Remarkable stereoselectivity in the hydrolysis of dioxolenium ions and orthoesters fused to anchored six-membered rings

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Hydrolysis of dioxolenium (acyloxonium) ions fused to anchored six-membered rings gives almost exclusively that hydroxyester in which the ester function is *axial* (and the hydroxyl group equatorial). With the exception of the orthoformate, a group of related orthoesters reacted similarly. The potential utility of these observations in stereoselective synthesis is suggested by the following examples. (*a*) With *trans*-decalin-*cis*-2,3-diol (**21**) formation of the mono-benzoate via the orthoester leads to the axial ester (**23***d*) in good yield; this procedure is complementary to reaction with benzoyl chloride and pyridine, which gives the equatorial ester (**24***d*) as the only isolated product. (*b*) The action of silver acetate and iodine in wet acetic acid (the Woodward–Prévost reaction) on *trans*-Δ^2-octalin gives the axial acetate – equatorial alcohol (**23***b*) again as the only significant product. The generality of this stereoselectivity is further supported by a number of individual examples drawn from the chemistry of carbohydrates. A rationalization is offered which qualitatively accounts for the observed stereoselectivity and its absence in the hydrolysis of the orthoformate, and which is based on the differences in steric strain among the possible transition states that fulfil the stereoelectronic requirements of dialkoxycarbonium ion formation.

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Introduction

We have recently described the synthesis of dioxolenium ions fused to anchored six-membered rings (e.g. **1**) and noted their preference for forming the diaxial product (**2**) rather than the diequatorial isomer (**3**) when allowed to react with halide anions (1). A number of nucleophilic reagents, however, form products derived from attack on C-1 rather than C-3 or C-4 of the dioxolenium ring; alcohols yield orthoesters and water gives the hydroxy-ester resulting from opening of the normally unstable "orthoacid" intermediate (e.g. **4**). When the dioxolenium ring is fused to an anchored cyclohexane system one oxygen is in an equatorial configuration and the other axial. As in the cleavage with halide ions, two products may in principle result from the hydrolysis, one from cleavage adjacent to the axial oxygen, the other by breaking of the bond to the equatorial oxygen. This is shown in Scheme 1, in which the dioxolenium salt (**1**) may yield either **5**, in which the hydroxyl group is equatorial and the acyloxy function axial, or **6**, the "axial alcohol – equatorial ester".

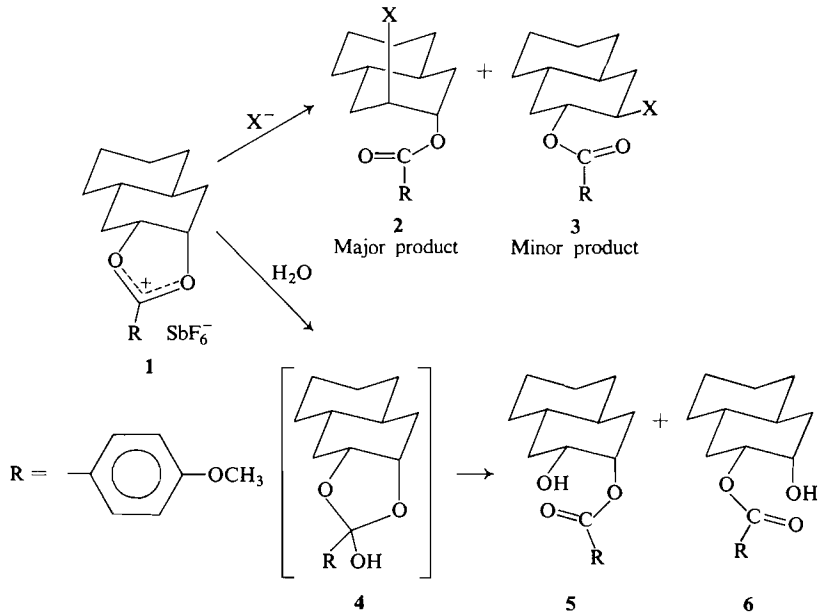
In the course of our work with dioxolenium salts we found that the hydrolysis of species such as **1** is remarkably stereoselective, the "axial ester – equatorial alcohol" (e.g. **5**) constituting more than 99.5% of the hydroxy-ester mixture obtained on hydrolysis. In this account we describe our study which rigorously proves the steric course of the hydrolysis, illustrates its scope, considers its ramifications with respect to the hydrolysis of orthoesters and the course of the Woodward–Prévost synthesis of *cis*-1,2-diols, and finally includes a rationalization of the observed stereoselectivity. Some of these results have been outlined already in a preliminary communication (2).

Results and Discussion

Hydrolysis of the Dioxolenium Hexafluoroantimonates

The dioxolenium hexafluoroantimonates (**1**, **7**, and **20**) were prepared by reaction of the corresponding diaxial bromohydrin esters with silver hexafluoroantimonate as described previously (1). The hydrolyses were normally carried out with aqueous acid, though in one experiment with **1**, aqueous base was used with essentially the same result. Examination of the hydrolysis products by thin-layer chromatography (t.l.c.) showed the presence of one major product plus a very small amount of a material running somewhat ahead of the main product. It is commonly, though not invariably, observed that axial alcohols run faster than their equatorial isomers. This suggested that if the two spots corresponded to the two readily derivable esters (e.g. **5** and **6**) then the ester formed in the greater amount had the hydroxyl group equatorial (as in **5**). That this was so was proved by the chemical correlations summarized in Scheme 2.

The essential features of this proof may be



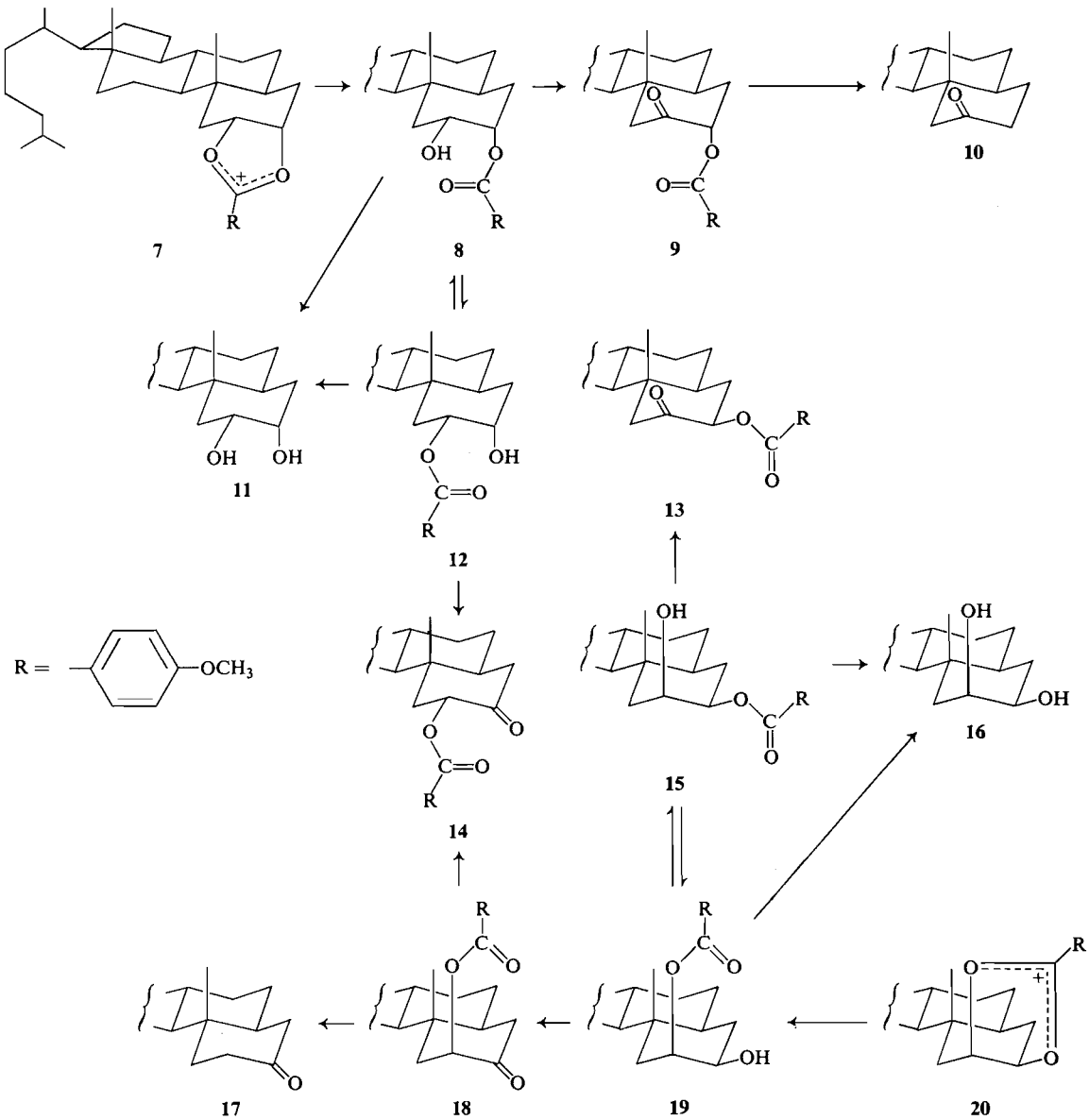
SCHEME 1

summarized with reference to the product (**8**) from the hydrolysis of the 2α,3α-anisoxonium hexafluoroantimonate **7**. Saponification of **8** gave 5α-cholestan-2α,3α-diol (**11**), showing the oxygen functions to be both on the alpha face of the molecule. Oxidation of **8** with Jones' reagent gave the α-anisoxyketone (**9**) which, on reduction with zinc and acetic acid yielded 5α-cholestan-2-one (**10**). Since the keto-function in **10** derives directly from the hydroxyl group in the product from the hydrolysis of the dioxolenium salt **7**, that hydroxyl group must be on C-2 and hence the ester function on C-3. Since the stereochemistry is already known from the formation of **11**, if no rearrangement has occurred the major hydrolysis product from **7** must have structure **8**. Analogous treatment of the major product obtained from the 2β,3β-anisoxonium salt **20**, gave respectively 5α-cholestan-2β,3β-diol (**16**), 2β-anisoxy-5α-cholestan-3-one (**18**), and 5α-cholestan-3-one (**17**), thereby showing it to have very probably the axial ester – equatorial alcohol structure also, in this case structure **19**.

Treatment of the 2α,3α-hydroxyester **8** with camphor-10-sulfonic acid in benzene led to partial conversion to the isomeric ester **12**, derived by migration of the anisoyl function from the 3α- to the 2α-oxygen. This material showed the same behavior on t.l.c. as the faster moving component of the mixture from hydrolysis of **7**. Structure **12** for this product follows from (*a*) the formation of the 2α,3α-diol (**11**) on saponification, and (*b*) production of 2α-anisoxy-5α-cholestan-3-one (**14**) on Jones' oxidation. The same material (**14**) was obtained by acid-catalyzed epimerization of **18**.

Starting with either **8** or **12** we obtained from the camphor-10-sulfonic acid treatment a mixture in which **12** predominated, showing that the equatorial ester–axial alcohol (**12**) is the more stable of the two isomers. This observation also demonstrates that the hydrolysis of the dioxolenium salt (**7**) is subject to kinetic rather than equilibrium control. The acid-catalyzed transesterification reactions **8** → **12** and **12** → **8** were not run to the point of obtaining a true equilibrium mixture owing to formation of by-products, but it can be estimated that **12** would constitute 60–75% of the ester mixture at equilibrium.

Similar acid treatment of the 2β,3β-ester-alcohol (**19**) gave **15**, which also apparently predominates at equilibrium, and which also shows the same behavior on t.l.c. as the faster moving material obtained from the hydrolysis of **20**. Oxidation of **15** gave **13**, identical with a specimen obtained in low yield along with **9** in the Jones' oxidation of **8**. Except for this instance the Jones' oxidation procedure took place without migration or epimerization of the anisoxyl group. Fear of such an occurrence in the usual



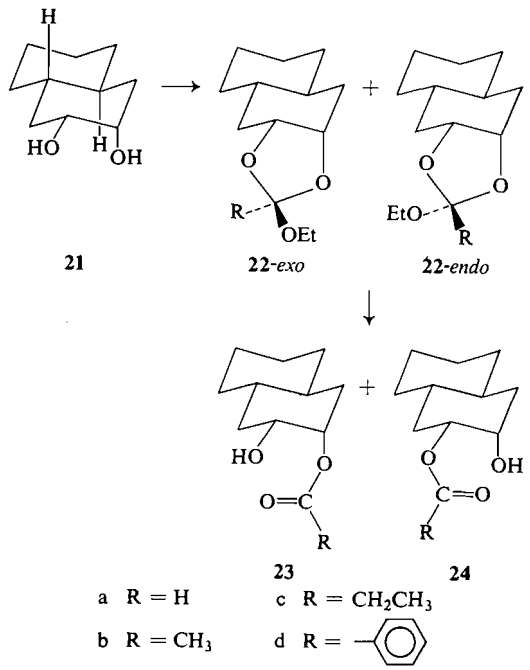
SCHEME 2

media for chromic acid oxidation had prompted us to use dimethyl sulfoxide–acetic anhydride as the oxidizing agent in some of our earlier experiments. This reagent worked well with **15** and **19**, but oxidation of **8** gave in addition to **9** a significant portion of an unidentified material.

The stereochemistry of the four keto-anisates (**9**, **13**, **14**, and **18**) follows not only from their mode of synthesis but also from their optical rotatory dispersion (o.r.d.) and nuclear magnetic resonance (n.m.r.) spectra. The o.r.d. spectra could not be observed below about 280 nm owing to the strong ultraviolet (u.v.) absorption of the anisoxyl group, but enough of the spectrum was measurable to show that the two keto-esters in which the anisoxyl group is axial (**9** and **18**) had large positive Cotton effects (amplitudes greater than 217 and 149, respectively), whereas

the two compounds with equatorial anisoxyl functions (**13** and **14**) showed much smaller positive Cotton effects (amplitudes 47 and 23, respectively). These findings are in excellent agreement with predictions based on the octant rule (3), though somewhat different from the observations reported by Williamson and Johnson (4). Because of the low solubility of our keto-esters in methanol, which was the solvent used by Williamson and Johnson, our o.r.d. spectra were obtained with methylene chloride solutions; the two sets of results may not be comparable. The n.m.r. spectra of the keto-anisates, however, were in good agreement with those described for the corresponding keto-acetates (4), the characteristic absorption patterns of the proton on the carbon bearing the ester function[1] being strikingly similar to those observed by Williamson and Johnson and interpreted by them as showing considerable distortion of ring-A from the normal chair conformation in 2β-acetoxy-5α-cholestan-3-one.

It is clear that the chemical interconversions summarized in Scheme 2 taken together with the spectroscopic properties found for compounds **9** to **18** allow no possibility of any kind of rearrangement or epimerization being the major course of any of these reactions, and that structures **8** and **19** are therefore established beyond question. The n.m.r. spectra of **8** and **19** (see Experimental) are in excellent agreement with these formulations and would provide strong independent support for the structures if any were needed. In the compounds derived from the decalin dioxolenium salt (**1**) it should be noted that no chemical proof of structure analogous to that summarized for the steroidal materials is possible owing to the symmetry of the decalin system. The proofs of the structures of the decalin hydroxy-esters rest on a comparison of physical data, notably n.m.r. spectra, with those obtained with the analogous steroids. In view of the virtual identity of the relevant parts of the n.m.r. spectra of the decalin hydroxy-esters to those from the steroid series it can be concluded that the structures of the decalin hydroxy-esters described in both this and subsequent sub-sections are also established beyond doubt. For the reaction which corresponds most directly with that of the steroidal materials, namely the hydrolysis of the decalin dioxolenium salt **1**, the product also proved to be almost entirely the axial ester – equatorial alcohol (**5**) with only a trace of a material presumed to be **6**, which showed the same R_f value on t.l.c. as the compound obtained by acid-catalyzed rearrangement of **5**.



Hydrolysis of Orthoesters of trans-Decalin-2β,3β-diol

Dialkoxycarbonium ions have long been regarded as intermediates in the acid-catalyzed hydrolysis of orthoesters; the evidence supporting this notion has recently been summarized by Cordes (6). For orthoesters derived from *trans*-decalin-2β,3β-diol (**21**) such an intermediate could (though it does not have to) be the dioxolenium ion, and therefore the hydrolysis of the corresponding orthoesters might well be expected to yield the axial ester – equatorial alcohol to the almost complete exclusion of the equatorial ester – axial alcohol. To test this simple extension of the results that we had obtained with the crystalline dioxolenium salts, we prepared the ethyl orthoesters **22***a–c*, by reaction of, respectively, ethyl orthoformate, ethyl orthoacetate, and ethyl orthopropionate with a solution of the diol (**21**) in benzene containing a small amount of camphor-10-sulfonic acid. Upon vacuum distillation the orthoesters were obtained as liquids

[1]This portion of the spectra is reproduced elsewhere (5).

which gave satisfactory analyses and showed no hydroxyl absorption in their infrared (i.r.) spectra. The n.m.r. spectra were in agreement with the orthoester formulation but suggested that each of the orthoester preparations was in fact a mixture of the two orthoesters epimeric at the orthoester carbon (**22** *exo* and **22** *endo*) in which one epimer was present in much greater amount than the other. In the spectrum of the ethyl orthoformate **22***a*, the orthoformyl proton region showed two singlets, at 5.73 and 5.79 p.p.m. (relative areas roughly 4:1), while the methylene of the ethoxyl group appeared as a quartet at 3.60 p.p.m. (J = 7 Hz) superimposed on a correspondingly smaller quartet at 3.65 p.p.m. (J = 7 Hz). Similarly, the spectrum of the orthoacetate **22***b* shows two methyl singlets, the larger one at 1.61 p.p.m., the smaller at 1.52 p.p.m., and the orthopropionate **22***c* displays a quartet at 3.53 p.p.m. (J = 7 Hz) together with what appears to be another quartet at 3.62 p.p.m.

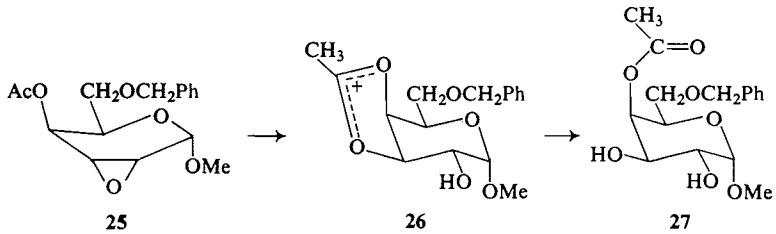
Perlin has found that formation of orthoacetates under the conditions of the Königs–Knorr synthesis leads to a mixture of epimers as demonstrated both by n.m.r. spectroscopy and actual isolation of the individual epimers (7). The major component of the mixture was suggested to have the alkoxyl group *exo* to the pyranose ring on the basis of the n.m.r. spectra and an earlier suggestion by Lemieux and Cipera (8) that the *exo* product would be expected to predominate because of the more facile approach of the alcohol to the side of the acetoxonium ion remote from the pyranose ring. Lemieux and Morgan (9), in another preparation of orthoesters believed to take place via the dioxolenium ion, also found the predominance of one isomer which was assigned the *exo* structure primarily on the basis of a cogent argument based on an imposing array of n.m.r. data.

Both the mode of preparation and the basic skeleton in our compounds are different from those of these authors, and it would not be surprising if the nature of our orthoester mixture proved to be different from theirs. Nonetheless using their correlations to interpret our n.m.r. data leads to the suggestion that the products that we obtain in the larger amount have the *exo* configuration of the ethoxyl group. This assignment is tentative because it is hard to be certain that the n.m.r. signals described above derive from one and the same minor component.

The hydrolysis of the orthoesters **22***a–c* was effected by dissolving in methanol, adding aqueous acetic acid, and letting the mixture stand at room temperature for 10–15 min. The orthoacetate (**22***b*) and orthopropionate (**22***c*) gave almost quantitative yields of the axial ester – equatorial alcohol (**23**) with only a very small amount of the isomer with the acyl function on the other oxygen (**24**). Both **23***b* and **23***c* underwent the acid-catalyzed transesterification to give **24***b* and **24***c* respectively. The structures of all of these compounds follow from analyses and the close correspondence of their spectra with those of the analogous materials already described (see Experimental).

Hydrolysis of the orthoformate **23***a*, however, gave a distinctly different result. The n.m.r. spectrum of the product showed the characteristic absorption of the axial ester – equatorial alcohol (in this case, **23***a*), but in addition there were equally characteristic bands indicating the presence of about 40% of the equatorial formate – axial alcohol (**24***a*). The axial formate (**23***a*) was obtained crystalline and characterized in the usual way but attempts to obtain a pure specimen of the equatorial formate (**24***a*) failed. Thin-layer chromatography on silica gel led to rapid equilibration of the two esters, a characteristic streaked double spot being obtained starting with either the mixture or with crystalline **23***a*. The ease with which **23***a* is converted to **23***b* on t.l.c. suggested the possibility that the mixture from the hydrolysis of **22***a* might merely be the product of a subsequent equilibration rather than that resulting from kinetic control of the reaction, as was the case with the other hydrolyses. The axial formate (**23***a*), however, was found to be completely stable to the conditions of the original orthoester hydrolysis. The orthoformate (**22***a*) is therefore also giving the kinetically controlled product which contains a much larger proportion of the equatorial ester – axial alcohol than the products of any of the other hydrolyses described in this paper. This observation is believed to be of significance in the rationalization of the steric course of these hydrolyses that is offered later in this account.

In addition to the orthoesters **22***a–c*, we also attempted to obtain the ethyl orthobenzoate **22***d*, following the same procedure as for the others. It was found, however, that distillation of the crude product led to extensive decomposition. The i.r. spectrum of the undistilled reaction prod-



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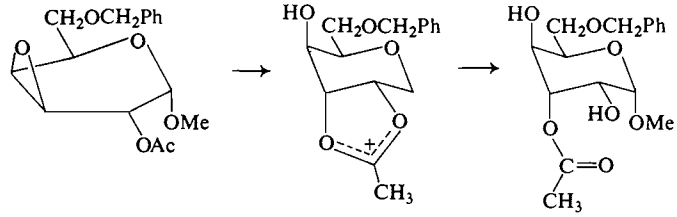


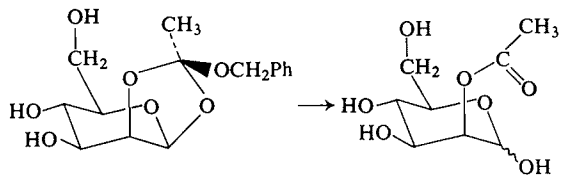
28 29 30

uct indicated that the material consisted primarily of the orthoester (**22***d*), and it was therefore hydrolyzed in the usual way. The t.l.c. showed the only significant components of this product to be the axial ester (**23***d*) and recovered diol (**21**); these were subsequently isolated in yields of 72% (88% based on reacted diol) and 18%, respectively.

It is interesting to compare this method of preparing a monobenzoate ester of **21** with direct esterification. When the diol (**21**) was treated with one equivalent of benzoyl chloride in the presence of pyridine, the other ester (**24***d*), in which the benzoyl group is attached to the *equatorial* oxygen was obtained in 93% yield (based on reacted diol). The complementary stereoselectivity of these methods of forming a mono-ester of such a *cis*-1,2-diol should prove useful in organic synthesis.

Stereoselective Hydrolysis of Carbohydrate Dioxolenium Ions

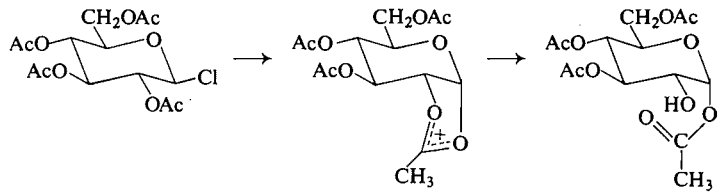
Reactions proceeding via dioxolenium ions have been used to a considerable extent in carbohydrate synthesis but the generality of the strong preference for forming axial esters on hydrolysis has not been pointed to. The following examples indicate that stereoselective hydrolysis does in fact occur with substituted pyranoses more or less anchored in one conformation. Buchanan and Fletcher (10) found that 80% acetic acid converted the anhydro sugars **25** and **28** to **27** and **30**, respectively, presumably via the acetoxonium ions **26** and **29**. Making the reasonable assumption that **26** and **29** have the C1 conformation as shown, these results are examples of the preferential formation of axial esters by hydrolysis of dioxolenium ions.[2] Perlin (7, 11) has shown that certain mannopyranose 1,2-orthoesters lead to



31 32

the axial ester, as for example in the reaction **31** to **32**. It could perhaps be argued that in the case of a dioxolane ring incorporating the anomeric carbon, the reaction may proceed via a different mechanism and that our observations on dioxolenium ions fused to cyclohexane rings are not relevant to the pyranose 1,2-orthoesters. One of the more likely alternative mechanisms would involve cleavage of the bond between the anomeric carbon and the dioxolenium oxygen, assisted by the electrons on the oxygen of the pyranose ring. Lemieux and Morgan (12), however, have shown that tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**33**) with silver acetate in wet acetic acid, gives (presumably via **34**) the 1-acetyl derivative **35**. This result would suggest

[2]NOTE ADDED IN PROOF: The formation of an axial acetate following neighboring group participation of an equatorial acetoxyl function has also been encountered with steroidal systems; S. Julia and R. Lorne have recently (*Comptes Rendus* **268 C**, 1617 (1969)) used the results given in our preliminary communication (2) to help to rationalize these observations.



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that the direction of cleavage of pyranose 1,2-orthoesters is not controlled by electronic influences associated with the anomeric carbon but rather by the stereochemical factors common to dioxolenium systems fused to six-membered rings. An instance of an unselective opening of an acetoxonium ion has been described by Paulsen and co-workers (13) who report that an acetoxonium derivative of arabinopyranose gives both possible hydroxyacetates. It is unlikely, however, that the arabinopyranose system is anchored, and hence would not be expected to show the stereoselectivity found with species which are.

Stereochemistry of the Hydroxy-ester from the Woodward–Prévost Reaction

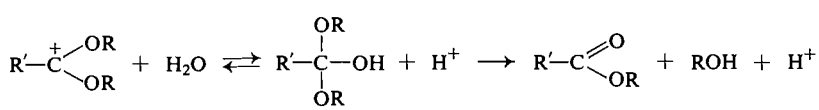
The reaction of an olefin with iodine and silver acetate in wet acetic acid (14), often referred to as the Woodward–Prévost reaction, is another process which is believed to proceed via a dioxolenium species, specifically an acetoxonium ion. If this is indeed the case, it would be expected that the hydroxy-acetate obtained as the direct product of the reaction, prior to the usual saponification to the glycol, would have the hydroxyl group equatorial and the acetoxyl function axial. We were unable to find any examples on searching the literature, all such hydroxy-acetates having been hydrolyzed directly to the glycols without any examination of their stereochemistry. We therefore investigated the product of the reaction with *trans*-2-octalin. The t.l.c. of the crude product showed it to consist almost entirely of one compound. After the usual workup we obtained a 79% yield of **23***b*, the major product obtained from hydrolysis of the orthoacetate **22***b*.

Origin of the Stereoselectivity Observed in the Hydrolysis of the Dioxolenium Ions and Orthoesters

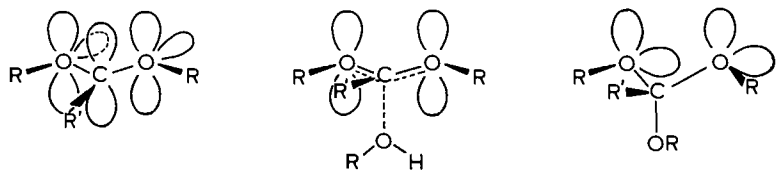
According to current informed opinion (6) the hydrolysis of dialkoxycarbonium ions requires at least the steps shown in Scheme 3. In addition to the above minimum number of intermediates, conjugate acid forms of both the "orthoacid" and ester species are probably involved, though proton loss or addition concerted with another bond formation or cleavage is regarded as possible (6). By representing the conjugate acids as discrete species and thereby multiplying the number of steps in the reaction sequence, each individual step becomes simpler and may be represented more easily. The stereochemical argument is essentially the same, however, whether or not addition or loss of a proton is concerted with another process.

Hydrolysis of an orthoester requires, of course, another step leading to formation of a dialkoxycarbonium ion. With the orthoesters incorporating a dioxolane ring, this step may yield either a dioxolenium ion or one in which the dioxolane ring has been opened. In the latter case the ring opening reaction leading to such a species would be stereochemically virtually identical with the second step of the sequence given above, i.e. the formation of the ester (or its conjugate acid). It follows then, that starting with an orthoester the reaction sequence either joins the same path as if it had started at the dioxolenium ion stage, or else it follows a parallel route that is sterically very closely related and which does not require additional special comment.

In our view the origin of the stereoselectivity observed with all of the substrates in this study except the orthoformates, is to be found in a

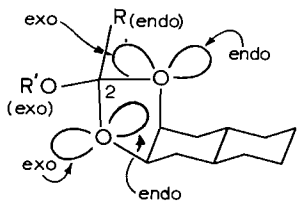


SCHEME 3



36 37 38

combination of steric and stereoelectronic effects. The latter effect is perhaps most clearly illustrated in terms of a nucleophilic attack on a hydroxyalkoxycarbonium ion, a reaction which is the reverse of the cleavage of an "orthoacid". We will first consider an unstrained system as in **36**, and its reaction with ROH. Simple theoretical considerations which are supported by the results of n.m.r. studies (15–20), require that all six of the atoms indicated in **36** and the localized non-bonding electrons on the oxygen atoms lie in a common plane; structure **36** depicts one of the possible arrangements which satisfies this requirement (the others may be obtained by successive interchange of the positions of the localized non-bonding electrons and the R group on each oxygen). Attack of ROH will take place on a line running through the charged carbon orthogonal to the common plane. This will lead through a transition state imagined to look like **37**, to the product in the conformation shown in **38**. For the reverse reaction **38** to **36**, which is the generalized version of the reaction which forms the basis of this paper, it is evident that in order to achieve maximum stabilization of the positive charge on carbon by the electrons on the two oxygen atoms, one free electron pair on each oxygen must be *anti* (or at least *anti*-periplanar) to the leaving group ROH.[3] If one now considers a specific version of this reaction with the corresponding species derived from a dioxolenium ion fused to an anchored six-membered ring, it is apparent from inspection of molecular models that the fusion of the five- and six-membered rings places restrictions on how to achieve a conformation even approaching one in which a pair of free electrons on each oxygen is *anti*-periplanar with the leaving group (as in **38**). For example, the *endo* electron pair on the axial oxygen (shown in **39**) can become *anti*-periplanar with the equatorial oxygen (which would be the leaving group in the formation of the equatorial alcohol – axial ester by this route) *only* by introducing severe steric strain, either by distorting the five-membered ring or alternatively



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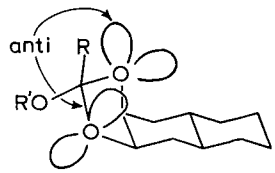
by flipping the six-membered ring into a boat conformation. Similarly the *exo* electrons of the equatorial oxygen can also only become *anti*-periplanar to the axial oxygen by introducing a good deal of strain. As is shown in **40**, however, the *exo* electrons of the axial oxygen can comparatively readily become *anti*-periplanar to the equatorial oxygen. Similarly as indicated in **41**, the *endo* electrons of the equatorial oxygen and the axial oxygen can also be so arranged, but in so doing the *endo* substituent on C-2 (shown as R in **41**) moves very close to the nearest axial hydrogen of the cyclohexane ring (H in **41**).[4] It would be expected that all species in which the *endo* function is either an aryl, alkyl, alkoxyl, or

[3]A good example of this requirement has very recently been given by Eliel and Nader (21).

[4]In the mannose derivatives studied by Perlin (7, 11) the non-bonding interaction is not with an axial hydrogen but rather a free electron pair of the pyranose oxygen. This interaction resembles the *syn*-axial non-bonded interaction between a *t*-butyl group and the free electron pairs in 2-alkyl-5-*t*-butyl-1,3-dioxanes, and which has been found by Eliel and Knoeber (22) to be much smaller than the analogous interaction between an axial *t*-butyl group and an axial hydrogen. This would suggest that the stereoselectivity with the mannose derivatives (though *not* with compounds **25**, **28**, and **33**) should be distinctly smaller than that found with the cyclohexane derivatives. Perlin (7) has noted the formation of a little of the 1-acetate from **31**, and has informed us (private communication) that in the hydrolysis of the fully acetylated orthoacetate from mannose he has found "almost equimolar yields of both products". We thank Professor Perlin for telling us of these results and for kindly giving permission to mention them here.



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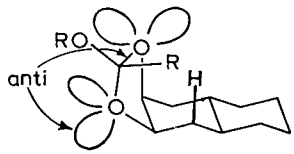

41

hydroxyl group, the interaction of the *endo* group with the neighboring axial hydrogen would make the transition state derived from **41** of much higher energy than the one derived from **40**. It is concluded from this argument that except when the *endo* substituent on C-2 is a hydrogen atom, the route derived directly from **40** would have much the lowest energy of the possible pathways. Such a route, of course, leads to the axial ester – equatorial alcohol, which is found experimentally in these cases to be the predominant product by a large measure.

When one *endo* group on C-2 is a hydrogen atom, the compound is an orthoformate ester (or the derived "orthoacid"). From the work of Lemieux and Perlin described earlier, it would appear that the major portion of a sample of orthoformate or of its derived "orthoacid" should in fact have the C-2 proton in the *endo* configuration. When the *endo* C-2 substituent is hydrogen one would expect that the transition states derived from **40** and **41** be not nearly as different in energy as when the substituent is larger than hydrogen. It is therefore not surprising in the context of this argument to find that the hydrolysis of the orthoformate ester (**22***a*) apparently gives nearly as much of the axial alcohol – equatorial ester (**24**) as of its isomer (**23**).[5]

[5]It might perhaps be mentioned that the mechanism of hydrolysis of orthoformates is believed to be essentially the same as that of the other orthoesters (6), and that any rationalization of the loss of stereoselectivity with the orthoformates must, as is the case here, be in terms of this same mechanism.

Another factor which may contribute in some measure to the stereoselectivity of hydrolysis is the greater ease of protonation of an equatorial oxygen (leading to the equatorial alcohol – axial ester) vs. protonation of an axial oxygen (leading to the axial alcohol – equatorial ester). In general an axial ion is of somewhat higher energy than its equatorial epimer, presumably because of poorer solvation of the axial ion resulting from the less open environment of an axial substituent (cf. ref. 23). An analogous, though perhaps smaller, energy difference would presumably be found between the *transition states* from the axially and the equatorially protonated species as well. Data for the relative basicities of axial and equatorial oxygen do not seem to be at hand but the difference between axial and equatorial amino groups is comparatively small: *cis*-4-*tert*-butylcyclohexylamine (axial NH_2) is less basic than the *trans* (equatorial NH_2) isomer by only 0.25 pK units in 80% methylcellosolve–water (24). Unless oxygen behaves quite differently from nitrogen in such cases, this factor alone could not account for the degree of stereoselectivity observed in the hydrolysis of dioxolenium ions, nor for the behavior of the orthoformates. Its effect, however, may be to increase the amount of the axial ester – equatorial alcohol to some extent.

Experimental

Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were obtained with Beckman IR-5 or IR-10 spectrophotometers using sodium chloride cells, and were determined on chloroform (Fisher Spectranalyzed grade) solutions. Rotations (at the D line) were determined on approximately 1% solutions in chloroform with a Rudolph model 80 polarimeter. Optical rotatory dispersion measurements were carried out with a Jasco ORD/UV-5-CD spectropolarimeter. Nuclear magnetic resonance spectra were run on $CDCl_3$ solutions using a Varian A-60 spectrometer. "Half-width" in the description of n.m.r. bands refers to the width of the band (in Hz) along a line midway between the baseline and the top of the band, cf. ref. (25). Refractive indices were determined with a thermostatically controlled Bausch and Lomb refractometer. Thin-layer chromatography was carried out using Camag silica gel DF 5. Petroleum ether refers to the fraction of boiling range 30–60°. Organic extracts were dried with anhydrous magnesium sulfate.

Acid-catalyzed Hydrolysis of Acyloxonium Hexafluoroantimonates

A solution of the acyloxonium salt in methylene chloride (10 ml) was shaken with aqueous acetic acid (10 ml, 10%) for several minutes. The reaction mixture

was then washed with dilute sodium bicarbonate solution, water, dried, the solvent evaporated under reduced pressure, and the residue treated as indicated below.

To obtain a semi-quantitative estimate of the composition of the reaction mixture, the product was dissolved in chloroform to give a suitable concentration for t.l.c. Standard mixtures of the two possible hydrolysis products were prepared, i.e. of the equatorial alcohol – axial ester and axial alcohol – equatorial ester compounds, and were dissolved in chloroform to give the same concentration as that of the hydrolysis product. A standard number of drops of each solution (from the same dropping pipette) were applied to t.l.c. plates which were then eluted with ether–benzene (1:1). The plates were sprayed with 30% sulfuric acid and charred, and the intensities of the resulting spots were compared.

In the products from 5α-cholestan-2α,3α-*p*-anisoxonium, 5α-cholestan-2β,3β-*p*-anisoxonium, and 9β,10α-decalin-2β,3β-*p*-anisoxonium salts the amount of axial alcohol – equatorial ester was in each case estimated at less than 0.5% of the product.

(a) 5α-Cholestan-2α,3α-p-anisoxonium Hexafluoroantimonate (7)

A solution of the salt (1) (370 mg) in methylene chloride was treated as described above. The t.l.c., eluting with ether–benzene (1:1), showed the product (255 mg) to consist of almost entirely one compound (R_f 0.54) together with a trace of a second compound (R_f 0.64), both being visible under u.v. light as well as upon charring. Crystallization from acetone–water gave 2α-hydroxy-5α-cholestan-3α-yl *p*-anisate (**8**); m.p. 146–148°; $[\alpha]_D$ +45°; ν_{max} 3580, 1700 cm^{-1}. The n.m.r. spectrum showed signals at 0.82 (s), 2.47 (s, OH), 3.80 (s), a broad band at 3.87 (half-width 20 Hz), a narrow band at 5.29 (half-width 6 Hz) and a signal interpreted as an AB quartet: δ_A 6.87, δ_B 7.96 p.p.m., J_{AB} 9 Hz. These signals were assigned to the C-19 methyl group, the hydroxyl group, the methoxyl group, the C-2 hydrogen (axial), the C-3 hydrogen (equatorial), and to the aromatic hydrogens respectively.

Anal. Calcd. for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 77.68; H, 10.08.

(b) 5α-Cholestan-2β,3β-p-anisoxonium Hexafluoroantimonate (20)

A solution of the salt (1) (250 mg) in methylene chloride was treated as above. The t.l.c., eluting with ether–benzene (1:1), showed the product (180 mg) to consist of almost entirely one compound (R_f 0.64), together with a trace of a second compound (R_f 0.85), both spots being visible under u.v. light as well as on charring. Crystallization from acetone – petroleum ether gave 3β-hydroxy-5α-cholestan-2β-yl *p*-anisate (**19**); m.p. 132–133°; $[\alpha]_D$ −22°; ν_{max} 3570, 1700 cm^{-1}. The n.m.r. spectrum had bands at 0.98 (s), 2.48 (s, OH), 3.78 (s), a broad band at 3.87 (half-width 22 Hz), a narrow band at 5.29 (half-width 8 Hz) and a quartet: δ_A 6.82, δ_B 7.93 p.p.m., J_{AB} 9 Hz, assigned to the C-19 methyl group, the hydroxyl group, the methoxyl group, C-3 hydrogen (axial), C-2 hydrogen (equatorial), and the aromatic hydrogens respectively.

Anal. Calcd. for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: 77.73; H, 9.95.

(c) 9β,10α-Decalin-2β,3β-p-anisoxonium Hexafluoroantimonate (1)

A solution of the salt (1) (500 mg) in methylene chloride was treated with aqueous acetic acid as outlined above. The t.l.c., eluting with ether–benzene (1:1) showed the product (286 mg) to consist of almost entirely one compound (R_f 0.32) together with a trace of a second compound (R_f 0.50). Crystallization from ether – petroleum ether gave 3β-hydroxy-9β,10α-decalin-2β-yl *p*-anisate (**5**); m.p. 92–94°; ν_{max} 3580, 1700 cm^{-1}. The n.m.r. spectrum showed bands at 2.88 (s, OH), 3.71 (broad band, half-width 21 Hz), 3.77 (s), 5.30 (narrow band, half-width 7 Hz), and a quartet δ_A 6.85, δ_B 7.94 p.p.m., J_{AB} 9 Hz. These bands were assigned to the C-3 hydroxyl group, the C-3 hydrogen (axial), the methoxyl group, the C-2 hydrogen (equatorial), and to the aromatic hydrogens respectively.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.90; H, 7.87.

(d) 9β,10α-Decalin-2β,3β-benzoyloxonium Hexafluoroantimonate

A solution of the benzoyloxonium salt (1) (100 mg) in methylene chloride (10 ml) was treated with aqueous acetic acid as described above. The t.l.c., eluting with benzene–ether (1:1), showed the product (52 mg) to be almost entirely one compound. Crystallization from ether–pentane gave 3β-hydroxy-9β,10α-decalin-2β-yl benzoate (**23***d*); m.p. 105–107°; ν_{max} 3600, 1705 cm^{-1}. The n.m.r. spectrum had signals at 2.40 (s, OH), 3.78 (broad band, half-width 21 Hz), 5.37 (narrow band, half-width 7 Hz), 7.42, and 8.05 (both multiplets). These signals were assigned to the C-3 hydroxyl group, the C-3 hydrogen (axial), the C-2 hydrogen (equatorial), and the phenyl hydrogens respectively.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.40; H, 8.09. Found: C, 74.34; H, 7.83.

Reaction of 9β,10α-Decalin-2β,3β-p-anisoxonium Hexafluoroantimonate (1) with Base

A solution of the decalin anisoxonium salt (200 mg) in methylene chloride (10 ml) was shaken with aqueous potassium hydroxide solution (10 ml; 5%) for 2 min. The methylene chloride was washed several times with water, dried, and evaporated under reduced pressure. The t.l.c., eluting with benzene–ether (1:1), showed the product to consist of one compound with the same R_f value as 3β-hydroxy-9β,10α-decalin-2β-yl *p*-anisate (**5**). Crystallization from ether – petroleum ether gave 3β-hydroxy-9β,10α-decalin-2β-yl *p*-anisate (112 mg) identified with an authentic specimen by m.p., mixed m.p., and i.r. spectra.

Alkaline Hydrolyses of Hydroxyanisates

A solution of the hydroxyanisate (50–100 mg) and potassium hydroxide (200–300 mg) in methanol (5 ml) and ether (1 ml) was allowed to react overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed several times with water, dried, and evaporated under reduced pressure, and further purified as described below for each reaction.

(a) 2α-Hydroxy-5α-cholestan-3α-yl p-Anisate (8)

This compound gave a product which was recrystallized

from chloroform–acetone; m.p. 222–224°; $[\alpha]_D$ +31°. Henbest and Smith (26) have prepared 5α-cholestan-2α,3α-diol (**11**) and report m.p. 212–214° and $[\alpha]_D$ +32°. Repetition of their procedure gave a sample melting at 214–217° and which on admixture with the material from the saponification, melted at 223–225°.

(b) 3α-Hydroxy-5α-cholestan-2α-yl Anisate (12)

Upon hydrolysis as described above, this anisate gave a material which on recrystallization showed essentially the same properties as the 5α-cholestan-2α,3α-diol (**11**) prepared from **8**: m.p. 225–226°, $[\alpha]_D$ +29°, and mixed m.p. with an authentic specimen 224–226°.

(c) 2β-Hydroxy-5α-cholestan-3p-yl Anisate (15)

Compound **15** was hydrolyzed similarly; the product was recrystallized from ether–methanol; m.p. 174–176°; $[\alpha]_D$ +40°; mixed m.p. with an authentic sample of 5α-cholestan-2β,3β-diol (**16**) (prepared as described below) 177–179°.

(d) 3β-Hydroxy-5α-cholestan-2β-yl Anisate (19)

On hydrolysis as above, **19** gave a product which on recrystallization from ether–methanol melted at 174–176°; $[\alpha]_D$ +42°; mixed m.p. with an authentic specimen of 5α-cholestan-2β,3β-diol (**16**) (see below) 175–177°.

(e) 2β-Hydroxy-9β,10α-decalin-3β-yl Anisate (6)

Compound **6** gave a hydrolysis product which was recrystallized from benzene – petroleum ether to give a sample melting at 140–141°; mixed m.p. 139–140° with an authentic specimen of 9β,10α-decalin-2β,3β-diol (**21**), prepared by the method of Henbest *et al.* (27).

(f) 3β-Hydroxy-9β,10α-decalin-2β-yl Anisate (5)

On similar treatment, **5** gave a product which after recrystallization melted at 141–142°; mixed m.p. with an authentic sample of 9β,10α-decalin-2β,3β-diol (**21**) (27), 141–142°.

5α-Cholestan-2β,3β-diol (16)

This compound was prepared from cholest-2-ene by the method of Henbest and Smith (26), with the exception that the reaction mixture was heated for 3½ h at 80°. The product, after alkaline hydrolysis, was purified by t.l.c., eluting with ether–benzene (1:1); m.p. 177–180° and $[\alpha]_D$ +37°; reported m.p. 174–177° and $[\alpha]_D$ +43° (26).

Oxidation of the Steroid Hydroxyanisates with Dimethyl Sulfoxide and Acetic Anhydride

(a) 3β-Hydroxy-5α-cholestan-2β-yl p-Anisate (19)

A solution of the hydroxyanisate (**19**) (147 mg) in dimethyl sulfoxide (2 ml) and acetic anhydride (2 ml) was allowed to react at room temperature for 36 h. The reaction mixture was diluted with ether and washed with dilute sodium bicarbonate solution, several times with water, dried, and the ether evaporated. Crystallization from ether–pentane gave 5α-cholestan-3-one-2β-yl *p*-anisate (**18**) (124 mg), m.p. 68–74°; $[\alpha]_D$ +51°; ν_{max} 1705 cm^{-1}. The n.m.r. spectrum had bands at 0.95 (s), 3.81 (s), 5.52 (apparent triplet, *J* 7.75 Hz) and a quartet, δ_A 6.88, δ_B 8.00 p.p.m., J_{AB} 9 Hz. These bands were assigned to the C-19 methyl, the methoxyl group, the C-2 hydrogen (equatorial), and to the aromatic hydrogens respectively. Optical rotatory dispersion in methylene chloride (*c*, 0.04): $[\alpha]_{650}$ +25, $[\alpha]_{589}$ +50, $[\alpha]_{307}$ +950, $[\alpha]_{290}$ 0, and $[\alpha]_{280}$ −1825°; amplitude > 149. Ultraviolet spectrum in methylene chloride, λ_{max} 257 nm, log ε 4.35.

Anal. Calcd. for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 77.96; H, 9.92.

(b) 2α-Hydroxy-5α-cholestan-3α-yl p-Anisate (8)

The hydroxyanisate (**8**) (304 mg) was treated with dimethyl sulfoxide (3 ml) and acetic anhydride (3 ml) as described in (*a*) above. Attempted crystallization of the product from several solvent mixtures failed. The t.l.c., single elution with ether–benzene (1:1), showed only one spot; however, two successive elutions with ether–benzene (5:95) showed two compounds to be present having R_f values of 0.53 and 0.49, respectively, and which were separated by preparative t.l.c.

The slower running of the two proved to be the major product (192 mg) and on recrystallization from ether – petroleum ether gave 5α-cholestan-2-one-3α-yl *p*-anisate (**9**), m.p. 86–88°; $[\alpha]_D$ +88°; ν_{max} 1720 cm^{-1}. The n.m.r. spectrum showed bands at 0.80 (s), 3.83 (s), 5.05 (narrow band, half-width 5 Hz) and a quartet δ_A 6.90, δ_B 7.96 p.p.m., J_{AB} 9 Hz. These bands were assigned to the C-19 methyl group, the methoxyl group, the C-3 hydrogen (equatorial), and to the aromatic hydrogens respectively. Optical rotatory dispersion in methylene chloride (*c*, 0.039): $[\alpha]_{650}$ +100, $[\alpha]_{589}$ +100, $[\alpha]_{320}$ +1715, $[\alpha]_{298}$ 0, and $[\alpha]_{280}$ −2330°; amplitude > 217.

Anal. Calcd. for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 78.55; H, 9.96.

The material of R_f value 0.53 above (85 mg) was recrystallized from ether – petroleum ether; m.p. 108–110°; $[\alpha]_D$ +65°; ν_{max} 1700 cm^{-1}. The n.m.r. spectrum showed bands at 0.90 (s), 3.83 (s), 4.66 (half-width 11 Hz), 5.50 (half-width 8 Hz) and a quartet: δ_A 6.88, δ_B 7.97 p.p.m., J_{AB} 9 Hz. Qualitative tests for halogen and sulfur were negative.

(c) 2β-Hydroxy-5α-cholestan-3β-yl p-Anisate (15)

The hydroxyanisate (**15**) (134 mg) was treated with dimethyl sulfoxide (2 ml) and acetic anhydride (2 ml) for 72 h, and the product was isolated as described in (*a*) above. This oxidation appeared to be slower than the previous ones as t.l.c., eluting with ether–benzene (1:9) showed that besides the keto-anisate (R_f 0.66) a small amount of starting material was present. The keto-anisate was purified by t.l.c. using ether–benzene (1:9) and the product (77 mg) was recrystallized from chloroform – petroleum ether, giving 5α-cholestan-2-one-3β-yl *p*-anisate (**13**), m.p. 178–179°; $[\alpha]_D$ +45°; ν_{max} 1725, 1705 cm^{-1}. The n.m.r. spectrum had bands at 0.82 (s), 3.80 (s), 5.4 (broad diffuse band), and a quartet: δ_A 6.88, δ_B 8.03 p.p.m., J_{AB} 9 Hz. These signals were assigned to the C-19 methyl group, the methoxyl group, the C-3 hydrogen (axial), and to the aromatic hydrogens respectively. Optical rotatory dispersion in methylene chloride (*c*, 0.04): $[\alpha]_{650}$ +37, $[\alpha]_{589}$ +44, $[\alpha]_{310}$ +700, $[\alpha]_{292}$ 0, $[\alpha]_{285}$ −175, and $[\alpha]_{280}$ 0°; amplitude 47.

Anal. Calcd. for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 78.52; H, 9.53.

Oxidation of the Steroid Hydroxyanisates with Jones' Reagent

The oxidizing agent used in these experiments consisted of a solution of sodium dichromate (13 g) and concentrated sulfuric acid (8.7 ml) in water (30 ml). To a

stirred solution of the hydroxyanisate (150–250 mg) in acetone (10–25 ml), at room temperature, was added a few drops of the above oxidizing agent (usually 0.3 ml) so that the solution was a red–orange color. After 3 min a dilute aqueous solution of sodium metabisulfite ($Na_2S_2O_5$) was added to the reaction mixture until a blue–green color was obtained. After dilution with water, the reaction mixture was extracted with ether. The ether extracts were washed with dilute sodium bicarbonate solution and water, and then dried and the ether evaporated under reduced pressure.

(a) 2α-Hydroxy-5α-cholestan-3α-yl p-Anisate (8)

The hydroxyanisate (**8**) (214 mg) in acetone (10 ml) on oxidation as described above gave 195 mg of crude product. The t.l.c., eluting with ether–benzene (5:95) showed that there was very little starting material present and that the product consisted of almost entirely one compound (R_f 0.48) with a small amount of a second product running slightly ahead of the main spot. Preparative t.l.c. separated the material into two fractions weighing respectively 15 mg and 150 mg. Recrystallization from methylene chloride – petroleum ether gave materials identified by melting point, mixed m.p. with an authentic specimen and i.r. spectra as respectively 5α-cholestan-2-one-3β-yl *p*-anisate (**13**) and 5α-cholestan-2-one-3α-yl *p*-anisate (**9**).

(b) 3α-Hydroxy-5α-cholestan-2α-yl p-Anisate (12)

The hydroxyanisate (**12**) (180 mg) in acetone (15 ml) was oxidized as described above. The crude product (176 mg) showed no OH peaks in the i.r. spectrum. Crystallization from pentane gave 5α-cholestan-3-one-2α-yl *p*-anisate (**14**); m.p. 148–150°; $[\alpha]_D$ +105°; ν_{max} 1725, 1705 cm^{-1}. The n.m.r. spectrum had bands at 1.17 (s), 3.78 (s), a doublet of doublets at 5.50 (J_{AB} 6.5 Hz, J_{AC} 12.5 Hz, presumed to be due to coupling with the equatorial and axial protons on C-1, respectively) and a quartet: δ_A 6.88, δ_B 8.00 p.p.m. (J_{AB} 9 Hz). These bands were assigned to the C-19 methyl group, the methoxyl group, C-2 hydrogen (axial), and the aromatic hydrogens respectively. Optical rotatory dispersion in methylene chloride (*c*, 0.04): $[\alpha]_{650}$ +50, $[\alpha]_{589}$ +100, $[\alpha]_{312}$ +550, $[\alpha]_{288}$ +125, and $[\alpha]_{280}$ +625°; amplitude 23.

Anal. Calcd. for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 77.97; H, 9.68.

(c) 3β-Hydroxy-5α-cholestan-2β-yl p-Anisate (19)

The hydroxyanisate (**19**) (215 mg) in acetone (15 ml) was oxidized as described above. The t.l.c., eluting with ether–benzene (5:95), showed the crude product to consist mainly of one compound (R_f 0.52) together with a small amount of starting material. Purification by t.l.c. gave 5α-cholestan-3-one-2β-yl *p*-anisate (**18**) (139 mg) which was recrystallized from ether–pentane; m.p. 65–75°. The i.r. spectrum was identical to that of the product obtained by oxidation of 3β-hydroxy-5α-cholestan-2β-yl *p*-anisate (**19**) with dimethyl sulfoxide and acetic anhydride.

(d) 2β-Hydroxy-5α-cholestan-3β-yl p-Anisate (15)

The hydroxyanisate (**15**) (233 mg) in acetone (25 ml) was oxidized as described above. The t.l.c., eluting with ether–benzene (1:9), showed the presence of two materials. The slower moving of these was obtained as an oil (60 mg) with bands in the i.r. at 1740 and 1700 cm^{-1} and was not further characterized. The faster running material (130 mg) on recrystallization melted at 180–181°, and was shown by m.p., mixed m.p., and i.r. spectrum to be identical with the specimen of 5α-cholestan-2-one-3β-yl *p*-anisate (**13**) obtained from the dimethyl sulfoxide – acetic anhydride oxidation of 2β-hydroxy-5α-cholestan-3β-yl *p*-anisate (**15**).

Epimerization of 5α-Cholestan-3-one-2β-yl p-Anisate (18) to 5α-Cholestan-3-one-2α-yl p-Anisate (14)

A solution of 5α-cholestan-3-one-2β-yl *p*-anisate (**18**) (35 mg) and D-10-camphorsulfonic acid (5 mg) in benzene (5 ml) was refluxed overnight. The reaction mixture, after dilution with ether, was washed with dilute sodium bicarbonate solution and water, dried, and the solvent removed by evaporation under reduced pressure. The crude product had an i.r. spectrum very similar to that of 5α-cholestan-3-one-2α-yl *p*-anisate (**14**). The product was purified by t.l.c. eluting with ether–benzene (1:9); two recrystallizations from ether–pentane gave 5α-cholestan-3-one-2α-yl *p*-anisate (**14**), m.p. 146–148°; mixed m.p. with an authentic sample 146–148°. The i.r. spectrum was also identical with that of 5α-cholestan-2-one-2α-yl *p*-anisate (**14**).

Reduction of 5α-Cholestan-3-one-2β-yl p-Anisate (18) with Zinc and Acetic Acid

To a solution of the keto-anisate (**18**) (69 mg) in ether (4 ml) and acetic acid (1.5 ml) was added zinc dust (1.0 g); the mixture was refluxed for 4 h. More ether was added to the mixture, which was then filtered through Supercel. The filtrate was washed with dilute sodium carbonate solution and water, dried, and the ether evaporated under reduced pressure. The t.l.c., eluting with ether–benzene (1:9), showed the product to consist of one compound which had the same R_f value as 5α-cholestan-3-one (R_f 0.56) and differed from 5α-cholestan-2-one (R_f 0.66) and from the keto-anisate (R_f 0.61). Recrystallization from ether–methanol yielded 5α-cholestan-3-one, (30 mg), m.p. 128–129°. Mixed m.p. with authentic sample of 5α-cholestan-3-one, 127–129°; mixed m.p. with authentic sample of 5α-cholestan-2-one,[6] 103–118°.

Reduction of 5α-Cholestan-2-one-3α-yl p-Anisate (9) with Zinc and Acetic Acid

2α-Hydroxy-5α-cholestan-3α-yl *p*-anisate (**8**) (150 mg) was oxidized with dimethyl sulfoxide (2 ml) and acetic anhydride (2 ml), as described above. The crude keto-anisate (123 mg) was dissolved in acetic acid, zinc dust (2.5 g) was added, and the mixture was refluxed for 3 h. The product was isolated as described for the 5α-cholestan-3-one-2β-yl *p*-anisate reduction. The t.l.c., eluting with ether–benzene (5:95), showed the product to consist of more than one compound. The major reaction product had the same R_f value (0.45) as 5α-cholestan-2-one, which differed from that of 5α-cholestan-3-one (R_f 0.37). Separation of the major product by t.l.c. yielded 5α-cholestan-2-one (**10**) (42 mg) which on recrystallization from ether–methanol melted at 128–130°; mixed m.p. with authentic 5α-cholestan-2-one 129–131°; mixed m.p. with 5α-cholestan-3-one 103–123°.

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[6]We thank Professor E. W. Warnhoff for the specimen of 5α-cholestan-2-one.

9β,10α-Decalin-2β,3β-diyl Ethyl Orthoformate (22a)

A solution of 9β,10α-decalin-2β,3β-diol (**21**), prepared by the method of Henbest *et al.* (27) (2.02 g), triethyl orthoformate (Eastman Practical grade) (1.75 g) together with a few crystals of D-10-camphorsulfonic acid in benzene (10 ml) was refluxed for 15 min. The benzene and alcohol produced by the reaction were distilled off at atmospheric pressure, a few crystals of calcium carbonate were added, and the residue distilled under vacuum. The product (1.75 g) distilled at 108–109° (0.5 mm), n_D^{25} 1.4755. The n.m.r. spectrum showed signals at 1.22 (triplet, *J* 7 Hz), 3.60 (quartet, *J* 7 Hz), 4.2 (broad band), 4.25 (narrow band, half-width 7 Hz), 5.73 (s) and 5.80 p.p.m. (s); the last two peaks were in the ratio 2:7. These signals were assigned to the methyl and methylene of the ethoxyl group, the C-3 and C-2 hydrogens of the decalin ring, and the formyl hydrogens (of the two epimers) respectively.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.05; H, 9.82. Found: C, 68.97; H, 9.65.

9β,10α-Decalin-2β,3β-diyl Ethyl Orthopropionate (22c)

A solution of 9β,10α-decalin-2β,3β-diol (**21**) (27) (2.0 g), triethyl orthopropionate (Eastman practical grade, 2.17 g), and a few crystals of D-10-camphorsulfonic acid in benzene (10 ml) was refluxed for 30 min. The benzene and alcohol were distilled off slowly at atmospheric pressure and, after the addition of a few crystals of sodium carbonate, the residue was distilled under vacuum. The product (1.23 g) distilled over at 112° (0.6 mm), n_D^{25} 1.4735. The n.m.r. spectrum showed in addition to a complex multiplet in the region 0.8 to 1.3 an apparent quartet centered at 3.52 (*J* 7 Hz) with a smaller multiplet (quartet ?) superimposed, a broad band centered at approximately 4.17 (half-width 12 Hz) and a narrow band at 4.38 p.p.m. (half-width 7 Hz). These bands were assigned to the methylenes of the two ethyl groups, and the C-3 and C-2 hydrogens of the decalin ring respectively.

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.84; H, 10.30. Found: C, 70.76; H, 10.37.

9β,10α-Decalin-2β,3β-diyl Ethyl Orthoacetate (22b)

This compound was prepared as described above from 9β,10α-decalin-2β,3β-diol (**21**) (27) (1.53 g) and triethyl orthoacetate (Eastman practical grade) (1.62 g). The product (1.77 g), distilled at 106–108° (0.6 mm), n_D^{25} 1.4717. This compound had n.m.r. bands at 1.18 (triplet, *J* 7 Hz), 1.62 (s), 3.57 (quartet, *J* 7 Hz), 4.17 (broad band), and 4.38 (narrow band, half-width 7 Hz). These bands were assigned to the methyl of the ethoxyl group, the acetate methyl, the methylene of the ethoxyl group, and the C-3 and C-2 hydrogens of the decalin ring respectively.

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.97; H, 10.07. Found: C, 70.21; H, 10.12.

Hydrolysis of 9β,10α-Decalin-2β,3β-diyl Ethyl Orthoformate (22a)

The orthoformate (150 mg) in methanol (5 ml) was treated with a few drops of aqueous hydrochloric acid (50%). The reaction solution was allowed to stand at room temperature for 10 min, diluted with water and extracted with ether. The ether extract was washed with dilute sodium bicarbonate solution and water, dried, and the ether removed under reduced pressure. The t.l.c., eluting with ether–benzene (1:9), showed the product to be mainly 9β,10α-decalin-2β,3β-diol (**21**).

In a second experiment the orthoformate (**22a**) (829 mg) in methanol (10 ml) was treated with aqueous acetic acid (5 ml, 10%) for 10 min at room temperature. The reaction was diluted with water and extracted with ether, and the ether extract was washed with dilute sodium bicarbonate solution and water, dried, and the solvent removed under reduced pressure. The t.l.c., eluting with ether–benzene (1:1), showed the product (700 mg) to consist of two compounds in roughly equal proportions. The i.r. spectrum had bands at approximately 3580 (m), 1720 (s), 1165 (m), 1145 (m), 1130 (m), 1000 (w), 980 (m), 970 (w), 960 (m), and 938 cm^{-1} (w).

Separation of these two materials was attempted by t.l.c. One half of the hydrolysis product was applied to t.l.c. plates (silica gel) which were then eluted with ether–benzene (1:1). The material was detected on the plates with iodine vapor and showed up as a broad band. This band was divided in half and each half was removed from the plates and extracted with ether. The i.r. spectra of the two fractions were identical to each other and to that of the original hydrolysis product. Upon further t.l.c. using ether–benzene (1:1), each fraction showed two spots, the same as were found in the original material. Thin-layer chromatography upon alumina was also unsuccessful.

The remaining half of the original hydrolysis product was crystallized from pentane and gave 3β-hydroxy-9β,10α-decalin-2β-yl formate (**23a**) (237 mg); m.p. 70–72°; ν_{max} 3580 (m), 1720 (s), 1165 (m), 1145 (m), 1130 (w), 1000 (w), 970 (w), 938 cm^{-1} (w). The n.m.r. spectrum had bands at 2.45 (s, OH), 3.70 (broad multiplet, half-width 21 Hz), 5.22 (narrow multiplet, half-width 6 Hz) and 8.15 (s). These bands were assigned to the C-3 hydroxyl group, the C-3 and C-2 hydrogens, and to the formyl hydrogen respectively.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.65; H, 9.13. Found: C, 66.27; H, 9.14.

A sample of crystalline hydroxyformate (**23a**) was chromatographed upon silica gel as described above. The product was recovered by extraction of the silica gel and was found to have an i.r. spectrum identical to that of the hydrolysis product, and contained the two extra peaks at 980 and 960 cm^{-1}.

In a third experiment the orthoformate (501 mg) was hydrolyzed as above. The product (433 mg) had an i.r. spectrum identical to that obtained previously. The n.m.r. spectrum included the following signals: 3.13 (s, OH), 3.70 (broad band, half-width 22 Hz), 4.07 (narrow band, half-width 7 Hz), 4.87 (broad multiplet), 5.20 (narrow band, half-width 7 Hz), 8.08 and 8.17 (both singlets). The signals at 3.70, 5.20 and 8.17 were assigned to the C-3 (axial) and C-2 (equatorial) hydrogens and to the formyl proton respectively of 3β-hydroxy-9β,10α-decalin-2β-yl formate (**23a**). The signals at 4.07, 4.87, and 8.08 were assigned to the C-2 (equatorial) and C-3 (axial) hydrogens and to the formyl proton respectively of 2β-hydroxy-9β,10α-decalin-3β-yl formate (**24a**).

Stability of 3β-Hydroxy-9β,10α-decalin-2β-yl Formate (23a) to Hydrolysis Conditions

The hydroxyformate (**23a**) (49 mg) in methanol (10 ml) was treated with aqueous acetic acid as described pre-

viously. The residue had an i.r. spectrum identical with that of the starting material.

9β,10α-Decalin-2β,3β-diyl Ethyl Orthopropionate (22c)

The orthopropionate (**22***c*) (267 mg) in methanol (10 ml) was treated with aqueous acetic acid (5 ml; 10%) for 15 min as described above. The t.l.c., eluting with ether–benzene (1:1), showed that the product (235 mg) consisted of almost entirely one compound (R_f 0.44) with only a slight trace of a second material (R_f 0.53). Crystallization from petroleum ether gave 3β-hydroxy-9β,10α-decalin-2β-yl propionate (**23***c*); m.p. 45–48°; ν_{max} 3580, 1720 cm^{-1}. The n.m.r. spectrum: 1.15 (triplet, *J* 7 Hz), 2.38 (quartet, *J* 7 Hz), 2.57 (s, OH), 3.77 (broad band, half-width 20 Hz), and 5.17 (narrow band, half-width 8 Hz). These bands were assigned to the methyl and methylene of the propionate ethyl group, the C-3 hydroxyl, and to the C-3 (axial) and C-2 (equatorial) hydrogens respectively.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 69.08; H, 9.81.

The second material in the hydrolysis product had the same R_f value as 2β-hydroxy-9β,10α-decalin-3β-yl propionate (**24***c*) (see below).

9β,10α-Decalin-2β,3β-diyl Ethyl Orthoacetate (22b)

The orthoacetate (214 mg) in methanol (5 ml) and ether (1 ml) was treated with a few drops of aqueous acetic acid (50%) as described previously. The t.l.c., eluting with ether–benzene (1:1), showed the product (188 mg) to consist of almost entirely one compound (R_f 0.39) together with a slight trace of a second material (R_f 0.45). Crystallization from ether–pentane gave 3β-hydroxy-9β,10α-decalin-2β-yl acetate (**23***b*), m.p. 73–75°, ν_{max} 3570, 1720 cm^{-1}. The n.m.r. spectrum showed absorption at 2.10 (s), 2.67 (s, OH), 3.70 (broad band, half-width 21 Hz) and 5.13 (narrow band, half-width 7 Hz). These signals were assigned to the acetate methyl group, the C-3 hydroxyl group, and to the C-3 (axial) and C-2 (equatorial) hydrogens respectively.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.51. Found: C, 68.23; H, 9.45.

Acid-catalyzed Rearrangement of the Hydroxyesters

A solution of the hydroxyester and D-10-camphorsulfonic acid in benzene was refluxed overnight. The products of the reaction were separated by t.l.c., eluting with benzene, the compounds being detected under u.v. light. In all cases, the compounds with an equatorial alcohol group ran slower than the compounds with an axial alcohol group, and were easily separated.

(a) 2α-Hydroxy-5α-cholestan-3α-yl p-Anisate (8)

A solution of the hydroxyester (**8**) (142 mg) and D-10-camphorsulfonic acid (14 mg) in benzene (15 ml) was treated as described above and gave starting material (48 mg) and 3α-hydroxy-5α-cholestan-2α-yl *p*-anisate (**12**) (48 mg), which was recrystallized from chloroform–methanol; m.p. 186–188°; $[\alpha]_D$ +61°; ν_{max} 3590, 1700 cm^{-1}. The n.m.r. spectrum showed signals at 0.90 (s), 2.25 (s, OH), 3.78 (s), 4.13 (narrow band, half-width 6 Hz), 5.1 (broad band, half-width 21 Hz), and a quartet: δ_A 6.82, δ_B 7.93 p.p.m. and J_{AB} 9 Hz. These signals were assigned to the C-19 methyl group, the hydroxyl group, the methoxyl group, the C-3 (equatorial), and C-2 (axial) hydrogens, and to the aromatic hydrogens respectively.

Anal. Calcd. for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 78.08; H, 9.86.

In two other rearrangements the following results were obtained: (*i*) the hydroxyanisate (372 mg) gave starting material (**8**) (93 mg) and 3α-hydroxy-5α-cholestan-2α-yl *p*-anisate (**12**) (147 mg); (*ii*) from the hydroxyanisate (456 mg) was obtained starting material (155 mg) and the rearranged hydroxyanisate (222 mg).

(b) 3β-Hydroxy-5α-cholestan-2β-yl p-Anisate (19)

The hydroxyester (**19**) (416 mg) and D-10-camphorsulfonic acid (17 mg) in benzene (5 ml) gave starting material (211 mg) and 2β-hydroxy-5α-cholestan-3β-yl *p*-anisate (**15**) (168 mg), which was recrystallized from chloroform–cyclohexane; m.p. 210–212°; $[\alpha]_D$ +27°; ν_{max} 3560, 1700 cm^{-1}. The n.m.r. spectrum had bands at 1.07 (s), 1.87 (s, OH), 3.75 (s), 4.18 (narrow band, half-width 6 Hz), 4.95 (broad band, half-width 21 Hz), and a quartet: δ_A 6.82, δ_B 7.93 p.p.m., J_{AB} 9 Hz. These bands were assigned to the C-19 methyl group, the C-2 hydroxyl group, the methoxyl group, the C-2 hydrogen (equatorial), the C-3 hydrogen (axial), and the aromatic hydrogens respectively.

Anal. Calcd. for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 78.10; H, 10.37.

(c) 3α-Hydroxy-5α-cholestan-2α-yl p-Anisate (12)

The hydroxyanisate (**12**) (63 mg) plus D-10-camphorsulfonic acid (3 mg), in benzene (3 ml) gave starting material (**12**) (46 mg) and 2α-hydroxy-5α-cholestan-3α-yl *p*-anisate (**8**) (13 mg), both compounds being identified by t.l.c., R_f values, and i.r. spectra.

(d) 2β-Hydroxy-5α-cholestan-3β-yl p-Anisate (15)

From this hydroxyester (**15**) (57 mg) plus D-10-camphorsulfonic acid (3 mg) in benzene (2 ml) was obtained starting material (40 mg) and 3β-hydroxy-5α-cholestan-2β-yl *p*-anisate (**19**) (15 mg), both identified by t.l.c., R_f values, and i.r. spectra.

(e) 3β-Hydroxy-9β,10α-decalin-2β-yl p-Anisate (5)

The hydroxyanisate (**5**) (404 mg) plus D-10-camphorsulfonic acid (67 mg) in benzene (5 ml) gave starting material (130 mg) and 2β-hydroxy-9β,10α-decalin-3β-yl *p*-anisate (**6**) (170 mg), which was recrystallized from ether – petroleum ether; m.p. 96–98°; ν_{max} 3600, 1700 cm^{-1}. The n.m.r. spectrum had signals at 2.62 (s, OH), 3.75 (s), 4.13 (narrow band, half-width 6 Hz), 4.95 (broad multiplet) and a quartet: δ_A 6.81, δ_B 7.94 p.p.m., J_{AB} 9 Hz. These signals were assigned to the methoxyl group, the C-2 (equatorial) and C-3 (axial) hydrogens, and to the aromatic hydrogens respectively.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.71; H, 7.80.

In addition to the above two materials, a third fraction (139 mg) was isolated from the t.l.c. plates which ran faster than either of the hydroxyanisates. The i.r. spectrum had absorption at 1745 and 1710 cm^{-1}. Thin-layer chromatography, eluting with benzene, showed this material to consist of at least three compounds; it was not investigated further.

(f) 2β-Hydroxy-9β,10α-decalin-3β-yl p-Anisate (6)

From the hydroxyester (**6**) (59 mg) plus D-10-camphorsulfonic acid (7 mg) in benzene (3 ml) was obtained starting material (**6**) (43 mg) and 3β-hydroxy-9β,10α-decalin-2β-yl *p*-anisate (**5**) (15 mg), both compounds being identified by t.l.c., R_f values, and i.r. spectra.

(g) 3β-Hydroxy-9β,10α-decalin-2β-yl Acetate (23b)

From the hydroxyacetate (**23***b*) (641 mg) and D-10-camphorsulfonic acid (50 mg) in benzene (10 ml) was obtained starting material (225 mg) and 2β-hydroxy-9β,10α-decalin-3β-yl acetate (**24***b*) (236 mg), which was recrystallized from ether–pentane; m.p. 81–83°; ν_{max} 3500, 1720 cm^{-1}. The n.m.r. spectrum: 2.07 (s), 2.38 (s, OH), 4.08 (narrow band, half-width 7 Hz), and 4.8 (broad multiplet). These bands were assigned to the acetate methyl group, the hydroxyl group, the C-2 hydrogen (equatorial) and the C-3 hydrogen (axial), respectively.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.51. Found: C, 67.89; H, 9.40.

(h) 3β-Hydroxy-9β,10α-decalin-2β-yl Propionate (23c)

The hydroxypropionate (**23***c*) (400 mg) and D-10-camphorsulfonic acid (22 mg) in benzene (4 ml) gave starting material (159 mg) and 2β-hydroxy-9β,10α-decalin-3β-yl propionate (**24c**) (213 mg), which was recrystallized from ether–pentane; m.p. 59–61°; ν_{max} 3590, 1730 cm^{-1}. The n.m.r. showed bands at 1.13 (triplet, *J* 7 Hz), 2.18 (s, OH), 2.35 (quartet, *J* 7 Hz), 4.05 (narrow band, half-width 6 Hz), and 4.8 (broad multiplet). These bands were assigned to the methyl group, the C-2 hydroxyl group, the propionyl methylene group, the C-2 hydrogen (equatorial) and the C-3 hydrogen (axial), respectively.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 69.18; H, 9.74.

(i) 3β-Hydroxy-9β,10α-decalin-2β-yl Benzoate (23d)

The hydroxybenzoate (**23***d*) (820 mg) and D-10-camphorsulfonic acid (40 mg) in benzene (10 ml) gave starting material (345 mg) and 2β-hydroxy-9β,10α-decalin-3β-yl benzoate (**24***d*) (433 mg), which was recrystallized from ether–pentane; m.p. 102–103°; ν_{max} 3580, 1700 cm^{-1}. The n.m.r. showed signals at 2.23 (s, OH), 4.18 (narrow band, half-width 5 Hz) and 5.0 (broad multiplet), assigned to the C-2 hydroxy group, the C-2 hydrogen (equatorial) and to the C-3 hydrogen (axial) respectively, and also complex aromatic absorption centered at 7.47 and 8.03 p.p.m.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.40; H, 8.09. Found: C, 74.53; H, 8.19.

Preparation of 3β-Hydroxy-9β,10α-decalin-2β-yl Benzoate (23d) from the Diol (21) via the Orthoester (22d)

A solution of 9β,10α-decalin-2β,3β-diol (500 mg) and trimethyl orthobenzoate (28) (567 mg) together with a small amount of D-10-camphorsulfonic acid in benzene (5 ml) was refluxed for 30 min. The benzene was distilled off at atmospheric pressure leaving an oily product with only small absorption in the hydroxyl and carbonyl regions of the i.r. spectrum. A solution of the residue in methanol (20 ml) and ether (5 ml) was treated with aqueous acetic acid (5 ml, 20%) for 15 min, after which the reaction mixture was extracted with ether, and the ether solution was washed with dilute sodium bicarbonate solution, water, dried and the solvent removed under reduced pressure. The t.l.c., eluting with ether–benzene (1:1), showed the product (799 mg) to consist mainly of the hydroxybenzoate (**23***d*) together with some decalindiol (**21**). These two materials were separated by column chromatography (B.D.H. silica gel, 3 g), the hydroxybenzoate (**23***d*) (597 mg) being eluted with ether–benzene (1:9) and the diol (93 mg) with ether. The hydroxybenzoate was identified as 3β-hydroxy-9β,10α-decalin-2β-yl benzoate (**23***d*) by m.p., mixed m.p. with authentic sample prepared from the benzoyloxonium salt (above), and i.r. spectrum.

Preparation of 2β-Hydroxy-9β,10α-decalin-3β-yl Benzoate (24d) from the Diol (21)

9β,10α-Decalin-2β,3β-diol (**21**) (250 mg) in pyridine (5 ml) was treated with benzoyl chloride (209 mg) overnight. The t.l.c., eluting with ether–benzene (1:1) showed the crude product (310 mg) to consist of a mixture of the hydroxybenzoate and unreacted diol. Separation by t.l.c. gave 275 mg of the hydroxybenzoate (**24***d*) which was recrystallized from ether–pentane; m.p. 102–104°; mixed m.p. with an authentic sample (prepared by acid-catalyzed rearrangement of **23***d*, above) 101–103°. 9β,10α-Decalin-2β,3β-diol (66 mg) was also recovered from the t.l.c. plates and was identified by m.p. and mixed m.p.

The Woodward-Prévost Reaction with Δ^2-9β,10α-Octalin

To a solution of Δ^2-9β,10α-octalin (2.0 g) in glacial acetic acid (300 ml) was added silver acetate (6.2 g). The mixture was stirred vigorously and powdered iodine (3.3 g) added slowly over 30 min. After a further 30 min, when no iodine was visible, the mixture was treated with aqueous acetic acid (4 ml, 80%) and then stirred overnight. A solution of sodium chloride (6.4 g) in water (20 ml) was added and the stirring stopped. After a few minutes the mixture was filtered and the filtrate evaporated. The residue was dissolved in ether and washed with dilute sodium bicarbonate solution, dilute sodium bisulfite solution, water, dried, and the ether removed by evaporation. The t.l.c., eluting with benzene–ether (1:1), showed the product (2.96 g) to be nearly all one compound, with the same R_f value as 3β-hydroxy-9β,10α-decalin-2β-yl acetate (**23***b*). Column chromatography using silica gel and eluting with ether–benzene gave 3β-hydroxy-9β,10α-decalin-2β-yl acetate (**23***b*) (2.46 g); this was recrystallized from methylene chloride – petroleum ether and identified by m.p., mixed m.p. with authentic sample, and i.r. spectrum.

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