The general dienol : benzene rearrangement of ring A of the steroids

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The dienol : benzene type of rearrangement of steroids, to form compounds with an aromatic ring A, occurs under acid-catalysed conditions with a wide range of substrates containing two double bond equivalents and a carbonium ion source on rings A and B.

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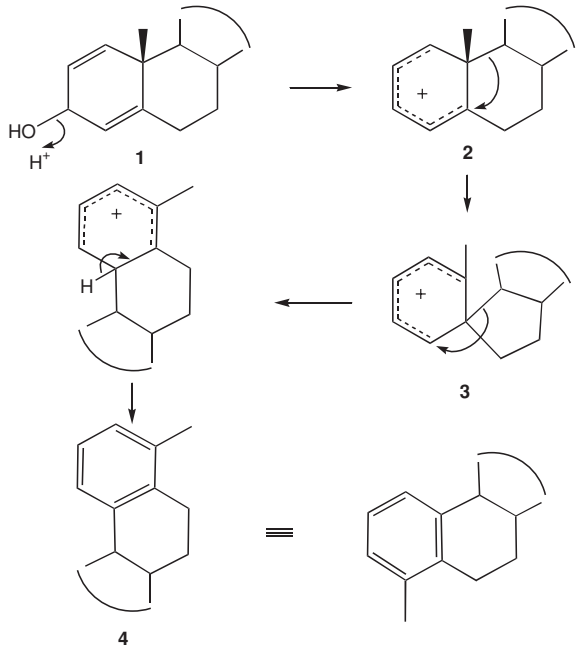
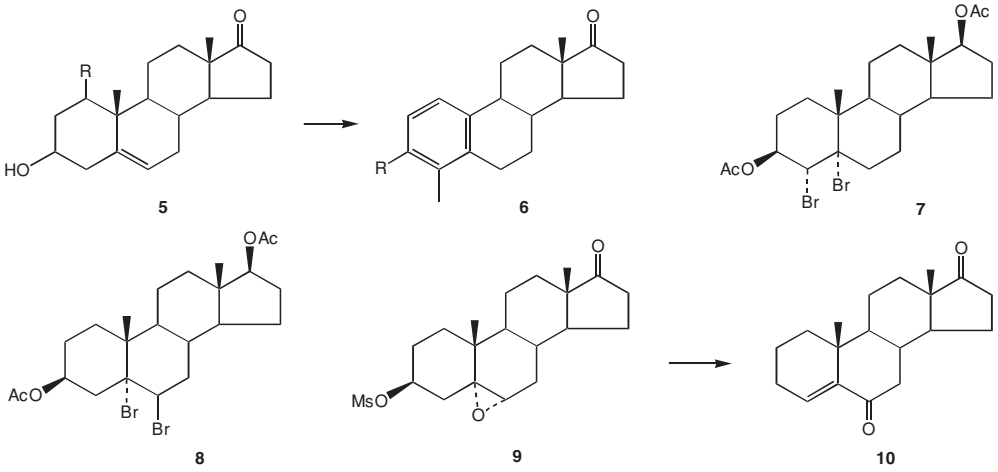
Chemical methods for the aromatisation of ring A of the steroids have attracted interest in the light of the relationship of the aromatic estrogens to the other hormonal steroids such as the androgens. Consequently rearrangement reactions leading to aromatisation, although unrelated to the biosynthetic processes, have been studied.[1] The dienone: phenol rearrangement, leading to the formation of 3-hydroxy-1-methyl and 1-hydroxy-4-methylestratrienes from 1,4-dien-3-ones, is the best known of these reactions. The dehydration of 1,4-dien-3-ols **1** under acid-catalysed conditions has been shown to follow similar pathways affording 1-methyl and 4-methylestratrienes **4**. Protonation of the 3-hydroxyl group of the dienol **1** followed by the loss of a molecule of water may generate a resonance stabilised carbonium ion **2**. Methyl group rearrangement to C-1 affords the 1-methyl steroid. On the other hand migration of the C-9:C-10 bond to C-5 forms a spiranic intermediate **3**. Further rearrangement of this intermediate leads to a 4-methylestratriene **4**.[1] (Scheme 1)



Scheme 1

A number of observations have led to the suggestion that the reaction might be more general. Firstly, in connection with the preparation of some ring B dienes, it was found that treatment of 3β-hydroxyandrost-5-en-17-one **5** (R = H) with an allylic brominating agent gave products which included 4-methylestra-1,3,5(10)-trien-17-one **6** (R = H).[2] The formation of a 3,4-dimethylestratriene **6** (R = Me; 17β-OAc) in which the methyl groups have remained adjacent to each other, from 17β-acetoxy-3β-hydroxy-1-methylandrost-5-ene **5** (R = Me; 17β-OAc), rather than a 1,4-dimethylestratriene, indicated that the rearrangement followed a spiranic pathway involving skeletal rather than methyl group migration.[3] Secondly, both 3β-acetoxy-4,5-dibromo- **7** and 5,6-dibromo-steroids **8** formed 4-methylestra-1,3,5(10)-trienes on treatment with acetyl bromide in propan-2-ol in a sealed tube at 85 °C.[4] Testosterone acetate also gave the 4-methylestratriene under these conditions. Testosterone has also been shown to rearrange to a 4-methylestratriene in the presence of either a trichloroacetic acid/anhydride mixture or in the presence of acetyl bromide and 2-bromopropionic acid.[4,5] These rearrangement reactions of androst-4-en-3-ones are interesting because they involve replacing a carbonyl group in the starting material by a =CH- in the product, possibly via an internal hydride shift. Finally, it was observed that treatment of 5α,6α-epoxy-3β-methanesulfonyloxy-androstan-17-one **9** with lithium bromide and lithium carbonate in dimethylformamide gave 4-methylestratrien-17-one **6** (R = H) along with androst-4-



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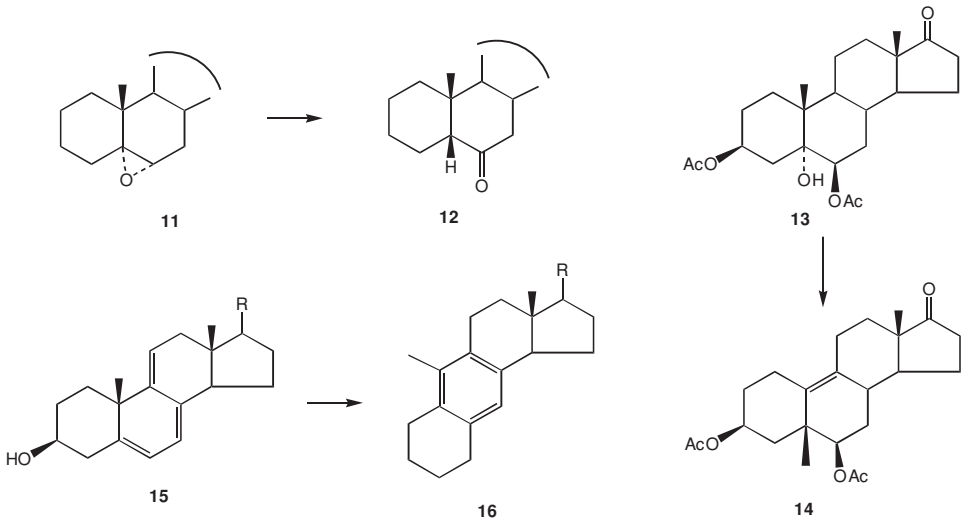
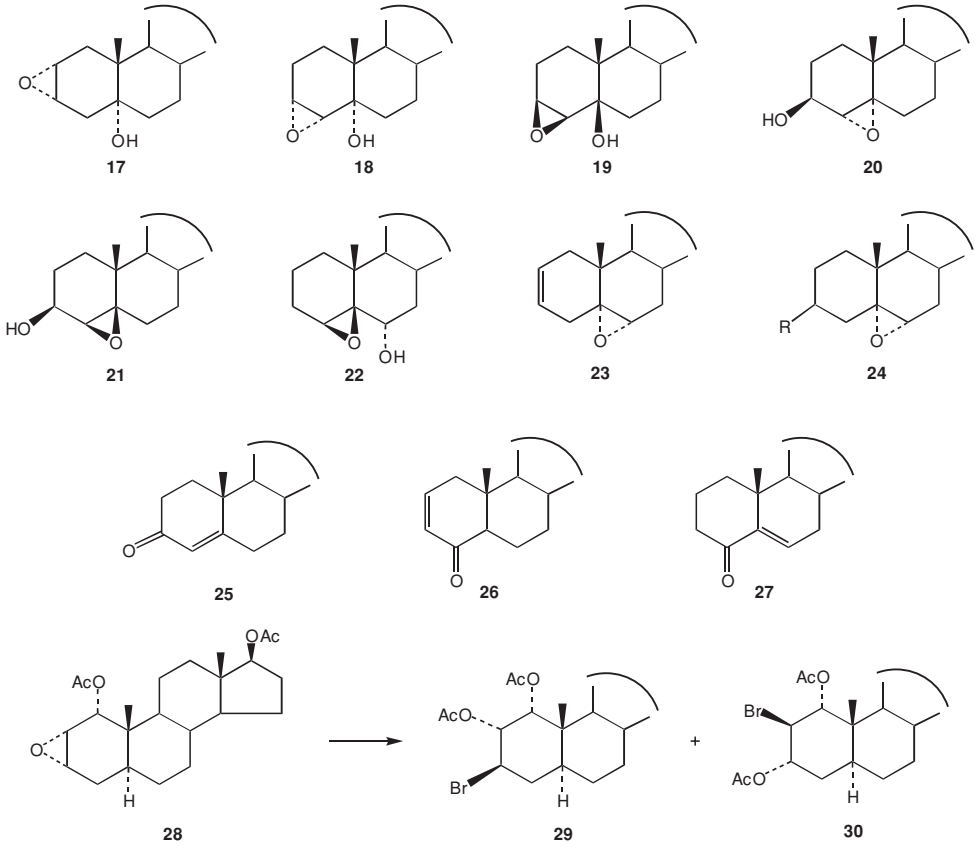


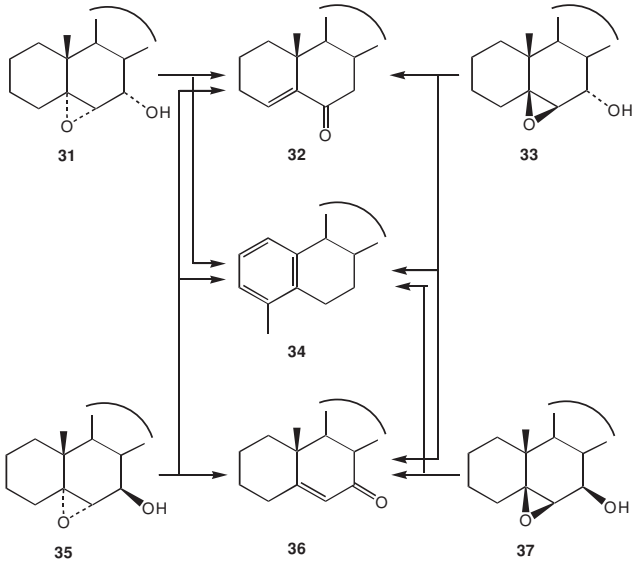
ene-6,17-dione **10**.[6] This led to the suggestion that the acid-catalysed steroidal dienol:benzene spiranic rearrangement might be a more general reaction requiring the presence of two double bond equivalents and a carbonium ion source on rings A or B of the steroid.[7]

These aromatisation reactions need to be seen in the context of some other acid-catalysed steroidal rearrangements. Thus treatment of a 5α,6α-epoxysteroid **11** with boron trifluoride etherate affords the 5β(H)-6-ketone **12**.[8] Secondly, a 5α-hydroxy steroid **13** undergoes the Westphalen backbone rearrangement in the presence of sulfuric acid in acetic anhydride.[9-11] In this rearrangement the C-10 methyl group migrates to C-5, generating a 9(10)-ene **14**. Thirdly, steroids with dienes or trienes on ring B may undergo aromatisation of ring B with the formation of an anthrasteroid, *e.g.* **15**–**16**.[12,13] Hence there are a number of competing reaction pathways.

The rearrangements of hydroxy-epoxides

The acid-catalysed hydrolysis of a hydroxy-epoxide can generate the two double bond equivalents and a carbonium ion source required for the generalised dienol:benzene rearrangement. The scope of the reaction was explored with a series of ring A and B hydroxy-epoxides and their derivatives (**17**–**24**).[14-18] These compounds differed not only the location of the substituents but also in their stereochemistry at C-3 and C-5, [*e.g.* **18** and **19**, **20** and **21**, and **24** (R = α- and β-OMs)]. In many cases the 4-methylestratriene was accompanied by an unsaturated ketone **10**, **25**–**27**. A large scale experiment with the methanesulfonate **9** also revealed a trace of an anthrasteroid involving the aromatisation of ring B. However, when the substrate was a 1α-acetoxy-2α,3α-epoxide **28** aromatisation did not occur, and the products (**29** and **30**) were those to be expected of hydrolysis of the epoxide with the intervention of an acetoxylinium ion.[19]





Scheme 2

Ring A aromatic products **34**, rather than anthrasteroids, were the major products even when the epoxide and the hydroxyl group were located on ring B as in **31**, **33**, **35** and **37**.[20] The formation of the unsaturated ketones (**32** and **36**) in these cases can be rationalised in terms of the initial opening of the 5,6-epoxide to form a 4-en-6-ol. In the case of the 7α-alcohol there is a trans diaxial relationship to the 6β-hydrogen and elimination can take place with the formation of the 4-en-6-one **32**. Where a 6β-alcohol is present and *trans* to a 7α-hydrogen, elimination to form a 5-en-7-one **36** takes place. (Scheme 2)

When the substrate was a B-norsteroid **38**, the product was a 1-methyl-B-norestratriene **39**.[21] Presumably the strain in forming a four-membered spiranic intermediate was too great for the reaction to follow this pathway. A bromo-olefin **40** and a Westphalen backbone rearrangement product **41** were also isolated. These aromatisation reactions are not restricted to the androstane series but have also been observed with pregnanes and with cholestanes.[22]

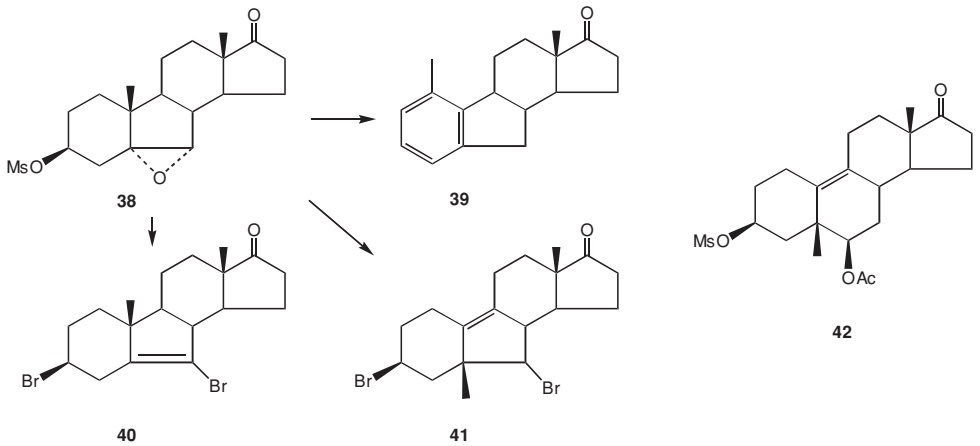
When 5α,6α-epoxy-3β-methanesulfonyloxyandrostan-17-one **9** was treated with an acetic acid/anhydride mixture containing sulfuric acid instead of hydrogen bromide in acetic acid, the product **42** was that of a Westphalen backbone rearrangement revealing the sensitivity of these pathways to the reaction conditions.[23] Treatment of the methanesulfonate **9** with hydrobromic acid in chloroform at room temperature gave the corresponding 6β-bromo-5α-alcohol by simple hydrolysis of the epoxide.[15]

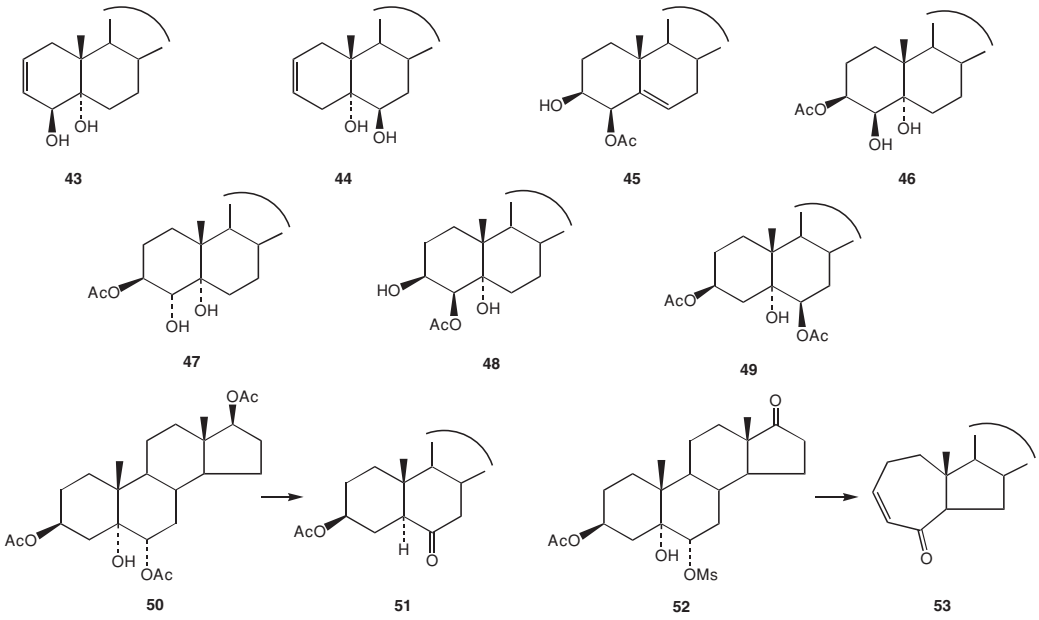
The rearrangements of enediols and triols

The requirement for two double bond equivalents and a carbonium ion source may also be met by the reaction of enediols and triols with hydrogen bromide in glacial acetic acid. Examples of structures which underwent the aromatisation reaction are represented by the partial structures **43**–**49**.[24, 25] As with the hydroxy-epoxides, the aromatic products were also accompanied by unsaturated ketones. On treatment with hydrogen bromide in glacial acetic acid, 3β,6β-diacetoxy-5α-hydroxy steroids **49** gave 4-methylestratrienes and no detectable backbone rearrangement product. However, the 6α-epimer, 3β,6α,17β-triacetoxy-5α-hydroxyandrostane **50**, gave 3β,17β-diacetoxy-5α-androstan-6-one **51** while the 6α-methanesulfonate **52** gave an A-homo-B-norsteroid **53**.

Evidence for the spiranic pathway

Two mechanistic pathways can be envisaged for the formation of the 4-methylestratriene from the hydroxy-epoxides. The first is the spiranic pathway typical of the dienol: benzene rearrangement.[1] The second involves a sequence of methyl group migrations. The first step in this pathway involves a methyl migration to C-5 and has an analogy in the Westphalen rearrangement[9] whilst the second step involves the migration of the methyl group from C-5 to C-4, paralleling the rearrangement of a methyl group from C-10 to C-1. These pathways can be differentiated by following the fate of a deuterium label at C-3 by ^{13}C and ^{2}H NMR.[26-29] If the reaction follows a dienol : benzene spiranic pathway, the label will appear at C-1 in the estratriene. If the methyl migration occurs, the label will be at C-3. In the event, when a series of epoxides were examined, the label appeared at C-1, consistent with a spiranic pathway. However, when a 19-norsteroid was used as the substrate the label remained at C-3, showing that the reaction in this case had probably followed a simple sequence of hydrolysis and elimination. When the aromatisation of the 5α,6α-epoxy-3β-methanesulfonate was carried out in a deuteriated medium, deuterium was incorporated at C-6 and C-7. Although both C-7 positions were labelled, at C-6 the β-position was predominantly labelled. This is in accord with a pathway involving a sequence of elimination and double bond rearrangements involving the formation of a 2,4,6-triene which then isomerises to a 1,3,5-triene prior to the generation of the penta-1,3-dien-5-yl cation and the spiran intermediate. Only a trace of deuterium was incorporated at C-6 when a 1,4-dien-3-ol was the substrate. This suggested that in this case the pentadienyl cation, and thence the spiran, are formed without the intervention of a 1,3,5-triene.



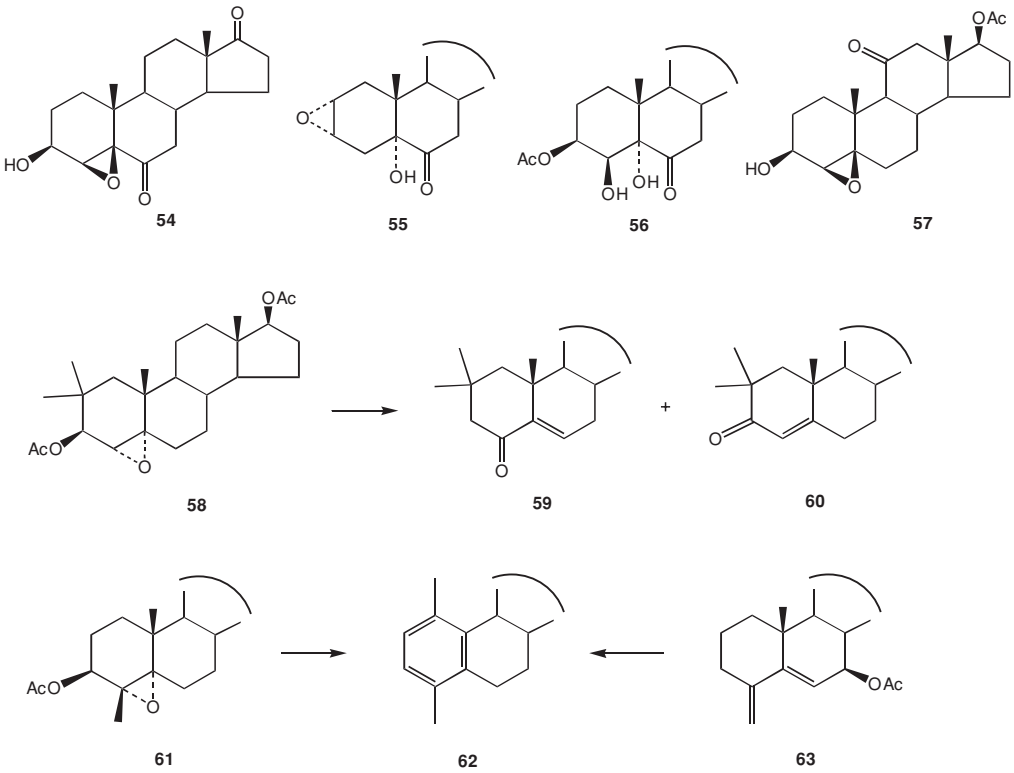


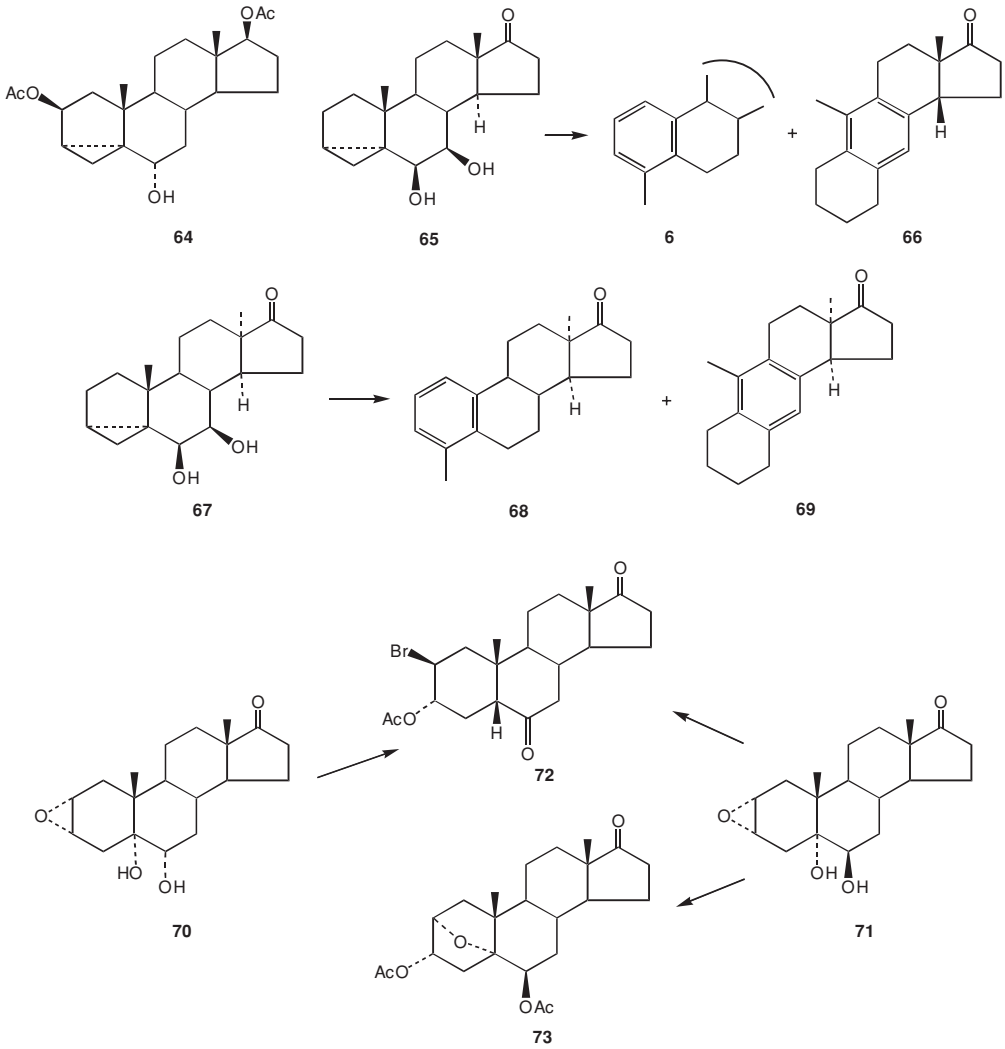
The initial steps prior to the formation of the spiran involve a positive charge at C-5. A carbonyl group at C-6, destabilises this C-5 carbonium ion. Consequently, when the 6-ketones **54**–**56**[14,16,25] were treated with hydrogen bromide in glacial acetic acid, the 1-methylestratrien-6-ones were formed by a simple methyl group migration rather than via a spiran. Reaction of the 11-ketone **57** gave only a low yield of 17β-acetoxy-4-methylestratrien-11-one.[16] The 11-carbonyl group has reduced the migratory aptitude of the C-9 : C-10 bond.

The effect of modification of ring A

Methylation at various sites on ring A, apart from providing mechanistic information, can favour alternative pathways. The consequences of methylation at C-1 have already been described. However the presence of 2,2-dimethyl groups, as in **58**, blocked the pathway and the substrate gave the 2, 2-dimethyl-unsaturated ketones **59** and **60**.[30] The presence of a 4-methyl group, as in **61**, also blocked the spiranic pathway although a 1,4-dimethylestratriene **62** was formed.[30] When the substrate contained a 4-deuteriomethyl group a 1-methyl-4-deuteriomethyl-17β-acetoxyestratriene was formed. Hence the C-4 methyl group had prevented aromatisation by the spiranic pathway and aromatisation had taken place by a methyl group migration from C-10 to C-1.

Treatment of 7β,17β-diacetoxy-4-methyleneandrost-5-ene **63** with HBr-AcOH gave 17β-acetoxy-1,4-dimethylestra-1,3,5(10)-triene **62** rather than an anthrasteroid.[31] When the reaction was repeated in a deuteriated medium, deuterium was incorporated inter alia on the 4-methyl rather than the 1-methyl group, consistent with a methyl group migration from C-10 to C-1. Other workers [32] found that 4,4-dimethyl-5-en-





3-ones rearrange in the presence of acetic acid and toluene-*p*-sulfonic acid or a trichloroacetic acid/anhydride mixture to give 1,3,4-trimethylaromatic compounds. When the 4,4-dimethylestra-5-en-3-one was used as the substrate, the 4,4-dimethylestra-1-en- and 5(10)-en-3-ones were amongst the minor products, indicating the mobility of the double bond under these reaction conditions.

3,5-Cyclosteroids, formed from the i-steroid reaction, undergo the aromatisation reaction to form 4-methylestratrienes. Thus 2β,17β-diacetoxy-6α-hydroxy-3α,5-cycloandrostane **64** gave 17β-acetoxy-4-methylestratriene accompanied by 17β-acetoxy-5α-androst-2-en-6-one and the related 2-bromo- and 3-bromo-6-ones.[33] 6β,7β-Dihydroxy-3α,5-cycloandrostan-17-one **65** gave 4-methylestratrien-17-one **6** accompanied by the *cis* C/D 13β,14β-anthrasteroid **66**. When the reaction was repeated[34] with the 13α-methyl epimer **67**, the 4-methyl-13α-estratriene **68** and the enantiomeric 13α,14α-anthrasteroid **69** were obtained. However, a 1,2-methylene steroid gave non-aromatic products in which the cyclopropane ring had opened.[35]

The dienone : phenol rearrangement effectively utilises a substrate with three double bond equivalents and a carbonium ion source. Hence there was a possibility that this might be a more general reaction provided that there was a group present in the molecule which might generate a ring A ketone. Androsta-2,5-diene-4,17-dione undergoes an acid-catalysed dienone : phenol rearrangement to form 4-hydroxy-1-methylestratrien-17-one.[36] Whereas the reaction of 2α,3α-epoxy-5α-hydroxyandrostane with hydrogen bromide in acetic acid readily gave 4-methylestratrienes, the presence of an additional 4β-acetoxy or a 6α- or 6β-hydroxyl group in the substrate led to non-aromatic products.[37] For example, the 6α-alcohol **70** gave 3α-acetoxy-2β-bromo-5β-androstan-6,17-dione **72**, and the 6β-alcohol **71** gave the same ketone and also 3α,6β-diacetoxy-2α,5α-epoxyandrostane **73**.

In conclusion, a wide range of substrates containing two double bond equivalents and a carbonium ion source on rings A and B of the steroids have been shown to undergo the dienol : benzene type of acid-catalysed rearrangement. In the presence of hydrogen bromide in glacial acetic acid, the reaction is accompanied by the formation of unsaturated ketones. The reaction requires a means of generating a C-5 carbonium ion. If the sequence involves the possibility of this being trapped by the formation of an acetoxylinium ion, the reaction does not proceed. The formation of the spiranic intermediates involves the release of interactions between C-1 and C-11 and between C-4 and C-6 and this may form part of the driving force for the initial stages of the reaction. Alternative aromatisation reactions can occur when key steps are blocked by methylation or disfavoured by the presence of a C-6 or C-11 carbonyl group.

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