The reactions of B-norsteroidal 4- and 5-enes

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Aspects of the stereochemistry of addition reactions to B-norsteroidal 4- and 5-alkenes are compared to the corresponding reactions in normal 6:6 A/B series.

Keywords: B-norandrostanes, B-norcholestanes, reduction, hydroboration, bromination, epoxidation

The application of conformational analysis to the reactions of cyclic alkenes has often been exemplified by the stereochemistry of the reactions of steroidal 5-enes such as those of cholesterol and its relatives. In many cases the stereochemical relationship between the addends in addition reactions to a 5-ene may be established by the mechanistic requirement either for a *trans* diaxial relationship between the components or by the constraints of a cyclic transition state whilst the facial selectivity of the initial addition to the alkene may be determined either by *trans*-annular interactions with the β-oriented methyl group at C-10 or by the neighbouring group participation of adjacent functional groups. In general, a *trans* fused 6:6-decalin is more stable than the *cis* isomers whilst the reverse is true for the 6 : 5 fusion of a hydrindane.[1-3] This can affect the stereochemistry of those reactions which are under thermodynamic control.

The regio- and stereochemistry of many reactions in the B-norsteroid series, *e.g.* **1** in which ring B is five-membered, differ from that of the normal six-membered series. In some instances, rearrangements occur in the B-nor series which are not found under comparable conditions in the normal series. There are dangers in extending well-established generalisations based on examples from the 6 : 6- series to the 6:5 series. In this review, we will consider some of the differences in the regio- and stereochemistry of reactions of alkenes between the B-norsteroids and the normal series. Previous reviews[4-6] have described the earlier work on the chemistry and biological activity of the B-norsteroids without necessarily highlighting these differences.

In the 6 : 6 series a distinction can be made between compounds with a *cis* or a *trans* geometry for the A/B ring junction by the chemical shift of the C-10 methyl group (C-19) in the ^{13}C NMR spectrum. A similar distinction applies in the 6:5-series.[7] In the B-nor-5α-androstanes, the resonance lies in the range δ_C 13–15 whereas in the B-nor-5β-androstanes it lies in the range δ_C 22–25 ppm.

In the B-nor series, the nature of the ring junction can affect the geometry of ring A.[8] The X-ray crystal structures of B-nor-5β-androstanes-3,6-dione **2**, 6β-methoxycarbonyl-3β,5β -dihydroxy-B-norandrostan-17-one **3** and 6β-toluene-*p*-sulfonyloxymethyl-5β-hydroxy-B-norandrostan-3,17-dione **4** reveal that ring A exists in a boat or twisted boat form in these B-nor-5β-androstanes. On the other hand, ring A existed in a more normal chair form in 3β, 6β-dihydroxy-B-nor-5α-androstane **5**. The formation of these boat forms needs to be considered when rationalising neighbouring group interactions between rings A and B in the B-norsteroid series.

Hydrogenation

Although it was at first assumed that catalytic hydrogenation of B-norcholesteryl acetate proceeded from the α-face, it has been reported that hydrogenation over platinum in acetic acid affords 75% B-nor-5β-cholestanyl acetate and only 25% B-nor-5α-cholestanyl acetate.[9] Under similar conditions cholesteryl acetate gave 95% 5α-cholestanyl acetate. Catalytic reduction of B-norpregnenolone[10] over palladium in ethanol gave the 5β-B-norpregnanolone. The 3α-alcohol was obtained from this by a Mitsonubu reaction.

Catalytic hydrogenation and lithium in ammonia reduction of B-norcholest-4-en-3-one **6** (R = H_2) both gave the 5β-H products unlike the normal series in which mixtures of 5α- and 5β-products were obtained depending on the detail of the catalytic conditions. 5α-Cholestanes were obtained by reduction with sodium in liquid ammonia. The reduction of B-norcholest-4-en-3,6-dione **6** (R = O) with zinc in acetic acid gave B-nor-5β-cholestan-3,6-dione whilst reduction of the corresponding cholest-4-en-3,6-dione gave 5α- cholestan-3,6-dione.[9]

Hydroboration

The hydroboration of cholest-5-enes proceeds predominantly from the α-face to afford, after oxidation with alkaline hydrogen peroxide, 5α-cholestan-6α-ols. In a comparative study of androst-5-ene and B-norandrost-5-ene, the major products in the B-nor series arose from reaction on the α-face.[11] Hydroboration of 3α-acetoxy-B-norcholest-5-ene also gave the 6α-alcohol **7** (unpublished work). However, these results do not parallel the difference in calculated energies for α- and β-5,6-cyclobutane models of the four-membered transition state. These would favour β-face addition for the B-norandrost-5-ene. This suggested that the facial selectivity of the hydroboration reaction may be determined by the relative ease of formation of the initial π-complex between the borane and each face of the alkene rather than the relative stabilities of the four-membered transition state. This rationalisation would also accommodate the influence of an allylic hydroxyl group which directs the borane to the *trans* face through a repulsive interaction between the oxygen lone pairs and the π-system.

Reduction with di-imide also proceeds through a four-centre transition state. In this case a 3β-hydroxy-B-norandrost-5-ene gave the B-nor-5α-androstane. This provided a facile route to B-nor-5α-dihydrotestosterone which was required for a study of its *anti*-hormonal activity.[12]

Addition of bromine

In the normal steroid series, the *trans* diaxial addition of bromine to a Δ^5 – steroid leads to the formation of the 5α,6β-dibromide which subsequently undergoes a slow epimerisation to the 5β,6α-dibromide. In contrast, treatment of 17β-acetoxy-B-norandrost-5-ene with bromine gave the bromoalkene **8** and a backbone rearrangement product **9**.[13] 3β-Hydroxy-B-norandrost-5-en-17-one gave a 3β-hydroxy-6-bromo-5-ene **10** and a 6-bromo-3,5-diene **11**. The 1-methyl-B-norestratrien-17-one **12** was a minor product. The formation of these products may be rationalised through the opening of the initial 5α,6α-bromonium to form a 6α-bromo steroid and C-5 carbocation. The latter can initiate the elimination of a

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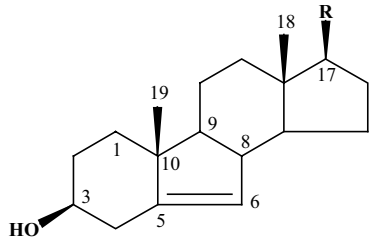

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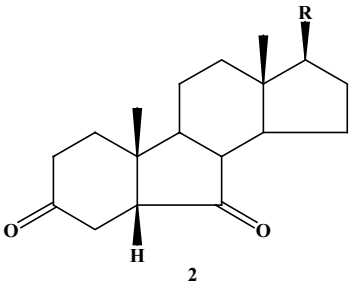

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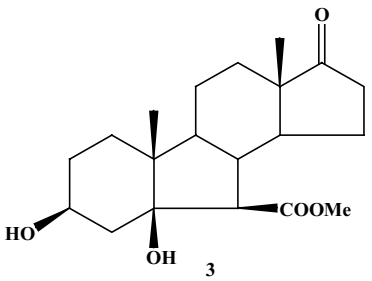

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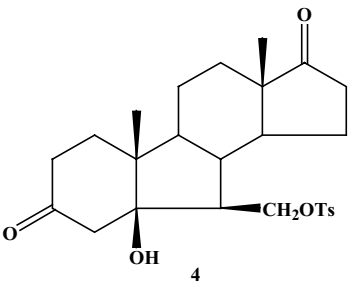

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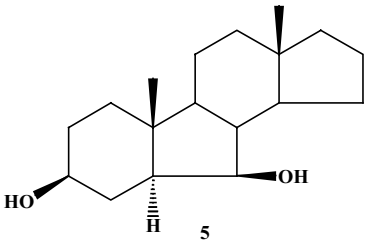

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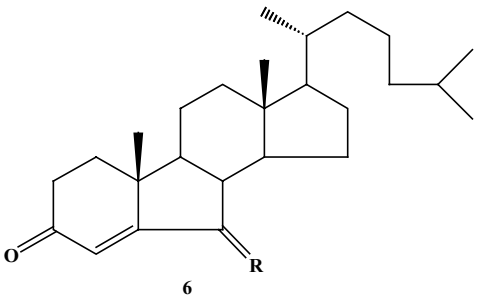

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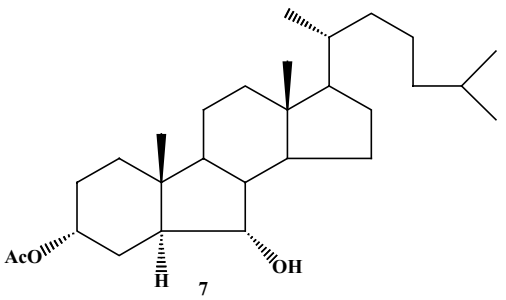

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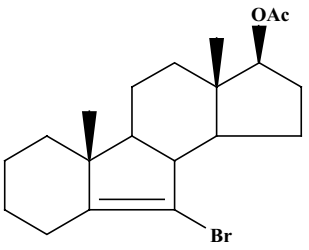

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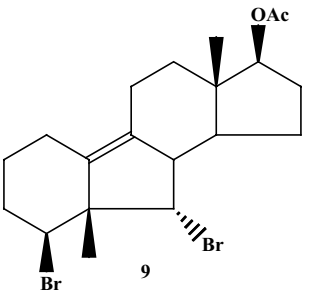

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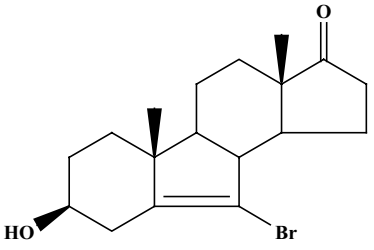

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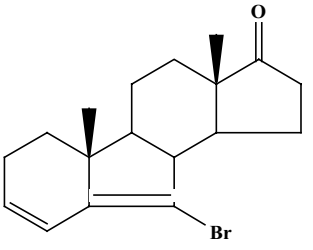

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proton to give either a C-4 or a C-5-ene. Further bromination and elimination followed by rearrangement afforded the aromatic steroid.

The allylic acetoxylation of 3-substituted androst-5-enes and B-norandrost-5-enes with bromine and silver acetate revealed further differences between the two series. In the normal steroid series, it provided a useful means of introducing a 4β-acetoxyl substituent.[14,15] However, treatment of 3β-hydroxy-B-norandrost-5-en-17-one gave the fragmentation product **13** and a mixture of the expected 4β-acetoxy-3β-hydroxyandrost-5-en-17-one and a smaller amount of the isomeric 3β-acetoxy-4β-hydroxy-B-norandrost-5-en-17-one. When 3β-acetoxy-B-norandrost-5-ene was used as a substrate, apart from acetoxylation products and 6-bromo-5-alkene compound, backbone rearrangement products were obtained. The reaction may be rationalised in terms of the reactions of a C-5 carbocation as in Scheme 1. The fragmentation product might arise via a β-face attack on the 5-ene.

Bromohydrin formation

In the normal steroid series, the addition of hypobromous acid to the 5-enes proceeds by a *trans* diaxial opening of the 5α,6α-bromonium ion to give the 5α-bromo-6β-hydroxy steroid. The stereochemistry of this addition by generating a 6β-hydroxyl group, has played an important role in facilitating the *trans*-annular activation of C-19. On the other hand the addition of hypobromous acid and acetyl hypobromite to the corresponding B-norsteroids affords the 6α-bromo-5β-hydroxyderivatives **14**.[16] These products arise by the Markovnikov opening of the 5α,6α-bromonium ion. In the norsteroid series, treatment of the bromohydrin with methanolic potassium hydroxide gave the 5β,6β-epoxide, for example to give the 5β,6β-epoxide of B-norpregnanolone.[10] Interestingly, treatment of 3β-acetoxy-5β, 6β-epoxy-B-norandrostan-17-one **15** with hydrogen bromide was reported to give 3β-acetoxy-6α-bromo-5β-hydroxy-B-norandrostan-17-one.

In the normal steroid series, the outcome of the addition of hypobromous acid to a 4,5-ene is influenced by neighbouring group participation from a 3β-substituent. Thus the addition of hypobromous acid to a 3β-acetoxy-4-ene gives the 4α-bromo-5β-alcohol. On the other hand in the B-nor series both the 3β-alcohol and the 3β-acetate give the 4β-bromo-5α-alcohol.[17]

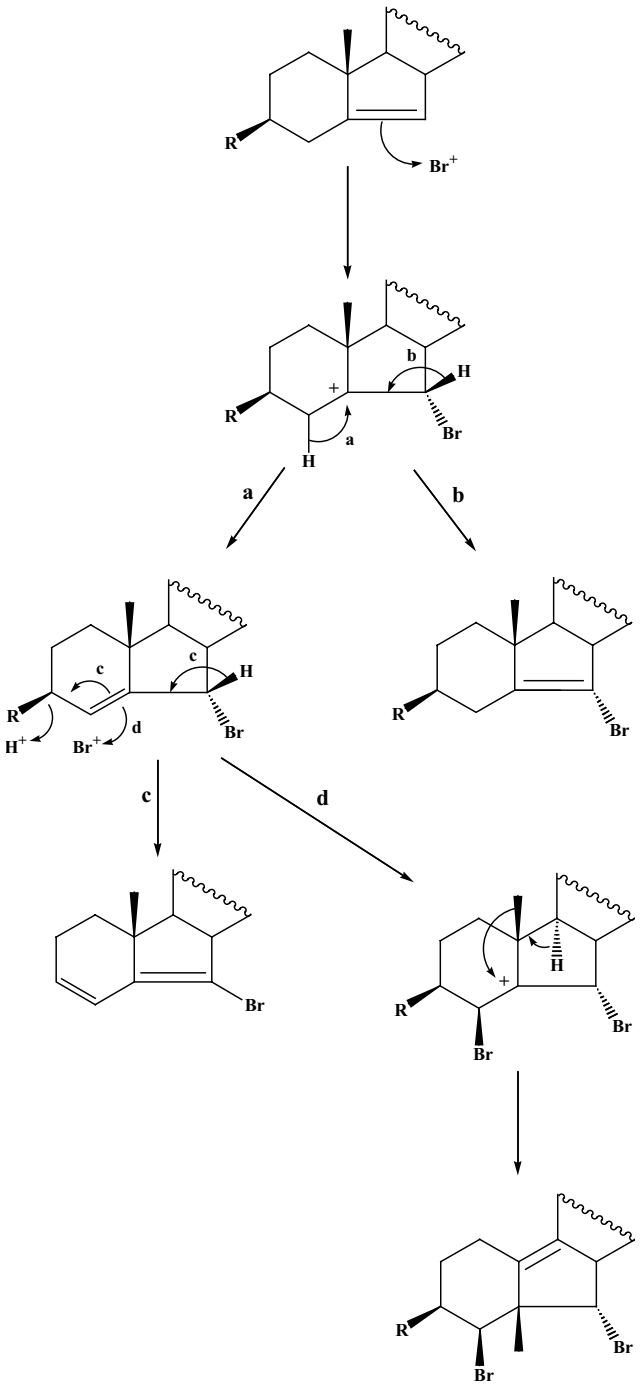
Epoxidation

In both series, epoxidation with peracids normally proceeds predominantly from the α-face of the molecule to provide the 5α,6α-epoxide. In the case of the B-norsteroids, a greater proportion of the product is the 5α,6α-epoxide.[18,19] Epoxidation with magnesium bis(monoperoxyphthalate) hexahydrate has been reported[20] to be a highly efficient method for producing the 5α,6α-epoxides in the B-norsteroid series. Whereas epoxidation with $KMnO_4$:$FeSO_4$ gives the 5β,6β–epoxide in the normal 6:6 series, in the B-norsteroids the product is the 5α,6α-epoxide.[21] In the B-norsteroid series, the 5β,6β–epoxide has to be obtained via the bromohydrin. Epoxidation of 3β-acetoxy-B-norandrost-5-en-17-one with sodium perborate and a potassium permanganate catalyst gave the α-epoxide whilst 3β-acetoxyandrost-5-en-17-one gave a 1:4 ratio of the α:β-epoxides.[22] As in the normal series, there is the potential for interaction between a 3α-substituent and a reagent for example, m-chloroperbenzoic acid. However, epoxidation of 3α-acetoxy-B-norandrost-5-en-17-one and the corresponding cholest -5-ene both gave the 5α,6α-epoxide.[12]

In the normal series, epoxidation of the 3β-hydroxy-4-enes with peracid gave the 4β,5β-epoxide whilst the acetate gave the 4α,5α-epoxide. However, in the B-norsteroid series both the 3β-alcohol and acetate gave the 4β,5β-epoxide paralleling the addition of HOBr.[23]

Reduction of the both the 5α,6α- and 5β,6β-epoxides in the B-norsteroid series with lithium aluminium hydride gave the corresponding 5-alcohols whilst catalytic hydrogenation gave the C-6 alcohols.

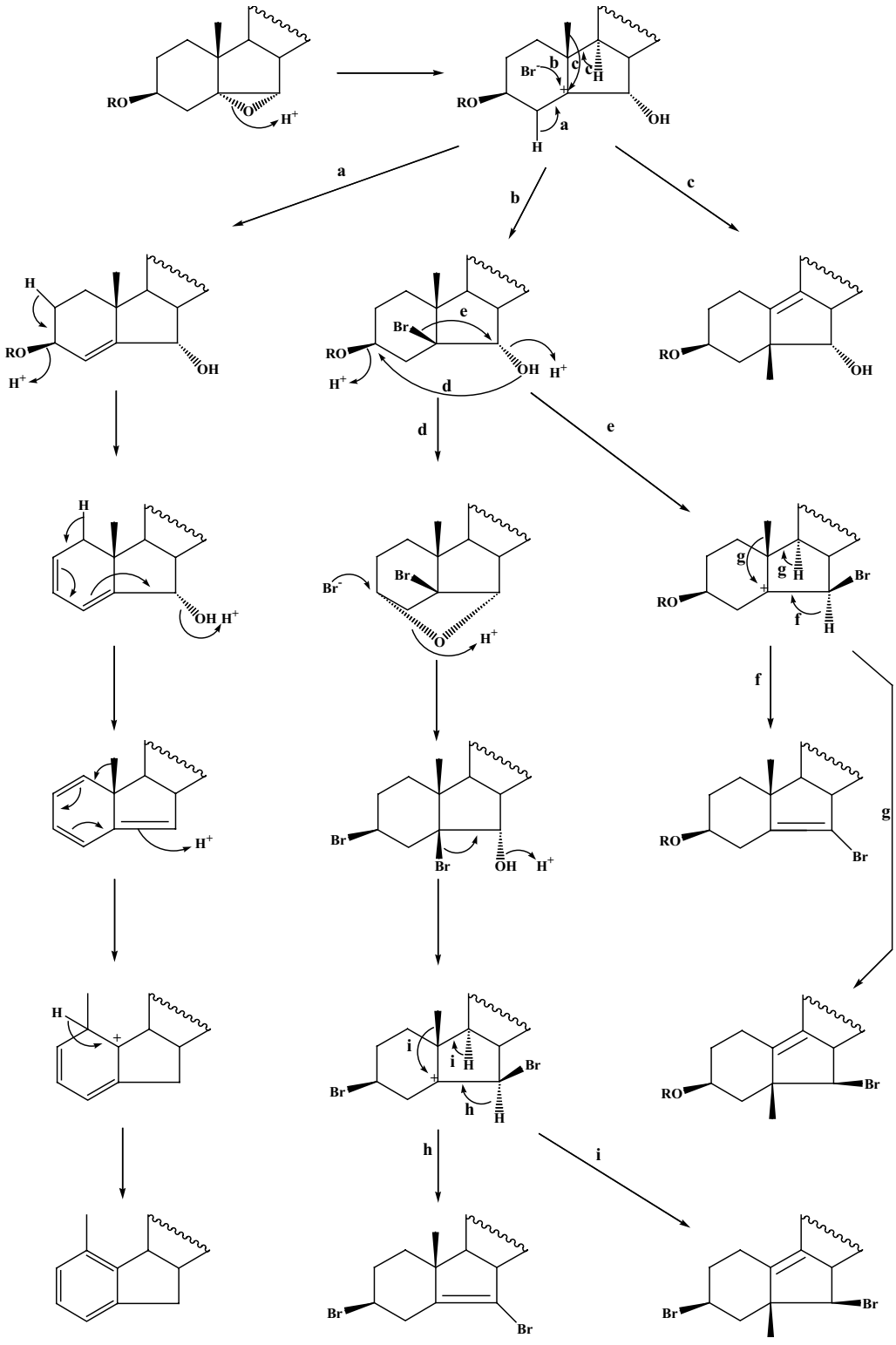
The acid-catalysed cleavage of steroidal 5,6-epoxides can initiate a number of molecular rearrangements. The generalised dienol : benzene rearrangement leading to the aromatisation of ring A of the steroids requires substrates possessing three double bond equivalents on rings A and B.[24] An epoxide can furnish two of these. The estratrienes that are



Scheme 1

formed contain the original C-10 methyl group at either C-1 or C-4. The formation of a 1-methyl-B-norestratriene involves a C-10–C-1 shift of a methyl group whilst the formation of the 4-methylestratrienes involves a spiranic intermediate which would become highly strained in the B-norsteroid series.

The reaction of 5α,6α-epoxy-B-norsteroids with either boron trifluoride or acetic acid gave backbone rearrangement products.[25] These reactions occur much more readily in the B-norsteroid series. Thus 3β-acetoxy-5α,6α-epoxy-B-norandrostan-17-one gave the backbone rearrangement product **16** and some of the 3,5,6-triol. Cleavage of the epoxide with perchloric or periodic acid gave the unrearranged 5β,6α-diol. When the reaction was carried out with hydrogen bromide in glacial acetic acid the products were 3β,6-dibromo-7-norandrost-5-en-17-one, the corresponding 3β-acetate and the 5β-bromo-3α,6α-ether **17**. Under the same conditions the 3β-methanesulfonate gave the backbone rearrangement product **18** and 1-methyl-B-norestratrien-17-one **12**. The formation of these products can be rationalised [26] by various modes of collapse of the C-5 carbocation (see Scheme 2). The retention of configuration



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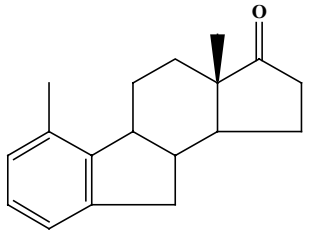

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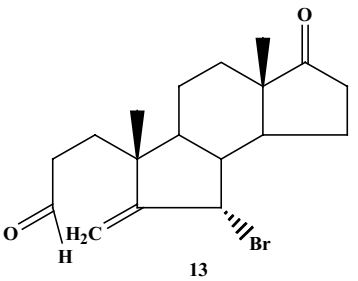

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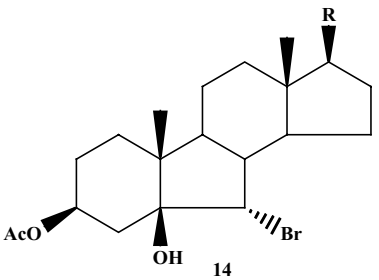

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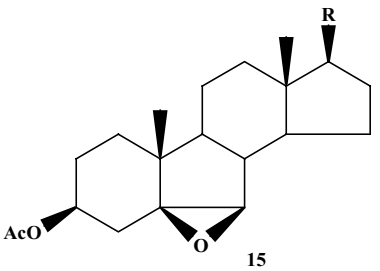

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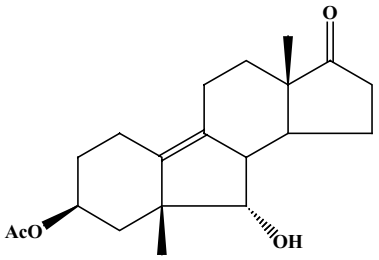

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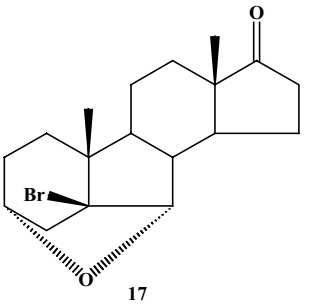

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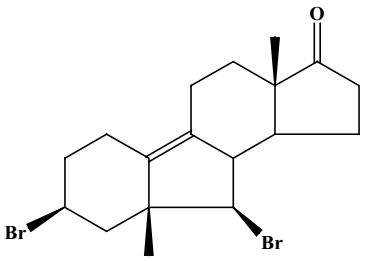

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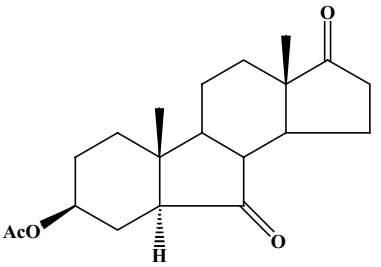

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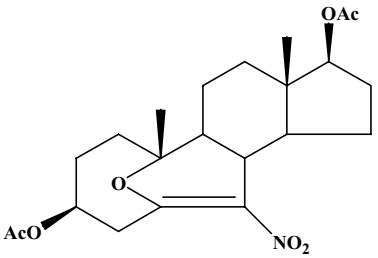

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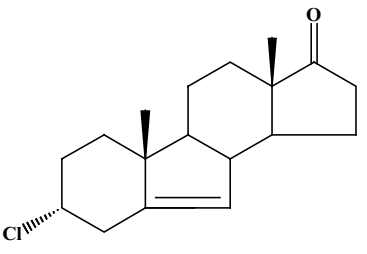

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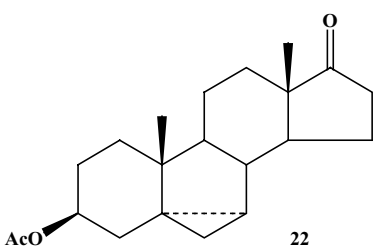

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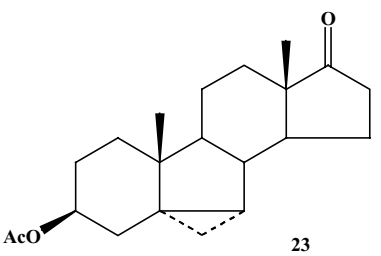

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at C-3 in the introduction of the bromine is a reflection of the ready formation of the 3α,6α-ether in the presence of a 5β-bromine.

The fission of the 5β,6β-epoxides in the B-norsteroid series has been examined.[27] Treatment with boron trifluoride etherate gave the 5α-6-ketone **19** as the sole product whilst the reaction with acetic acid gave the same ketone together with the backbone rearrangement product. This has been used in the B-norandrostane, B-norcholestane and B-norpregnane series. Although the chemistry of these B-nor-6-ketones is outside the scope of this review, it is worth noting that the Beckmann rearrangement of B-nor-6-oximes has been used to prepare 6- and 7-aza steroids.[28-30]

Osmylation

As in the normal 6:6-series, catalytic osmylation of both 3α- and 3β-hydroxy-B-norandrost-5-en-17-ones gave the corresponding 5α,6α-diols (unpublished work).

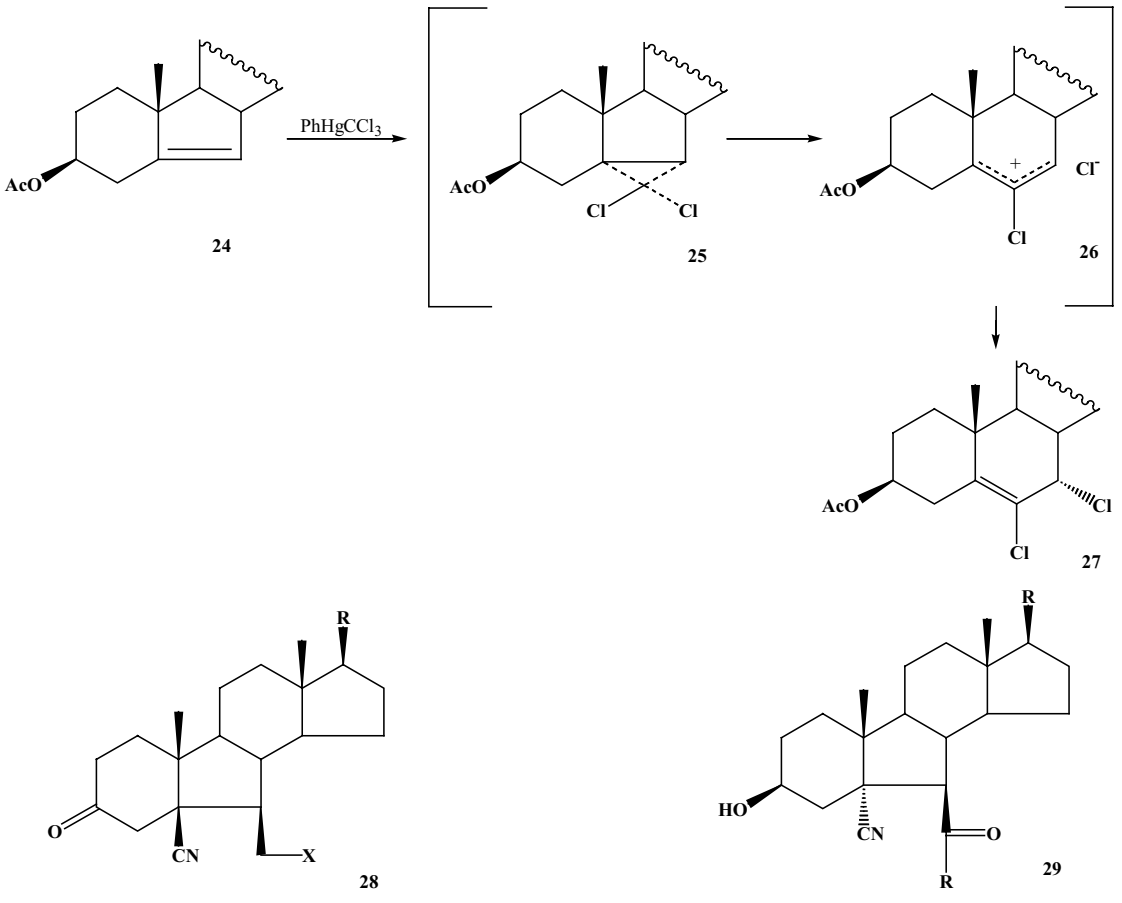
Nitration

The nitration of cholest-5-enes has been shown to form 6-nitrocholest-5-ene. Nitration of 3β-acetoxyandrost-5-en-17-one with fuming nitric acid gave 3β-acetoxy-6-nitroandrost-5-en-17-one in good yield. Under identical conditions 3β, 17β-diacetoxy-B-norandrost-5-ene gave a complex mixture from which two major components were isolated.[31] These were identified as 3β,17β-diacetoxy-5β-nitroxy-6α-nitro-B-norandrostane and a unusual 5,10-ether **20** formed by a rearrangement including cleavage of the A/B ring system. The minor products included some nitroalkenes comparable to the major products which were formed in the normal series.

The i-steroid reaction

The homoallylic participation of the C-5 : C-6 double bond in the reactions of equatorial C-3 substituents leading to the i-steroid carbocation is a well-established example of neighbouring group participation. Examination of the rate of acetolysis of 3β-toluene-*p*-sulfonoxy-B-norcholest-5-ene showed that it was approximately half that of the corresponding cholesterol derivative whilst a comparison of the rates of acetolysis of the toluene-*p*-sulfonates of 3β-hydroxy-5α-androstan-17-one, 3β-hydroxyandrost-5-en-17-one and 3β-hydroxy-B-norandrost-5-en-17-one showed that they were in the ratio 1 : 36 : 10 revealing the diminished participation of a Δ^5-double bond in the acetolysis of B-nor-3β-toluene-*p*-sulfonates.[32] Whilst under some conditions cyclosteroid products comparable to those in the 6:6 series such as 6β-hydroxy-3α,5α-cyclo-B-norandrostan-17-one were isolated from these reactions, in the B-norsteroid series a greater proportion of the products arose from attack on ring A at C-3 rather than at C-6.[33]

The diminished homoallylic participation of the C-5 : C-6 double bond is also revealed by the products of halogenation at C-3.[34] The major product of halogenation of both 3β-hydroxyandrost-5-en-17-one and the corresponding B-norsteroid with phosphorus pentachloride were the 3β-chlorides. However, with triphenylphosphine:carbon tetrachloride, the product from the B-norsteroid was 3α-chloro-B-norandrost-5-en-17-one (54%) **21** accompanied by some B-norandrost-3,5-dien-17-one (22%). In the normal series, the product obtained from 3β-hydroxyandrost-5-



Scheme 3

en-17-one whilst containing a substantial amount (47%) of the 3α-chloroandrost-5-en-17-one, also contained 3α, 5-cycloandrost-6-en-17-one (34%) rather than the 3,5-diene.

Microbiological hydroxylation

Whereas the microbiological hydroxylation of 3β-hydroxy-androst-5-en-17-one takes place predominantly at the allylic C-7 methylene, this position is not available in the corresponding B-norsteroid. However, rather than attack at C-8, the microbial transformation which is observed[35] is that of epoxidation to give the 5α,6α-epoxide. In this context, it is worth noting that when an unsaturated centre replaces a saturated centre that is hydroxylated, the outcome is often epoxidation.

5,7-Cyclosteroids

The Simmons–Smith methylenation of the 5,6-unsaturated B-norsteroids formed the 5,7α- and 5,7β-cyclosteroids substituted at C-3. When 3β-acetoxy-B-norandrost-5-en-17-one was treated with methylene diiodide and a zinc-copper couple, 3β-acetoxy-5,7α-cyclo-5α-androstan-17-one **22** and 3β-acetoxy-5,7β-cyclo-5β-androstan-17-one **23** were formed. The latter was the major product.[36,37] When a dihalogenocarbene was used in place of methylene, either a stable bicyclo [3.1.0] hexane ring system was formed or rearrangement occurred readily to give a 6,7-dihalo-Δ^5-steroid. The use of phenyl (trichloromethyl) mercury resulted in the effective addition of dichlorocarbene to the Δ^5-B-norsteroid **24**,[38] In contrast to 6,6-dichlorobicyclo [3.1.0] hexane, which is thermally stable in tetrahydrofuran,[39] the strained 6,6-dichlorobicyclo [3.1.0] hexane system present in compound **25** has undergone a spontaneous rearrangement at 80 °C *via* the ion pair **26** to form the allylic product **27**. In contrast to the β-face addition of the normal Δ^5-steroids, the reaction took place from the α-face as in Scheme 3.

Hydrocyanation

In the normal steroid series, the addition of cyano group to the α,β–unsaturated ketones proceeds by coordination of a proton or an alkylaluminium cation to ketone oxygen to give an activated species, a rate-determining nucleophilic attack of a cyanoaluminate anion at the β–carbon to give a 1,4 adduct and its conversion of a dicyano compound.[40] However, in the B-nor steroid series a cyano group was introduced into C-5 with two different ways. Both Δ^4- and Δ^5-B-norsteroids gave 5-cyano-B-norsteroids. The stereochemistry of the addition was exclusively β-oriented **28** in case of Δ^4-B-norsteroids and α-oriented **29** in case of Δ^5-B-norsteroids.[41,42]

Conclusion

In conclusion there are sufficient differences between the reactions of the alkenes in the B-norsteroids and those in the normal series to act as a warning not to extend analogies and stereochemical conclusions from one series to the other without careful attention to other stereochemical evidence for the structures of the products. These differences illustrate the importance of evaluating the varied contributions of facial selectivity, the structures of intermediates and the relative thermodynamic stability of the products in rationalising the overall stereochemical outcome of the reactions of cyclic alkenes.

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