), 62(100).

Mol. wt. Calcd. for $C_{20}H_{32}O_3$: 320.2351. Found: 320.2327.

*17β-Acetoxy-4β-bromo-5β-androstan-3-one (**16**) (26)*

To a solution of 17β-acetoxy-5β-androstan-3-one (**5**, 9.197 g, 0.027 mol) in glacial acetic acid (50 ml) was added a solution of bromine (1.53 ml, 28.5 mmol) in acetic acid (40 ml) over a period of 20 min with vigorous stirring at 10°, decoloration of bromine was rapid, and 30 min later water (300 ml) was added and the mixture was allowed to stand for 1 h at 10°. The precipitated product was collected, washed with water (3 × 100 ml), and dissolved in ethyl ether (300 ml). The organic layer was washed with saturated sodium chloride (2 × 20 ml) solution, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to give 10.44 g (92%) of a crystalline solid, m.p. 135–151°. Vapor phase chromatographic analysis (column *D*, 250°, 45 ml/min) of this product indicated the presence of two compounds (retention times 9.0 and 8.9 min) in *ca.* a 4:1 ratio. Two recrystallizations from ethyl ether gave compound **16** as a crystalline solid, m.p. 174–175°, $[\alpha]_D$ +43.0° (c, 1 MeOH) (lit. (26) m.p. 174–175°, $[\alpha]_D$ +44.7 ± 2° $CHCl_3$); i.r. ($CHCl_3$), 1730 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.82 (singlet, 3H, C-18 CH_3), 1.10 (singlet, 3H, C-19 CH_3), 2.03 (singlet, 3H, acetate), 4.63 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 5.0 (doublet, J = 12 Hz, 1H, C-4 H_{ax}); mass spectrum *m/e* (relative intensity), 412(30), 410(30), 353(70), 351(70), 333(100), 332(70), 273(100), 258(80), 245(70), 273(100).

*2β,17β-Diacetoxy-5β-androstan-3-one (**17**)*

A solution of crude 17β-acetoxy-4β-bromo-5β-androstan-3-one (**16**, 10.3 g, 0.025 mol) and anhydrous sodium acetate (50.2 g, 0.612 mol) in glacial acetic acid (730 ml) was refluxed for 2.5 h. After cooling the solution was poured into water (500 ml) and extracted with ethyl ether (2 × 200 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate (4 × 50 ml) and saturated sodium chloride (2 × 50 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford a crystalline residue. Recrystallization of the residue from methanol gave 6.80 g (70%) of diacetate **17**, m.p. 170–173°. Vapor phase chromatographic analysis (column *D*, 250°, 45 ml/min) indicated the presence of one compound (retention time 16.8 min). The analytical specimen was obtained by two recrystallizations from methanol, m.p. 161–162°; i.r. ($CHCl_3$), 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.80 (singlet,

3H, C-18 CH_3), 1.05 (singlet, 3H, C-19 CH_3), 2.00 (singlet, 3H, acetate), *ca.* 2.2 (double doublet, J = 5 and 13 Hz, 1H, C-4 H_β), 2.81 (broad triplet, J = 13 Hz, 1H, C-4 $H\alpha$), 4.57 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 5.15 (double doublet, J = 6 and 14 Hz, 1H, C-2 $H\alpha$); mass spectrum *m/e* (relative intensity), 390(4), 348(15), 346(9), 331(7), 330(30), 304(10), 288(14), 270(12), 55(100).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.77. Found: C, 70.70; H, 8.82.

*Zinc – Acetic Acid Reduction of 2β,17β-Diacetoxy-5β-androstan-3-one (**17**)*

To a solution of diacetate **17** (100 mg, 0.25 mmol) in glacial acetic acid (30 ml) was added dry zinc dust (500 mg). The reaction mixture was refluxed for 30 h, then cooled, and poured into water (50 ml). The aqueous solution was extracted with ethyl ether (3 × 30 ml). The combined ethereal extracts were washed with water (3 × 10 ml), saturated sodium bicarbonate (3 × 10 ml), and sodium chloride (2 × 10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 72.5 mg of a yellow oil which was chromatographed on a 5 × 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluant. After elution, the band lying in the region R_f 0.52–0.59 was removed and extracted with ethyl acetate (50 ml). The solvent was removed by evaporation under pressure to yield 25.7 mg (extrapolated yield, 31%) of a clear oil. This material was identical (t.l.c., i.r., n.m.r., and mass spectrum) with 17β-acetoxy-5β-androstan-3-one (**5**).

*4β-Bromo-2β,17β-diacetoxy-5β-androstan-3-one (**18**)*

A solution of diacetate **17** (95 mg, 0.24 mmol) in 25 ml of glacial acetic acid was treated with bromine (12.4 μl, 0.23 mmol). The bromine color had disappeared after 2 h, and the acetic acid solution was poured into water (100 ml) and extracted with ethyl ether (150 ml). The ether was washed with saturated sodium bicarbonate (50 ml) and brine (50 ml), dried over sodium sulfate, filtered, and the solvent removed under reduced pressure to yield 120 mg of clear oil. This material was purified by t.l.c. on silica gel with chloroform development to yield 84 mg (74%) of **18** as a clear oil; i.r. ($CHCl_3$), 1735, 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.82 (singlet, 3H, C-18 CH_3), 1.15 (singlet, 3H, C-19 CH_3), 2.05 (singlet, 3H, acetate), 2.17 (singlet, 3H, acetate), 4.64 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 4.98 (doublet, J = 13 Hz, 1H, C-4 $H\alpha$), 5.21 (double doublet, J = 5 and 13 Hz, 1H, C-2 $H\alpha$);

Mol. Wt. Calcd. for $C_{23}H_{33}O_5Br$: 468.1512 and 470.1492. Found: 468.1506 and 470.1501.

*3,17β-Diacetoxy-5β-androst-3-ene (**19**) (11)*

To a solution of 17β-acetoxy-5β-androstan-3-one (**5**, 250 mg, 0.75 mmol) in isopropenyl acetate (5 ml) was added hydroquinone (30 mg) and concentrated sulfuric acid (10 μl) under an atmosphere of nitrogen. The reaction mixture was heated to a gentle reflux and the acetone formed during the reaction was collected. Isopropenyl acetate was periodically added to maintain a solvent volume of *ca.* 5 ml. After refluxing under nitrogen for 2 h, the reaction mixture was cooled to 0° and diluted with ethyl ether (30 ml). This organic mixture was washed with saturated sodium bicarbonate (3 × 25 ml) and sodium chloride (15 ml) solutions, dried over sodium sulfate, and filtered. The solvent was distilled to afford 361 mg of a light yellow oil. Vapor phase chromatographic analysis (column *A*, 225°, 60 ml/min) of the crude product indicated the presence of 59% 3,17β-diacetoxy-5β-androst-3-one (**19**) and 23% 3,17β-diacetoxy-5β-androst-2-ene (retention times 12 and 14 min, respectively); i.r. ($CHCl_3$), 1750, 1725, 1685 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.88 (singlet, 3H, C-18 CH_3), 2.02 and 2.10 (singlets, 6H, acetates), 4.64 (triplet, J = 9 Hz, 2H, C-17 $H\alpha$), 5.05 (singlet, C-4 H), 5.20 (multiplet, C-2 H).

Equilibration of Enol Acetates (11)

The enol acetate mixture from above (150 mg) was dissolved in benzene (12 ml), carbon tetrachloride (6 ml), and acetic anhydride (2.4 ml). To this solution was added 70% perchloric acid (30 μl) under an atmosphere of nitrogen. The reaction mixture was stirred under nitrogen at room temperature for 22 h. Then the reaction mixture was poured into ethyl ether (50 ml) and washed with water (25 ml), saturated sodium bicarbonate (4 × 20 ml), and sodium chloride (20 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed by evaporation under reduced pressure to yield 121 mg of a light yellow oil. Vapor phase chromatographic analysis (column *A*, 225°, 60 ml/min) of this product indicated 88% of 3,17β-diacetoxy-5β-androst-3-ene (**19**, retention time 12 min) and 2% of 3,17β-diacetoxy-5β-androst-2-ene (retention time 14 min); i.r. ($CHCl_3$), 1750, 1725, 1685, 1660 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.88 (singlet, 3H, C-18 CH_3), 0.98 (singlet, 3H, C-19 CH_3), 2.03 (singlet, 3H, acetate), 2.11 (singlet, 3H, vinyl acetate), 4.64 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 5.05 (singlet, 1H, C-4 H).

*3α,17β-Diacetoxy-3β,4β-oxido-5β-androstane (**20**)*

The equilibrated enol acetate mixture containing predominantly compound **19** (53 mg, 0.14 mmol) was dissolved in chloroform (5 ml). To this solution was added *m*-chloroperoxybenzoic acid (70 mg, 0.40 mmol) and sodium bicarbonate (50 mg). The reaction mixture was stirred at 0° for 4 h and then allowed to stand at −5° for 40 h. The reaction mixture was poured into cold saturated sodium bicarbonate solution (10 ml) and extracted with ethyl ether (3 × 10 ml). The organic layer was separated and washed with 20% sodium carbonate (3 × 15 ml) and saturated sodium chloride (10 ml) solutions, dried over sodium sulfate, and filtered. Removal of the solvent under reduced pressure afforded 46 mg (84%) of β-epoxide **20** as a light yellow oil, with no trace of the starting enol acetate **19** by v.p.c.; i.r. ($CHCl_3$), 1720–1745, 860 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.80 (singlet, 3H, C-18 CH_3), 0.87 (singlet, 3H, C-19 CH_3), 2.03 (singlet, 3H, acetate), 2.07 (singlet, 3H, acetate), 3.07 (singlet, 1H, C-4 H), 4.64 (triplet, 1H, C-17 $H\alpha$).

Mol. Wt. Calcd. for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2417.

*4β,17-Diacetoxy-5β-androstan-3-one (**21**)*

3α,17β-Diacetoxy-3β,4β-oxido-5β-androstan-3-one (**20**, 25 mg, 0.064 mmol) was pyrolyzed at 160° for 5 min under an atmosphere of nitrogen to afford 20.0 mg (80%) of compound **21**. Vapor phase chromatographic analysis (column *A*, 225%, 60 ml/min) of this product indicated one compound (retention time 24 min); i.r. ($CHCl_3$), 1740, 1725 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.79 (singlet, 3H, C-18 CH_3), 1.10 (singlet, 3H, C-19 CH_3), 2.03 (singlet,

3H, acetate), 2.15 (singlet, 3H, acetate), 4.62 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 5.41 (doublet, J = 8 Hz, 1H, C-4 H_β).

Mol. Wt. Calcd. for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2400.

4β,17β-Diacetoxy-5β-androstan-3-one (22)

Hydrogen chloride was bubbled through a stirred solution of 3α,17β-diacetoxy-3β,4β-oxide-5β-androstane (**20**, 25 mg, 0.064 mmol) in ethyl ether at 12° for 5 min. The solution was stirred for 30 min, then allowed to stand at −5° for 20 h. The reaction mixture was diluted with ethyl ether (30 ml), washed with saturated sodium bicarbonate (3 × 20 ml), and sodium chloride (20 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed by evaporation under reduced pressure to afford 20.0 mg (80%) of crude compound **22**. Vapor phase chromatographic analysis (column *A*, 225°, 60 ml/min) of the crude product indicated the presence of one compound (retention time 24 min); i.r. ($CHCl_3$), 1740, 1725 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.79 (singlet, 3H, C-18 CH_3), 1.07 (singlet, 3H, C-19 CH_3), 2.02 (singlet, 3H, acetate), 2.15 (singlet, 3H, C-4 acetate), 4.61 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 5.52 (doublet, J = 12 Hz, 1H, C-4 $H\alpha$).

Mol. Wt. Calcd. for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2409.

*Isomerization Studies of **21** and **22***

(*a*) To a solution of 4α,17β-diacetoxy-5β-androstan-3-one (**21**, 19 mg, 0.048 mmol) in hexamethylphosphoramide (1.5 ml) was added a crystal of *p*-toluenesulfonic acid and the reaction mixture was heated under nitrogen at 160° for 15 min. The reaction mixture was then cooled to room temperature and diluted with ethyl ether (25 ml). This organic layer was washed with water (3 × 20 ml), saturated sodium bicarbonate (2 × 15 ml), and sodium chloride (15 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 12 mg of compound **22** with no trace of compound **21** detectable by n.m.r. spectroscopy or t.l.c.

(*b*) To a solution of 4α,17β-diacetoxy-5β-androstan-3-one (**21**, 30 mg, 0.076 mmol) in glacial acetic acid (4.5 ml) was added sodium acetate (300 mg, 3.65 mmol). The reaction mixture was refluxed under an atmosphere of nitrogen for 2 h. The reaction mixture was then cooled to 0°, diluted with cold water (25 ml), and extracted with ethyl ether (3 × 25 ml). The extracts were washed with saturated sodium bicarbonate (3 × 20 ml) and sodium chloride (2 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 19 mg (63%) of 4β,17β-diacetoxy-5β-androstan-3-one (**22**).

(*c*) Compound **22** was recovered unchanged in 83% yield when subjected to conditions in *a* above and in 76% yield when subjected to conditions in *b* above.

2-Hydroxymethylene-5β-androstan-17β-ol-3-one (21f)

To a suspension of sodium hydride (31.2 mg, 1.3 mmol) in dry benzene (5 ml), under nitrogen, was added absolute methanol (40 ml). The mixture was stirred and heated briefly to boiling. After the mixture was cooled to room temperature, 17β-hydroxy-5β-androstan-3-one (200 mg, 0.68 mmol) and ethyl formate (50.3 mg, 0.68 mmol) were added. The mixture was stirred at room temperature under nitrogen for 30 h. After the careful addition of water (10 ml) to destroy the excess sodium hydride, the mixture was diluted with water (5 ml) and ethyl ether (25 ml). The ether–benzene layer was separated and re-extracted with water (10 ml). The combined aqueous layers were washed once with ethyl ether (10 ml) and then neutralized with carbon dioxide to p*H* 7. The mixture was filtered and the collected solid washed thoroughly with water (3 × 20 ml). Recrystallization of this material from acetonitrile gave 131 mg (60%) of the hydroxymethylene derivative as a crystalline solid, m.p. 153–159° (evacuated sealed tube), $[\alpha]_D^{25}$ +30.2° (c, 1 MeOH), λ_{max} 290 mμ (ε 8000) (lit. (21*f*) m.p. 157–163°, $[\alpha]_D$ +26.9°, λ_{max} 284 mμ (ε 7900)).

17β-Acetoxy-2β-bromo-5β-androstan-3-one (27)

Following the method of Hanson and Organ (33) an ethyl ether solution (20 ml) of the above hydroxymethylene derivative (200 mg, 0.63 mmol) was extracted with 0.05 *N* sodium hydroxide (3 × 10 ml). The aqueous extracts were combined and treated with a solution of bromine (100 mg, 0.63 mmol) and potassium bromide (*ca.* 200 mg) in 5 ml of water. The bromine color was discharged immediately. The reaction mixture was stirred at room temperature for ½ h, acidified with concentrated hydrochloric acid and extracted with methylene chloride (4 × 15 ml). The extracts were combined, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield 82 mg of a white semisolid which was treated with acetic anhydride (1 ml) and pyridine (5 ml) overnight. This mixture was poured onto ice (10 g) and extracted with ethyl ether (3 × 15 ml). The ethereal extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate and water, dried over magnesium sulfate, filtered, and the solvents removed under reduced pressure to yield 80 mg of a pale yellow liquid which was chromatographed on sliica gel (25 g) using chloroform – ethyl acetate (6:1) as eluant. Fractions containing compound with R_f 0.7–0.8 on t.l.c. (silica gel, chloroform – ethyl acetate, 6:1) were combined and solvents removed under reduced pressure to yield a white solid which was recrystallized from acetone – isopropyl ether to yield 32 mg (12%) of **27**, m.p. 198–200° (lit. (11) m.p. 201–202°).

*Preparation of **17** from **27***

A solution of bromoketone **27** (15 mg, 0.036 mmol) and anhydrous sodium acetate (100 mg) in acetic acid (1 ml) was refluxed for 1.5 h and worked up as before for **17**, when no starting material could be detected by t.l.c. The yield of **17** was 11 mg (78%) of product m.p. 168–170°. A parallel reaction of bromoketone **16** gave 76% yield of **17** after 1.5 h. These products were compared with the previously prepared **17** by i.r., t.l.c., and v.p.c.

*Hydrolysis of **17***

To a solution of 2β,17β-diacetoxy-5β-androstan-3-one (**17**, 100 mg, 0.255 mmol) in methanol (4 ml) and water (1 ml) was added sodium bicarbonate (100 mg). The reaction mixture was heated at 50° for 30 min and then stirred for *ca*, 1 h at room temperature. The solvent was removed under reduced pressure and the resulting residue was dissolved in water (10 ml) and extracted with ethyl ether (2 × 10 ml). The combined ethereal extracts

were washed with saturated sodium chloride (2 × 5 ml), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 75 mg (84%, crude) of a mixture of 17β-acetoxy-2β-hydroxy-5β-androstan-3-one (**30**) and 17β-acetoxy-3α-hydroxy-5β-androstan-2-one (**31**). Thin-layer chromatographic analysis of the crude product on silica gel with a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluant indicated the presence of two compounds, R_f 0.75 and R_f 0.78; i.r. ($CHCl_3$), 3350, 1720 cm^{-1}; n.m.r. ($CDCl_3$), 0.75 and 0.80, (singlets, 3H, C-18 CH_3), 1.03 and 1.10, (singlets, 3H, C-19 CH_3), 3.40–4.20 (multiplet, 1H, C-2 $H\alpha$, **30** and C-3 H_β, **31**), 4.60 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$).

anti-17β-Acetoxy-2β-hydroxy-5β-androstan-3-one Oxime (32)

A solution of 2β,17β-diacetoxy-5β-androstan-3-one (**17**, 5.10 g, 0.013 mol), hydroxylamine hydrochloride (21.0 g, 0.302 mol), and sodium acetate trihydrate (27.5 g, 0.202 mol) in 90% methanol (400 ml) was refluxed for 48 h and then the methanolic solution was concentrated to 20 ml under reduced pressure. Water (100 ml) was added to the solution and the resulting suspension was extracted with ethyl ether (2 × 200 ml). The combined ethereal extracts were washed with aqueous sodium bicarbonate (2 × 30 ml), and saturated sodium chloride (2 × 20 ml) solutions, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to afford 4.01 g (85%) of hydroxyoxime **32**, m.p. 176–182°. Thin-layer chromatographic analysis of this material on silica gel, using a mixture of ethyl acetate and benzene (5:1, v/v) as eluant, indicated one major compound, R_f 0.78. The analytical specimen was obtained by three recrystallizations from methanol, m.p. 214–215°, $[\alpha]_D^{25}$ +21.42° (c, 0.7 MeOH); i.r. ($CHCl_3$), 3550, 3350, 1720, 1660 cm^{-1}; n.m.r. ($CDCl_3$), 0.75 (singlet, 3H, C-18 CH_3), 0.97 (singlet, 3H, C-19 CH_3), 2.79 (double doublet, J = 4 and 14 Hz, 1H, C-4 H_β), 4.20 (double doublet, J = 5 and 13 Hz, 1H, C-2 $H\alpha$), 4.60 (triplet, 1H, C-17 $H\alpha$); mass spectrum *m/e* (relative intensity), 363(1), 362(6), 347(3), 345(4), 344(5), 334(17), 333(78), 316(6), 303(3), 271(3), 43(100).

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.62; H, 9.37; N, 4.02.

17β-Acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (36)

(*a*) To a solution of *anti*-17β-acetoxy-2β-hydroxy-5β-androstan-3-one oxime (**32**, 1.0 g, 2.75 mmol) in pyridine (45 ml) was added *p*-toluenesulfonyl chloride (500 mg, 2.62 mmol). The reaction mixture was refluxed under an atmosphere of nitrogen for 5 h. The solution was cooled, poured into dilute sodium bicarbonate solution (50 ml), and extracted with ethyl ether. The organic layer was separated and washed with water (4 × 20 ml), saturated sodium bicarbonate (2 × 15 ml), and sodium chloride (2 × 10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed by evaporation under reduced pressure to yield 985 mg of a brown oil. This material was chromatographed on a 20 × 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (5:1, v/v). After development, the band lying in the region R_f 0.62–0.68 was removed and extracted with ethyl acetate (100 ml). The solvent was removed by evaporation under reduced pressure to afford 190 mg (20%) of cyanoaldehyde **36** as a clear oil; i.r. ($CHCl_3$), 2750, 2250, 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.79 (singlet, 3H, C-18 CH_3), 1.32 (singlet, 3H, C-19 CH_3), 4.60 (triplet, 1H, C-17 $H\alpha$), 9.80 (double doublet, J = 1 and 3 Hz, 1H, CHO); mass spectrum *m/e* (relative intensity), 345(2), 318(5), 302(6), 301(11), 290(4), 258(7), 242(8), 241(16), 43(100).

Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.06. Found: C, 72.82; H, 9.16; N, 3.88.

(*b*) *anti*-17β-Acetoxy-2β-hydroxy-5β-androstan-3-one oxime (**32**, 1.0 g, 2.75 mmol) was treated with distilled thionyl chloride (10 ml) at −20° (methanol–ice). After 1.5 min the resulting colorless solution was at once slowly poured into a mixture of 3 *N* potassium hydroxide (300 ml) and diethyl ether (100 ml) at 0°. The organic phase was separated and the aqueous solution was extracted with ethyl ether (2 × 50 ml). The combined ethereal extracts were washed with saturated sodium chloride (2 × 50 ml) solution, dried over sodium sulfate, and filtered. The solvent was removed under pressure to afford 1.10 g of an oily residue which was chromatographed on fluorisil (50 g). Elution with a mixture of chloroform and benzene (1:2, v/v) afforded 805 mg (85%) of cyanoaldehyde **36** as a clear oil which crystallized on standing, m.p. 110–112°, $[\alpha]_D^{20}$ +23.3° (c, 1 MeOH). Cyanoaldehyde **36** was also converted into its 2,4-DNP derivative, m.p. 238–240°, for analysis.

Anal. Calcd. for $C_{27}H_{35}N_5O_6$: C, 61.70; H, 6.71; N, 13.32. Found: C, 61.90; H, 6.84; N, 13.13.

17β-Acetoxy-2-hydroxy-2,3-seco-5β-androstane-3-nitrile (38, X = OH)

To a solution of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (**32**; 80 mg, 0.23 mmol) in ethanol (10 ml) was added sodium borohydride (4.4 mg, 0.46 mmol), and the reaction mixture was stirred for 3 h at room temperature under an atmosphere of nitrogen. The solvent was removed under reduced pressure, water (20 ml) and ethyl ether (40 ml) were added to the residue. The organic layer was separated and the aqueous layer was extracted with ethyl ether (2 × 20 ml). The combined ethereal extracts were washed with 1 *N* hydrochloric acid (2 × 20 ml), saturated sodium bicarbonate (3 × 10 ml) and sodium chloride (10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to yield 80.2 mg of a crystalline solid. Recrystallization of this material from methanol yielded 68.1 mg (85%) of compound **38** (X = OH), m.p. 139–144°. An analytical specimen was obtained by two recrystallizations from methanol, m.p. 138–140°, $[\alpha]_D^{20}$ +34° (c, 5 MeOH); i.r. ($CHCl_3$), 3450, 2250, 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.75 (singlet, 3H, C-18 CH_3), 1.03 (singlet, 3H, C-19 CH_3), 2.0 (singlet, 3H, acetate), 4.53 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 3.70 (triplet, J = 10 Hz, 2H, C-2 H_2); mass spectrum *m/e* (relative intensity), 348(6), 347(23), 329(6), 332(5), 303(10), 302(39), 288(9), 287(24), 270(31), 260(14), 43(100).

Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.43; H, 9.56; N, 3.88.

17β-Acetoxy-2-tosyloxy-2,3-seco-5β-androstane-3-nitrile (38, X = Ts)

To a solution of 17β-acetoxy-2-hydroxy-2,3-seco-5β-androstane-3-nitrile (**38**, X = OH; 200 mg, 0.57 mmol) in pyridine (15 ml) was added *p*-toluenesulfonyl chloride

(180.0 mg, 0.94 mmol). The reaction mixture was stirred at room temperature for 24 h and then cold saturated sodium bicarbonate (20 ml) solution and ethyl ether (40 ml) were added. The organic layer was separated and washed with 0.1 *N* hydrochloric acid (3 × 10 ml), saturated sodium bicarbonate (2 × 15 ml), and sodium chloride (10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 310 mg of a crystalline solid. This material was recrystallized from ethyl ether to give 232 mg (81%) of compound **38** (X = Ts) m.p. 128–129°. An analytical specimen was obtained by three recrystallizations from diethyl ether, m.p. 129–131°; $[\alpha]_D^{20}$ +37° (c, 1 MeOH); i.r. ($CHCl_3$), 2250, 1720, 1600, 1190 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.76 (singlet, 3H, C-18 CH_3), 1.01 (singlet, 3H, C-19 CH_3), 2.0 (singlet, 3H, acetate), 2.48 (singlet, 3H, tosyl CH_3), 4.08 (triplet, J = 9 Hz, 2H, C-2 H_2), 4.60 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 7.40 and 7.85 (doublets, J = 10 Hz, 4H, tosylate group); mass spectrum *m/e* (relative intensity), 501(10), 440(16), 346(15), 301(15), 269(35), 368(45), 241(29), 43(100).

Anal. Calcd. for $C_{28}H_{39}NO_5S$: C, 67.03; H, 7.83; N, 2.79; S, 6.39. Found: C, 67.02; H, 7.96; N, 2.89; S, 6.18.

*cis- and trans-2,17β-Diacetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (**39**)*

To a solution of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (**36**, 612 mg, 1.774 mmol) in isopropenyl acetate (15 ml) was added 2,5-di-*tert*-butyl-*p*-benzoquinone (60 mg) and 15 μl of concentrated sulfuric acid, and the mixture was heated to reflux. During addition and reflux a stream of nitrogen was passed through the solution. After 36 h of refluxing the mixture was cooled to room temperature, poured into dilute aqueous sodium bicarbonate (15 ml), and extracted with ethyl ether (2 × 100 ml). The combined ethereal extracts were washed with saturated sodium chloride (2 × 20 ml) solution, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 930 mg of a brown oil which was chromatographed on silica gel (45 g). Elution with chloroform gave 472 mg (68%) of a mixture of *cis* and *trans* enol acetates **39** as a colorless oil. Thin-layer chromatographic analysis of this material on a 20 × 5 cm silica coated plate, adsorbant thickness 0.1 mm, using chloroform as eluant indicated the presence of two compounds, R_f 0.81 and R_f 0.72, in *ca.* a 1:1 ratio; i.r. ($CHCl_3$), 1745, 1725, 1600 cm^{-1}; n.m.r. ($CDCl_3$), 0.80 (broad singlet, 3H, C-18 CH_3), 1.20 and 1.30 (singlets, 3H, C-19 CH_3), 1.98 (singlet, 3H, acetate), 2.07 and 2.14 (singlets, 3H, vinyl acetate), 4.58 and 5.26 (two doublets, J = 8 and 13 Hz, respectively, 1H, C_1H), 6.96 and 7.04 (two doublets, J = 8 and 13 Hz, respectively, 1H, C_2H); mass spectrum *m/e* (relative intensity), 387(25), 360(9), 359(35), 345(52), 344(45), 327(34), 318(22), 311(46), 303(36), 302(54), 301(23), 285(45), 49(100).

Mol. Wt. Calcd. for $C_{23}H_{33}NO_4$: 387.2409. Found: 387.2389.

*17β-Acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (**40**)*

A solution of *cis*- and *trans*-2,17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (**39**; 510 mg, 1.318 mmol) in ethyl acetate (20 ml) at Dry Ice – acetone temperature was treated with ozone (50 ml/min) for 20 min. The resulting dark blue solution was allowed to stand at Dry Ice – acetone temperature for 35 min and then the excess ozone was removed with a stream of nitrogen. The solvent was removed under reduced pressure to give an oily residue. Methanol (30 ml) and aqueous sodium sulfite (5%, 70 ml) were added to the residue. The mixture was allowed to stand at room temperature for 2.5 h and then concentrated (70 ml). The aqueous solution was then extracted with ethyl ether (3 × 50 ml). The combined etheral extracts were washed with saturated sodium chloride (2 × 50 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford 378 mg (86%) of compound **40** as a clear oil. Thin-layer chromatographic analysis of this material on silica gel with a mixture of chloroform and ethyl acetate as the eluant indicated one compound, R_f 0.73. Vapor phase chromatographic analysis (column *D*, 250°, 45 ml/min) indicated one compound (retention time, 9 min); i.r. ($CHCl_3$), 2725, 1720 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.76 (singlet, 3H, C-18 CH_3), 1.03 (singlet, 3H, C-19 CH_3), 1.99 (singlet, 3H, acetate), 4.59 (triplet, 1H, C-17 $H\alpha$), 9.54 (singlet, 1H, CHO); mass spectrum *m/e* (relative intensity), 331(15), 330(8), 303(15), 302(20), 301(15), 270(12), 243(36), 242(70), 241(20), 202(15), 201(24), 200(15), 43(100). Compound **40** was converted into its 2,4-DNP derivative, m.p. 186–188°, for analysis.

Anal. Calcd. for $C_{26}H_{33}N_5O_6$: C, 61.04; H, 6.50; N, 13.68. Found: C, 60.90; H, 6.70; N, 13.48.

*17β-Acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (**37**)*

n-Butyllithium (2.1 *M*, 1.3 ml, 2.7 mmol) was added to methyltriphenylphosphonium bromide (1.00 g, 2.8 mmol) in dry benzene (50 ml) under an atmosphere of nitrogen. After 1.5 h, 17β-acetoxy-1-oxo-2,3-seco-A-nor-5-androstane-3-nitrile (**40**, 160 mg, 0.48 mmol) was added and the solution was stirred for 6 h at room temperature. Water (50 ml) was then added, and the organic layer separated. The aqueous phase was extracted with benzene (3 × 30 ml). The combined benzene extracts were washed with saturated sodium chloride (2 × 20 ml), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford a brown oil (630 mg) which was chromatographed on silica gel (36 g). Elution with a mixture of chloroform ethyl acetate (3:1, v/v) afforded a clear oil which was dissolved in acetic anhydride (3 ml) and pyridine (0.4 ml). The solution was stirred at room temperature for 15 h, and then the solvent was removed under reduced pressure to give an oily residue which was taken up in ethyl ether (40 ml). The ether solution was washed with 1 *N* hydrochloric acid (2 × 10 ml), saturated sodium bicarbonate (2 × 20 ml) and sodium chloride (2 × 10 ml) solutions, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to give 81.2 mg (51%) of compound **37** as a crystalline solid, m.p. 132–135°, which was sublimed at 125°, 0.1 mm pressure, to afford needles, m.p. 134–135°, $[\alpha]_D^{25}$ +31.2° (c, 8 MeOH); (lit. (4) m.p. 147–148°); i.r. ($CHCl_3$), 2250, 1720, 1630, 980, 920 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.80 (singlet, 3H, C-18 CH_3), 1.17 (singlet, 3H, C-19 CH_3), 4.59 (triplet, 1H, C-17 $H\alpha$), 4.90–5.80 (multiplet, 3H, vinylic protons); mass spectrum *m/e* (relative intensity), 329(15), 303(10), 302(7), 301(20), 288(6), 287(11), 286(6), 254(10), 243(20), 242(16), 241(23), 43(100).

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.49; H, 9.54; N, 4.19.

17β-Hydroxy-2,3-seco-5β-androst-1-ene-3-nitrile

n-Butyllithium (2.4 *M*, 2 ml, 5.0 mmol) was added to methyltriphenylphosphonium bromide (1.80 g, 5.04 mmol) in dry tetrahydrofuran (20 ml) at 0° under an atmosphere of nitrogen. After 1.5 h the mixture was cooled to −78°, 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (**40**, 360 mg, 1.08 mmol) in dry tetrahydrofuran (10 ml) was added, and the solution was stirred for 6.5 h at room temperature. Water (4 ml) was then added, the tetrahydrofuran was evaporated, and the residue was dissolved in ethyl ether (100 ml). The ether solution was washed with saturated sodium chloride (5 × 60 ml), dried over sodium sulfate, and filtered. Removal of the solvent under reduced pressure afforded 1.04 g of a brown oil which was chromatographed on silica gel (36 g). Elution with a mixture of chloroform ethyl acetate (3:1, v/v) gave 205 mg (65%) of compound which was sublimed at 125°, 0.1 mm pressure, to yield a crystalline solid, m.p. 129–131°; i.r. ($CHCl_3$), 3400, 2250, 1630, 920, 990 cm^{-1}; n.m.r. ($CDCl_3$), δ 0.77 (singlet, 3H, C-18 CH_3), 1.20 (singlet, 3H, C-19 CH_3), 3.66 (triplet, J = 9 Hz, 1H, C-17 $H\alpha$), 4.0–5.0 (multiplet, 3H, vinylic protons); mass spectrum *m/e* (relative intensity), 288(32), 287(100), 272(20), 269(15), 260(20), 245(25), 228(34).

Mol. Wt. Calcd. for $C_{19}H_{29}NO$: 287.2248. Found: 287.2254.

We are grateful to the British Columbia Heart Foundation and the National Research Council of Canada for financial support, and to Professor E. W. Warnhoff for preprints.

1. (*a*) C. Schöpf. Experientia, **17**, 285 (1961); (*b*) G. Habermehl. Naturwissenschaften, **53**, 123 (1966); (*c*) G. Habermehl. *In* The alkaloids. Vol. IX. *Edited by* R. H. F. Manske. Academic Press, Inc. New York, N.Y. 1967. p. 427; (*d*) G. Habermehl. *In* Progress in organic chemistry. Vol. VII. Butterworth, London. 1968. p. 35.
2. O. Gessner and G. Urban. Arch. Exptl. Pathol. Pharmakol. **187**, 378 (1937) and earlier papers.
3. (*a*) S. Hara and K. Oka. J. Am. Chem. Soc. **84**, 1041 (1967); (*b*) K. Oka and S. Hara. Tetrahedron Lett. 1987 (1969).
4. Y. Shimizu. Tetrahedron Lett. 2919 (1972).
5. M. H. Benn and R. Shaw. Chem. Commun. 288 (1973).
6. G. Habermehl and A. Haaf. Z. Naturforschg. **23b**, 1551 (1968).
7. G. Habermehl and A. Haaf. Liebigs Ann. Chem. **722**, 155 (1969).
8. (*a*) K. Oka and S. Hara. Tetrahedron Lett. 1193 (1969); (*b*) K. Oka and S. Hara. Tetrahedron Lett. 1189 (1969).
9. O. Jeger and H. Wehrli. Swiss Patent No. 482,721 (1970); Chem. Abstr. **72**, 121834 (1970).
10. J. K. Paisley and L. Weiler. Tetrahedron Lett. 261 (1972).
11. A. J. Liston. J. Org. Chem. **31**, 2105 (1966).
12. C. W. Shoppee and G. Kruger. J. Chem. Soc. 3641 (1961).
13. G. Habermehl and A. Haaf. Tetrahedron Lett. 3815 (1969).
14. (*a*) K. Oka and S. Hara. Chem. Ind. London, 911 (1968); (*b*) K. Oka and S. Hara. Chem. Ind. London, 168 (1969).
15. (*a*) V. Burchardt and T. Reichstein. Helv. Chim. Acta, **25**, 821 and 1434 (1942); (*b*) L. Ruzicka, V. Prelog, and P. Meister. Helv. Chim. Acta, **28**, 1251 (1945).
16. S. Hara, N. Matsumota, and M. Takeuchi. Chem. Ind. London, 2086 (1962).
17. M. Uskoković, J. Gutzwiller, and T. Henderson. J. Am. Chem. Soc. **92**, 203 (1970).
18. (*a*) E. H. White. J. Am. Chem. Soc. **77**, 6011 and 6014 (1955); (*b*) H. R. Nace and A. C. Watterson. J. Org. Chem. **31**, 2109 (1966).
19. J. K. Paisley. Ph.D. Thesis. University of British Columbia, Vancouver, British Columbia. 1973.
20. L. F. Fieser and M. Fieser. Steroids. Reinhold Publishing Corp. New York, N.Y. 1959. Chap. 8.
21. (*a*) E. Caspi, Y. Shimizu, and S. N. Balasubrahmanyam. Tetrahedron, **20**, 1271 (1964). (*b*) W. G. Dauben, R. A. Michili, and J. F. Eastman. J. Am. Chem. Soc. **74**, 3852 (1952); (*c*) L. F. Fieser and X. A. Dominguez. J. Am. Chem. Soc. **75**, 1704 (1953); (*d*) M. Rubin and B. H. Ambrecht. J. Am. Chem. Soc. **75**, 3513 (1953); (*e*) B. Camerino, B. Patelli, and R. Sliaky. Tetrahedron Lett. 554 (1961); (*f*) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, K. K. Jennings, and D. F. Phillips. J. Org. Chem. **27**, 2800 (1962); (*g*) A. K. Rose, G. Mina, M. S. Manhas, and E. Rzucidlo. Tetrahedron Lett. 1467 (1963); (*h*) M. Garodetsky, E. Levy, R. D. Youssefyeh, and Y. Mazur. Tetrahedron, **22**, 2039 (1966).
22. F. Johnson. Chem. Rev. **68**, 375 (1968).
23. (*a*) I. S. Y. Wang and E. W. Warnhoff. Chem. Commun. 1158 (1969); (*b*) J. B. Stothers, I. S. Y. Wang, D. Ouchi, and E. W. Warnhoff. J. Am. Chem. Soc. **93**, 6702 (1971).
24. (*a*) J. C. Sheehan and R. M. Wilson. J. Am. Chem. Soc. **89**, 3457 (1967); (*b*) D. H. R. Barton, P. D. Magnus, and M. J. Pearson. Chem. Commun. 550 (1969).
25. (*a*) Y. Satoh, M. Mukoh, Y. Ogaki, T. Takahasi, T. Kimura, H. Aoki, and A. Hagitani. Chem. Pharm. Bull. Tokyo, **39**, 855 (1966); (*b*) T. Takahasi, Y. Satoh, and A. Hagitani, Nippon Kagaku Zasshi, **89**, 974 (1968); Chem. Abstr. **70**, 78247 (1969); (*c*) E. W. Warnhoff and I. S. Y. Wang. Personal communication. 1971.
26. L. F. Fieser and M. Romero. J. Am. Chem. Soc. **75**, 4716 (1953).
27. K. L. Williamson and W. S. Johnson. J. Org. Chem. **26**, 4563 (1961).
28. K. Takeda, T. Okanishi, H. Osaka, A. Shimaoka, and N. Aezono. Chem. Pharm. Bull. Tokyo, **9**, 388 (1961).
29. K. Tori, T. Komeno, and T. Nakagawa. J. Org. Chem. **29**, 1136 (1964).
30. R. F. Zurcher. Helv. Chim. Acta, **46**, 2054 (1967).
31. K. L. Williamson, J. I. Coburn, and M. F. Herr. J. Org. Chem. **32**, 3934 (1967).
32. J. Y. Satoh and T. T. Takahashi. Chem. Commun. 1714 (1970).
33. J. R. Hanson and T. D. Organ. J. Chem. Soc. C, 1065 (1970).
34. P. L. Julian, L. Bauer, C. L. Bell, and R. E. Hewitson. J. Am. Chem. Soc. **91**, 1690 (1969).

35. R. NOYORI, Y. HAYOKAUA, M. FUNAKURA, H. TAKAYA, S. MURAI, R. KOBAYASHI, and S. TSUTSUMI. J. Am. Chem. Soc. **94**, 7202 (1972).
36. R. L. AUTRY and P. W. SCULLARD. J. Am. Chem. Soc. **90**, 4924 (1968).
37. R. K. HILL. J. Org. Chem. **27**, 29 (1962).
38. C. W. SHOPPEE and S. K. ROY. J. Chem. Soc. 3774 (1963).
39. S. ITO, H. TAKESHITA, and M. HIRAMA. Tetrahedron Lett. 1181 (1971).
40. C. W. M. GRANT. Ph.D. Thesis, University of British Columbia, Vancouver, British Columbia. 1972.
41. R. B. RAO and L. WEILER. Tetrahedron Lett. 4971 (1973).