STUDIES RELATED TO THE TOTAL SYNTHESIS OF TETRACYCLINE

a thesis presented by

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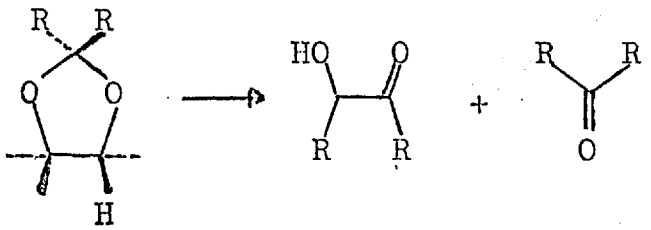
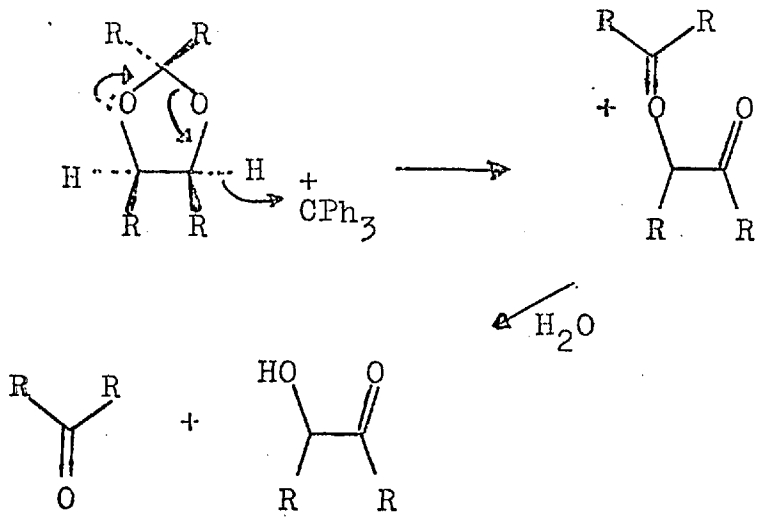
ABSTRACT.

This thesis describes the development of a new and synthetically promising oxidation that involves hydride abstraction from ethylene ketals by the trytil-carbonium ion:



The review covers published work on intermolecular hydride transfer involving carbonium ions, with emphasis on the synthetic application of the process. This section is followed by the work of the tetracycline group in this laboratory that led to the present experiments. Mechanistic studies establish that hydride abstraction from an ethylene ketal proceeds in a concerted manner to an oxonium ion which is quenched with water during workup.



Synthetically, the reaction can be used to regenerate protected ketones under neutral conditions or to oxidize glycols to ketols. The very mild deketalisation process is illustrated for simple ketones and applied in the steroid field. The oxidative aspect is exemplified by conversion to hydroxyketones of a number of carbohydrate and steroidal glycols, (protected against the usual oxidizing agents as their ketals). In particular a route to vitamin C was developed which is not dependent on microbiological oxidation. Diosgenin was converted to the natural product kryptogenin. Further experiments showed that hydride abstraction with trityl-fluoroborate serves for cleavage of the methylenedioxy

groups when it is attached to a benzene ring or incorporated into a bis-methylenedioxy (BMD) system.

ACKNOWLEDGEMENTS.

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Thanks are due to the technical staff of the Chemistry Department for their assistance. N.m.r. and mass spectra were measured by the staff of the Spectroscopy Department, and combustion analyses were performed in the Analytical Laboratory.

Daniel Zurr,
Whiffen Laboratory,
June, 1971.

CONTENTS.

REVIEW.

Intermolecular-hydride transfer.

Introduction.

Intermolecular hydride transfers have been extensively examined since 1950. The researches have led to a significant improvement of industrial processes. Such as cationic polymerization[1] and high octane gasoline synthesis[2]. Hydride transfer is also of biochemical importance and plays a vital role in redox systems such as those involving DPN$^+$ - DPNH[3,4].

Intermolecular hydride transfer has been reviewed twice[5,6], the more recent work covering the literature through 1969. The present review is confined to those reactions* in which the hydride ion is accepted by a carbonium ion. The driving force is obviously formation of the strong C-H bond[7].

Kinetic and mechanistic aspects.

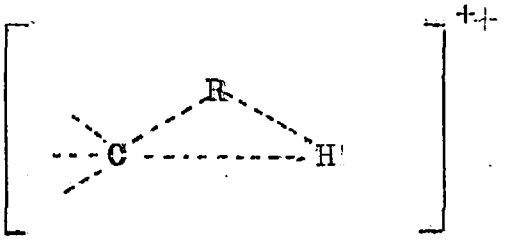
The hydride ion $\ddot{H}^-$ is relatively stable species, as inferred from quantum mechanical calculations.

* Ambiguous cases such as the Meerwein-Ponndorf-Verley reduction, Oppenauer oxidation, and the base catalysed Cannizzaro reaction are not included in this review.

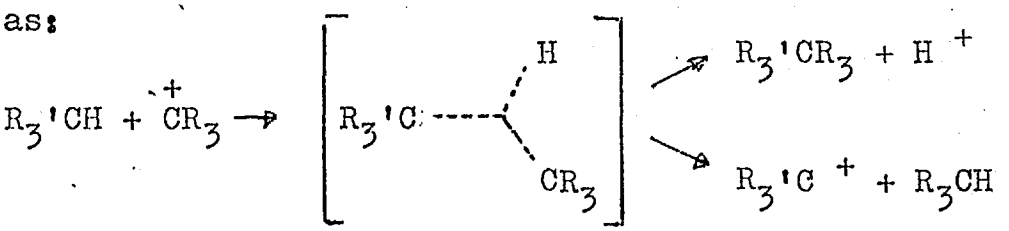
($H + e^- \longrightarrow H:^-$ = 17.4 kcal/mole[8]) and from its existence in the solid state in salt-like hydrides. However, the hydride transfer reaction has the characteristic that the hydrogen transferred does not react with the labile protons in the media. Extensive evidence[9,10] has shown that the transfer reaction is first order both in hydride acceptor and in donor.

Log. K for the reaction (K = rate constant) is directly proportional to the difference in PK_{R^+} (PK_{R^+} = -log K_{R^+} for the reaction $R^+ + H_2O \rightleftharpoons ROH + H^+$) between the two carbonium ions exchanging the hydride[11]. The linear relationship is equivalent to the linear relationship between log K and the modified Hammet σ^+ - value since ΔPK_{R^+} and σ^+ are linearly related[11,12]. On the basis of differences in reaction rate when the steric environment of the reaction centre is varied, a linear transition state has been suggested[11] $C^+ \cdots\cdots H \cdots\cdots C^+$. Such a situation inevitably implies considerable charge delocalization in the transition state compared with the initial and final states. In such a case the general theory of solvent effects[13] leads to the prediction that an increase of solvent polarity should cause a decrease in reaction rate. This expectation has been demonstrated recently[9]. A second

plausible mode of raction involves a triangular transition state[12].



In the case of 1,2 intramolecular shifts the C-----H-----C system must of necessity pass through a triangular state. In the intermolecular reactions such a concept expresses the idea that attack of the electrophile takes place preferentially at the position of maximum σ -electrons density of the C-H bond. With a grossly distorted triangular transition state direct alkylation via proton elimination has been proposed recently[15] as:



A choice between the two transition states (Linear and Triangular) is not possible at the present stage.

Hydrocarbons as hydride donors.

Formation of a reactive tertiary alkyl carbonium ion may result in a hydride shift between two

saturated hydrocarbons. Aluminium halides or sulfuric acid are the most common catalysts used for generation of carbonium ions[16,17].

$(CH_3)_3CCL + AlBr_3 \rightleftharpoons (CH_3)_3C^+ \; AlClBr_3^-$

$(CH_3)_3C^+ + HC(CH_3)_2CH_2CH_3 \rightleftharpoons (CH_3)_3CH + C(CH_3)_2CH_2CH_3$

$CH_3CH_2(CH_3)_2C^+ + AlClBr_3 \rightleftharpoons CH_3CH_2(CH_3)_2CBr + AlClBr_3$

$$(CH_3)_3CH + CH_3CH_2CD(CH_3)_2 \overset{H_2SO_4}{\rightleftharpoons} (CH_3)_3CD + CH_3CH_2CH(CH_3)_2$$

This type of reaction has no synthetic utility because a large number of side reactions, such as deprotonation of the carbonium ions to alkene, addition of carbonium ion to the latter and β-cleavage of the higher carbonium ion occur simultaneously.

Secondary alkyl carbonium ions can also be formed by aluminium haldies and they may be used like the tertiary ions as hydride acceptors[16]. The formation of secondary ions in sulfuric acid[2,18,19] has not been reported. Alkylation of alkenes by alkanes is applied on an industrial scale[17,20]. Mechanistically the process can be regarded as alkylation of the olefin by the carbonium ion derived by intermolecular hydride transfer from the isoalkane[15].

$$R_2'C = CH_2 \xrightarrow{H^+} R_2'C\,{}^+CH_3$$

$$R_2'C\,{}^+CH_3 + R_3CH \longrightarrow R_2'CHCH_3 + R_3C^+$$

$$R_3C^+ + R_2'C = CH_2 \longrightarrow R_2C^+ - CH_2CR_3 \xrightarrow{:H^-} R_2'CHCH_2CR_3$$

Thorough reviews on this topic are available[20,21].

Isomerization of alkanes and cycloalkanes can be interpreted in many cases by intermolecular hydride shift and many reviews on this subject are also available[22,23]. The isomerization is catalysed by Lewis acids and protic acids. In addition a cocatalyst (A) has been used as an initiator[16].

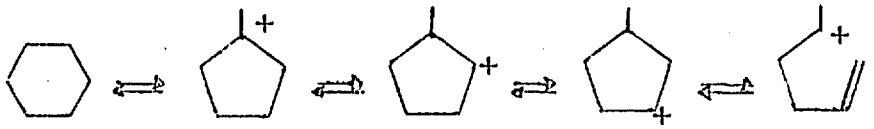
$$CH_3CH_2CH_2CH_3 + A^+ \longrightarrow CH_3\overset{+}{C}HCH_2CH_3 + AH$$

$$CH_3\overset{+}{C}HCH_2CH_3 \rightleftharpoons CH_3-\underset{CH_3}{CH}-\overset{+}{C}H_2 \rightleftharpoons CH_3-\underset{CH_3}{\overset{+}{C}}-CH_3$$

$$CH_3-\underset{CH_3}{\overset{+}{C}}-CH_3 + CH_3CH_2CH_2CH_3 \rightleftharpoons CH_3-\underset{CH_3}{CH}-CH_3 + CH_3\overset{+}{C}HCH_2CH_3$$

The main purpose of the cocatalyst (A) is to generate an active carbonium ion, A^+, which acts as an initiator for the reaction. A typical cocatalyst is RX which generates R^+[24] after complexation with AlX_3. In the case of the cyclohexanone-methyl cyclopentanone isomerization the major side product is n-hexane[25] and

the mechanistic interpretation led to use of a suitable hydride donor (such as isobutane) which completely eliminated this side reaction[27].



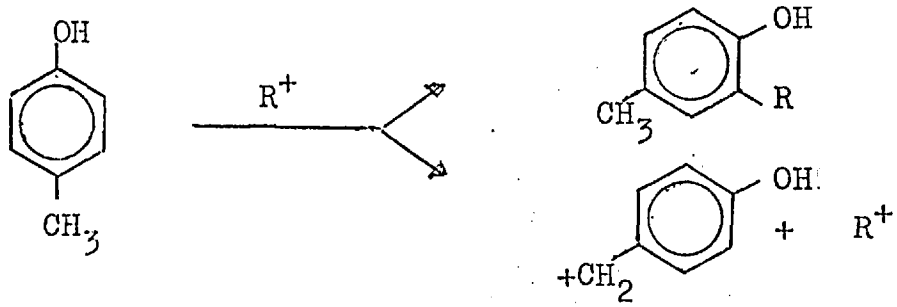
1): H^-

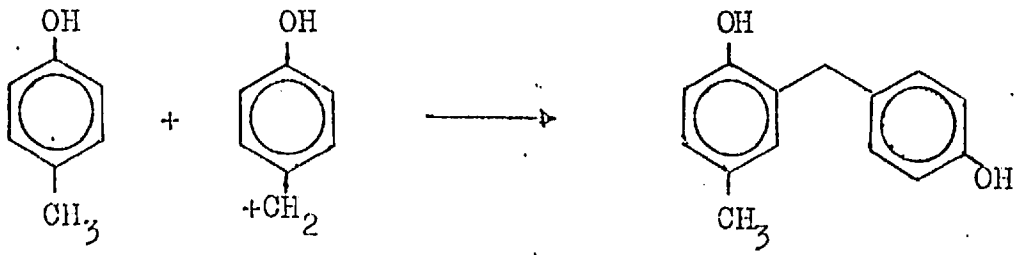
2) H^+

3): H-

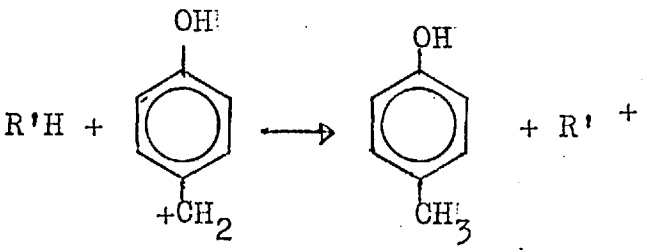
n-hexane.

Alkylation of aromatic hydrocarbons is very often associated with hydride transfer[27,28]. Alkylation of p-cresol with tertiary alkylation agents and BF_3 as catalyst proceeds in good yield, but with an excess of BF_3 bis methylenephenol is formed[29] in addition to the normal alkylation product.





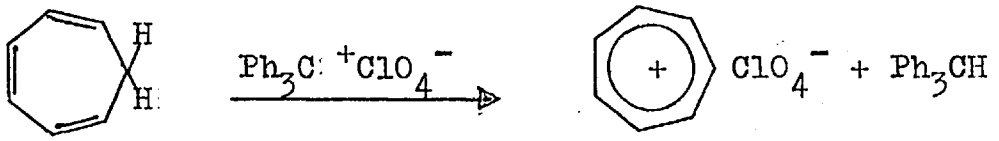
The origin of the bis methylenephenol presumably lies in the easy generation of the benzyl cation by hydride abstraction by the tert-alkyl cation R^+. This side reaction also can be suppressed by the addition of a hydride donor and in this case isopentane (R') has proved suitable:



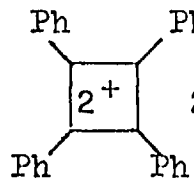
The alkylation versus hydride abstraction ratio is dependent on the catalyst as well as the two potential carbonium ions involved[27]. p.-Dialkylbenzenes are better hydride donors than isoalkanes. Consequently p.-dialkylbenzenes undergo normal alkylation to a less extent[28]. Isomerization of the side chain in phenylalkanes through intermolecular hydride shift are more complex to study than in the aliphatic series. Numerous side reactions may occur[30,31] together with competition from the normal process of Friedel-Crafts alkylation[32,33].

Unsaturated hydrocarbons as hydride donors.

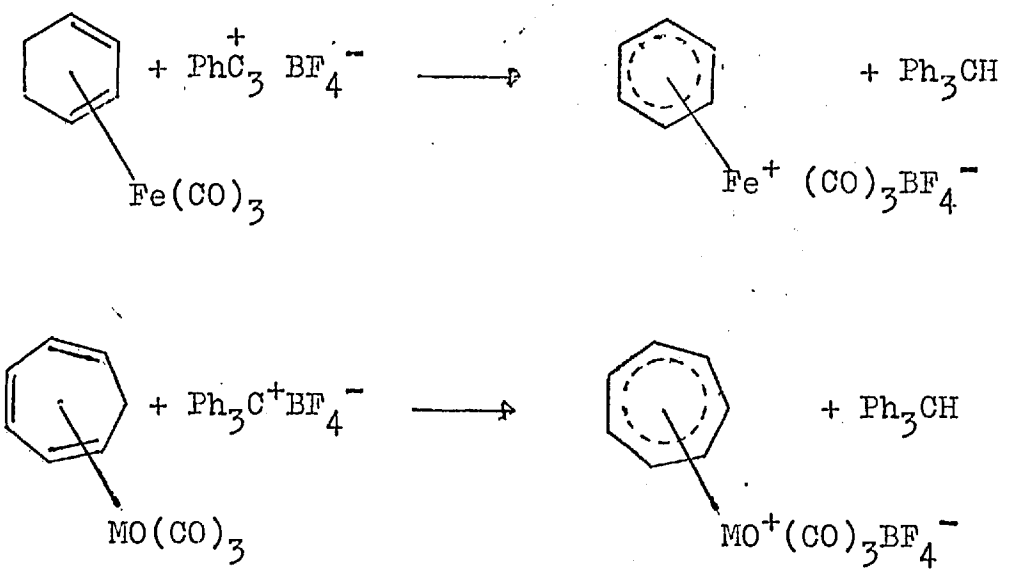
Olefins might be expected to be good hydride donors in view of the stabilization available to the resulting allyilic cation. However such cations have been found to polymerize with great ease[34]. The situation is different when the donor is cyclic polyene, for loss of two electrons can generate aromatic $(4n+2)\pi$ - electrons system[35].



Typical hydride acceptors in this type of reaction are shown in the table:

Hydride acceptor	Ref.
$Ph_3C^+BF_4^-$	35
$Ph_3C^+ClO_4^-$	35,36
	37,38
$SnCl_6^{-2}((CH_3)_3C^+)_2$	40-39
$Ph_3C^+SbCl_6^-$	42
$SbCl_5$	41

The tendency of dienes and triens to lose hydride ion is appreciably enhanced on complexation with transition metals. π-Complexes of cyclic cations are formed and these are probably stabilized through the back donation of electrons from the metal to the ligand[6,43,44].



Alcohols and ethers as hydride donors.

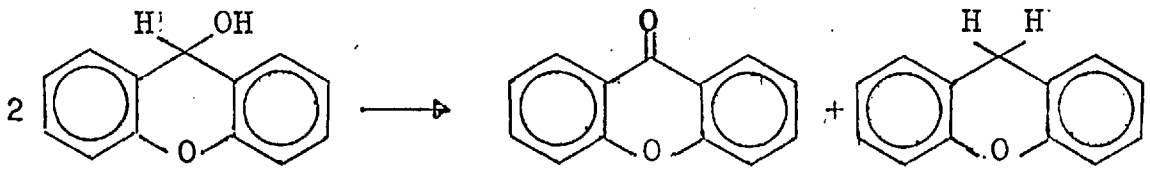
Primary and secondary alcohols are excellent

hydride donors. The hydride shift occurs from the α position of the alcohols to the hydride acceptor[7].

$$Ph_3C^+ + CDOH(CH_3)_2 \qquad Ph_3CD + (CH_3)_2C = OH^+$$

A protonated ketone is formed first and it then undegoes very rapid equilibration with the deprotonated ketone.

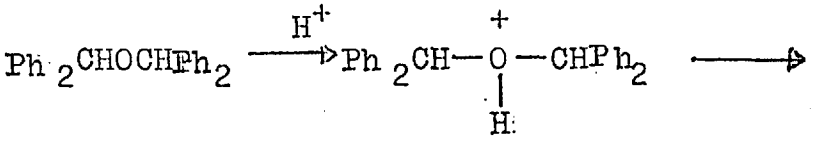
Using high concentrations of mineral acid as carbonium ion generator has the disadvantage of converting the alcohol into its unreactive protonated form[7]. On the other hand when low acid concentrations are used the carbonium (oxonium) ion is not generated in sufficient concentration. Therefore only a narrow range of acid concentration gives satisfactory results. Disproportionation reactions may take place in the case of diaryl carbinols. This system serves simultaneously as a hydride acceptor and donor[45,46].

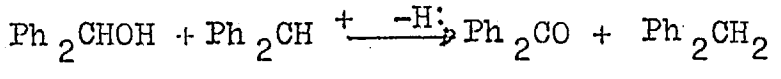


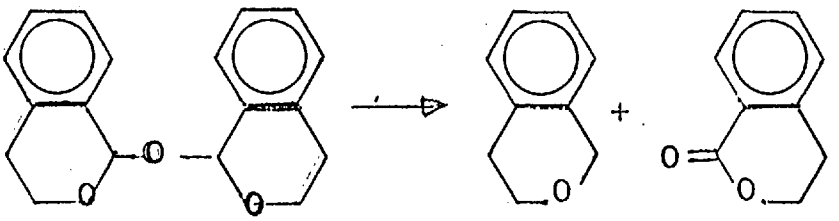
When the reaction was carried out in CCl_3COOD no

deuterium was incorporated into the diarlymethane[7] confirming the intermolecular nature of the hydride transfer.

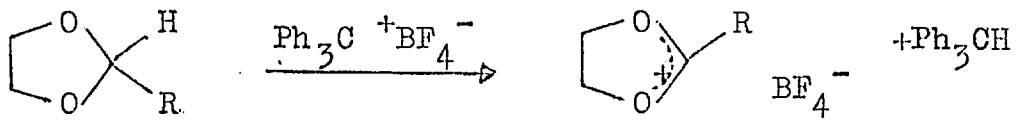
Ethers also are a good hydride donors. A well-known method of preparing triphenylmethane consists of treating triphenyl-chloromethane with ether in the presence of $AlCl_3$[47]. Disproportionation reactions may take place in strong acid provided a stable carbonium ion is formed from the protonated ether[48,49].



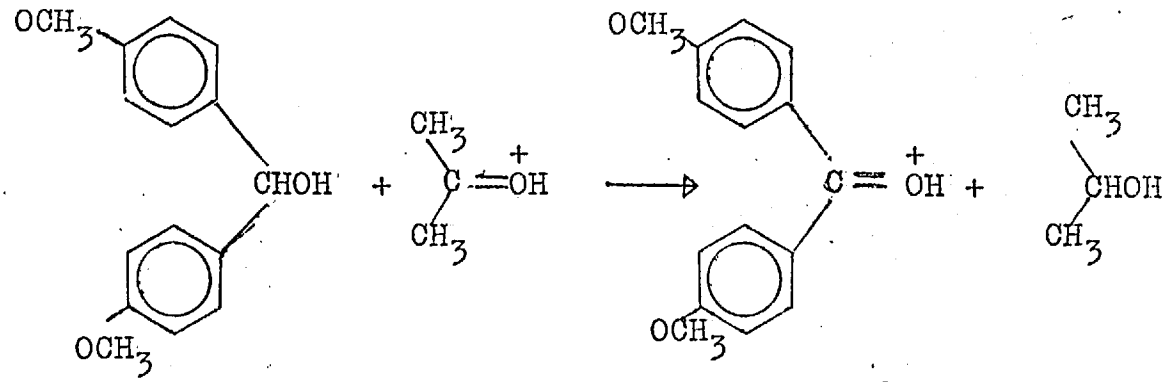




1,3-Dioxolane derivatives are excellent hydride donors[10,50], yielding stable crystalline dioxolonium salts



The transfer of hydride between aliphatic alcohols and ketones can be catalysed by mineral acids (this is the counterpart of the well known base catalysed Meerwein-Ponndorf reaction[5].) Only a narrow range of acid concentration enables the free alcohol to react with the protonated ketone[7].



The poor yields which are obtained in this type of process make it synthetically inferior to the aluminium alkoxide-catalysed reactions.

Formic acid and alkyl amine as hydride donors.

Formic acid is another excellent hydride donor[51].

Triphenyl carbinol is quantitatively reduced by deuterated formic acid to deuterated triphenylmethane.

$$Ph_3C^+ + DCOOH \longrightarrow Ph_3CD + CO_2 + H^+$$

The isotope effect with 99.9% formic acid is $K_H/K_D = 4.9$. The reductive alkylation of alkyl amines by aldehyde and ketone in the presence of formic acid has been recognised as involving hydride transfer[52]. The carbinolamine formed by the amine and the carbonyl in the acid solution can form a imminium ion, which abstracts hydride from the formic acid.

$$R_2N\text{-}CR_2'OH \xrightarrow{H^+} R_2N^{\pm}{=}CR_2'$$

$$R_2N^{\pm}{=}CR_2' + HCOOH \longrightarrow R_2NCHR_2'$$

If formaldehyde is used the reaction proceeds without addition of formic acid. The formaldehyde probably donates hydride to the immonium salt to form formic acid which then donates hydride to the same carbonium ion[53].

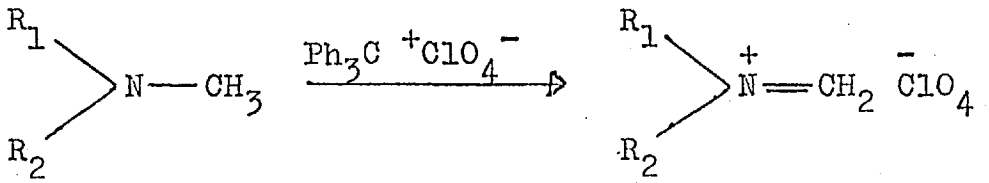
$$R_2N^{\pm}{=}CH_2 + CH_2(OH)_2 \longrightarrow R_2NCH_3 + HCOOH + H^+$$

$$R_2N^{\pm}{=}CH_2 + HCOOH \longrightarrow R_2NCH_3 + CO_2 + H^+$$

The well known Leuckart reaction (conversion of ketone to an amine) uses ammonia instead of substituted

amine[54,55].

A related mechanism has been proposed for the Sommelet reaction[56]. Recently methyleneimmonium salts have been isolated by hydride abstraction from tertiary amines[57].



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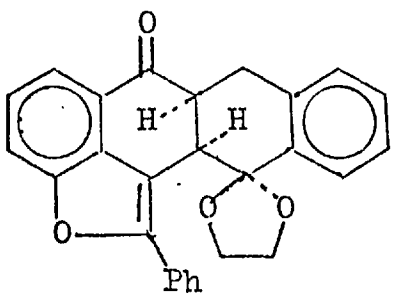
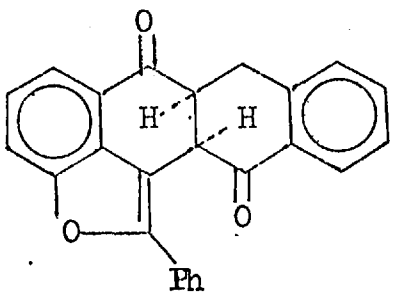
DISCUSSION.

Part 1. Introduction.

The trityl carbonium ion is well known as a hydride ion acceptor[7] and its ability to convert an ethylene acetal to a stable acetoxonium ion[2] is particularly relevant to the present work. However the possiblity that a similar reaction might take place with ketals has not hitherto been explored. During work in this laboratory directed towards the total synthesis of tetracycline[3,4] the need arose to convert the ketal (1) to the diketone (2).

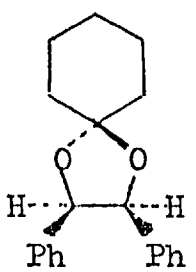


1.



2.

Conventional deketalization procedures (aqueous acid) gave (2) in very low yield (> 10%). It was observed that treatment of the ketal (1) with tritylfluoroborate in dichloromethane followed by aqueous workup gave the desired diketone (2) in 65% yield[5]. Further investigations readily established that tritylfluoroborate is a useful reagent for deketalization when neutral conditions are required. Cyclohexanone ethyleneketal gave cyclohexanone in 70% yield. Benzophenone ethylene ketal gave benzophenone in 100% yield. In each case triphenyl methane was the major product from the trityl salt (traces of trityl methanol were present from the use of excess reagent). In order to establish the nature of the oxidized ethylene glycol moiety the ketal (3) was prepared by a trans-ketalization reaction between cyclohexanone dithioethylene-ketal and meso-dihydrobenzoin[6,7,8].



Treatment of (3) with tritylfluoroborate revealed another aspect of the hydride abstraction process for besides the cyclophexanone it was possible to isolate benzoin (64%). Further investigations have established that α-ketol formation is general and several α-ketols have been synthesised by hydride abstraction.

These results illustrate a useful method for deketalisation under neutral conditions with concommitant oxidation of a diol to the α-ketol level.

The reaction can be used for either purpose.

Part 2. The Mechanism of oxidation with Trityl Carbonium Ion.

The results presented in this work are accommodated by a mechanism involving hydride abstraction from the ethylene ketal with concerted formation of an oxonium ion (4). This species is quenched by water during work-up to give the isolated products (figure 1).

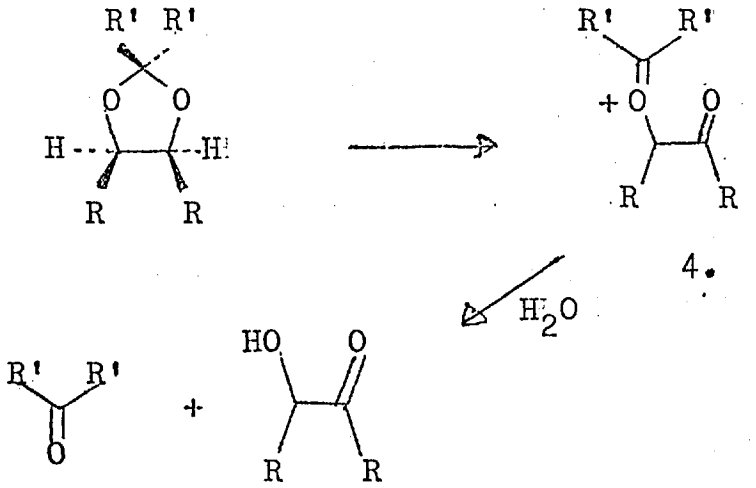
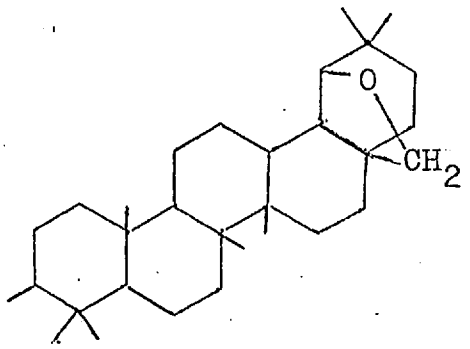


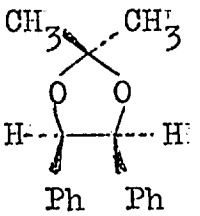
Figure 1.

The concerted nature of the process is established by the fact that simple ethers are dehydrogenated by the trityl carbonium ion very much more slowly than ketals. No reaction was observed when allobetulin[9] (5) was treated with tritylfluoroborate under the usual conditions.



5.

meso-Dihydrobenzoin acetonide (6) was prepared by trans ketalisation with 2'2-dimethoxypropane and meso-hydrobenzoin[6].



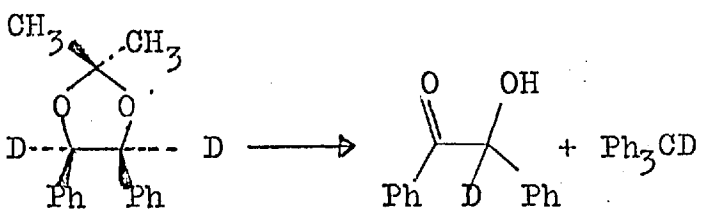
6.

Under the standard conditions (6) gave benzoin and triphenylmethane in good yield. The n.m.r. spectrum of (6) exhibited two singlets for the methyl groups at 1.25 p.p.m. and 1.4 p.p.m. When the oxidation of (6) was carried out in n.m.r. tube these singlets coalesced to a six proton singlet at 1.8 p.p.m. This observation indicates that a symmetrical species is formed and the n.m.r. data are therefore compatible

with the intermediate (4).

Further evidence for this species was obtained by treating cyclohexanone ethyleneketal with tritylfluoroborate in an infrared cell[5]. A strong band developed at 1700cm^{-1} prior to aqueous work-up, indicative of a carbonyl group. These results are in agreement with the proposed intermediate.

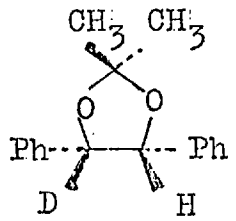
Deuterated meso-dihydrobenzoin acetonide (7) (incorporation of D = 87%) was prepared from benzil by reduction with $NaBD_4$ followed by trans ketalisation with 2'2-dimethoxypropane.



7.

Treatment of (7) with tritylfluoroborate furnished deuterated benzoin (incorporation of D = 84%) and triphenylmethane (incorporation of D = 71%). These results establish the occurrence of an intermolecular hydride abstraction from the ethyleneketal by the

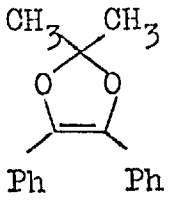
trityl carbonium ion. Mono deuterated meso-dihydrobenzoin acetonide (8) (incorporation of D = 89%) was also prepared. Reduction of benzoin with $NaBD_4$ followed by trans ketalisation with 2'2-dimethoxypropane, and on treatment with tritylfluoroborate gave highly deuterated



8.

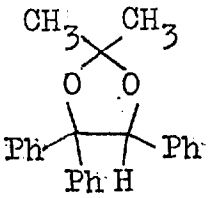
benzoin (incorporation of D = 84%) and mainly a non-deuterated triphenylmethane (incorporation of D = 16.5%). The distribution of the label compounds in the reaction products reveals a strong primary isotope effect. Calculations based on the triphenylmethane/deuterated triphenylmethane ratio gave $\frac{K_H}{K_D} = 4.2$ and those on the benzoin/deuterated benzoin gave $\frac{K_H}{K_D} = 4.9$ (the calculations were based on mass spectrum and ignore the secondary isotope effect). The relatively high[10] isotope effect indicates that the hydride abstraction is the rate determining step in this reaction.

The intervention of an intermediate such as (9) was ruled out by the work described above but (9) was

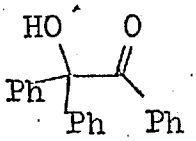


9.

also excluded in an alternative manner. The triphenyl glycol acetonide (10) was prepared from triphenyl ethylene by performic acid oxdiation[11] followed by exchange with 2'2-dimethoxypropane.



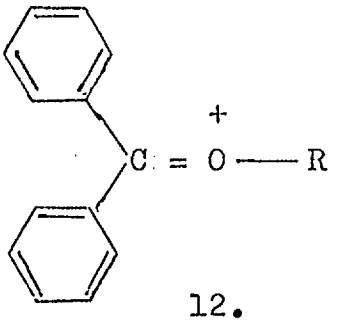
10.



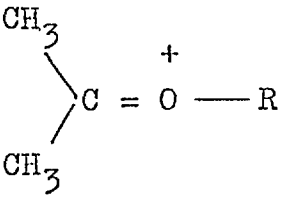
11.

Treatment of (10) with tritylfluoroborate gave triphenylmethane and α',α-diphenyl-α-hydroxy acetophenone[12] (11) a compound which cannot arise from (9). Finally it was observed in several cases (see Part 3 and Part 4) that benzophenone ketals when treated with tritylfluoroborate gave a better yield of the normal products than the corresponding isopropylidene derivatives, and this trend is expected on the basis of the proposed mechanism.

An intermediate of type (12) is stabilised by the two aromatic rings (several resonance forms can be



12.



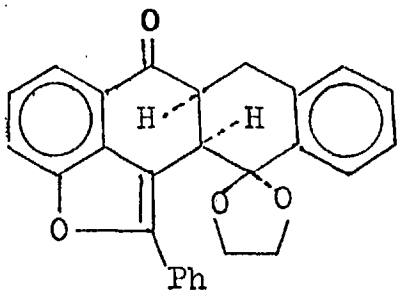
13.

assignated to (12)) more extensively than by two methyl groups (13).

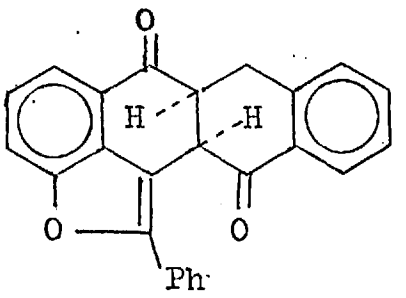
Part 3. Deketalisation of ethylene ketals with trityl carbonium ion.

Ketalisation is a useful method for protection of a keto-group during operations on the other functions present under non-acidic conditions. The keto-group is easily regenerated by hydrolysis with dilute mineral acid[13]. However, the conventional method of deketalisation is unsuitable for acid sensitive ketones and in such cases the carbonium ion method represents a useful alternative as it involves operation under neutral conditions.

The nature of the reaction is illustrated by the work with the tetracycline ketal (1)[5].

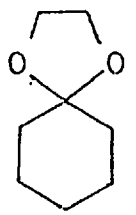


1.



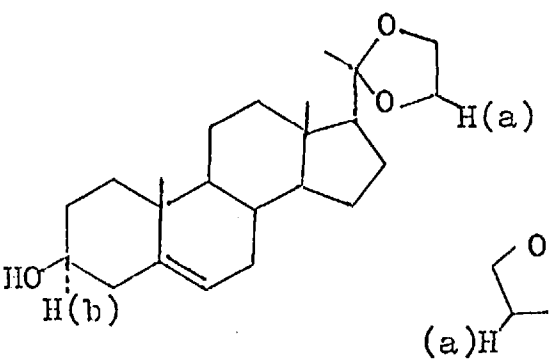
2.

Deketalisation by the conventional method (aqueous acid) gave the diketone (2) in less than 10% yield. By using the oxidative deketalisation method (2) was obtained in a much better yield (65%). Similarly cyclohexanone ethyleneketal (14) was converted into cyclohexanone in 70% yield.



14.

11α-Hydroxy progesterone ethylene ketal[14] (15) and pregnenolone ethylene ketal[15] (16) reacted smoothly



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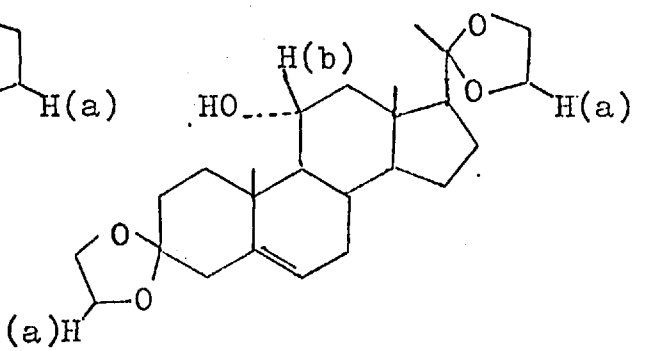
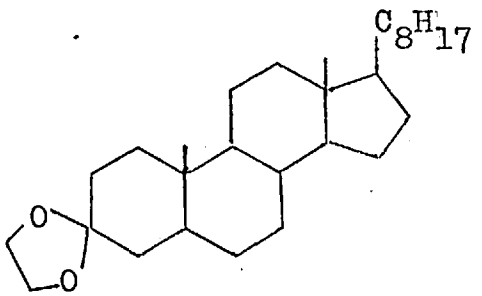


15.

with tritylfluoroborate to give pregnenolone (80%) and 11α-hydroxy progesterone (70%). It is interesting to note that no hydride abstraction from position 3 (α to the hydroxy group) occurred presumably the rate of the trityl oxidation (abstraction of hydrogen (a)) is much higher than the rate of the well known oxidation of secondary alcohols[16] (abstraction of hydrogen (b)).

Treatment of cholestanone ethyleneketal (17) with triphenylfluoroborate afforded cholestanone (80%).

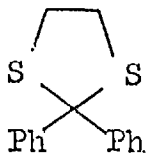


17.

In all these reactions triphenylmethane was the main product derived from the trityl carbonium.

Oxidative deketalisation of benzophenone ethyleneketal gave benzophenone in quantitative yield.

Benzophenone hemithioketal (18) and benzophenone thioketal (19) are structurally related to the compounds considered so far but distinct in that sulfur atom replaces one (18) or two (19) of the oxygen bonded to the central carbon atom.



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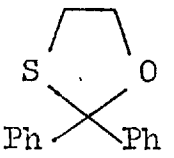


18.

Treatment of the hemithioketal (18) with trityl-fluoroborate gave benzophenone in quantitative yield, but no reaction was observable between the thioketal (19) and the trityl cation. Even after a reaction period of 24 hours the thioketal (19) could be recovered quantitatively. Moreover, when the reaction mixture was monitored by n.m.r. technique none of the signal changes expected for an equilibrium (Figure 2)

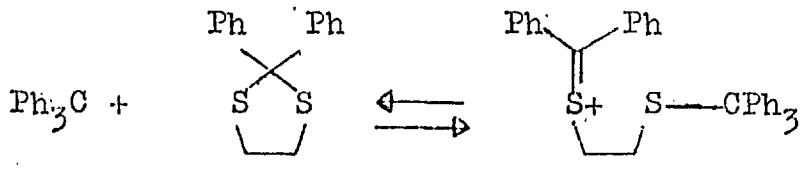
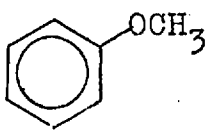


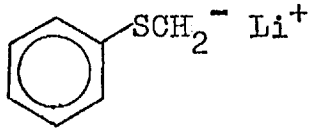
Figure 2.

could be observed. The dithioketone is completely inert to the reagent. This selectivity of the oxidative deketalisation widens the scope of this reaction, and theoretically can be interpreted on the basis of lower stability of sulfonium ion[17] relative to that of oxonium ion (by analogy siliconium ion to carbonium ion).

A further example illustrates this difference. While anisole (20) is unreactive towards butyl lithium the sulfur analogue readily loses a porton to give a stable anion[18] (21).



20.

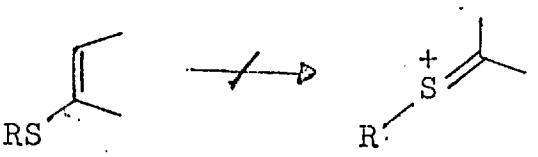


21.

In principle the reverse order should occur for loss of a hydride ion.

The resistance of enolthioether towards acids is also evidence that sulfonium ion is a high energy

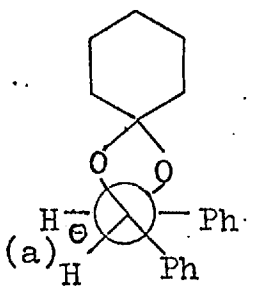
species.



Part 4. Oxidation of diols by hydride abstraction from their derived ketals.

In Part 3 one aspect of the trityl reaction has been considered. The other use of this reaction is for oxidation of diols protected against the usual electron removal reagents, as an acetonide or other ketals to the corresponding hydroxy ketones.

The reaction was first observed in the case of cyclohexanone meso-dihydrobenzoin ketal (3).

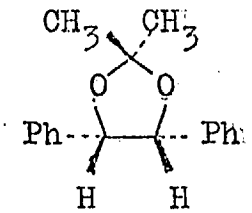


3.

Conventional ketalisation procedures are unsuitable for meso-dihydrobenzoin. Since the diol rearranges very easily (pinacol rearrangement) in the presence of acid. Neutral conditions throughout the reaction can be maintained by using a trans ketalisation method[7]. (3) was prepared by treating equimolar quantities of cyclohexanone ethylenethioketal and

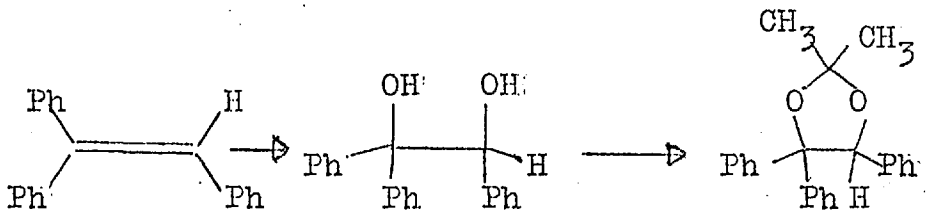
meso-dihydrobenzoin[6] in dry tetrahydrofuran with mercuric chloride/mercuric oxide. (A neutral pH is maintained by combination of the mercuric oxide with the HCl formed). The n.m.r. spectrum of (3) revealed that the configuration has a very low dihedrol angle Θ[19] because the two protons (a) appeared as a singlet.

meso-Dihydrobenzoin acetonide (6) was prepared from meso-dihydrobenzoin, 2'2-dimethoxypropane, and p-toluenesulfonic acid as catalyst. 2'2-dimethoxypropane was used as a solvent in this reaction, and being a water scavenger[20,21], it eliminated the possibility of rearrangement of the dihydrobenzoin molecule.



6.

The n.m.r. spectrum of (6) also had showed evidence for a low dihedral angle. Trityl oxidation of (3) and (6) gave in both cases benzoin in 65% yield. The acetonide (10) was prepared from triphenyl-ethylene.



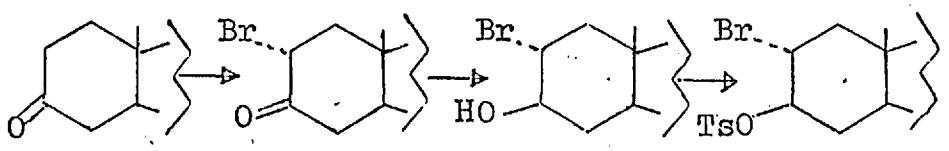
22. 10.

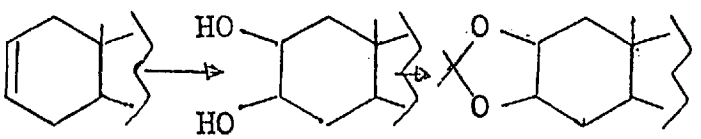
Silver acetate/iodine[22] cis hydroxylation of triphenylethylene gave the diol (22) in a poor yield (10%). A better yield of (22) (25%) was obtained by performic acid oxidation[11] of triphenylethylene. Trans ketalisation of them gave the acetonide (10), and trityl oxidation furnished α'α diphenyl-α-hydroxy-acetophenone[12] in>10% yield.

a) Steroid series.

An important development in steroid chemistry is the growing interest in procedures for selective oxidation[30] such as the use of microbiological techniques.

In the steroid series the trityl oxidation method was first applied to the isopropylidene derivative of cholestan-2β-hydroxy, 3β-hydroxy[23] (23). The acetonide (24) was prepared from cholestan-3-one[24] (figure 3).



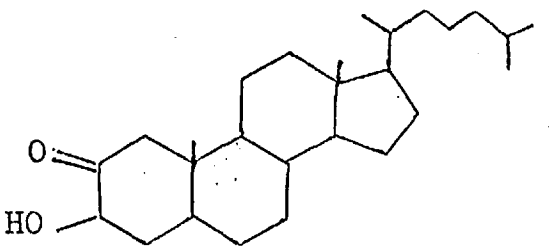


23. 24.

Figure 3.

Bromination of the ketone gave 2α-bromo-cholestane-3-one and reduction with sodium borohydride furnished

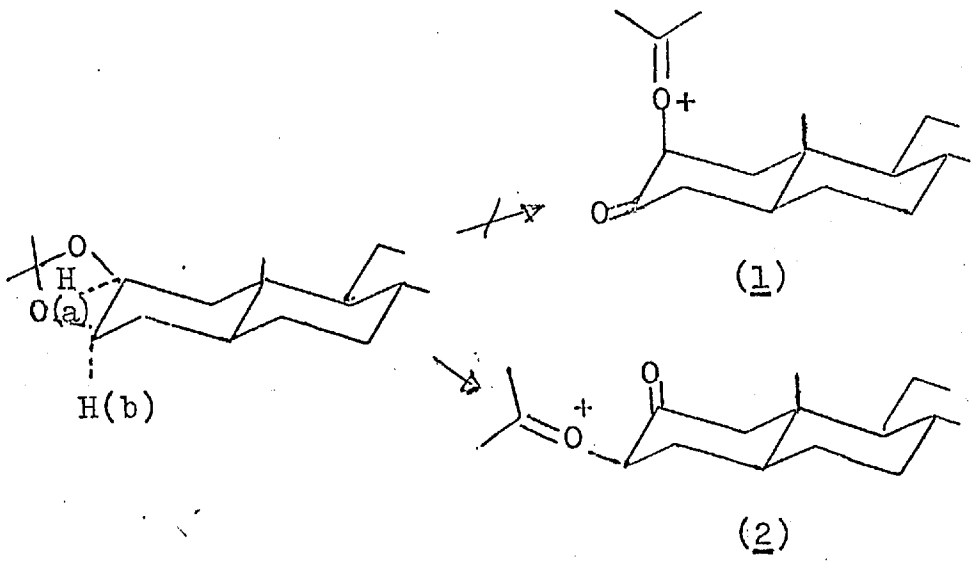
cholestane-2α-bromo-3β hydroxy. Tosylation afforded the vicinal bromo-tosylate which on treatment with zinc dust in acetic acid gave the Δ^2-cholestene[24]. Cis-hydroxylation (Woodward method) gave cholestane-2β, 3β diol (23). Trans-ketalisation with 2'2-dimethoxypropane using the crude diol (23) afforded the isopropylidene derivative (24). Trityl oxidation of (24) gave cholestane-2β-hydroxy-3-one* (25) in good yield (79%).



25.

* Two other methods reported in the literature are DMSO-oxidation of both 2β,3β epoxycholestane and 2α, 3α epoxy cholestane[25] (50%) and the acyloin condensation of 2,3-secocholestane-2,3-dioic acid dimethyl ester (82%)[26].

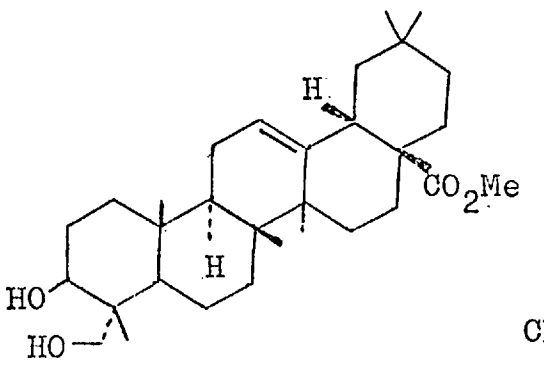
The specific oxidation at position 2 can be explained in terms of the proposed intermediate (see Part 2).



Abstraction of the axial hydrogen (b) by the trityl cation results in an equatorial oxonium ion intermediate (2) which is less sterically hindered (and therefore more stable) than the axial oxonium ion (1) obtained by abstraction of the equatorial hydrogen (a).

Cholestane-2β-hydroxy-3-one (25) is also thermodynamically more stable[26] than the cholestane-3β-hydroxy-2-one (the product from intermediate (1)) and equilibration of these isomers is possible through enol formation such a transformation is, however, very unlikely under the experimental conditions.

The naturally occurring 1,3 diol, methyl hederagenin[27,28] (26) readily afforded the acetonide (27) by trans ketalisation, and the benzophenone ketal (28) by exchange with benzophenone ethylenedithioketal[29] (see Part 3).



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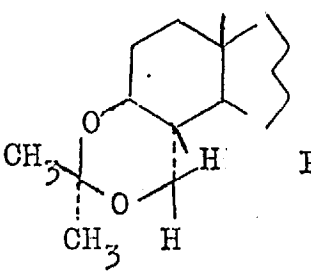

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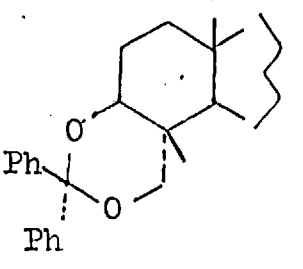
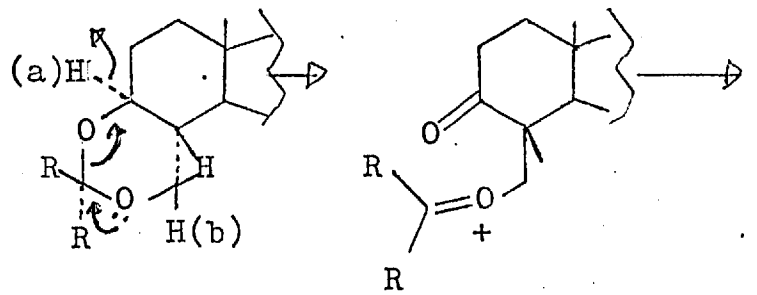


28.

Trityl oxidation of (27) afforded methyl hederagonate* (29) (20%) identical with an authentic sample, but as expected (see Part 2) a slightly better yield (25%) was obtained from (28) mechanistically these reactions of 1,3-diols are readily interpreted by the general mechanism already given - Scheme 4.



29.

1) R = CH_3

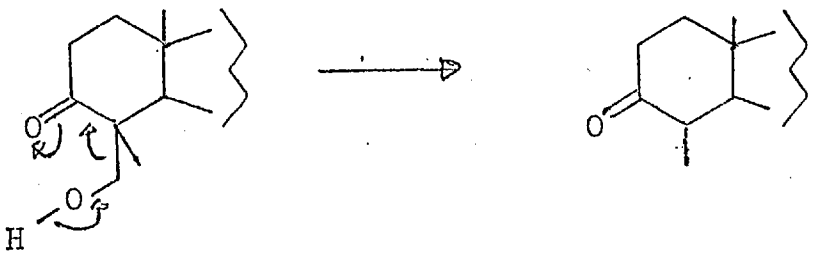
2) R = Ph

Scheme 4

The "secondary" hydrogen (a) is abstracted more easily by the trityl cation than the "primary" hydrogen (b) (see Part 2). The other mode of oxidation maybe present since the yield was low. The structure of (29) was further substantiated by its retro aldol transformation

* also prepared by permanganate oxidation[27].

to methyl hedragonate (30)[28].

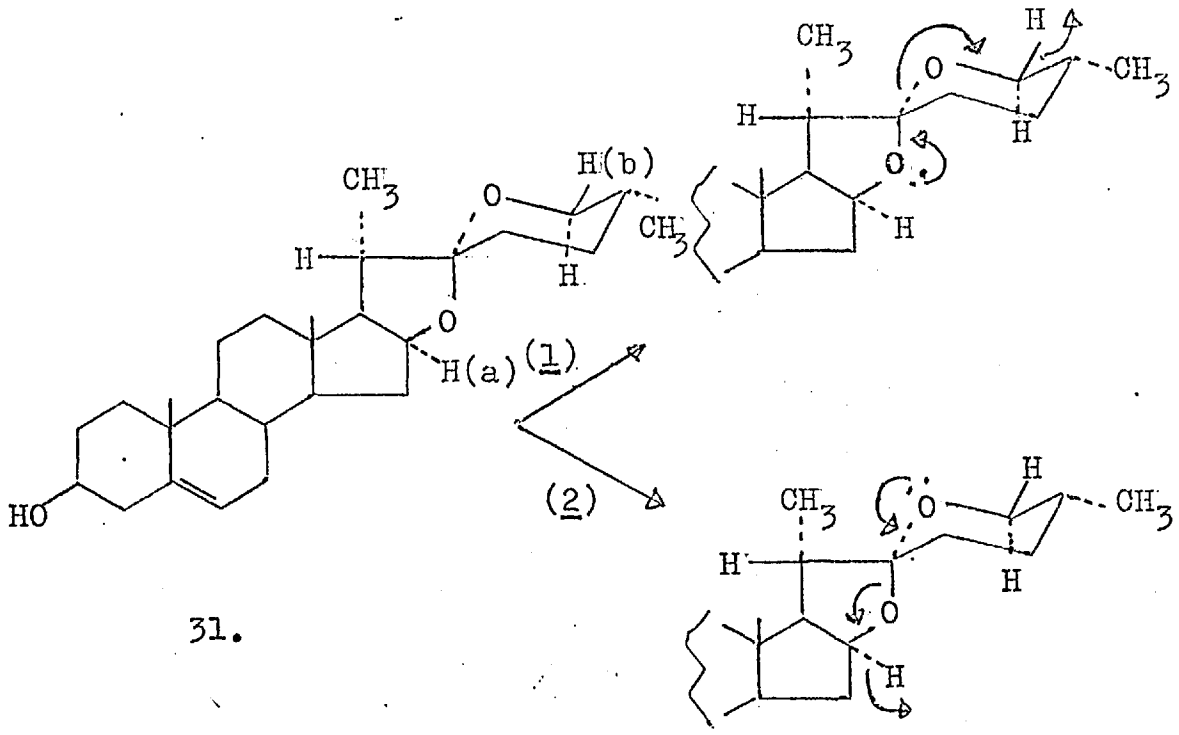


29. 30.

The natural product diosgenin (31) serves as a starting material for a large number of the steroids. Key reaction sequences involve degradation of the side chain of this sapogenin. Nearly all the steroids in therepeutic use can now be obtained on industrial scale from diosgenin[30] (31).

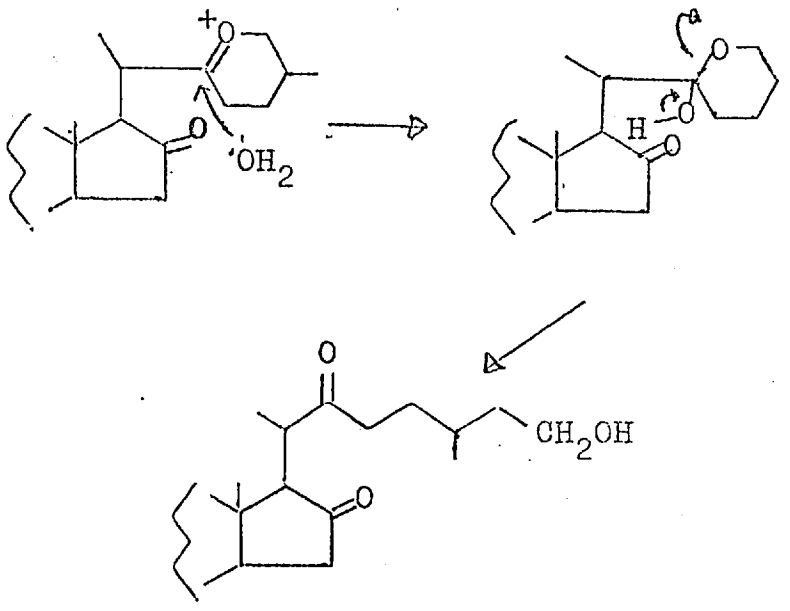
Formally the side chain of (31) represents a ketal, and in principle, two modes of hydride abstraction (1) and (2) are possible.

Abstraction of hydrogen (a) (mode 2) is more



31.

likely than the alternative (b) (mode 1) (see Part 2). The product from route (2) is kryptogenin (32) which is itself a natural product first isolated along with diosgenin[31,32] from Beth root.

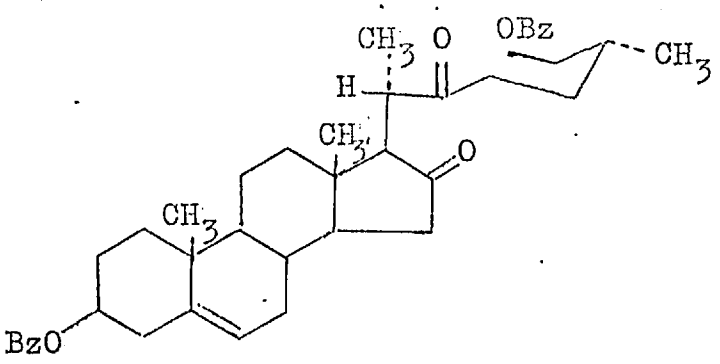


32.

Trityl oxidation of diosgenin benzoate (the benzoate derivative is highly crystalline and purified easily) gave kryptogenin monobenzoate (35%) which on further benzoylation furnished kryptogenin dibenzoate[*] (33) identical with an authentic sample.[≠]

[*] also prepared from benzoylation of kryptogenin[32].

[≠] Authentic sample of kryptogenin was kindly supplied by Prof. G. Rosenkranz.

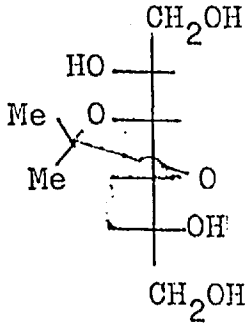


33.

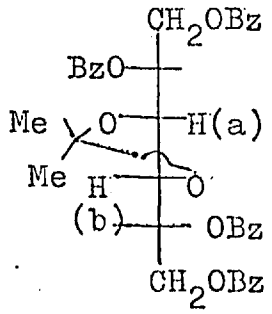
b) Carbohydrate Series.

As a result of the successful application of some newly developed oxidation procedures to carbohydrate chemistry[33,34,35], there has been considerable interest during the last decade in the chemistry of keto-sugars. This class of compound often represents the starting material of choice for the synthesis of desoxy-amino- and branched chain sugars. An added incentive in the search and development of better selective oxidation procedures has been the occurrence of unusual keto-sugars in natural products, notably in antibiotics[36].

Trityl oxidation was first applied in the case of D-mannitol-3,4-acetonide (34).

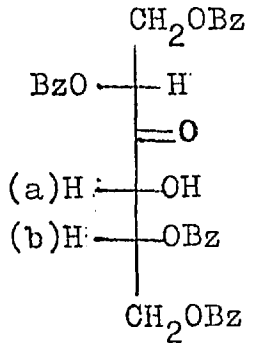


34.



35.

D-mannitol was converted by standard procedures[37] into the 3,4-acetonide (34) and benzoylated to give (35). (Free sugars were converted into the benzoyl derivatives prior to the trityl oxidation in order to render them less polar, and hence soluble in methylene-chloride and to improve the ease of handling them[38]). Treatment of (35) with tritylfluoroborate gave (36)*[39] in 65% yield. (35) is a symmetrical molecule, therefore abstraction of either hydrogen (a) or (b) by the trityl cation gives the same product (36).

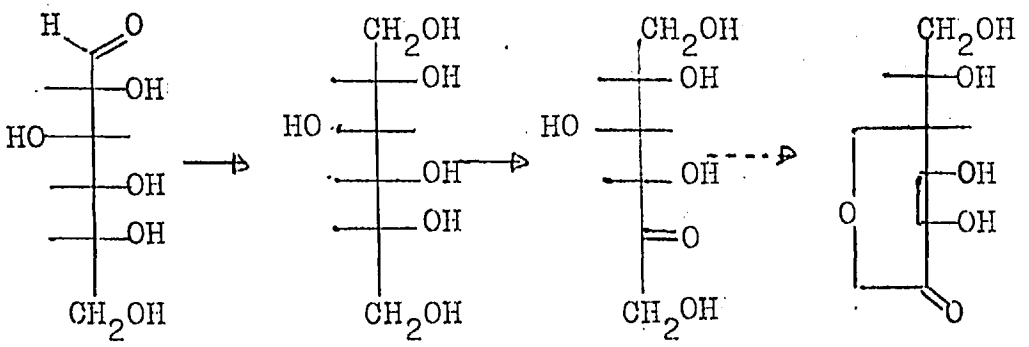


36.

* The acetate derivative of (36) has recently been synthesised by chromic oxidation of the 3:4 methylene dioxy-mannitol[39].

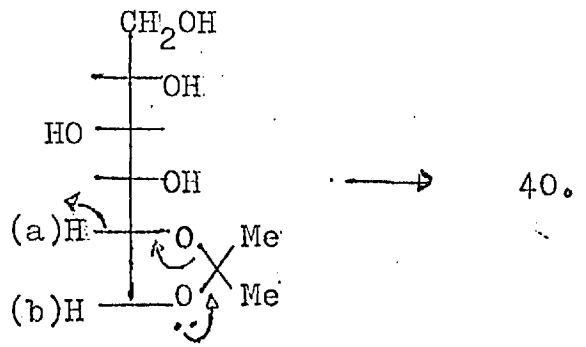
As expected the n.m.r. spectrum exhibited one exchangeable proton (with D_2O) proton (a) appeared as a multiplet at 4.1 p.p.m. which on removal of the hydroxyl proton coupling (exchanged with D_2O) transformed into a doublet J_{ab} = 10Hz.

Vitamin C (37) is synthesised conventionally[40] by hydrogenation of L-glucose (38) to D-glucitol (39) (sorbitol) followed by micro organism oxidation specifically at position 2 to L-sorbose (40). The latter is further converted into the 2:3, 4:6 diacetonide of sorbofuranose, and the unprotected terminal hydroxyl group is oxidised to give the diacetonide derivative of 2-keto-2-gluconic acid. Hydrolysis gives the unprotected acid which undergoes lactonisation and enolisation to



38. 39. 40. 37.

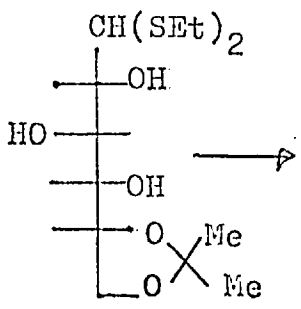
L-ascorbic acid (37). An attractive chemical alternative to the microbiological oxidation would be trityl oxidation of the sorbitol-5:6-acetonide (41) to give L-sorbose (40).



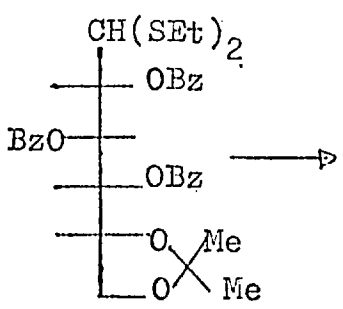
40.

41.

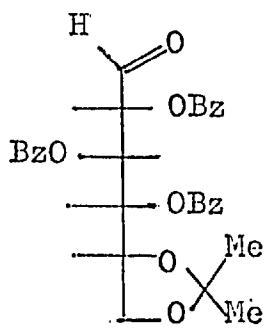
The hydrogen on position 5 (a) is more likely to be abstracted by trityl cation than the hydrogen (b) on position 6 (see Part 2). However, (41) was unknown and a route to it was developed as follows:



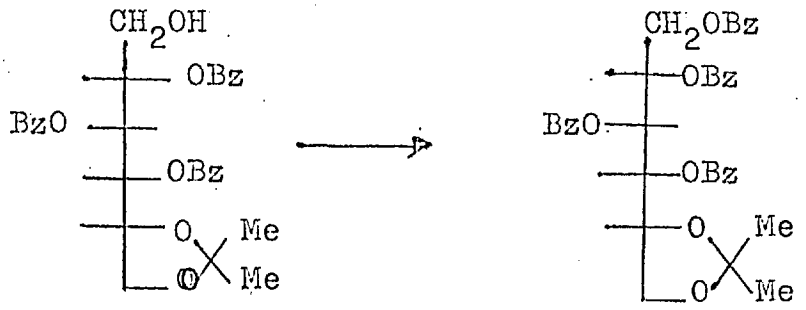
42.



44.



45.

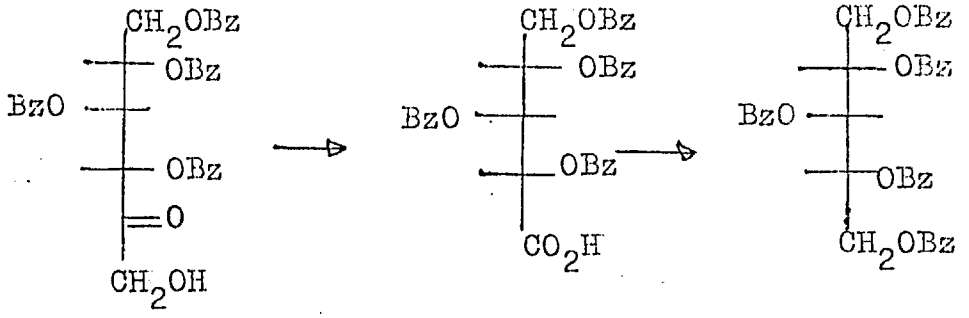


46. 43.

D-Glucosedithioethane-5,6-acetonide[41] (42), prepared from D-glucose in 60% yield, was converted into the benzoyl derivative of the required acetonide (43).

Benzoylation of (42) gave the tri-benzoate acetonide (44) and treatment with mercuric chloride/mercuric oxide[42,43] in aqueous acetone gave D-glucose-5,6-acetonide (45). Reduction of (45) with sodium borohydride gave (46) and benzoylation furnished sorbitol-O-tetra-benzoate-5,6-acetonide (43) (which is the benzoyl derivative of the desired (41)) which was a suitable substance for trityl oxidation. The expected sorbose-O-tetrabenzoate (47) (ν_{max} 3500cm^{-1} 1720cm^{-1} 1700cm^{-1} (shoulder)) was produced in 50% yield. The structure of (47) was confirmed by periodate oxidation to the acid (48) followed by diborane reduction[44] and benzoylation to xylitol pentabenzoate (49) identical

with an authentic specimen*.



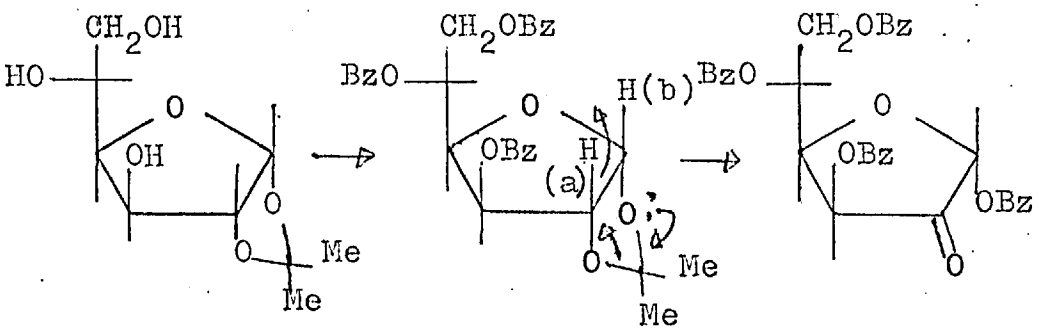
47. 48. 49.

The production of (47) represents a partial synthesis of sorbose and hence of Vitamin C, which is not dependent on microbiological transformation[46,45≠].

* Xylitol pentaacetate was kindly supplied by Prof. L. Owen.

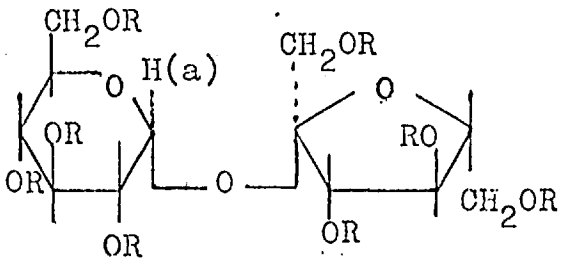
≠ A recent modification uses direct oxidation of 1,2-O-isopropylidene-α-D-glucofuranose to give Vitamin C in a shorter route[47].

α-D-Glucofuranose was converted by standard procedures into 1,2-O-isopropylidene-α-D-glucofuranose (50)[48] and benzoylated to give the tribenzoate (51).



50. 51. 52.

Treatment of (51) with trityl fluoroborate followed by benzoylation gave (52) in 20% yield. Next the possibility of finding a new cleavage method for the glycoside linkage was explored in the expectation that H (a) of (53) (a) or (b) would be removable[49].



a) R = Ac
b) R = Me

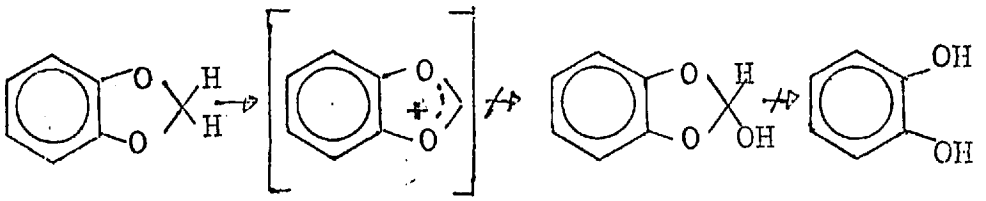
53.

These substances were each treated with tritylfluoroborate but they failed to react. It was not surprising therefore to observe that (51) lost H (a) (to give (52)) rather than h (b) (to afford a lactone).

Part 5. Other synthetic applications of hydride abstraction with tritylfluoroborate.

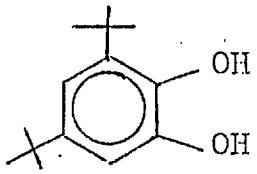
Many natural products contain the methylene-dioxy group attached to an aromatic nucleus[50]. The ability to remove this group under neutral conditions should be of great value.

Benzo-1,3-dioxole (54) was chosen as a model compound, but treatment with tritylfluoroborate gave a

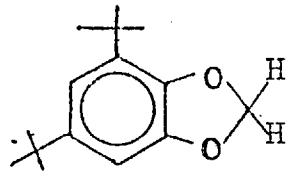


54. 55.

polymeric product, probably as a result of attack of the carbonium ion (trityl cation or (55)). On the exposed aromatic ring[51] 2,5-tert-butyl catechol (56) represents a case where the aromatic ring is shielded against such attack.



56.



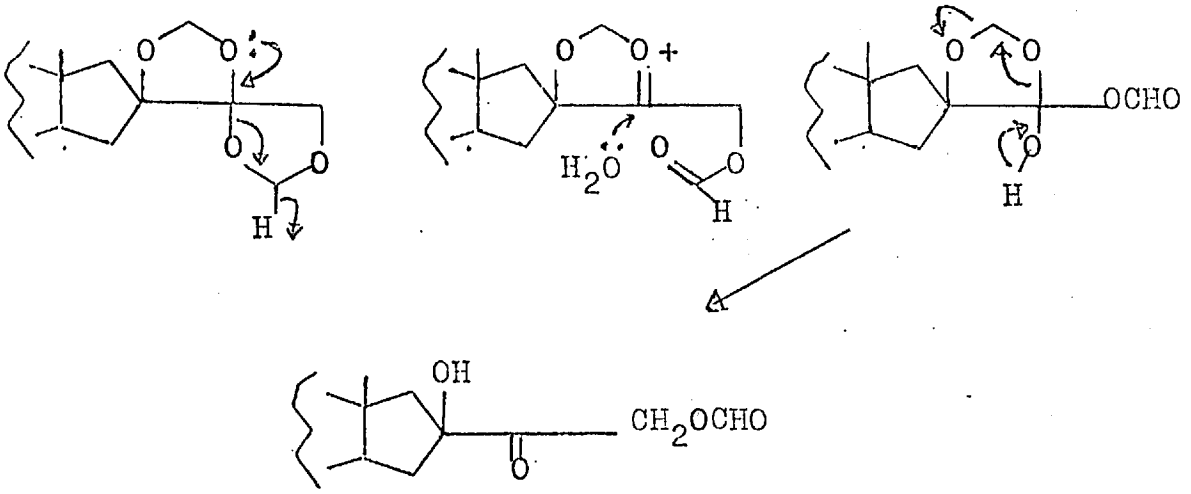
57.

The methylene derivative (57) was prepared from (56) and methylene chloride[52] to give (57) in 85% yield. Treatment with tritylfluoroborate followed by aqueous sodium carbonate (to hydrolyse the formate) furnished 2,5-tert-butyl catechol (56) in 80% yield.

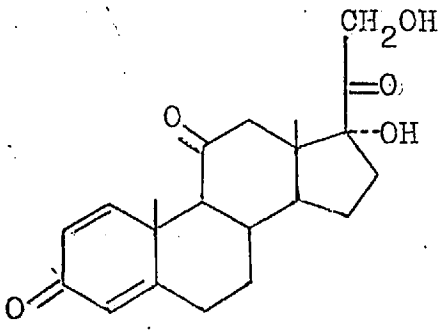
The bis methlenedioxy group occurs extensively in protection of α,α'-dihydroxyketones, expecially the adrenocortical hormone series. It can be removed by treating with aqueous formic acid, but the yield is low* (40%). Triphenylfluoroborate reacted with BMD derivatives to give the free dihydroxyketone compound and a monoformate derivative, (which was easily transformed to the dihydroxyketone compound by treatment with aqueous alkali carbonate) however, the yields were at the same range as the conventional method (30-40%) (but much starting material could be recovered unchanged).

* recently HF was reported a a good agent[54].

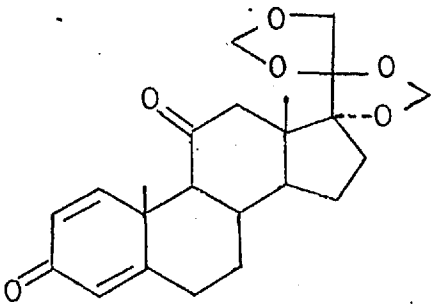
Mechanistically the process can be explained in the manner shown:



Although the formate was never isolated because it is readily converted to dihydroxyketone. The evidence for its intermediacy, at least comes from n.m.r. measurement (1 proton singlet at τ 1.9) and from the charateristic infrared absorption (ν_{max} 1725cm^{-1}). Formylation of prednisone[55] gave a compound with the same Rf (t.l.c.) as the one derived from prednisone-BMD. Treatment of prednisone-BMD (58) with tritylfluoroborate gave prednisone (59) in 40% yield.

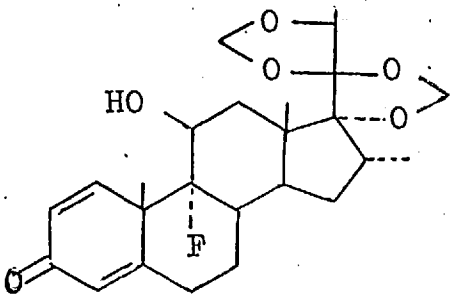


59.



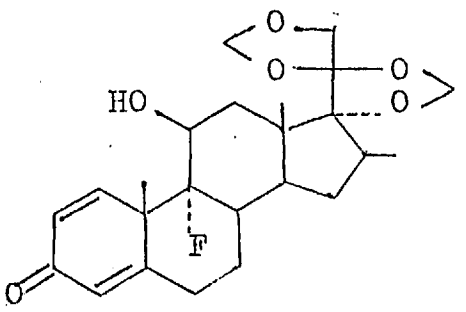
58.

Similarly, dexamethasone BMD[56] (60) gave dexamethasone in 30% yield.



60.

Betamethasone BMD (61) previously unknown was prepared from betamethasone and formalin in a two phase reaction (CH_2Cl_2).



61.

Treatment with triphenylfluoroborate gave betamethasone in 40% yield.

EXPERIMENTAL.

Unless otherwise specified, the following data apply to the experiments described in this section.

Measurements.

Melting points were determined on a Kofler block. Infrared were measured in nujol with a Unicam S.P. 200 spectrometer. N.m.r. spectra were taken in deuterochloroform on a Varian A 60 or HA 100 spectrometer. Mass spectra were taken with an A.E.I. MS 9 high resolution mass spectrometer.

Technique.

The phrase "in the usual way" implies, in general, dilution with aqueous sodium hydrogen carbonate (5% w/v), extraction with dichloromethane washing with water drying and evaporation of the organic phase *in vacuo*. Chromatography refers to the preparative layer chromatography on 1mm. layers. Bands were extracted with Analar aceton. Reactions were monitored by t.l.c. technique.

Sodium sulphate was used to dry solutions of organic compounds.

Materials.

Dichloromethane was dried over calcium chloride, decanted, and distilled from powdered calcium hydride. The middle fraction was used directly. Other solvents were dried, when necessary, by standard techniques.

Petroleum ether refers to the fraction (40-60°). Nitrogen was dry and oxygen free. Solvent mixture proportions refer to the volumes mixed. Silica for chromatography was type GF_{254} (Merck).

General procedure for oxidation with tritylfluoroborate.

The following general procedure was used. The ketal and tritylfluoroborate were placed in a dry flask and stirred gently under nitrogen at room temperature while anhydrous dichloromethane was distilled into the vessel. When the reaction was over (t.l.c. control) an excess of aqueous sodium hydrogen carbonate was added and the two phase mixture was stirred vigorously for 10 minutes. More dichloromethane was added and the organic layer was washed with water, dried, and evaporated *in vacuo*. The residue was chromatographed over silica for isolation of the required product.

Tritylfluoroborate.

This compound was prepared from triphenylmethanol and hydroborofluoric acid[57]. The salt was dried under high vacuum for 48 hours before use and had m.p. 200° dec.

Benzophenone ethyleneketal.

Benzophenone (1.8g) in dry benzene (40ml) and ethyleneglycol (2ml) and p-toluenesulfonic acid monohydrate (5mg) was heated under reflux while water was

removed by Dean and Stark apparatus for 12 hours. After the reaction was worked up in the usual way, recrystallisation from absolute ethanol furnished benzophenone ethyleneketal (1.9g), m.p. 135°; ν_{max} 1100cm^{-1}; λ_{max} 215nm (ε 12,000); τ 5.9 (4H,s) and 2.5 (10H,m). (Found: C, 79.41; H, 6.48, $C_{15}H_{14}O_2$ requires C, 79.64; H, 6.19%.).

Cyclohexanone from cyclohexanone ethyleneketal (14).

Cyclohexanone ethyleneketal (14) (149mg) and tritylfluoroborate in dichloromethane (10ml) were allowed to react for 30 minutes in the standard manner. The yield (70%) was evaluated by quantitative G.L.C. analysis (S.E. 30. 1m. t°, 100°).

Benzophenone from benzophenone ethyleneketal.

Benzophenone ethyleneketal (226mg) and tritylfluoroborate (330mg) in dichloromethane (20ml) were allowed to react for 15 minutes in the standard manner. The yield (100%) was evaluated by quantitative u.v. spectra.

λ_{max} 251 nm (ε, 14,000).

Dideuterated dihydrobenzoin acetonide (7).

Benzil (0.45g) was dissolved in hot ethanol 95% (5ml). The solution was cooled to produce a fine suspension and sodium borodeuteride (99.9%, 0.2g) was added. The solid dissolved and the yellow color of the diketone was discharged. After 10 minutes water (15ml) was added and the dideuterated dihydrobenzoin (0.38g) crystallised directly. The crude diol was dissolved in 2'2-dimethoxypropane and p-toluenesulfonic acid monohydrate (10mg) was added. The solution was stirred at room temperature for 1 hour (protection from moisture) and worked up in the usual way. Chromatography over silica and elution with acetone petroleum ether (1:9) gave dideuterated dihydrobenzoin acetonide (7) m/e 256 ($M^{+\cdot}$).

Monodeuterated dihydrobenzoin acetonide (8).

Starting from benzoin (0.5g) and sodiumboro-deuteride (0.1g) and following the same procedure as above gave monodeuterated dihydrobenzoin acetonide (8) m/e 255 ($M^{+\cdot}$).

Benzophenonehemithioketal (18).

Benzophenone (1g) in dry benzene (30ml) was treated with β-mercaptoethanol (1ml) and p-toluenesulfonic acid monohydrate (5mg) was added. The mixture was heated under reflux for 12 hours while water was removed by the use of a soxhlet thimble packed with calcium hydride. The mixture was poured into an aqueous solution of sodium hydrogen carbonate (5% w/v, 40ml) and extracted with chloroform. The organic phase was washed with water, dried and evaporated *in vacuo*. Chromatography of the residue over silica and elution with benzene gave benzophenonehemithioketal (18) (0.4g), m.p. (from ethanol) 46°; τ 6.8 (2H, t, J 5 Hz), 5.8 (2H, t, J 5 Hz) and 2.8 (10H, m).

Benzophenone from benzophenonehemithioketal.

Benzophenonehemithioketal (240mg) and trityl fluoroborate (330mg) in dichloromethane (10ml) were allowed to react for 15 minutes in the standard manner. Chromatography over silica with benzene as eluent gave benzophenone (175mg), m.p. 49° undepressed on mixing with an authentic sample.

Benzophenone ethylenethioketal (19).

Benzophenone (1g) in glacial acetic acid (10ml) was treated with ethanedithiol (1ml) and boron trifuoride etherate (1ml) at 60° for 3 hours. The mixture was diluted with water (50ml) and extracted with dichloromethane. After working up in the usual way crystalisation from ethanol afforded benzophenone ethylenethioketal (19) (1.38g) m.p. (from ethanol) 106°; τ 6.6 (4H,s) and 2.6 (10H,m) (Found: C, 69.92; H, 5.51; S, 24.68. $C_{15}H_{14}S_2$ requires C, 69.74; H, 5.42; S, 24.83%).

11α-Hydroxy progesterone from 11α-hydroxy progesterone ethyleneketal (15).

11α-Hydroxy progesterone ethyleneketal[14] (15) (209mg) and tritylfluoroborate (340mg) in dichloromethane (15ml) were allowed to react for 30 minutes in the standard manner. The product was chromatographed over silica and eluted with acetone petroleum ether (3:7) to give 11α-hydroxy progesterone (115mg), m.p. (from methanol) 166-168°, undepressed on mixing with an authentic specimen $[\alpha]_D^{23}$ + 176° (C, 1).

Pregnenolone from pregnenolone ethyleneketal (16).

Pregnenolone ethyleneketal (16)[15] (360mg) and tritylfluoroborate (450mg) in dichloromethane (15ml) were allowed to react for 30 minutes in the standard manner. Chromatography over silica by double elution with acetone petroleum ether (1:9) gave pregnenolone (255mg), m.p. (from alcohol) 193°, undepressed on mixing with an authentic sample. $[\alpha]_D^{23}$ + 28° (C, 1.1).

Cholestanone from cholestanone ethyleneketal (17).

Cholestanone ethyleneketal (17) (215mg) and tritylfluoroborate (165mg) in dichloromethane (15ml) were allowed to react for 30 minutes in the standard manner. The product was chromatographed over silica and eluted with acetone petroleum ether (1:9) to furnish cholestanone (154mg), m.p. 128-129°, undepressed on mixing with an authentic sample. $[\alpha]_D^{23}$ + 43° (C, 1.1).

Cyclohexanone meso-dihydrobenzoin (3).

Cyclohexanone ethylenethioketal (0.43g) in dry

tetrahydrofuran (50ml) was treated with meso-dihydrobenzoin[6] (0.5g) and mercuric oxide (2.7g) (yellow). The mixture was stirred under reflux, and a solution of mercuric chloride in dry tetrahydrofuran (40ml, 5% w/v) was then added at such a rate as to maintain gentle reflux. After a further 15 hour period the hot solution was filtered and mercuric oxide (0.1g) was added to the filtrate. The mixture was concentrated in vacuo, diluted with dichloromethane, and filtered. The solution was then washed successively with water, aqueous potassium iodide (10% w/v), and water. The organic phase was dried and evaporated in vacuo. Chromatography of the residue over silica and elution with benzene gave cyclohexanone meso-dihydrobenzoin (3) (0.54g), m.p. (from ethanol) 63°; ν_{max} 1050, 1110cm^{-1}; τ 8.2 (10H, m), 4.35 (2H,s) and 3.1 (10H,s) (Found: C, 81.45; H, 7.55, $C_{20}H_{12}O_2$ requires C, 81.63; H, 7.48%).

meso-Dihydrobenzoin acetonide (6).

meso-Dihydrobenzoin (0.4g) in 2'2-dimethoxypropane was stirred at room temperature with p-toluenesulfonic acid (10mg) for 1 hour. Chloroform (50ml) was added and the solution was washed successively with water, aqueous hydrogen carbonate (5% w/v), and water. The

organic phase was dried and the solvent was evaporated to give isopropylide meso-dihydrobenzoin (6) (0.41g) m.p. (from ethanol) 58°; ν_{max} 1060cm^{-1}; τ 8.8 (3H,s), 8.57 (3H,s), 4.75 (2H,s) and 3.2 (10H,s) (Found: C, 80.51; H, 7.03 $C_{17}H_{18}O_2$ requires C, 80.31; H, 7.08%).

Formation of Benzoin from (3).

Cyclohexanone meso-dihydrobenzoin (3) (300mg) and tritylfluoroborate (450mg) in dichloromethane (15ml) were allowed to react for 4 hours in the standard manner. Chromatography over silica with acetone petroleum ether (1:9) as eluent gave benzoin (145mg) m.p. (from ethanol) 134°; undepressed on mixing with an authentic sample, ν_{max} 1680, 3450cm^{-1}.

Formation of Benzoin from (6).

meso-Dihydrobenzoin acetonide (6) (250mg) and tritylfluoroborate (450mg) in dichloromethane (15ml) were allowed to react for 4 hours in the standard manner. Chromatography over silica with acetone petroleum ether (1:9) as eluent gave benzoin (135mg),

m.p. (from ethanol) 134°, undepressed on mixing with an authentic specimen; ν_{max} 1680, 3450cm^{-1}; m/e 244 (M^+).

1,2-Dihydroxy-triphenylethylene (22).

Triphenylethylene (256mg) was treated with formic acid (99.9%, 4ml) and hydrogen peroxide 30% (1ml). The solution was heated (40°) and kept at this temperature for 3 hours. Formic acid was removed *in vacuo* (50°/125 mm. Hg.) and the residue was treated with an excess of sodium hydroxide (15ml; 3N) in methanol (15ml) for 30 minutes. The solution was diluted with dichloromethane (50ml), and the organic phase was washed with water 3 times, dried and evaporated *in vacuo*, to give a crude diol (22) ν_{max} 3500cm^{-1}.

1,2-O-isopropylidene triphenylethylene (10).

The crude diol (22) (250mg) was dissolved in 2'2-dimethoxypropane (15ml) and p-toluenesulfonic acid monohydrate (15mg) was added. The mixture was stirred at room temperature for 1 hour (protection from moisture).

After work up in the usual way, chromatography over silica and elution with acetone petroleum ether (0.5:9.5) gave the acetonide (10) (250mg), m.p. (from ethanol) 113°; ν_{max} 1100cm^{-1}; τ 8.5 (3H,s), 8.2 (3H,s), 4.2(1H,s), and 7.2 (15H,m) (Found: C, 83.63; H, 6.76. $C_{23}H_{22}O_2$ requires C, 83,60; H, 6.71%).

Acetophenone α-hydroxy-α'α-diphenyl.

1,2-O-isopropylidene triphenylethylene (66mg) and tritylfluoroborate (100mg) in dichloromethane (10ml) were allowed to react for 4 hours in the standard manner. Chromatography over silica with acetone petroleum ether (1:9) as eluent gave acetophenone α-hydroxy-α'α-diphenyl[12] (5mg), m.p. 89°; ν_{max} 3400 and 1690cm^{-1}.

Cholestan-3β,ol-2β,ol (23).

Δ^2 Cholestene[24] (215mg) was dissolved in glacial acetic acid (3ml). Silver acetate (0.2g) was added and the mixture was stirred at room temperature under nitrogen for 1 hour. Finely divided iodine (0.18g) was added in portions over a period of 15 minutes. After a further 2 hours water (0.03ml) was added and the mixture was

stirred overnight, diluted with chloroform and the combined filtrate was washed successively with water, aqueous sodium hydrogen carbonate (5% w/v), and water. The organic phase was dried and evaporated *in vacuo*. The crude monoacetate was dissolved in dry ether (30ml) and lithium aluminium hydride (50mg) was added. The mixture was refluxed for 1 hour and excess of the reagent was then destroyed by addition of ethyl acetate and water. Work up and chromatography over silica by elution with acetone petroleum ether (2:8) gave crude cholestan-3β,ol-2β,ol, (23) ν_{max} 3400-3500cm^{-1}.

2β,3β-*O*-isopropylidene Cholestane (24).

Crude cholestane-3β,ol-2β,ol (200mg) was dissolved in 2'2-dimethoxypropane (10ml) and treated with *p*-toluenesulfonic acid monohydrate (8mg). The mixture was stirred at room temperature for 1 hour (protected from moisture). After work up in the usual way crystallisation from methanol furnished the acetonide (24), $[\alpha]_D^{26}$ (240mg), m.p. 111°; ν_{max} 1060cm^{-1}.

Cholestane-3β,ol-2,one (25).

2β,3β-O-isopropylidene cholestane (24) (110mg) and tritylfluoroborate (250mg) in dichloromethane (10ml) were allowed to react for 2 hours in the standard manner. Chromatography over silica by triple elution with benzene gave cholestane-3β,ol-2,one (25)[26] (80mg), m.p. (from methanol) 107°; $[\alpha]_D^{23}$ + 63° (C, 1.3); ν_{max} 1715 and 3500cm^{-1}. (Found; C, 80.78; H, 11.54, $C_{27}H_{46}O_2$ requires C, 80.68; H, 11.53%).

Methyl hedera genin acetonide (27).

Methyl hederagenin[27] (26) (0.5g) was dissolved in 2'2-dimethoxypropane (15ml) and p-toluenesulfonic acid monohydrate (20mg) was added. The mixture was stirred at room temperature for 3 hours (protected from moisture). Work up in the usual way furnished methyl hederagenin acetonide[28] (27) (0.51g), m.p. (from methanol) 250-251°; ν_{max} 1720, 1185cm^{-1}; τ 6.35 (2H,s), 6.5 (1H,s) and 4.65 (1H,m).

Benzophenone methyl hederagenin-ketal (28).

Benzophenone ethylenethioketal (19) (128mg) in dry tetrahydrofuran (40ml) was treated with methyl hederagenin (295mg) and mercuric oxide (2g) (yellow). The mixture was stirred under reflux and solution of mercuric chloride in dry tetrahydrofuran (30ml 5% w/v) was added at such a rate as to maintain gentle reflux. After a further 15 hour period the hot solution was filtered and mercuric oxide (0.1g) was added to the filtrate. The mixture was concentrated *in vacuo*, diluted with dichloromethane, and filtered. The solution was then washed successively with water, aqueous potassium iodide (10% w/v), and water. The organic phase was dried and evaporated *in vacuo*. Chromatography of the residue over silica and elution with benzene furnished the benzophenone ketal (28) (260mg), m.p. (from methanol) 275-277°; $[\alpha]_D^{23}$ + 31° (C, 0.98); ν_{max} 1725, 720cm^{-1}. A sample for microanalysis was sublimed at 260°/0.6mm.Hg (Found: C, 81.15; H, 8.92. $C_{44}H_{58}O_4$ requires C, 81.3; H, 8.99%).

Formation of Methyl hederagonate (29) from (27).

Methyl hederagenin acetonide (27) (250mg) and tritylfluoroborate (275mg) in dichloromethane (15ml) were allowed to react for 15 hours in the standard manner. Chromatography over silica by successive elution with benzene and acetone petroleum ether (1:9) gave methyl hederagonate[28] (29) (50mg), m.p. (from methanol) 217°; $[\alpha]_D^{23}$ + 78° (C, 1.1), ν_{max} 1680, 1722 and 3450cm^{-1}. Undepressed in m.p. on mixing with an authentic specimen. (Found: C, 76.74; H, 10.71. $C_{31}H_{48}O_4$ requires C, 76.96; H, 9.99%).

Formation of Methyl hederagonate (29) from (28).

Benzophenonemethyl hederagenin ketal (28) (0.32g) and tritylfluoroborate (300mg) in dichloromethane (15ml) were allowed to react for 15 hours in the standard manner. Chromatography over silica by successive elution with benzene and acetone petroleum ether (1:9) gave methyl hederagonate[28] (29) (49mg), m.p. (from methanol) 217°; $[\alpha]_D^{23}$ + 78° (C, 1.1); ν_{max} 1680, 1722 and 3450cm^{-1}. Undepressed in m.p. on mixing with an authentic sample.

Retro-aldol reaction of Methyl hederagonate.

Methyl hederogonate (29) (10mg) in methanol (7ml) was treated with a solution of potassium hydroxide (0.4g) in water (3ml) for 1 hour. Work up and chromatography of the total product over silica by elution with acetone petroleum ether (1:9) gave methyl hedragonate[28] (30) (7mg), m.p. 203°; undepressed on mixing with an authentic sample. $[\alpha]_D^{23}$ + 101° (C, 1); ν_{max} 1722 and 1680cm^{-1}.

Kryptogenin dibenzoate (33).

Diosgenin benzoate (100mg) and tritylfluoroborate (150mg) in dichloromethane (15ml) were allowed to reat for 15 hours in the standard manner. Chromatography over silica with acetone petroleum ether (2:8) as eluent gave crude kryptogenin monobenzoate (32) (35mg).

The crude material (32) (35mg) in dry pyridine (7ml) was treated with freshly distilled benzoyl chloride (0.3ml) and left at room temperature overnight. The solution was poured into ice-water (150ml) containing sodium hydrogen carbonate (1.5g) and the mixture was

stirred for 1 hour and then extracted with chloroform (3x30ml). The organic phase was dried and evaporated in vacuo. Chromatography of the residue over silica and elution with acetone petroleum ether (1:9) gave kryptogenin dibenzoate[32] (33) (35mg), m.p. (from ethanol) 183°; undepressed on mixing with an authentic specimen. ν_{max} 1715, 1710 and 1700cm^{-1}. m/e 638 (M^+); τ 5.8 (2H, d, J 5Hz), 5 (1H,m), 4.6 (1H,m), and 2.5 (10H,m). (Found: C, 77.23; H, 7.80 $C_{27}H_{41}O_4$ requires C, 77.08; H, 7.89%).

3,4-O-isopropylidene-Mannitol tetrabenzoate (35).

3,4-O-isopropylidene-mannitol[37] (34) (200mg) in dry pyridine (10ml) was treated with freshly distilled benzoyl chloride (0.3ml) at room temperature for 15 hours. The solution was poured into ice-water (150ml) containing sodium hydrogen carbonate (1g) and the mixture was stirred for 1 hour and then extracted with chloroform (3x30ml). The organic phase was dried and evaporated in vacuo. Chromatography of the residue over silica and elution with acetone petroleum ether (2:8) afforded 3,4-O-isopropylidene-mannitol tetrabenzoate (35) (270mg), m.p. (from ethanol) 101° ; $[\alpha]_D^{23}$ + 1.1°

(C, 1); ν_{max} 1710, 1110 and 1290cm^{-1}; τ 8.4 (6H,s), 5.3 (6H,m), 4.3 (2H,m) and 2.5 (20H, m) (Found: C, 69.66; H, 5.44. $C_{37}H_{34}O_{10}$ requires C, 69.58; H, 5.37%).

4-O-Hydroxy-D-arabino-3-hexulose (36).

3,4-O-isopropylidene mannitol tetrabenzoate (35) (314mg) and tritylfluoroborate (215mg) in dichloromethane (15ml) were allowed to react for 4 hours in the standard manner. Chromatography over silica with acetone petroleum ether (2:8) as eluent gave the hydroxy ketone (36) 190mg, m.p. (ethylacetate petroleum ether 60°-80°) 103°; $[\alpha]_D$ + 20.7 (C, 0.3); ν_{max} 1705, 1710 and 3500cm^{-1}; τ 5.9 (2H, d, J 10Hz became clear after exchanging with D_2O), 5.2-4.3 (5H,m) and 2.5 (20H, m) (Found: C, 68.21; H, 4.92. $C_{34}H_{28}O_{10}$ requires C, 68.45; H, 4.73%).

D-Glucosedithioethane.

D-Glucose (20g) was dissolved in hydrochloric acid (sp.gr. 1.19, 100 ml) at room temperature. Ethanethiol (20ml) was added and the securely stopped vessel was shaken vigorously while kept at room

temperature by periodic addition of small amounts of ice. Shaking was continued the mixture crystallised. After a further 30 minutes the mixture was filtered and the crystals were washed with ice-water and recrystallised from hot water containing some sodium hydrogen carbonate. The product was collected and washed successively with ice-water, ethanol and ether to give D-glucosedithioethane[41] m.p. 127°.

D-Glucosedithioethane-5,6-acetonide (42).

D-Glucosedithioethane (6g) was shaken in Analar acetone (100ml) containing anhydrous copper sulphate (25g) for 3 hours. The mixture was filtered and the filtrate was evaporated at room temperature. Column chromatography of the residue over silica and elution with chloroform gave D-glucosedithioethane-5,6-acetonide[41] (42) (3.2g), m.p. 68-69°; $[\alpha]_D$ - 11° (C, 1.1); ν_{max} 3500, 1080 and 1615cm^{-1}; τ 8.6 (6H,s), 8.7 (6H, T, J 7Hz), 7.3 (4H, 9, J 7Hz) and 6.8-5.4 (7H,m).

5,6-O-isopropylidene-D-Glucosedithioethane tribenzoate (44).

D-Glucosedithioethane-5,6-acetonide (42) (250mg) in dry pyridine (10ml) was treated with freshly distilled benzoyl chloride (0.4ml) at room temperature for 15 hours. The solution was poured into ice-water (150ml) containing sodium hydrogen carbonate (1g) and the mixture was stirred for 1 hour and then extracted with chloroform (3x30ml). The organic phase was dried and evaporated *in vacuo*. Chromatography of the residue over silica and elution with acetone petroleum ether (2:8) gave (44) as an oil (318mg). ν_{max} 1710, 1110 and 1280cm^{-1}; τ 8.9 (6H, t, J 6Hz), 8.5 (6H,s), 7.5 (4H, 9, J 6Hz), 5.8-4.8 (7H,m) and 2.5 (15H, m).

5,6-O-Isopropylidene-2,3,4-O-tribenzoate-D-glucose (45).

D-Glucosedithioethane-5,6-acetonide tribenzoate (44) (200mg) was dissolved in aqueous acetone (acetone water (9:1); 10ml) and mercuric oxide (250mg) (yellow) was added. The mixture was stirred and heated under reflux. A solution of mercuric chloride (250mg) in Analar acetone (5ml) was added dropwise at such a rate as to maintain

gentle reflux. After a further 4 hours the hot solution was filtered. Sodium hydrogen carbonate (0.3g) was added and the filtrate was concentrated and then diluted with chloroform (60ml). The solution was washed successively with water, aqueous potassium iodide (30ml, 10% w/v), and water. Chromatography of the residue over silica and elution with acetone petroleum ether (2:8) gave D-glucose-5,6-aceonide-2,3,4-O-benzoate (45) as an oil, ν_{max} 1710, 1110 and 1280cm^{-1}; τ 8.6 (6H, d, J 2Hz), 5.8-4.4 (6H,m), 2.5 (15H, m) and 1 (1H,s).

Sorbitol-5,6-acetonide tetrabenzoate (43):

D-Glucose-5,6-acetonide tribenzoate (45) (100mg) in methanol (20ml) was treated with sodium borohydride (20mg). The mixture was stirred at room temperature for 1 hour and then the pH was adjusted to 7 (aqueous acetic acid 10%). The solution was evaporated to dryness and the residue was dissolved in methanol and evaporated to dryness. This last process was repeated once more and the product was chromatographed over silica and eluted with acetone petroleum ether (2:8) to give sorbitol-5,6-acetonide-2,3,4-benzoate (46) (90mg) which upon further benzoylation (see above) gave sorbitol-5,6-

acetonide tetrabenzoate (43) (93mg) m.p. 119° crystallised from ethylacetate petroleum ether 60-80°, m.p. 119-123° $[\alpha]_D$ + 24.8 (C, 0.5), ν_{max} 1710 and 1100cm^{-1}; τ 8.6 (6H,s), 6 - 4.5 (8H,m) and 2.5 (20H, m) (Found: C, 69.48; H, 5.48. $C_{37}H_{34}O_{10}$ requires C, 69.58; H, 5.37%).

1,2,3,4-O-Tetrabenzoate sorbose (47).

Sorbitol-5,6-acetonide tetrabenzoate (43) (165mg) and tritylfluoroborate (250mg) in dichloromethane (15ml) were allowed to react for 5 hours in the standard manner. Chromatography over silica with acetone petroleum ether (2:8) as eluent gave sorbose tetrabenzoate (47) 77mg., m.p. (from ethylacetate petroleum ether 60-80°) 101-103°; $[\alpha]_D$- 8.6 (C, 0.6); ν_{max} 3500, 1710 and 1700cm^{-1}. (Found: C, 68.27 ; H, 4.19 . $C_{34}H_{28}O_{10}$ requires C, 68.45 ; H, 4.73%).

Xylitol pentabenzoate (49).

Sorbose-1,2,3,4-tetrabenzoate (47) (150mg) was added to a soltuion of potassium periodate (300mg) in water acetone (2:8, 7ml) and the mixture was stirred at

5° for 15 minutes under nitrogen. Potassium permanganate (10mg) in water acetone (1:1 2ml) was then added and stirring at 5°-10° was continued overnight. The mixture was filtered and the filtrate was extracted with dichloromethane (3x30ml) washed with water, dried and evaporated to give the crude acid (48) directly suitable for the next stage.

The crude acid in dry tetrahydrofuran (5ml) was treated with diborane[44] (generated by addition of sodium borohydride in diglyme to boron trifluoride etherate in diglyme). After the mixture was stirred at room temperature for 1 hour excess of the reagent was destroyed by addition of water. Work up gave a crude material which was benzoylated (see p. 87) to afford a crystalline product which, after chromatography over silica and elution with acetone petroleum ether (1:9) furnished xylitol pentabenzoate (49) (10mg), m.p. (from ethanol) 106°-107°, undepressed on mixing with an authentic specimen (prepared from xylitol penta acetate); $[\alpha]_D^{23}$ - 0.17 (C, 1.1) (Found: C, 71.43; H, 4.75. $C_{40}H_{32}O_{10}$ requires C, 71.42; H, 4.80%).

1,2-O-Isopropylidene-D-glucofuranose tribenzoate (51).

1,2-O-Isopropylidene-D-glucofuranose[48] (50) (200mg) in dry pyridine (20ml) was treated with freshly distilled benzoyl chloride (0.3ml) at room temperature for 15 hours. The solution was poured into ice-water (150ml) containing sodium hydrogen carbonate (1.5g) and the mixture was stirred for 1 hour and then extracted with chloroform (3x30ml). The organic phase was dried and evaporated *in vacuo*. Chromatography of the residue over silica and elution with acetone petroleum ether (2:8) gave 1,2-O-isopropylidene-D-glucofuranose tribenzoate (51) (380mg), m.p. (from ethanol) 115°; $[\alpha]_D^{23}$ - 99.7 (C, 0.76); ν_{max} 1710, 1110 and 1270cm^{-1}; τ 8.65 (3H,s), 8.4 (3H,s), 3.9-5.2 (7H,m) and 2.4 (15H,m). (Found: C, 67.74; H, 5.30. $C_{30}H_{28}O_9$ requires C, 67.74; H, 5.08%).

1,3,5,6-O-Tertabenzoyl-D-*ribo*-hexofuranos-2-ulose (52).

1,2-O-isopropylidene-D-glucofuranose tribenzoate (51) (260mg) and tritylfluoroborate (200mg) in dichloromethane (15ml) were allowed to react for 14 hours in the standard manner. Chromatography over silica with

acetone petroleum ether (2:8) as eluent gave an oily product. $[\alpha]_D$ - 97.2 (C, 0.9); ν_{max} 3500, 1712 and 1705cm^{-1}; τ 5.8 - 4 (6H,m) and 2.5 (15H,m). The oily product was benzoylated (see above) to give (52), 37mg., m.p. (ethylacetate-petroleum ether 60°-80°) 150-151°; $[\alpha]_D$ - 61.4 (C, 0.2); ν_{max} 1712 and 1705cm^{-1}; τ 5.8 - 4 (6H,m) and 2.5 (20H,m). (Found: C, 68.79; H, 4.72. $C_{34}H_{31}O_{10}$ requires C, 68.80; H, 4.21%).

3,5-Di-tert-butyl benzo-1,3-dioxole (57).

Anhydrous dichloromethane (2ml) and dimethylsulfoxide (10ml) were stirred under nitrogen at 125-130°. 3,5-Di-t-butyl-catechol (56) (4g) and sodium hydroxide (1.7g) were added together in portions over a period of 2 hours. While the temperature was maintained. More dichloromethane (2ml) was added and the mixture was heated for a further 1 hour. The mixture was then cooled, diluted with water and extracted with chloroform (3x30ml). The extract was washed with water, dried and evaporated to give a brown oil. Filtration through a short column of silica with chloroform furnished the 1,3-dioxole (57) (3.2g) b.p. 101°/0.1mm.Hg. τ 8.8 (18H,s), 4.2 (2H,s) and

3.3 (2H,s). (Found: C, 76.07; H, 9.11. $C_{15}H_{22}O_2$ requires C, 76.07; H, 9.40%).

3,5-Di-tert-butylcatechol (56).

3,5-Di-tert-butyl benzo-1,3-dioxole (57) (120mg) and tritylfluoroborate (330mg) in dichloromethane (15ml) were allowed to react for 15 minutes in the standard manner. The red solution was diluted with aqueous potassium hydrogen carbonate (10% 30ml) and stirred for 1 hour. The organic phase was washed with water and evaporated in vacuo. Chromatography of the residue over silica and elution with acetone and petroleum ether (0.5:9.5) gave the catechol (56) (95mg), m.p. 98° undepressed on admixture with an authentic sample.

Prednisone (59) from prednisone-B.M.D. derivative (58).

Prednison-B.M.D. derivative (200mg) and tritylfluoroborate (300mg) in dichloromethane (15ml) were allowed to react for 24 hours in the standard manner. The product was dissolved in aqueous methanol (90% v/v, 40ml) and potassium hydrogen carbonate (0.5g) was added and the mixture was stirred at room temperature

overnight. Dichloromethane (50ml) as added and the organic phase was washed with water, dried, and evaporated. The residue was chromatographed over silica and eluted with acetone petroleum ether (3:7) to give prednisone (59) (71mg), m.p. (from chloroform methanol) 233-235° decomp., undepressed on mixing with an authentic specimen. $[\alpha]_D^{23}$ + 172 (dioxáne), ν_{max} 3500, 1703, 1660 and 1620cm^{-1}; τ 5.7 (2H, 9), 4 (2H,m) and 2.3 (2H, d, J 5Hz); m/e 358 (M^+).

Dexamethasone from dexamethasone-B.M.D.-derivative (60).

Dexamethasone-B.M.D. derivative[56] (60) (150mg) and tritylfluoroborate (300mg) in dichloromethane (15ml) were allowed to react for 24 hours in the standard manner. The product in methanol (70ml) was treated with a solution of potassium hydroxide (10% w/v, 30ml) and the mixture was stirred for 5 hours. Dichloromethane (50ml) was added and the organic phase was washed with water, dried, and evaporated. The residue was chromatographed over silica and eluted with acetone petroleum ether (3:7) to give dexamethasone (40mg), m.p. 256°; undepressed on mixing with an authentic sample. $[\alpha]_D^{23}$ + 86° (C, 1.1).

Betamethasone-B.M.D.-derivative (61).

Betamethasone (500mg) in chloroform (25ml) was stirred with aqueous formaldehyde (37%m 10ml) and concentrated hydrochloric acid (sp.gr. 1.19, 10ml) for 24 hours at room temperature. An additional 25ml of chloroform was added and the layers separated. The chloroform layer was washed with saturated solution of sodium hydrogen carbonate, dried and evaporated in vacuo. Chromatography over silica and elution with acetone petroleum ether (3:7) gave the B.M.D. (61) (260mg), m.p. (from dichloromethane-methanol) 300°; ν_{max} 1650 and 1600cm^{-1}; τ 2.9 (1H, d, J 5Hz), 3.9 (1H, d, J 5Hz), 4.15 (1H,s), 5.2 (4H,m) and 6 (2H, 9, J 4Hz); m/e 434 (M^+). (Found: C, 66.28; H, 7.26; F, 4.40. $C_{24}H_{31}O_5F$ requires C, 66.35; H, 7.30; F, 4.37%).

Betamethasone from betamethasone-B.M.D. derivative.

β-methasone B.M.D. derivative (61) (150mg) and tritylfluoroborate (300mg) in dichloromethane (15ml) were allowed to react for 24 hours in the standard manner. The product in methanol (20ml) was treated with a solution of potassium hydroxide (10% w/v, 30ml) and

the mixture was stirred for 5 hours. Dichloromethane (50ml) was added and the organic phase was washed with water, dried, and evaporated. The residue was chromatographed over silica and eluted with acetone petroleum ether (3:7) to give betamethasone (55mg), m.p. 233-235°; undepressed on mixing with an authentic specimen. $[\alpha]_D$ + 108° (Me_2CO).

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