Steroids and Steroidases. XI.[1] Synthetic Approaches to C-17 Bis(2-hydroxyethyl)-amino Compounds as Potential Precursors of 17-Hydroxyandrostane Nitrogen Mustards[2]

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The synthesis of some potential nitrogen mustard precursor 17α-bis(2-hydroxyethyl)aminomethyl androst-17β-ol derivatives has been achieved by two routes. During the investigation, unequivocal proof was obtained that addition of cyanide to 17-keto steroids gives predominantly 17β-hydroxy-17α-cyano epimers.

On rapporte la synthèse par deux voies différentes de quelques dérivés de bis(hydroxy-2 éthyl) aminométhyl-17α-androstol-17β qui sont possiblement actifs comme moutardes azotés. Au cours de ces travaux, on a pu obtenir des preuves sans équivoques que l'addition du cyanure sur les 17-cétastéroïdes conduit principalement aux épimères hydroxy-17β cyano-17α.

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In the search for anti-tumor effective nitrogen mustards many compounds in which a steroid molecule has been used as a carrier for the bis(2-chloroethyl)amino group have been examined.[3] We have previously synthesized and evaluated some androstane C-17 mustard compounds in which hormonally important ring A functional groups were present (2) and this communication describes our attempts to extend the investigation to androstane mustards in which *both* the ring A Δ^4-3-keto and ring D 17β-hydroxyl functions of 17β-hydroxyandrost-4-en-3-one (testosterone) were retained.

The compound selected as the initial target was the 17α-bis(2-chloroethyl)aminomethyl testosterone (**1***a*). The reservations expressed (2) regarding the usefulness of aliphatic nitrogen mustards in cancer chemotherapy owing to their high reactivity potential do not necessarily apply to hydroxy mustards of this type since for such compounds formation of a five-membered hydrogen bonded ring (3) should prolong the physiological activity by retarding the formation of the active ethylenimmonium ion species (4, 7–9).[4]

Our earlier studies (2) had indicated syntheses involving chlorination of bis(2-hydroxyethyl)-amino precursors in the final step to be the most satisfactory for the preparation of steroid mustards. Similar pathways to **2***a* were therefore examined and, as summarized in Schemes 1 and 3, two routes to the precursor triol **2***b* proved satisfactory. In the cyanohydrin approach (Scheme 1), 5α-androstan-17-one (**3**) was found to react smoothly with potassium cyanide in acetic acid to give in 87% yield a mixture of the C-17 cyanohydrin epimers in which the 17β-hydroxy compound **4** predominated to a large extent.[5] Reduction of **4** with lithium aluminum hydride followed by reaction with ethylene oxide gave the 2-hydroxyethylamino compound **2***b* in 38% overall yield.

The synthesis of the analogous bis(2-hydroxyethyl)amino precursor **1***b* of androst-4-en-3-one was also achievable via cyanohydrin routes and the two pathways followed are outlined in Scheme 2. The sequence **6** → **7** → **8** → **9** was explored first and although ketalization of testosterone (**6**) followed by Sarett oxidation of the C-17 hydroxyl group proceeded smoothly to give the 17-keto-3-ketal **8** in good yield, the presence of the ketal function posed problems with regard to the subsequent C-17 cyanohydrination reaction. The use of the acidic potassium

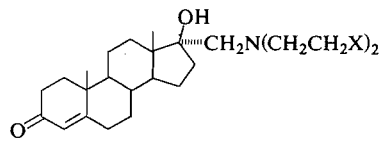
[1]For Part X see ref. 2.

[2]Abstracted from ref. 1. First presented in part at the C.I.C. Conferences, Montreal, Quebec, May 1969 and Toronto, Ontario, May 1970.

[3]A comprehensive review of nitrogen mustards is included in ref. 1 and the most relevant steroid literature is cited and discussed in ref. 2.

[4]It has been pointed out by Ross (4) and others (5, 6) that competition with chlorine for the lone pair of electrons on nitrogen produces modifications of biological actions of nitrogen mustards.

[5]That the desired 17β-hydroxy-17α-cyano compound would be the major product was expected from a consideration of the known preference for α-attack of the 17-carbonyl group by the cyanide ion in closely related steroids (10).



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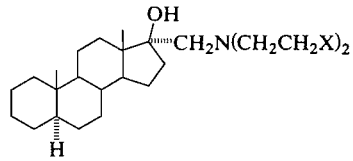
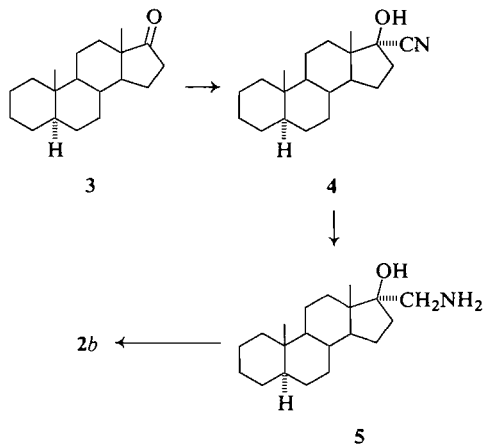


2

a X = Cl
b X = OH

cyanide conditions found to be satisfactory in the case of the model compound **3** was precluded by the acid sensitivity of the 3-ketal of **8** and it was found necessary to employ *trans*-cyanohydrination with acetone cyanohydrin. Again one epimer predominated in the mixture produced and this was assigned the 17β-hydroxy configuration shown in **9** for the reasons cited above for the 5α-androstane analogue.



SCHEME I

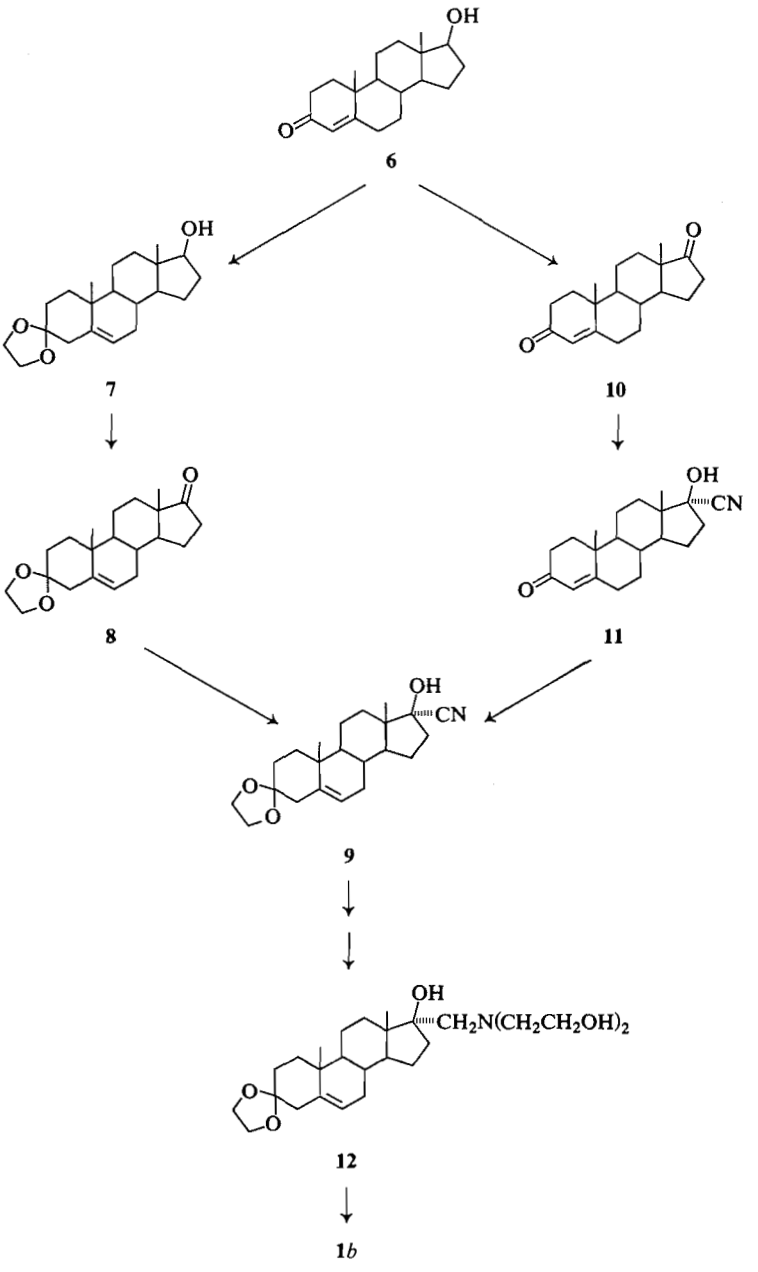
Since the yields obtained of **9** in the last step of the above sequence were influenced quite markedly by minor variations in the *trans*-cyanohydrination reaction conditions, the alternative route to **9** via intermediates **10** and **11** was also investigated. On treatment of **10** with acetone cyanohydrin, selective reaction (11) at C-17 was achieved to give the 17β-hydroxy epimer **11** in 74% yield. Its subsequent ketalization was readily accomplished to give samples of **9** of superior purity and in higher overall yield (53% as opposed to 38%) than obtained by the initial route.

The subsequent transformations of **9** into the bis(2-hydroxyethyl)amino ketal **12** by lithium aluminum hydride reduction followed by ethylene oxide alkylation were accomplished in 46 and 73% yields respectively and preliminary experiments showed that acid-catalyzed deketalization of **12** to give the Δ^4-3-keto compound **1***b* could be readily achieved when required.

The cyanohydrin routes discussed above suffer from the disadvantage that the final yields obtained of the desired mustard precursors are rather low owing to the problems encountered in the cyanohydrin reduction steps where partial dissociation of the hydroxynitriles to the corresponding ketones during reduction could not be prevented even when the cyanohydrin acetates were used (12). A further cause for dissatisfaction with the cyanohydrin routes was that although the C-17 configurational assignments made were felt to be fairly secure on the basis of their analogy with earlier work in similar steroidal systems (10) no physical or chemical data had been obtained which would permit the C-17 stereochemistries of the cyanohydrins and their derivatives to be accepted unequivocally. Therefore, in an attempt to improve the yields of **1***b* and **2***b* and in order to remove all ambiguity from the assignment of their C-17 geometries, the alternative approaches involving the oxiranes **13** and **17** outlined in Schemes 3 and 4 were investigated.

5α-Androstan-17-one (**3**) was converted stereospecifically[6] by reaction with dimethylsulfonium methylide to give spiro-17β-oxiranyl-5α-androstane (**13**) in 84% yield. The 17β-configuration of the epoxide group was verified by reduction of **13** with lithium aluminum hydride to 17α-methyl-5α-androstan-17β-ol (**14**, 70% yield) which showed peaks in the p.m.r. spectrum for the C-17 proton, and C-18 and -19 methyl groups at chemical shifts characteristic of 17β-hydroxy-17α-methyl steroids (13, 14) and which was identical in all respects with an authentic sample prepared unambiguously from 17α-methyltestos-

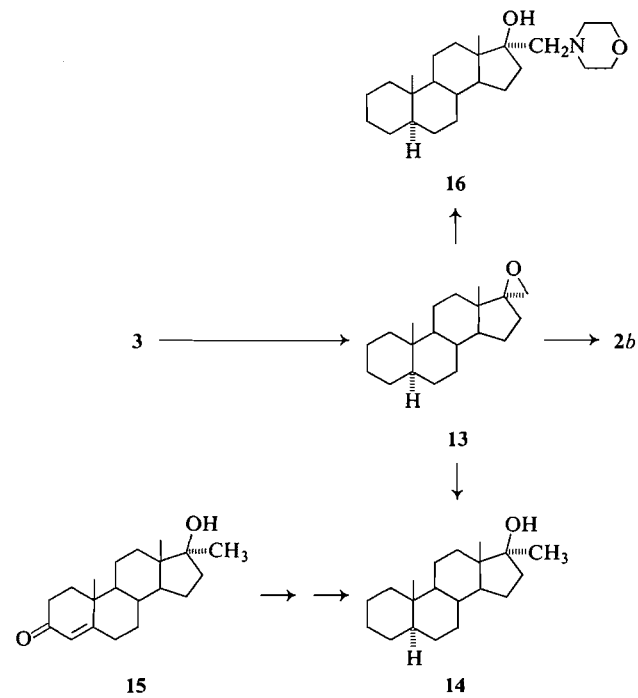
[6]That a single C-17 epimer only was formed was confirmed by the p.m.r. spectrum which showed the C-18 methyl protons as a sharp *singlet* at δ 0.86 p.p.m. only.



SCHEME 2

terone (**15**). The oxirane **13** was condensed with bis(2-hydroxyethyl)amine in ethylene glycol at 160° (15) and 92% of the mustard precursor triol **2***b* was obtained directly as the sole product.[7] A comparison of this sample of **2***b* of chemically verified C-17 stereochemistry with that obtained by the cyanohydrin route of Scheme 1 showed both to be identical in all respects. This therefore established unambiguously that the major products of cyanide ion addition to the C-17 carbonyl group of **3**, and by analogy to those of **8** and **10**,

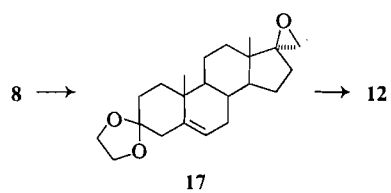
[7]When water was used as a catalyst (16), a 42% yield only was obtained.



SCHEME 3

were the cyanohydrins **4**, **9**, and **11** respectively as had been predicted from steric considerations.[5] The overall yield (80%) of the triol **2*b*** from the starting ketone **3** by the oxirane route was much higher than that obtained via the cyanohydrin intermediates (38%) and thus was much the preferred synthetic method. Unfortunately, the preparation of the Δ^4-3-keto mustard precursor **1*b*** via reaction of the oxirane **17** with bis(2-hydroxyethylamine to give the ketal **12** (Scheme 4), followed by mild hydrolysis, turned out to be less satisfactory than for the analogous route described above for the model series (Scheme 3) the overall yield of **12** from testosterone (**6**) being only 15%.

Disappointingly, all attempts to effect the conversion of the mustard precursors **1*b***, **2*b***, and **12** into the corresponding bis(2-chloroethyl)amino derivatives were unsuccessful. Application of such reagents as thionyl chloride, phosphoryl chloride, and methane sulfonyl chloride under the conditions delineated previously (2) for other sensitive androstane compounds afforded extensively decomposed, complex, reaction mixtures in which none of the desired or related mustards could be detected even by the sensitive p.m.r. and mass spectral diagnostic methods (2). Major difficulties in achieving the desired selective chlorinations had, of course, been anticipated but surprisingly the products of the expected competitive reactions, such as $\Delta^{16,17}$, perhydrooxazino, and morpholino[8] derivatives, were not formed in isolable quantities either. Direct conversion of the oxiranes **13** and **17** to the corresponding nitrogen mustards by condensation with bis(2-chloroethyl)amine (17) was also attempted under a variety of conditions but in most cases the starting oxiranes were recovered quantitatively. Under forcing conditions (130° in alcoholic solvents in sealed tubes) multiple reactions occurred but in no instance was any steroid mustard detectable. The marked instability of nitrogen mustard itself to elevated tempera-



SCHEME 4

[8]For reference purposes a sample of one such possible product, **16**, was prepared by the phenol-catalyzed reaction of the oxirane **12** with morpholine.

tures (18) was presumably a major factor in the failure of this approach.

In view of the discouraging results encountered in the final stages it is considered unlikely that the approaches described above can be modified sufficiently to provide satisfactory syntheses of the mustards **1***a* and **2***a* and alternative routes to these latter compounds are now being explored.

Experimental

Melting points were determined on a Fisher–Johns block and are corrected. The i.r. spectra were recorded on a Perkin–Elmer 237 B or 257 spectrometer. The p.m.r. spectra were determined in deuteriochloroform with tetramethylsilane as the internal standard on a Varian A-60 or HA-100 instrument. Column chromatographic separations were effected with Fisher Scientific Co. Florisil or neutral alumina deactivated with 2% w/w of water. The t.l.c. and preparative layer chromatography was performed on silica gel G and the compounds were visualized with iodine vapor or under u.v. light. Unless otherwise stated, all compounds described were purified until they were homogeneous to t.l.c. analysis.

17α-Bis(2-hydroxyethyl)aminomethyl-5α-androstane (2b)

(a) Cyanohydrin Route

A solution of 5α-androstan-17-one (1 g, 3.7 mmol) in absolute ethanol (125 ml) was added to a solution of potassium cyanide (11 g) in water (50 ml). The mixture was cooled in an ice bath and glacial acetic acid (15 ml) was added dropwise with stirring. The resulting solution was stirred for 1 h, and was then diluted with water (200 ml) and filtered to give the *17α-cyano-5α-androstan-17β-ol* (**4**, 0.96 g, 87%), m.p. 120–124°; i.r. (KBr) 3448, 2232, and 1730 cm^{-1} (C-17 carbonyl impurity).[9]

A solution of the above cyanohydrin (2.50 g, 8.3 mmol) in anhydrous benzene–ether (1:1, 500 ml) was added dropwise during 1 h at 0° to a well-stirred slurry of lithium aluminum hydride (0.48 g, 12.5 mmol) in anhydrous ether (250 ml). The mixture was then refluxed 18 h, and water (50 ml) followed by 10% aqueous sodium hydroxide (50 ml) were added dropwise in the presence of Celite. The resulting mixture was filtered, and the filtrate dried ($MgSO_4$) and evaporated. The residual solid (1.3 g) was combined with the material (0.95 g) obtained by Soxhlet extraction[10] of the filter cake with chloroform–methanol (1:1). The product so obtained was shown by g.l.c., t.l.c., and p.m.r. analyses to contain 18% of 5α-androstan-17β-ol[11] and 82% of the desired *17α-aminomethyl-5α-androstan-17β-ol* (**5**) which was used without further purification.

A solution containing the aminomethyl alcohol **5** (0.5 g, 1.27 mmol) in the minimum amount of chloroform (*ca.* 15 ml) was added rapidly to a stirred solution of ethylene oxide (10 ml) in methanol (20 ml), at 0°. The reaction flask was tightly stoppered and stirring was continued for a further 1 h at 0°. The solution was then kept at 20° for a further 2 days and was then refluxed for 8 h using an acetone – Dry Ice coating system to condense the remaining ethylene oxide. The solvent was removed by rotary evaporation at 20° and the yellow residue obtained (0.45 g) was purified by chromatography on Florisil. Elution with chloroform removed the 5α-androstan-17β-ol (35 mg) impurity and subsequent elution with chloroform–methanol–ammonia (90:15:1) afforded a colorless solid (0.39 g) which was recrystallized from methylene chloride to give *17α-bis(2-hydroxyethyl)-aminomethyl-5α-androstan-17β-ol* (**2***b*) (0.37 g, 58%),[12] m.p. 182–183°; i.r. ($CHCl_3$) 3448 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.78 (3H, s, C-19 CH_3), 0.85 (3H, s, C-18 CH_3), 2.68 (2H, midpoint of AB quartet superimposed on signal centered at 2.78 p.p.m., C-17 CH_2N), 2.78 (4H, 't', J = 4.8 Hz, NCH_2CH_2OH), 3.35 (3H, m, partially exchangeable with D_2O, OH), and 3.62 p.p.m. (4H, 't', J = 4.8 Hz, $NCHCH_2OH$).

(b) Oxirane Route

A mixture of spiro-17β-oxiranyl-5α-androstane (**13**, 60 mg, 0.21 mmol), bis(2-hydroxyethyl)amine (1 ml), and ethylene glycol (2 ml) was heated in a sealed tube at 160° for 5 h. The mixture was then poured into water and filtered. The solid obtained was dissolved in the minimum amount of anhydrous ether (20 ml) and hydrogen chloride was bubbled into the solution. The precipitate produced was filtered, washed with anhydrous ether, and dried *in vacuo* to give the hydrochloride (76 mg) which was resuspended in ether (50 ml) and then stirred with saturated aqueous sodium hydrogen carbonate (50 ml) for 1 h. The ether layer was then separated, washed with water (2 × 15 ml), and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue from methylene chloride gave the bis(2-hydroxyethyl)amino alcohol **2***b* (75 mg, 92%) which was identical in all respects to the material obtained above from the cyanohydrin route.

The analogous preparation of **2***b* using water as a solvent gave a 42% yield only.

Spiro-17β-oxiranyl-5α-androstane (13)

A 53.8% suspension of sodium hydride in mineral oil (0.65 g, 14.6 mmol) was washed with tetrahydrofuran by

[9]Recrystallization of this material from methanol did not remove the trace of the starting ketone **3** and attempted purification via column chromatography on alumina afforded 5α-androstan-17-one only. Accordingly the cyanohydrin **4** was used in its initially isolated form for the subsequent reaction.

[10]Several groups have observed that the filter cakes obtained during metal hydride reduction of cyanohydrins retain a considerable proportion of the desired amines (10, 19).

[11]The formation of the relatively large amount of this compound arises from the significant disproportionation which occurs during reduction of the cyanohydrin to the original C-17 ketone and cyanide ion (12).

[12]In spite of the application of various purification procedures satisfactory analytical data could not be obtained for this compound, nor for its hydrochloride. Analytical difficulties with steroid mustard compounds and intermediates have also been encountered previously (2, 20).

decantation. Dry dimethyl sulfoxide (10 ml) was added and the mixture was stirred for 45 min at 70° under nitrogen. Tetrahydrofuran (10 ml) was then added, the mixture cooled to −5°, and solution of trimethylsulfonium iodide (30 g, 14.6 mmol) in dimethyl sulfoxide (23 ml) added rapidly with stirring (13). During this addition the reaction mixture solidified and the addition of further tetrahydrofuran (14 ml) became necessary. 5α-Androstan-17-one (**3**) (1.0 g, 3.65 mmol) in tetrahydrofuran (30 ml) was then added to the mixture and after being kept at 20° for 15 h the whole was poured into water (150 ml) and extracted with ether (4 × 75 ml). The combined ether extracts were washed with water (2 × 25 ml), dried ($MgSO_4$), and evaporated. The residue (0.93 g) was purified by chromatography on alumina and elution with petroleum ether (60–70°). Recrystallization from acetone gave *spiro-17β-oxiranyl-5α-androstane* (**13**) as feathery plates (0.88 g, 84%), m.p. 160–161°; p.m.r. ($CDCl_3$) δ 0.78 (3H, s, C-19 CH_3), 0.86 (3H, s, C-18 CH_3), and 2.71 p.p.m. (2H, midpoint of AB quartet, δ_A 2.82, δ_B 2.52, J_{AB} = 5.0 Hz, C-17 CH_2).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.22; H, 11.31.

17α-Methyl-5α-androstan-17β-ol (**14**)

(a) From the Oxirane (**13**)

Spiro-17β-oxiranyl-5α-androstane (**13**) (300 mg, 1.04 mmol) was refluxed for 4 h with lithium aluminum hydride (0.30 g, 7.8 mmol) in tetrahydrofuran (50 ml). Ethyl acetate (50 ml) was then carefully added to the cooled reaction mixture following which it was poured into aqueous hydrochloric acid (5%, 150 ml). The mixture was extracted with benzene (3 × 40 ml) and the combined extracts were washed with water and dried ($MgSO_4$). Evaporation gave a colorless solid (225 mg) which recrystallized from acetone to produce *17α-methyl-5α-androstan-17β-ol* (**14**) as plates (210 mg, 70%), m.p. 165–166°; i.r. ($CHCl_3$) 3597 and 3472 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.79 (3H, s, C-19 CH_3), 0.82 (3H, s, C-18 CH_3), and 1.18 p.p.m. (3H, s, C-17 CH_3).

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.45; H, 11.95.

(b) From 17β-Hydroxy-17α-methylandrost-4-en-3-one (**15**)

17β-Hydroxy-17α-methylandrost-4-en-3-one (**15**, 4 g, 13.2 mmol) was converted, via lithium in liquid ammonia, followed by Wolff–Kishner reductions (21) into authentic 17α-methyl-5α-androstan-17β-ol (**14**, 1.95 g, 50%) which was identical in all respects with the material obtained above.

17α-Bis(2-hydroxyethyl)aminomethyl-3,3′-ethylenedioxyandrost-5-en-17β-ol (**12**)

(a) Cyanohydrin Routes

3,3′-Ethylenedioxy-17β-hydroxyandrost-5-ene (**7**) m.p. 183–184° (lit. (22) m.p. 182–184°) was obtained from testosterone (**6**) in 46% yield (22). Oxidation of **7** with chromium trioxide in pyridine (22) proceeded smoothly to give 3,3′-ethylenedioxyandrost-5-en-17-one (**8**) m.p. 196–197° (lit. (22) m.p. 197–198°) in 80% yield. Freshly prepared (23) acetone cyanohydrin (1 ml) was added to the ketal **8** (200 mg, 0.61 mmol) dissolved in the minimum quantity of warm methanol. The resulting solution was heated on a steam bath for 3 min and a few drops of a methanolic solution containing 2% w/w of potassium cyanide were added. After keeping for 4 h at 20° the crystalline precipitate was filtered off, washed with water, and then dried *in vacuo* to give 3,3′-ethylenedioxyandrost-5-ene-17-cyanohydrin (**9**, 180 mg, 83%), m.p. 205–209° (lit. (11) m.p. 185°); i.r. (KBr) 3390 and 1739 cm^{-1} (C-17 carbonyl impurity). This material was not further purified but was used directly in subsequent experiments (*cf.* footnote 9).

Alternatively, the cyanohydrin **9** could be prepared from androst-4-ene-3,17-dione (**10**).

Androst-4-ene-3,17-dione (2 g, 7.0 mmol) was dissolved by gentle warming and swirling in freshly prepared (23) acetone cyanohydrin (3 ml). The solution was allowed to stand for 2 h at 20° and was then diluted with water (15 ml) and extracted with ether (4 × 40 ml). The combined ether extracts were washed with water and the ether solution was then cooled in an ice bath. The precipitated crystalline mass was filtered and dried *in vacuo* to give crude androst-4-en-3-one-17-cyanohydrin (**11**) (1.62 g, 74%), m.p. 174–180° (lit. (11) m.p. 176–178°); i.r. (KBr) 2279, 2237, 1656, and 1739 cm^{-1} (C-17 C=O impurity). No attempt was made to further purify this material (*cf.* footnote 9).

A suspension of the above cyanohydrin **11** (1.0 g, 3.2 mmol) in benzene (65 ml) and ethylene glycol (1.30 ml) with toluene-*p*-sulfonic acid (0.1 g) was refluxed for 16 h in a Soxhlet extractor with the water formed during the reaction being removed with molecular sieves. Evaporation of the solvent and recrystallization of the residue from methanol containing a few drops of pyridine produced the cyanohydrin ketal **9** (0.91 g, 80%), m.p. 205–208°. The i.r. spectrum of this material indicated that less C-17 carbonyl impurity was present than in the previous material, m.p. 205–209°, obtained above.

3,3′-Ethylenedioxyandrost-5-ene-17-cyanohydrin (**9**) (1.20 g, 34 mmol) was treated with lithium aluminum hydride (0.19 g, 5.1 mmol) and the reaction mixture worked-up as described for the synthesis of the 5α-androstane analogue **5**. The product obtained by extraction of the filter cake[10] (0.51 g) was combined with the material obtained by evaporation of the supernatant (0.66 g) and the whole chromatographed on Florisil. Elution with chloroform gave 3,3′-ethylenedioxyandrost-5-en-17β-ol[9] (0.30 g) and elution with chloroform – methanol – ammonium hydroxide (90:15:1) produced the amino-carbinol **12** (0.56 g, 46%) which was recrystallized from benzene as prisms, m.p. 240°; i.r. (KBr) 3778, 3300, 3175, 1107, and 1093 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.90 (3H, s, C-18 CH_3), 1.02 (3H, s, C-19 CH_3), 2.70 (2H, midpoint of AB quartet superimposed on other H signals, δ_A 2.90, δ_B 7.50, J_{AB} = 12.8 Hz, C-17 CH_2N), 3.90 (4H, s, OCH_2CH_2O), and 5.31 p.p.m. (1H, m, vinyl H). Mass spectrum (70 eV) *m/e* 361 (parent ion).

3,3′-Ethylenedioxy-17β-hydroxy-17α-aminomethylandrost-5-ene (**12**) (0.30 g, 0.83 mmol) and ethylene oxide (6 ml) were reacted and worked-up as described above for the synthesis of the model compound **2***b*. Recrystallization of the product from methylene chloride gave *17α-bis(2-hydroxyethyl)aminomethyl-3,3′-ethylenedioxyandrost-5-en-17β-ol* (**12**) as plates (270 mg, 72%), m.p. 199–201°; i.r. ($CHCl_3$) 3425, 1663, and 1096 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.90 (3H, s, C-18 CH_3), 1.03 (3H, s,

C-19 CH_3), 2.69 (2H, m, superimposed on signal centered at 2.77 p.p.m., C-17 CH_2N), 3.40 (3H, m, partially exchangeable with D_2O, OH), 3.61 (4H, 't', $J = 5.5$ Hz, NCH_2CH_2OH), 3.90 (4H, s, OCH_2CH_2O), and 5.29 p.p.m. (1H, m, vinyl H). Mass spectrum (70 eV) *m/e* 449 (parent ion).

Anal. Calcd. for $C_{26}H_{43}NO_5$: C, 69.45; H, 9.64; N, 3.11. Found: C, 69.13; H, 9.48; N, 3.47.

(b) Oxirane Route

3,3'-Ethylenedioxyandrost-5-en-17-one (**8**, 1 g, 3 mmol) was reacted with dimethylsulfonium methylide as described above in the preparation of the oxirane **13**. 3,3'-Ethylenedioxy-spiro-17β-oxiranylandrost-5-ene (**17**) was obtained as feathery plates (0.88 g, 88%) from acetone, m.p. 185–190°; i.r. ($CHCl_3$) 1096 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.94 (3H, s, C-18 CH_3), 1.09 (3H, s, C-19 CH_3), 2.78 (2H, midpoint of AB quartet, δ_A 2.78, δ_B 2.63, $J_{AB} = 4.9$ Hz, oxiranyl CH_2), 3.97 (4H, s, OCH_2CH_2O) and 5.40 p.p.m. (1H, m, vinyl H).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.65; H, 9.36. Found: C, 76.75; H, 9.43.

A mixture of the spiro-17β-oxiranyl-3-ketal **17** (0.50 g, 1.45 mmol), bis(2-hydroxyethyl)amine (25 ml), and water (6 ml) was reacted and worked-up by the procedure described above for the conversion of the oxirane **13** into **2***b*. Recrystallization of the product from methylene chloride yielded 0.31 g (48%) of the aminotriol **12** identical in all respects with the material obtained via the cyanohydrin route.

17α-(N-Morpholinomethyl)-5α-androstan-17β-ol (16)

A solution of spiro-17β-oxiranyl-5α-androstane (**13**, 125 mg, 0.44 mmol) in morpholine (5 ml) containing phenol (55 mg) was refluxed for 24 h. The solution was then poured into water (25 ml) and extracted with ether (3 × 20 ml). The combined ether extracts were washed with aqueous sodium hydroxide (10%, 3 × 10 ml), then with water (2 × 15 ml), and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue (130 mg) from methanol gave *17α-(N-morpholinomethyl)-5α-androstan-17β-ol* (**16**, 108 mg, 66%), m.p. 160–161.5°; i.r. ($CHCl_3$) 3425 cm^{-1}; p.m.r. ($CDCl_3$) δ 0.78 (3H, s, C-19 CH_3), 0.87 (3H, s, C-18 CH_3), 2.24–2.68 (6H, m, NCH_2CH_2O and C-17 CH_2N), 3.48 (1H, s, OH), and 3.71 p.p.m. (4H, 't', NCH_2CH_2O, $J = 4.4$ Hz).

Anal. Calcd. for $C_{24}H_{41}NO_2 \cdot \frac{1}{2}H_2O$: C, 74.95; H, 11.07; N, 3.64. Found: C, 75.27; H, 10.98; N, 3.78.

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