Tetrahedron. Vol. 29, pp. 1941 to 1947. Pergamon Press 1973. Printed in Great Britain

STEROIDS AND STEROIDASES—XIX*

COMPARISON OF DIAZOMETHANE AND TIFFENEAU-DEMJANOV HOMOLOGATIONS OF 5α-3-OXOSTEROIDS. EVIDENCE FOR PREDOMINANT EQUATORIAL APPROACH OF THE C-3 CARBONYL GROUP BY DIAZOMETHANE

J. BRYAN JONES* and P. PRICE

Lash Miller Chemical Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada, M5S 1A1

(*Received in the USA* 11 *December* 1972; *Received in the UK for publication* 20 *February* 1973)

Abstract—Quantitative comparisons of the product ratios of the mechanistically similar diazomethane and Tiffeneau-Demjanov homologations of 17β-hydroxy-5α-androstan-3-one and 5α-cholestan-3-one have shown that equatorial approach of diazomethane to the C-3 CO group predominates to the extent of 70–79%. The data for both the C-17β-OH and $-C_8H_{17}$ substituted steroids are in close agreement thereby confirming that the C-17 substituents do not exert any significant long range effect on the reactions studied.

INTRODUCTION

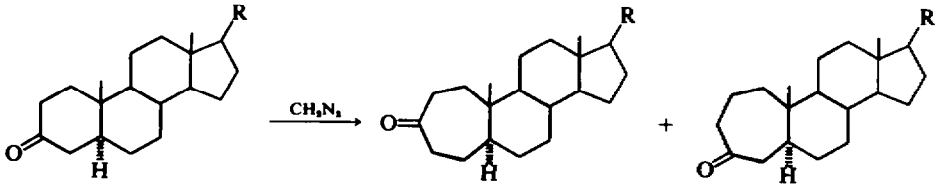
During the course of our investigations on the diazomethane homologation of ring A of steroid-3-ketones[2] such as **1** we became interested in whether axial or equatorial approach of diazomethane to the C-3 CO group was favoured and how this factor would affect the ratio of the isomeric A-homo-3- and 4-ones **2** and **3** produced in the subsequent homologation reaction.

Very little is known regarding the parameters controlling the direction of addition of diazomethane to cyclic ketones. Although diazomethane is a rod-like nucleophile the data available on the stereochemically analogous cyanide,[3,4] ethinyl,[3-5] and nitromethane[3,6] anions are not helpful since the products of their additions to ketones are formed under conditions of thermodynamic control. In contrast, diazomethane undoubtedly reacts under kinetically controlled conditions since equilibration of the starting ketone and diazomethane, and intermediates such as **4** and **5**, will be precluded by facile loss of nitrogen from the latter. However, on the basis of the studies carried out on the homologations of cyclopropanones,[7] 4-alkylcyclohexanones,[8] and *trans*-2-decalone,[9] for which diazoalkane addition to the ketone from the least hindered or equatorial direction was concluded to predominate to a greater or lesser extent, it would be predicted that equatorial attack by diazomethane of the CO group of **1** would be preferred.† The results presented in this communication confirm this prediction.

The initial intermediates arising from axial and

*For Part XVIII see J. B. Jones and K. D. Gordon, *Biochemistry* **12**, 71 (1973). Abstracted from the Ph.D. thesis of P. Price, University of Toronto (1972). A preliminary communication on some of these results has been published.[1]

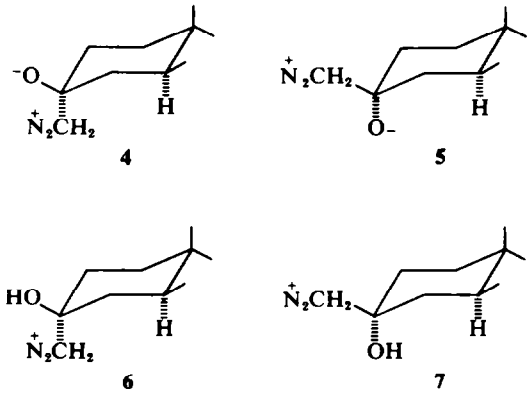
†Since the "effective bulk" of diazomethane is not easy to assess, consideration of the torsional and steric factors[10] involved is not possible.



1 **2** **3**

a: R = OH
b: R = C_8H_{17}

SCHEME 1



equatorial approach of diazomethane to compounds **1** would be **4** and **5** respectively. Unfortunately, since it is not possible to generate each of these (or their subsequent equally transient[11] derivatives) independently of the other, the consequences of the differences in configuration on the proportions formed of the possible products cannot be determined directly. However, the analogous intermediates **6** and **7** of the closely related Tiffeneau-Demjanov rearrangement[12] can be obtained from hydroxyamine precursors of establishable stereochemical integrity and purity. Accordingly, we turned our attention towards this reaction in the hope that it would provide an insight into the rearrangement consequences of the different configurations of the two epimeric diazomethane addition intermediates **4** and **5**. That epimeric Tiffeneau-Demjanov intermediates such as **6** and **7** do give rise to different product, or bond migration, ratios is well established[6,9,13–15] and several groups[9,16,17] have studied Tiffeneau-Demjanov analogues of diazomethane-cyclic ketone reactions in attempts to understand the factors involved in the two related processes. The investigation by Carlson and Behn[9] on *trans*-2-decalone has been the most rigorous of these previous studies and their general rearrangement procedures have therefore been followed in this investigation.*

RESULTS AND DISCUSSION

The comparative diazomethane and Tiffeneau-Demjanov homologation reactions were carried out on 5α-3-oxo-steroids with polar (OH) and non-polar (C_8H_{17}) C-17β substituents. The sequences of reactions performed were identical for both series of compounds and are summarized in Scheme 2.

Treatment of the 17β-hydroxy ketone **1a** with potassium cyanide in acetic acid, followed by acetylation, yielded a mixture of the epimeric cyanohydrin acetates **8c** and **12c** in which the axial cyano derivative **8c** predominated to the extent of ~ 8:1. The equatorial cyano epimer **12c** had not been isolated previously.[19] Reduction of the purified cyanohydrin acetates with lithium aluminum hydride gave the corresponding hydroxy aminomethyl compounds **9a** and **13a** which were difficult to purify and which were therefore converted directly to the more easily handled acetonides **10a** and **14a** respectively. The latter were further characterized as their acetate derivatives **11c** and **15c**.

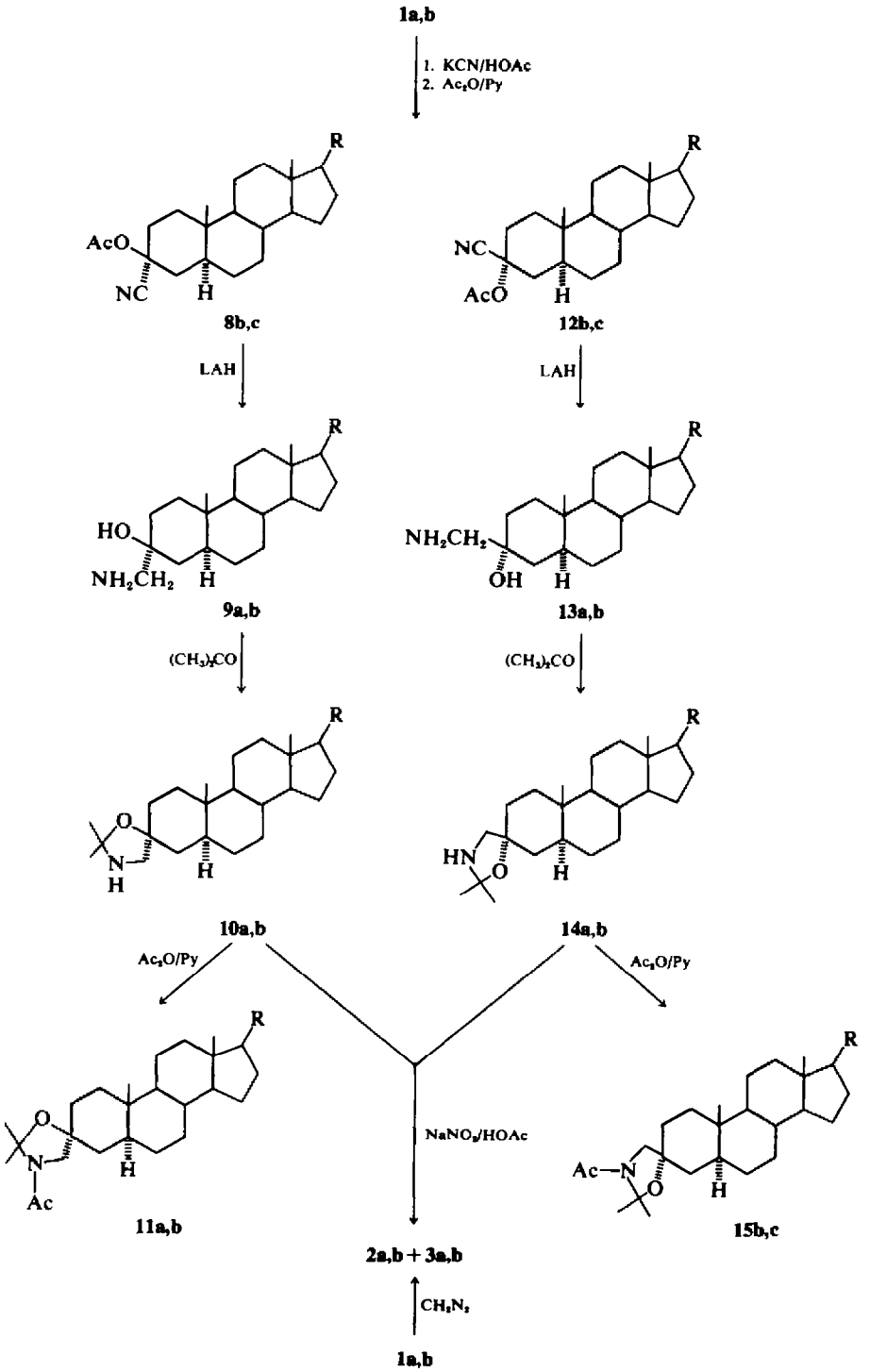
The designations of the C-3 configurations of the hydroxy aminomethyl intermediates **9a** and **13a** as shown in Scheme 2 follow from the initial assignments of the stereochemistries of their cyanohydrin precursors. For the latter, the predominance of the axial cyano product under conditions of thermodynamic control was expected from a consideration of the conformational free energy between hydroxyl and cyano groups,[20a] and by analogy with the course of addition of cyanide ions to other substituted cyclohexanones.[3,4] However, in view of the importance of unambiguous assignments of the C-3 stereochemistries of **9a** and **13a**, and of their acetonides **10a** and **14a**, to the study in hand, the configurations of **13a** and **14a** were rigorously established as outlined in Scheme 3. On treatment with sodamide in liquid ammonia, the α-oxirane **16a** of previously verified C-3 geometry[21] gave the equatorial amino methyl compound **13a**, the acetonide **14a** and N-acetate **15c** of which were identical with the samples derived from the minor cyanohydrin epimer **12c**.

The synthetic operations followed above for the C-17β-hydroxy compounds were then repeated in the cholestane series and the C-3 epimeric Tiffeneau-Demjanov intermediates **9b** and **10b**, and **13b** and **14b** were obtained without difficulty. The C-3 configurations were again rigorously established *via* the oxirane **16b**.†

Before proceeding with the evaluation of the influence of the C-3 configuration on the product ratios from Tiffeneau-Demjanov rearrangements of **9a**, **9b** and **13a**, **13b**, it was necessary to establish a reliable procedure for analyzing the properties

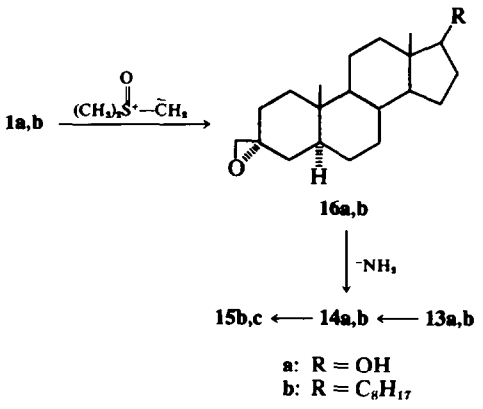
*Consideration of the Tiffeneau-Demjanov intermediates **6** and **7** as reasonable models for the corresponding diazomethane reaction species **4** and **5** can be questioned on the grounds that in **4** and **5**, an alkoxide anion is present whereas in **6** and **7**, the equivalent function is a hydroxyl group. However, since the homoketone ratios obtained with diazomethane in basic methanol are identical with those from analogous homologations in neutral methanol solutions[2] (for which the alkoxide anions of **4** and **5** will be largely protonated[8,18]), the assumption that the Tiffeneau-Demjanov and diazomethane intermediates are closely similar is considered valid.

†Shortly after the completion of this synthetic portion of our investigation, details of a virtually identical approach to the same cholestane compounds were reported by Sykes *et al.*[22] The properties of the Tiffeneau-Demjanov intermediates obtained were in total agreement except for the minor cyanohydrin acetate **12b**, which was only partially purified by the latter authors.



a, R = OH; b, R = C_8H_{17}; c, R = OAc

SCHEME 2



SCHEME 3

of the A-homoketone **2a**, **2b** and **3a**, **3b** produced since mixtures of such compounds are difficult to resolve. Furthermore, even when the isomers are separable, the yields obtained of the pure homoketones are often very low.[2] The problem is particularly acute for the homocholestanones with Levisalles and his coworkers having shown[23] that most of the literature data[2,16,19,22,24,25] on **2b** and **3b** are inaccurate to a greater or lesser degree owing to the failure of mixtures of these compounds to yield to even the most rigorous purification procedures. The only reliable analytical method has proven to be one based on ORD or CD differences.[2,23] The ORD Cotton effect amplitude calibration graphs obtained using pure samples of the 17β-hydroxyhomoketones **2a** and **3a** and the corresponding cholestanones **2b** and **3b*** were linear and, using mixtures of 3- and 4-ones of predetermined compositions, it was found that the A-homoketone ratios could be determined to within $< \pm 3\%$ by this method.

Diazomethane and Tiffeneau-Demjanov ring enlargements were then carried out in duplicate on **1a**, **1b** and **10a**, **10b**, **14a**, **14b** respectively. Following each reaction, the total products were analyzed by GLC in order to ascertain the percentage yields of the A-homoketones **2a**, **2b** and **3a**, **3b** and of the epoxides **16a**, **16b** and their C-3 epimers. The reaction mixtures were then chromatographed in order to separate the A-homoketones from all other components. The ORD spectrum of the total A-homoketone component of each reaction was then measured and the proportions of 3- and 4-ketones present determined from the amplitudes of the Cotton effects. The results are summarized in Table 1. They show clearly that Tiffeneau-Demjanov rearrangements of the C-3 epimeric precursors do give significantly different A-homo-3- to 4-ketone ratios. The product ratios from the corresponding diazomethane homologations are similar to those from the Tiffeneau-Demjanov precursors derived from the equatorial aminomethyl compounds thereby indicating that for the kinetically controlled diazomethane reaction, the incoming nucleophile approaches the C-3 carbonyl predominantly from the equatorial direction. Furthermore, since the two rearrangement processes are considered to proceed *via* the closely analogous intermediates **4**, **5**, **6** and **7**, the product ratios recorded in Table 1 can be used to provide a quantitative estimate of the preference of diazomethane for equatorial attack of the carbonyl groups of **1a**, **1b**. The relative percentages of equa-

*Authentic samples obtained by chemical fractionation were kindly provided by Professor J. Levisalles.

Table 1. Comparison of product ratios and influence of C-3 stereochemistry of intermediates on diazomethane and Tiffeneau-Demjanov homologations of 5α-androstane-17β-ol- and 5α-cholestan-3-ketones and their derivatives

Starting material	Homolog. method	% Yield 2+3	Mol. amp.[a] 2+3	% Ratio[b] 2:3	Calc % ratio 5:4
10a	TD	95 (~ 1)[c]	+32·2	49·5:50·5	
14a	TD	80 (~ 8)	+1·6	61·5:38·5	
1a	DM	75 (~ 7)	+9·0	59:41	79:21[d]
10b	TD	88 (~ 5)	+32·0	48:52	
14b	TD	73 (~ 15)[e]	−6·3	63:37	
1b	DM	80 (~ 13)	+5·2	58·5:41·5	70:30

The values cited are averages of the data obtained from duplicate runs reproducible to within $\pm 3\%$.

[a]From ORD spectra in MeOH.

[b]Obtained using calibration graphs prepared using *a* values of pure samples of **2a**, **3a**[2] and **2b**, **3b**.[23]

[c]Values in parentheses are % yields (GLC) of C-3 oxiranyl products.

[d]Preferred values. *cf* reference 1.

[e]Sykes *et al.*[22] observed 20% oxirane.

torial and axial approach calculated* on this basis (Table 1) are found to be similar for both steroid-3-ketones **1a**, **1b** with equatorial attack being favoured to the extent of 70–79%.† These conclusions are similar to those drawn by Carlson and Behn[9] for ring expansions of the related *trans*-2-decalone. For the latter compound, analysis of the product ratios as described above gives a calculated 56:44 equatorial/axial ratio for the direction of diazomethane approach of the carbonyl group. The increased proportion of equatorial diazomethane attack of the steroid ketones may be due to a slightly decreased accessibility of the C-3 carbonyl from the axial direction resulting from the convex character of the steroid skeleton.[28] The formation of greater amounts of epoxides from diazomethane homologation of **1a,b** and from **14a,b** than from **10a,b** (Table 1) is also in accord with predominant equatorial approach of diazomethane to the C-3 CO. The larger epoxide yields from the equatorial diazomethyl epimers is satisfactorily accounted for by the suggestion of Carlson and Behn[9] that transannular interactions between $CH_2N_2^+$ and C-1,5 hydrogens operates against the transition states leading to oxirane formation.

It has been noted previously[1,22] that studies of models and consideration of the factors affecting differential bond migration give little indication why formation of the 3- and 4-A-homoketones from epimers such as **6** and **7** should not be equally favoured. Qualitative conformational analyses of the probable carbonium ion transition states involved[9] are more helpful in this regard. They show that transannular interactions between the C-19 Me hydrogens and those of an equatorial methylene residue of a diazomethyl group would favour conformations leading to the experimentally observed preferential migrations of C-3,4 over C-2,3 bonds. In contrast, no similar preference of one bond migration is apparent from a consideration of axial methylene—C-5 H interactions. However, although these analyses are in accord with the experimental data (Table 1) they are not considered overly significant in view of the small free energy differences (< 350 cal mole^{-1})[20b] between the transition states that the product ratios reflect.

Note on Long Range Effects and Apparent Contradictions in the A-Homosteroid Literature

When this investigation was begun, one of the objectives was to have been an evaluation of the apparently unique long-range effect exerted by the C-17β C_8H_{17} function on the diazomethane homologation reaction.[2] However, as stated above, this effect was subsequently shown to be spurious[23] and the data of Table 1 confirm the conclusion that the nature of the C-17 substituent does not affect the homologation pathway to any significant extent. In view of the number of groups, including ourselves, who have been misled into considering their samples of A-homocholestanones to be pure,[2,16,19,22,24,25] and the continuing interpretations of these data as being contradictory with respect to the ratios of C-2 to C-3,4 migration,[29] it should be reemphasized[23] that the normal purification and analytical techniques do not effect satisfactory separations of the A-homocholestanones **2b** and **3b**. The usual spectroscopic or TLC and GLC analytical methods do not enable the isomers to be distinguished and the data based on these methods alone are of questionable validity. For example, although GLC has been used extensively in the studies on A-homosteroids, we have found that **2b** and **3b**, or their N,N-dimethylhydrazones,[30] cannot be distinguished using SE-30, QF-1, XE-60, NPGS, STAP, Carbowax-20M or PDEAS columns. This syndrome appears general for A-homosteroid ketones with non-polar C-17 groups such as C_8H_{17} and H. In such cases the pure isomers can only be obtained by chemical fractionation[23] or independent synthesis[2] and reliable determinations of the proportion of each isomer in mixtures of such compounds require analysis by the ORD (or CD) method.‡ As would be expected, the *a* values of pure samples of the variously C-17 substituted A-homo-3- and 4-ones respectively are very similar.[2,23] In the light of the total data now available, the conformational justifications presented for exceptional predominance of one bond migration over the other[22] are no longer required.

EXPERIMENTAL

Apparatus and materials. M.p's were determined on a Fisher-Johns block and are uncorrected. IR spectra were recorded on a Perkin-Elmer 237B spectrophotometer. NMR spectra were determined using TMS as the internal standard on a Varian A-60 or HA-100 instrument. Mass spectra were obtained with a Bell and Howell 21-490 mass spectrometer. ORD measurements were made in methanol on a Jasco-Durrum ORD/UV5 spectropolarimeter. GLC analyses were performed on an F and M 400 biomedical unit with the usual columns used being 3% SE-30, 1% QF-1, and 2% XE-60, all on silanized Chromosorb G. Column chromatographic separations were effected with deactivated alumina. Silica gel G was used for analytical and preparative TLC and the compounds were visualized with iodine vapour. All solvents were redistilled and, unless indicated otherwise, all compounds were purified at least until homogeneous to GLC analysis on 3 columns.

*The calculations were performed as illustrated below: If a = % axial diazomethyl epimer and e = % equatorial diazomethyl epimer, then $a+e=100\%$. For the 17β-hydroxy series. Tiffeneau-Demjanov homologation of the equivalent intermediates gives 49·5:50·5 (axial diazomethyl) and 61·5:38·5 (equatorial diazomethyl) ratios respectively of **2a**:**3a**. For the corresponding diazomethane reaction, the ratio is 59:41. Thus, provided **4** and **6**, and **5** and **7** are mechanistically analogous under the respective reaction conditions, $49{\cdot}5a+61{\cdot}5e=59$ and $50{\cdot}5a+38{\cdot}5e=41$. From these equations, and the fact that $a+e=100$, the individual values of e and a are 79 and 21 respectively (Table 1).

†For the presumably kinetically controlled addition of methyl Grignard reagent to **1b** a similar equatorial:axial (~ 60:40) product distribution is observed.[26,27]

‡Although several groups[2,24,25] have determined the ORD spectra of their 5α-A-homocholestanones, the *a* values reported show clearly that the samples were impure.

Preparations of 17β-hydroxy-5α-androstane derivatives

3α-Cyano-3β,17β-diacetoxy-5α-androstane (**8c**) *and 3β-cyano-3α,17β-diacetoxy-5α-androstane* (**12c**). A soln of **1a** (10 g, 34·5 mmoles) in abs EtOH (900 ml) was added to a soln of KCN (110 g, 1·7 moles) in water (600 ml) and the stirred soln cooled to 0°. AcOH (150 ml, 2·6 moles) was then added dropwise and stirring was continued for a further 1 hr.[19] The soln was then poured into water (1 l) and the precipitated solid 3,17β-dihydroxy-3α-cyano-5α-androstane (10·6 g, 97%) obtained was filtered, washed well with water, and then dried *in vacuo* over P_2O_5; IR(KBr) 3436 and 2240 cm^{-1}.

A soln of the above mixture of cyanohydrin epimers (10 g, 3·1 mmoles) in Ac_2O (300 ml) and pyridine (400 ml) was kept at 22° for 15 hr and was then poured into water (2 l). The solid which separated was filtered off and washed well with water. The product was then washed separately with a small portion of ether (30 ml) and the ethereal soln saved for work-up as described below. The residual material (8·6 g) was found by GLC analysis to be ~99% **8c**. Recrystallization from MeOH gave needles of pure material (6·1 g) m.p. 207·5–208·5° (lit.[19] m.p. 198–200°); IR(KBr) 1750 and 1727 cm^{-1}; NMR ($CDCl_3$) δ0·78 (3H, s, C-18 Me), 0·84 (3H, s, C-19 Me), 2·00 (3H, s, C-17β OAc), 2·03 (3H, s, C-3β OAc), 4·62 ppm (1H, 't',* $J = 8$ Hz, C-17α H); mass spectrum (70 eV) *m/e* 401 (parent ion). (Found: C, 71·72; H, 8·64; N, 3·44; Calcd. for $C_{24}H_{35}NO_4$: C, 71·79; H, 8·78; N, 3·49%.)

Chromatography of the material (3·8 g), obtained from the initial 30 ml ethereal washing, on Florisil (40% diethylether – 60% hexane elution) gave **12c** (0·71 g) which on recrystallization from MeOH afforded needles, m.p. 185·5–186°; IR(KBr) 1754 and 1727 cm^{-1}; NMR($CDCl_3$) δ0·80 (3H, s, C-18 Me), 0·86 (3H, s, C-19 Me), 2·01 (3H, s, C-17β OAc), 2·11 (3H, s, C-3α OAc), 4·60 ppm, (1H, 't', $J = 8$ Hz, C-17αH); mass spectrum (15 eV) *m/e* 401 (parent ion). (Found: C, 71·82; H, 8·67; N, 3·58. Calcd. for $C_{24}H_{35}NO_4$: C, 71·79; H, 8·78; N, 3·49%.)

17β-Hydroxy-3(S)-spiro-[5'-(2',2'-dimethyl-1',3'-oxazolidine)]-5α-androstane (**10a**). A soln of **8c** (5·0 g, 12·5 mmoles) in anhyd benzene-ether (1:1, 1 l) was added with stirring to a slurry of LAH (6·25 g, 165 mmoles) in anhyd ether (500 ml) over a period of 45 min. The mixture was stirred for a further 30 min at 22° and was then heated under reflux for 24 hr. The excess hydride was then decomposed by the cautious addition of water and NaOH (250 ml, 2 N) added to the resulting suspension. The solid material produced was filtered off, washed well with water, dried and extracted in a Soxhlet apparatus with acetone (300 ml) for 3 days. The acetone soln was evaporated and the solid obtained (3·7 g) was chromatographed on neutral alumina (prepared in chloroform). Compound **10a** was eluted with chloroform: MeOH: ammonia (9:1·5:1) which, after recrystallization from acetone, gave needles, m.p. 165–167°; IR($CHCl_3$) 3610 and 3333 cm^{-1}; NMR ($CDCl_3$) δ0·73 (3H, s, C-18 Me), 0·84 (3H, s, C-19 Me), 1·35 and 1·37 (6H, 2s, $Me_2(N)O$), 2·65 (2H, s (broad), NH and OH), 2·99 (2H, s, NCH_2), 3·59 ppm (1H, 't', $J = 8$ Hz, C-17αH); mass spectrum (15 eV) *m/e* 361 (parent ion). (Found: C, 76·37; H, 10·75; N, 3·90. Calcd. for $C_{23}H_{39}NO_2$: C, 76·42; H, 10·87; N, 3·87%.)

The acetonide **10a** was further characterized as its N-acetate by treatment of **10a** with Ac_2O in pyridine. The amide **11c** was recrystallized from 2,2,4-trimethylpentane as needles m.p. 187·5–188°; IR(KBr) 1736 and 1667 cm^{-1}; NMR($CDCl_3$) δ0·79 (3H, s, C-18 Me), 0·86 (3H, s, C-19 Me), 1·58 and 1·61 (3H, 2s, $Me_2C(N)O$), 2·03 (3H, s, C-17β OAc), 3·52 (2H, AB q, δ_A3·55, δ_B3·49, $J_{AB} = 10$ Hz, NCH_2), 2·07 (3H, s, NAc), 4·64 ppm (1H, 't', $J = 8$ Hz, C-17αH); mass spectrum (15 eV) *m/e* 430 (strong) (M-15) (no parent ion). (Found: C, 72·65; H, 9·63; N, 3·04. Calcd. for $C_{27}H_{43}NO_4$: C, 72·77; H, 9·73; N, 3·14%.)

17β-Hydroxy-3(R)-spiro-[5'-(2',2'-dimethyl-1',3'-oxazolidine)]-5α-androstane (**14a**)

(a) *By reduction of 3β-cyano-3α,17β-diacetoxy-5α-androstane* (**12c**). Compound **12c** (1·5 g, 3·75 mmoles) in anhyd benzene-ether (1:1, 300 ml) was reduced with LAH (2·3 g, 60·5 mmoles) in anhyd ether (150 ml) as described above. Compound **14a** was obtained as a colourless semi-solid oil which could not be crystallized; NMR ($CDCl_3$) δ 0·72 (3H, s, C-18 Me), 0·75 (3H, s, C-19 Me), 1·35 (6H, s, $Me_2C(N)O$), 2·08 (2H, s (broad), —NH and OH), 2·87 (2H, s, NCH_2), 3·62 ppm (1H, 't', $J = 8$ Hz, C-17αH), mass spectrum (15 eV) *m/e* 361 (parent ion).

(b) *By reaction of* (3R)-*spiro*(3,2'-*oxiranyl*)-5α-*androstan*-17β-*ol* (**16a**) *with sodium amide*. A mixture of liquid ammonia (100 ml), compound **16a**, m.p. 170–172° (lit.[21] 21 m.p. 174–176°) 2 g, 6·6 mmoles, (prepared by reaction of **1a** with dimethylsulfoxonium methylide[21]) in dry THF (25 ml), and $NaNH_2$ (4 g, 100 mmoles) was kept in a stainless steel bomb at 22° for 4 days. Water (30 ml) was then added dropwise to decompose any unreacted $NaNH_2$ and the residual ammonia allowed to evaporate. The aqueous mixture was extracted with chloroform (8 × 100 ml) and the chloroform extracts washed with sat NaCl aq (2 × 50 ml) and then dried ($MgSO_4$). Evaporation of the chloroform extract gave **13a** as a yellow solid (1·5 g) which was dissolved in acetone (150 ml) and then evaporated to give the corresponding acetonide as a yellow oil (1·68 g).

Chromatographic purification as described above again yielded the acetonide **14a** as a noncrystallizable oil.

The samples of the acetonide **14a** were further characterized by conversion to **15c** with Ac_2O in pyridine. The amide **15c** recrystallized from 2,2,4-trimethylpentane as needles m.p. 113–114°; IR(KBr) 1736 and 1664 cm^{-1}; NMR ($CDCl_3$) δ0·78 (6H, s, C-18 Me and C-19 Me), 1·58 (6H, s, $Me_2C(N)O$), 2·02 (3H, s, C-17β OAc), 2·03 (3H, s, NAc), 3·40 (2H, s, NCH_2), 4·65 ppm (1H, 't', $J = 8$ Hz, C-17αH); mass spectrum (15 eV) *m/e* 430 (M-15) (no parent ion). (Found: C, 72·68; H, 9·86; N, 3·09. Calcd. for $C_{27}H_{43}NO_4$: C, 72·77; H, 9·73; N, 3·14%.)

Preparations of 5α-cholestane derivatives

The procedures followed paralleled those described above for the corresponding 5α-androstane derivatives. Except where indicated otherwise, the analytical and spectroscopic data for the compounds prepared corresponded with those recorded by Sykes *et al.*[22]

3β-Acetoxy-3α-cyano-5α-cholestane (**8b**) *and 3α-acetoxy-3β-cyano-5α-cholestane* (**12b**). Treatment of **1b** with KCN in aqueous AcOH gave a quantitative yield of the expected cyanohydrin epimers which were acetylated to give **8b**, (76%) needles from EtOH m.p. 129–130° (lit.[22] m.p. 125–126°) and **12b** (19%) needles from m.p. 141–142° (lit.[22] m.p. 100–110°); IR($CHCl_3$) 1754 cm^{-1}, NMR ($CDCl_3$) δ0·66 (3H, s, C-18 Me), 0·85 (3H, s, C-19 Me), and 2·11 ppm (3H, s, C-3α OAc); mass spectrum (70 eV) *m/e* 455 (parent ion). (Found: C, 79·16; H, 10·80; N, 3·15. Calcd. for $C_{30}H_{49}NO_2$: C, 79·07; H, 10·84; N, 3·07%.)

3(S)-*spiro*-[5'-(2',2'-*dimethyl*-1',3'-*oxazolidine*)]-5α-*cholestane* (**10b**) was obtained in 95% yield by LAH

*The symbol 't' is used throughout to denote an apparent triplet.

reduction of **8b** followed by acetone treatment. It recrystallized from acetone as needles m.p. 146–147° (lit.[16,22] m.p. 145–146°). Acetylation afforded the N-acetate **11b**, needles from acetonitrile m.p. 139·5–140°; IR(KBr) 1672 cm^{-1}; NMR ($CDCl_3$) δ0·66 (3H, s, C-18 Me), 0·85 (3H, s, C-19 Me), 1·58 and 1·60 (6H, 2s, $Me_2C(N)O$), 2·07 (3H, s, NAc), 3·51 (2H, AB q, δ_A3·54, δ_B3·49, J_{AB} = 10 Hz, NCH_2); mass spectrum (11 eV) *m/e* 484 (M-15) (no parent ion). (Found: C, 79·34; H, 11·43; N, 2·88. Calcd. for $C_{33}H_{57}NO_2$: C, 79·30; H, 11·49; N, 2·80%.)

3(R)-*spiro*-[5′-(2′,2′-*dimethyl*-1′,3′-*oxazolidine*)]-5α-*cholestane* (**14b**) was obtained by two methods.

(a) By LAH reduction of **12b** followed by acetone treatment; a 50% yield of **14b** as a GLC pure oil was obtained; NMR($CDCl_3$) δ0·66 (3H, s, C-18 Me), 0·76 (3H, s, C-19 Me), 1·33 (6H, s, $Me_2C(N)O$) and 2·87 ppm (2H, s, NCH_2); mass spectrum (11 eV), *m/e* 457 (parent ion). It was more completely characterised as its N-acetate **15b**, needles from acetonitrile m.p. 163–164°, IR(KBr) 1664 cm^{-1}; NMR ($CDCl_3$) δ0·66 (3H, s, C-18 Me), 0·78 (3H, s, C-19 Me), 1·59 (6H, s, $Me_2C(N)O$), 2·03 (3H, s, NAc), 3·39 ppm (2H, s, NCH_2); mass spectrum (11 eV), *m/e* 484 (M-15) (no parent ion). (Found: C, 79·59; H, 11·47; N, 2·90. Calcd. for $C_{33}H_{57}NO_2$: C, 79·30; H, 11·49; N, 2·80%.)

(b) By reaction of **16b**, m.p. 131–132°, (lit.[31] m.p. 131–132°), prepared by treatment of **1b** with dimethylsulfoxonium methylide[21] with $NaNH_2$ in liquid ammonia followed by reaction of the product **13b** with acetone.

Tiffeneau-Demjanov rearrangements of **10a,b** *and* **14a,b**. The procedure followed was essentially that described by Carlson and Behn.[9] Each individual acetonide **10a,b**, **14a,b** (75–500 mg) was treated with $NaNO_2$ (5 molar excess) in 10% aqueous AcOH at 0°. After stirring for 30 min at 0° the soln was warmed to 22° for 30 min and finally heated on a steam bath for 20 min. The resulting suspension was cooled, thoroughly extracted with ether, and the ethereal extract washed with $NaHCO_3$ aq. Evaporation of the dried ($MgSO_4$) ether soln gave a solid which was analyzed by GLC for A-homoketone and epoxide content. The A-homoketone fraction was then separated from all other material by column chromatography on alumina (prepared in hexane for the cholestane series and in hexane-benzene (1:1) for the 17β-hydroxyandrostanes) using hexane and hexane–benzene elution.

The A-homoketone fractions were combined, evaporated and their ORD spectra determined. Using the average molecular amplitudes of duplicate runs, and the calibration graphs obtained from the ORD curves of pure **2a** ($a = -98$) and **3a** ($a = +159$),[2] and **2b** ($a = -97$) and **3b** ($a = -149$),[23] the proportions of the respective A-homo-3- and -4-ones were calculated. The results obtained are summarized in Table 1.

Diazomethane homologation of **1a,b**. The diazomethane homologations of **1a** and **1b** were carried out as described previously.[2] The A-homoketone mixtures were analyzed and separated as in the corresponding Tiffeneau-Demjanov procedure and their ORD amplitudes used to estimate the 3-one/-4-one ratios as before. The results are summarized in Table 1.

Acknowledgment—This work was supported by the National Research Council of Canada. The award (to P.P.) of a Province of Ontario Graduate Fellowship is gratefully acknowledged.

REFERENCES

[1]J. B. Jones and P. Price, *J. Chem. Soc. Chem. Commun.*, 1478 (1969)
[2]J. B. Jones and J. M. Zander, *Canad. J. Chem.* **46**, 1913 (1968); **47**, 3501 (1969) and refs therein
[3]A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron* **18**, 705 (1962)
[4]J. C. Richer, *J. Org. Chem.* **30**, 324 (1965)
[5]G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.* **80**, 614 (1958)
[6]H. Favre and D. Gravel, *Canad. J. Chem.* **41**, 1452 (1963)
[7]N. J. Turro and R. B. Gagosian, *J. Am. Chem. Soc.* **92**, 2036 (1970)
[8]J. A. Marshall and J. J. Partridge, *J. Org. Chem.* **33**, 4090 (1968)
[9]R. G. Carlson and N. S. Behn, *Ibid.* **33**, 2069 (1968)
[10]M. Cherest and H. Felkin, *Tetrahedron Letters* 2205 (1968); 383 (1971)
[11]C. D. Gutsche and D. Redmore, *Carbocyclic Ring Expansion Reactions* p. 81. Academic Press, New York (1968)
[12]P. A. S. Smith and D. R. Baer, *Org. Reactions* **11**, 157 (1960)
[13]H. Heusser, P. T. Herzig, A. Fürst and P. L. Plattner, *Helv. Chim. Acta* **33**, 1093 (1950)
[14]F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.* **77**, 134 (1955); **78**, 644 (1956)
[15]N. L. Wendler, D. Taub and H. L. Slates, *Ibid.* **77**, 3559 (1955)
[16]N. A. Nelson and R. N. Schut, *Ibid.* **81**, 6486 (1959)
[17]T. M. Jacob and S. Dev. *J. Indian Chem. Soc.* **30**, 674 (1961)
[18]H. O. House, E. J. Grubbs and W. F. Gannon, *J. Am. Chem. Soc.* **82**, 4099 (1960)
[19]M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta* **26**, 288 (1943)
[20]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, [a]p. 44 [b]p. 11. Wiley-Interscience, New York, N.Y. (1965)
[21]C. E. Cook, R. C. Corley and M. E. Wall, *J. Org. Chem.* **33**, 2789 (1968)
[22]J. D. Ballantine, J. P. Ritchie and P. J. Sykes, *J. Chem. Soc.* (C), 736 (1970)
[23]J. Levisalles, G. Teutsch and I. Tkatchenko, *Bull. Soc. Chim. Fr.* 3194 (1969)
[24]G. D. Meakins and D. J. Morris, *J. Chem. Soc.* (C), 394 (1967)
[25]H. Velgova and V. Cerny, *Coll. Czech. Chem. Comm.* **35**, 2408 (1970)
[26]D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956)
[27]C. S. Barnes and A. Palmer, *Austr. J. Chem.* **9**, 105 (1956)
[28]H. J. Giese, C. Altona and C. Romers, *Tetrahedron* **23**, 439 (1967)
[29]D. N. Kirk and P. J. May, *Terpenoids and Steroids* pp. 353–354, 449. Chemical Society, London (1971)
[30]E. C. Horning, W. J. A. Vandenheuvel and B. G. Creech, *Methods of Biochemical Analysis*, **11**, 112 (1965)
[31]J. D. Ballantine and P. J. Sykes, *J. Chem. Soc.* (C), 731 (1970)