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AN EFFICIENT METHOD FOR CONVERTING 17-OXO- INTO 17-ACETYL STEROIDS

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Abstract—A study of certain reaction parameters of the recently described procedure for converting ketones to the corresponding carbonitriles using tosylmethyl isocyanide, has led to a modified method suitable for the efficient synthesis of 17-cyanosteroids. These products readily undergo methylation to give the corresponding 17-acetyl compounds. This two-step conversion of steroidal 17- to 20-ketones proceeds in excellent overall yields, and constitutes a particularly mild and simple alternative method to those hitherto used for this purpose.

Several of the known[1] methods for converting androstan-17-ones and related 17-ketones to the analogous pregnan-20-ones are of limited applicability, owing to the need for protecting susceptible functionality elsewhere in the molecule throughout multi-step reaction sequences. This often results in product losses despite the efficiency of the two-carbon addition step. Attempts in this laboratory to reproduce claimed yields using well-known[1] procedures on steroidal 17-ketones were only moderately successful.

A recently described method[2-4] for the conversion of ketones (1) to their homologous nitriles (3), *via* reaction with tosylmethyl isocyanide (TosMIC, 2), appeared to offer a novel alternative pathway. An attractive feature of this route would be that alkylation of resulting 17-carbonitriles would circumvent the problems associated with similar alkylation of 17-cyanohydrins.[1,5] However, difficulty was envisaged in the introduction of the cyano-group at the 17-position, since it was reported[3] that the similarly hindered ketone, pinacolone (1, R = t-Bu, R' = Me), gave a relatively low yield (36%) of the corresponding carbonitrile upon reaction with TosMIC.

This was borne out by an experiment, in which oestrone methyl ether (4) was treated with TosMIC (2) under the conditions prescribed by van Leusen *et al.*[3] (viz., the addition of 2 equiv t-BuOK to equimolar amounts of the ketone and TosMIC in DME at 0°, followed by stirring for 2 hr), to give only 30% of a mixture of the epimeric 17-carbonitriles (5), together with the unreacted 17-ketone (49%).

The failure of more extended reaction times and higher reaction temperatures to improve the yield suggested that the reagent was being destroyed by competitive processes. This was verified by a blank experiment, in which TosMIC was added to a solution of t-BuOK in t-BuOH–DME. The mixture discoloured rapidly and a precipitate formed; the attempted recovery of TosMIC or other identifiable products from this gummy, water-soluble precipitate was unsuccessful. Some insight into the course of this reaction was gained through monitoring (GLC) the decreasing concentration of TosMIC under various conditions. It was shown that the addition of a solution of t-BuOK to a solution of TosMIC results in their mutual destruction in a 1:1 molar ratio, i.e. after the addition of each mmole aliquot of base, an equivalent decrease of TosMIC was detected in the reaction mixture.

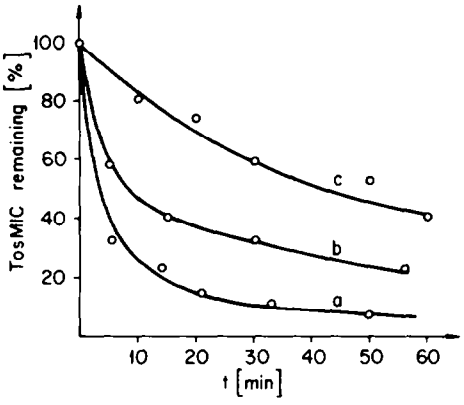
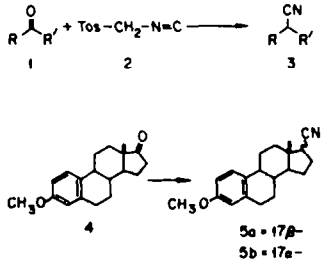
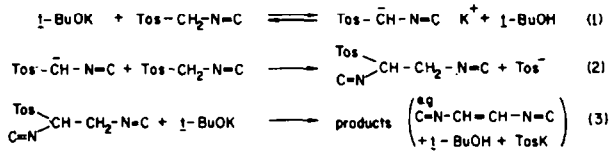


Fig. 1. Decrease in detectable TosMIC in the presence of (a) 2 equiv. t-BuOK, (b) 5 equiv. t-BuOK and (c) 10 equiv. t-BuOK, in t-BuOH-DME at 25°.

In another series of experiments, the rapidity of TosMIC destruction was measured at 25° in the presence of varying excesses of t-BuOK (Fig. 1). Thus, a 2-fold excess of base led to rapid destruction of the reagent, more than 65% being irreversibly consumed within 5 min (curve a). In the presence of a 5-fold excess of base this reaction was retarded since only 40% of the TosMIC was destroyed after 5 min (curve b), while a 10-fold excess of base resulted in only 20% reaction after 10 min (curve c).

These results are consistent with self-condensation as depicted in Scheme 1. Generation of the TosMIC anion (eqn 1) may be followed by nucleophilic attack upon neutral TosMIC (eqn 2), with subsequent reaction of the product, e.g. base-induced elimination of the elements of





Scheme 1.

toluenesulphinic acid (eqn 3). Such a Scheme would account for the 1:1 molar ratio for mutual destruction of base and reagent. Furthermore, the presence of a large excess of base would ensure that the right-hand side of the initial equilibrium (eqn 1) is strongly favoured, and that the resulting low concentration of neutral TosMIC would inhibit self-condensation (eqn 2) (cf. Fig. 1).

Attempts to obtain further evidence for the Scheme, through isolation of end-products of self-condensation, were unsuccessful but this was not surprising in view of their expected lability. However, the sequence is entirely plausible since the known[6] nucleophilicity of the TosMIC anion and the known[3,4,7] leaving-group property of the tosyl group are invoked.

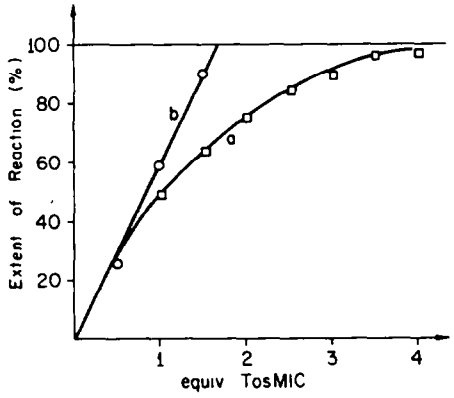


Fig. 2. Extent of reaction of 4 in the presence of 10 equiv. t-BuOK, as a function of the amount of TosMIC; (a) during addition of t-BuOK to 4 + TosMIC, (b) during addition of TosMIC to 4 + t-BuOK.

In view of the finding that the effective lifetime of the reagent is prolonged in the presence of a large excess of base, experiments were conducted, in which mixtures of oestrone methyl ether (4) and TosMIC were treated with 10 equiv t-BuOK. The quantities of TosMIC were varied for each experiment, in order to determine the minimum amount required to achieve complete conversion of (4) to the carbonitrile mixture (5). The extent of reaction was determined by GLC analysis after each experiment, and the results were plotted (Fig. 2, curve a). Increased yields of the nitriles (5) were obtained using increased excesses of TosMIC but, even with a 4-fold excess, a small amount (*ca.* 2%) of the ketone (4) failed to react. This procedure, apart from being wasteful of the reagent, had the further disadvantage of requiring laborious separation of the desired products (5) from starting material (4) and large amounts of reagent artefacts (e.g. 18).

Better results were obtained by reverse addition, of TosMIC to a mixture of the substrate and base. Very slow addition of the reagent ensured that a large excess of base was present throughout the reaction, thereby allowing ample opportunity for the TosMIC anion to form and react without excessive loss through self-condensation.

A solution of TosMIC in DME was added dropwise at the rate of *ca.* 1 equiv/hr to a solution of the ketone (4) and t-BuOK (10 equiv) in t-BuOH–DME at r.t. Aliquots were quenched and assayed by GLC during the addition in order to determine the progress of the reaction. Under these conditions a nearly linear relationship was obtained between the amount of reagent added and the extent of reaction (Fig. 2, curve b).

Although the reaction appeared to be essentially complete after the addition of 1.7 equiv TosMIC, a total of 2 equiv was used for preparative reactions. Furthermore, reaction mixtures were then stirred for 1 hr after addition of the reagent, before being worked up.

The preparative utility of this method was demonstrated on a variety of 17-oxo-steroids (4, 7, 10 and 13) and uniformly high isolated yields of the respective 17-carbonitrile mixtures were obtained (Table 1), without affecting olefinic bonds, hydroxy-, ethylenedioxy- or 11-oxo-groups. The latter function was completely inert under these conditions, as demonstrated by the failure of 16 to undergo any detectable reaction with TosMIC.

Table 1.

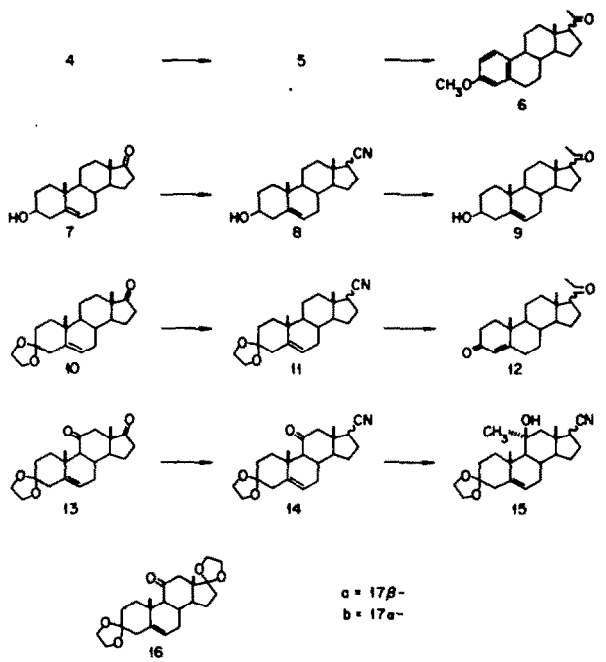
Cpd.	Yield (%)	Ratio 17β/17α	δ 13β-Me	δ 10β-Me
5a	91	60/40	0.96	–
5b			0.85*	–
8a	86	69/31	0.94	1.03
8b			0.84*	1.03*
11a	88	70/30	0.94*	1.04*
11b			0.84*	1.04*
14a	27	70/30	0.91	1.23
14b	63		0.82	1.22

* Determined from the NMR of the epimer mixture.

The reaction products (5, 8, 11 and 14) exhibited characteristic IR absorption for nitriles at $2240 \pm 2\ cm^{-1}$ which, taken in conjunction with other spectroscopic and analytical data, verified the structural assignments.

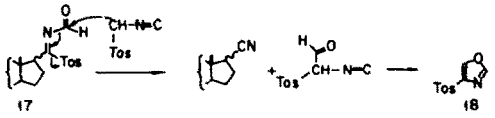
Difficulty was usually experienced in separating the 17-cyano-epimers, but this was achieved chromatographically in the case of 14a and 14b. The epimer mixtures 5, 8, and 11 were separated from other reaction products by chromatography. The major components 5a and 8a were obtained by several recrystallizations of 5 and 8 respectively, but attempted isolation of the pure minor isomers from mother-liquor residues was unsuccessful. The epimer ratio of 11 remained unchanged after two crystallizations, and this product was characterized as a mixture.

The epimer ratios of those mixtures (5, 8 and 11) which could not be quantitatively separated, were determined by integration of their 13-Me NMR signals (Table 1). Each mixture displayed two sharp singlets between δ 0·8 and



1·0, differing in chemical shift by δ *ca.* 0·1, which together integrated for 3 protons. In each case the lower field signal was more prominent and was assigned to the 17β-epimer. This is consistent with the mechanistic expectation that protonation of the intermediate 17-cyano-anion (or a precursor), generated in the TosMIC reaction, would occur preferentially from the α-side. Furthermore, the assignments are in accordance with the finding[8] that steroidal angular methyl groups undergo greater downfield shifts upon introduction of a vicinal *cis*- than of a *trans*-cyano-group. The assignments were unequivocally established by alkylation to give known 17-acetyl compounds (*vide infra*).

A persistent by-product, isolated in varying yields in the preparative TosMIC reactions, was shown to have properties consistent with 4-tosyloxazole (**18**). It may be envisaged as arising through nucleophilic attack of the TosMIC anion upon the presumed[4] intermediate (**17**) of nitrile formation. Some analogy may be found in reactions reported by van Leusen *et al.*[7] and Schoellkopf *et al.*[9]



The 17-carbonitriles were converted to the corresponding 17-acetyl steroids by brief treatment with methyl lithium under nitrogen at room temperature; hydrolysis of the intermediate imines occurred during work-up to give the 17-acetyl compounds in excellent yields. These reaction conditions were sufficiently mild to ensure that the configurational integrity of the 17-position was preserved. Thus, the pure 17β-carbonitriles (**5a** and **8a**) were converted to the known 17β-acetyl compounds (**6a** and **9a** resp.), uncontaminated with their 17α-isomers.

In the case of the inseparable isomer mixture (**11**, 70% 17β–CN, 30% 17α–CN), methyl lithium alkylation, followed by brief acidic treatment to hydrolyse the 3-acetal function and isomerize the olefinic bond, afforded a mixture of progesterone (**12a**) and isoprogesterone (**12b**) in a ratio (GLC) similar to that of starting material.

Alkylation of the epimeric mixtures of carbonitriles (**5**, **8** and **11**) afforded product mixtures from which the major 17β-isomers (**6a**, **9a** and **12a** resp.) could readily be isolated by crystallization.

The possibility was examined of achieving selective methylation of the 17-cyano-group of **14** in the presence of the unprotected 11-oxo-group. Although the reported[10,11] conditions for methylation of 11-ketones suggested that this might be possible, a model experiment on **16** revealed that the compound underwent quantitative methylation in the presence of 0·5N MeLi in THF-ether at −78° after only 20 min. By contrast, the 17β-carbonitrile (**5a**) failed to react at all under these conditions. It was therefore expected that the undesired selectivity would prevail in alkylation of **14a** and **14b** even at −78°, and indeed, this was shown to be the case since the respective 11-methyl compounds (**15a** and **15b**) were obtained in excellent yields. Although it is evident from the aforegoing results that more forcing alkylation conditions would lead to the derived 17-acetyl compounds, it is clearly necessary for prior protection of the 11-oxo-group to be carried out if that functionality is to be preserved.

The simple two-step method described here for converting 17-ketones to 17-acetyl steroids may be regarded as complementary to most other methods.[1] Apart from the protected cyanohydrin[5] and ethynyl carbinol routes,[1] which are more suited to the synthesis of Δ^{16}-and 17-OR-20-ketones, attention has recently been given to new methods[12] for efficient introduction of the corticoid and similarly functionalized side chains.

The ethylidene Wittig route,[1] with which this work may be most directly compared, suffers the disadvantage of requiring differentiation between the intermediate $\Delta^{17(20)}$-bond and olefinic bonds elsewhere in the molecule, during hydration. The TosMIC method may therefore be used in such cases, and in substrates without base-labile functionality or unprotected carbonyl groups other than at the 17-position.

EXPERIMENTAL

M.ps were determined with a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded as follows: IR spectra

(Perkin-Elmer 257) for solutions in CH_2Cl_2, NMR spectra (Varian HA 100) for solutions in $CDCl_3$ with TMS as internal standard, and mass spectra (AEI MS9). Optical rotations were determined for solns in $CHCl_3$ at 24°. CDs were determined for MeOH solns on a Jasco J-20 instrument. GLC was carried out on a Packard 800 instrument with FID; glass columns (2 m × 2 mm) were packed with solid support carrying 1% (unless otherwise specified) of liquid phase. Specific details and operating temperatures are indicated in the text (A°→B° refers to a linear temperature programme).

"Work-up" refers to dilution of the reaction mixture with a specified solvent, washing with specified aqueous solutions, drying over anhydrous $MgSO_4$ and evaporation *in vacuo*.

Column chromatography was carried out with Merck Kieselgel 60, 70-230 mesh. Methyl lithium refers to ethereal 2M solns (Fluka).

Reaction of tosylmethyl isocyanide (2) *with potassium t-butoxide.* (a) A standard soln (4 ml) of 0·1 M TosMIC in DME (containing 0·15% n-$C_{22}H_{46}$ as an internal GLC standard) was stirred at 25° under N_2. Aliquots (0·08 ml, 0·2 equiv) of M t-BuOK in t-BuOH were added at intervals, and an aliquot (0·05 ml) of the mixture was withdrawn 30 min after each addition, quenched with 5N HOAc (0·03 ml), diluted with DME (0·05 ml) and assayed by GLC (OV-210, 145°). The original concentration of TosMIC was shown to have diminished by 20% after each addition of base.

(b) In three separate experiments, the standard soln (1 ml) of TosMIC (see previous experiment) at 25° under N_2, was treated with an excess of M t-BuOK in t-BuOH (0·2, 0·5 and 1 ml respectively). Aliquots were withdrawn at intervals and assayed for TosMIC as described in the previous experiment. The resultant time-dependent destruction of TosMIC is depicted in Fig. 1.

Rate experiments. (a) Seven DME solns (each 2 ml) of **4** and TosMIC (**2**) were made up, each being 0·02 M in **4** but varying between 0·02 and 0·08 M in **2**. A soln (0·2 ml) of M t-BuOK in t-BuOH was added to each of these solns at 0° under N_2. After 1 hr the solns were quenched with HOAc (0·5 ml) and assayed by GLC (OV-210, 215°) to establish the extent of reaction, given by [5]/[4] + [5]. The results are depicted in Fig. 2 (curve **a**).

(b) A soln, 0·02 M in **4** and 0·2 M in t-BuOK was made up in DME–t-BuOH (4:1, 10 ml), and kept at r.t. under N_2. A soln of 0·15 M TosMIC in DME was added at *ca.* 1·3 ml/hr with vigorous stirring. At intervals the addition was stopped in order to withdraw an aliquot of the mixture for assay by the method described in the previous experiment. The results are depicted in Fig. 2 (curve **b**).

Conversion of steroidal 17-ketones to 17-carbonitriles. The general method, adopted for all the preparations described in this work, is as follows: a 0·04 M soln of the 17-ketone in DME under N_2 was treated with M t-BuOK-t-BuOH to provide a 10-fold excess of base. The soln was vigorously stirred at r.t. while 0·4 M TosMIC–DME was added very slowly by means of a syringe whose plunger was propelled by a motor-driven micrometer screw at *ca.* 1 r.p.m. In this way 2 equiv of TosMIC were delivered during *ca.* 2 hr. During the addition the soln became yellow, then brown, but remained clear. After completion of the addition, stirring was continued for 1 hr, then the mixture was poured into a suitable solvent and worked up.

The reagent-substrate artefact, 4-(toluene-4′-sulphonyl)-1,3-oxazole (**18**) was formed during all the reactions but its isolation and characterization is only described once.

(a) The reaction of **4** (586 mg) gave, after work-up (benzene extraction and aqueous NaCl) a slightly yellow crystalline product (850 mg), which was adsorbed on silica gel (70 g). Elution with benzene-EtOAc (6:1) afforded a mixture of the epimeric **5** (535 mg), ν_{max} 2241 cm^{-1}, δ 0·85 ('1·2 H', s, 13β-Me of 17α-CN compound), 0·96 ('1·8 H', s, 13β-Me of 17β-CN compound). Two crystallizations of the mixture, from $CHCl_3$-MeOH, afforded the pure 17β-*carbonitrile* (**5a**), m.p. 207–210°, $[\alpha]_D$ + 113° (*c* 0·8), ν_{max} 2241 cm^{-1}, δ 0·96 (3 H, s, 13β-Me), 3·75 (3H, s, 3-OMe), 6·62 (1H, s, 4-H), 6·69 (1H, q, *J* 8·5 and 2·5 Hz, 2-H) and 7·17 (1H, d, *J* 8·5 Hz, 1-H) (Found: C, 81·45; H, 8·5; N, 4·8; M$^+$, 295. $C_{20}H_{25}NO$ requires: C, 81·3; H, 8·5; N, 4·7%; M, 295).

Further elution of the column with the same solvent afforded the *oxazole* **18** (48 mg), m.p. 166° (from EtOH), ν_{max} 3165, 3143, 3055, 1596, 1333 and 1150 cm^{-1}, δ 2·43 (3 H, s, 1′-Me), 7·34 (2H, d, *J* 8·5 Hz, 3′- and 5′-H), 7·96 (2 H, d, *J* 8·5 Hz, 2′- and 6′-H), and 7·96 and 8·26 (each 1H, d, *J* 1·5 Hz, 2- and 5-H) (Found: C, 53·7; H, 4·1; N, 6·4; M$^+$, 223·0294. $C_{10}H_9NO_3S$ requires: C, 53·8; H, 4·1; N, 6·3%; M, 223·0303).

(b) Androst-5-en-3β-ol-17-one (**7**, 288 mg) gave, after work-up (EtOAc extraction and aqueous NaCl), a yellow crystalline product (512 mg), which was adsorbed on silica gel (27 g) and eluted with benzene-EtOAc (1:1) to give a mixture of the epimeric **8** (258 mg), ν_{max} 2240 cm^{-1}, δ 0·84 ('0·93 H', s, 13β-Me of 17α-CN compound) and 0·94 ('2·07 H', s, 13β-Me of 17β-CN compound). Two crystallizations from EtOAc gave the 17β-epimer (**8a**), m.p. 215–217°, $[\alpha]_D$ -11·4° (*c* 0·8), ν_{max} 3607 and 2240 cm^{-1}, δ 0·94 (3 H, s, 13β-Me), 1·03 (3 H, s, 10β-Me), 3·49 (1 H, m, 3α-H) and 5·31 (1H, br. d, *J* 5·5 Hz, 6-H) (Found: C, 80·4; H, 9·9; N, 4·8; M$^+$, 299. $C_{20}H_{29}NO$ requires: C, 80·2; H, 9·8; N, 4·7% M, 299) (lit.,[13] m.p. 209–210°, $[\alpha]_D$ - 10·4° and - 11·6°).

(c) The acetal (**10**, 440 mg) gave, after work-up (benzene extraction and aqueous NaCl), an oil (680 mg) which was adsorbed on silica gel (85 g) and eluted with benzene-EtOAc (20:1) to give a crystalline mixture of epimers (**11**, 398 mg), m.p. 195–210° (from EtOH), $[\alpha]_D$ - 33·5° (*c*, 1·1), ν_{max} 2238 cm^{-1}, δ 0·84 ('0·9 H', s, 13β-Me of 17α-CN compound **11b**), 0·94 ('2·1 H', s, 13β-Me of 17β-CN compound **11a**), 1·04 (3H, s, 10β-Me), 3·93 (4H, m, 3-acetal) and 5·32 (1H, br, $W_{1/2}$ 9 Hz, 6-H) (Found: C, 77·2; H, 9·1; N, 3·95; M$^+$, 341. $C_{22}H_{31}NO_2$ requires: C, 77·4; H, 9·15; N, 4·1%, M; 341). Repeated recrystallization from EtOH, of the mixture, m.p. 195–210°, failed to improve the m.p., or to alter the epimer ratio as measured by NMR.

(d) Compound **13** (240 mg) gave, after work-up (benzene extraction and aqueous NaCl), a yellow oil (328 mg), which was adsorbed on silica gel (25 g). Elution with $CHCl_3$-EtOAc (2:1) gave the 17α-carbonitrile **14b** (66 mg), m.p. 232–236° (from EtOH), $[\alpha]_D$ - 85° (*c* 0·4), ν_{max} 2238 and 1706 cm^{-1}, $\Delta\epsilon$ (MeOH) + 1·2 (301 nm) and - 0·38 (218 nm), δ 0·82 (3 H, s, 13β-Me), 1·23 (3H, s, 10β-Me), 3·94 (4 H, m, 3-acetal) and 5·34 (1H, br, $W_{1/2}$ 8 Hz, 6-H) (Found: C, 74·2; H, 8·1; N, 4·0; M$^+$, 355. $C_{22}H_{29}NO_3$ requires: C, 74·3; H, 8·2; N, 3·9%; M, 355).

Further elution with the same solvent gave the 17β-*carbonitrile* **14a** (156 mg), m.p. 287–289° (from $CHCl_3$-EtOH), $[\alpha]_D$ + 26° (*c* 1), ν_{max} 2240 and 1706 cm^{-1}, $\Delta\epsilon$ (MeOH) + 0·93 (301 nm) and - 0·31 (224 nm), δ 0·91 (3 H, s, 13β-Me), 1·22 (3H, s, 10β-Me), 3·91 (4 H, m, 3-acetal), and 5·3 (1 H, br d, *J* 5 Hz, 6-H) (Found: C, 74·2; H, 8·1; N, 3·8%; M$^+$, 355).

Methylation of 17-carbonitriles. (a) MeLi (5 ml) was added to the epimeric mixture (**5**, 200 mg) in THF (10 ml) under N_2 at 25°. After 30 min the reaction was quenched with H_2O and worked up (benzene extraction and H_2O, HCl aq, $NaHCO_3$ aq, NaCl aq) to give a mixture of 17-epimers (**6**, 200 mg). Two crystallizations from CH_2Cl_2-Et_2O afforded the pure **6a**, m.p. 134–136° (lit.,[14] m.p. 134–136°).

(b) Treatment of **5a** (57 mg) with MeLi, as described in (a), afforded the pure **6a** (53 mg) directly.

(c) A mixture of the 17-epimers **8**, (106 mg) was methylated as described in (a). After work-up (EtOAc extraction and $NaHCO_3$ aq, NaCl aq), chromatography of the crude product (139 mg) on silica gel (16 g) with benzene-EtOAc (1:1) gave the crystalline product **9** (89 mg) (separable by GLC on OV-210, 205°). Crystallization from EtOH gave **9a**, m.p. 189–191° (undepressed by admixture with authentic material).

(d) Methylation of the pure **8a** (3 mg), as described in (a), gave **9a**, which was shown by GLC to be essentially uncontaminated with the 17α-isomer.

(e) A mixture of the 17-epimers **11** (100 mg) was methylated as described in (a). The reaction was quenched with 2N HCl (4 ml) and the mixture was stirred at 50° for 1 hr. Work-up (EtOAc extraction and $NaHCO_3$ aq, NaCl aq) afforded an oil (121 mg) which was adsorbed on silica gel (22 g). Elution with benzene-EtOAc (4:1) afforded a mixture of **12**, (73 mg). GLC (3% OV-17, 240°→270°) showed a 17β-Ac (**12a**): 17α-Ac (**12b**) isomer distribution of 71:29. Several recrystallizations of the mixture from Et_2O gave pure **12a**, m.p. 130–132° (undepressed by admixture with authentic material).

Low temperature (-78°) methylations. (a) MeLi (1 ml) was added to **5a** (25 mg) in THF (3 ml) at -78° under N_2. After 20 min at -78°, H_2O (1 ml) was added and the mixture was worked up (benzene extraction and NaCl aq) to give unchanged starting material (25 mg).

(b) Treatment of **16** (18 mg) with MeLi (0·5 ml) as described in (a), gave a single product (GLC on OV-17, 240°), ν_{max} 3595 cm^{-1}, (Found: M^+, 404·2541. $C_{24}H_{36}O_5$ requires: M, 404·2563) presumed to be the 11β-hydroxy-11α-methyl derivative.

(c) The ketone **14a** (100 mg) was treated with MeLi as described in (a), and worked up (benzene extraction and aqueous NaCl) to give a product (122 mg) which was adsorbed on silica gel (13 g). Elution with $CHCl_3$-EtOAc (2:1) gave the *11β-hydroxy-11α-methyl compound* **15a** (97 mg), m.p. 198–201° (from EtOH), $[\alpha]_D$-20° (*c* 0·4), ν_{max} 3598 and 2241 cm^{-1}, δ 1·14 (3 H, s, 13β-Me), 1·38 (3 H, s, 10β-Me), 1·48 (3 H, s, 11α-Me), 3·93 (4H, m, 3-acetal), and 5·27 (1H, m, $W_{1/2}$ 9 Hz, 6-H) (Found: C, 74·4; H, 9·1; N, 3·7; M^+, 371. $C_{23}H_{33}NO_3$ requires: C, 74·4; H, 8·95; N, 3·8%; M, 371).

(d) Methylation of **14b** (60 mg) as described in (a) and chromatography of the product on silica gel (8 g) with $CHCl_3$-EtOAc (2:1) gave the *11β-hydroxy-11α-methyl compound* **15b** (52 mg), m.p. 152–155° (from EtOH), $[\alpha]_D$ −110° (*c* 0·6), ν_{max} 3590 and 2238 cm^{-1}, δ 1·04 (3 H, s, 13β-Me), 1·37 (3H, s, 10β-Me), 1·53 (3H, s, 11α-Me), 3·94 (4H, m, 3-acetal) and 5·29 (1H, br. d, *J* 4·5 Hz, 6-H) (Found: C, 74·3; H, 9·1; N, 4·0%; M^+, 371).

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