SOME REACTIONS OF 6-KETOCHOLESTANYL ACETATE

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ABSTRACT

Enol acetylation of 6-ketocholestanyl acetate by acetic anhydride-sulphuric acid or acetic anhydride-perchloric acid gave the Δ^5-enol acetate, which on bromination yielded the known 5α-bromo-ketone.

Isopropenyl acetate enol acetylation afforded a 1:1 mixture of Δ^5- and Δ^6-isomers, the ratio being determined by bromination of the enol acetate mixture followed by O.R.D. and specific rotation measurements on the mixed 5α- and 7α-bromo-ketone.

The 7α-bromo-ketone with pyridine-silver nitrate gave the known 3β-acetoxy-cholesta-6,7-dione together with the 6-keto-Δ^7-ketone. Dehydrobromination of the 7α-bromo compound by N,N-dimethyl formamide-lithium carbonate gave the 6-keto-Δ^7-compound in good yield.

From O.R.D. measurements the structure of the enol form of 3β-acetoxy-cholesta-6,7-dione has been assigned.

A preliminary study has been made of the enol acetylation of both 3β-acetoxy-7α-bromo-cholestan-6-one and 3β-acetoxy-cholest-4-en-6-one.

INTRODUCTION

The monobromination of 6-ketocholestanyl acetate has been studied [1], and it has been found that initial bromination occurs at the 5 position, but that this bromo-ketone is slowly converted into the 7α- bromo-ketone in the presence of acetic acid and hydrogen bromide.

It was decided to examine further the reactions of the 6-keto group, and in particular to endeavour to prepare the Δ^5- and Δ^6- enol acetates. This introduction discusses previous enol acetylation studies, and on the basis of these it was hoped to be able to predict the preferred direction of enolisation of the 6-ketone under different reaction conditions.

The known examples of enol acetylation of steroid ketones under specified reaction conditions are given in the following table, and further reference to these will be made in the subsequent discussion.

Position of keto-group	Compound	Conditions	Product	References
2-keto-(5α-H)	cholestan-2-one	acetic anhydride $CCl_4/HClO_4$	Δ^2-enol acetate	9
3-keto-(5α-H)	17β-acetoxy-androstan-3-one	isopropenyl acetate TsOH	Δ^2-enol acetate	10
3-keto-(5α-H)	2α-methyl-17β-acetoxy-androstan-3-one	isopropenyl acetate TsOH	Δ^2-enol acetate	10
3-keto-(5α-H)	4α-methyl-cholestan-3-one	isopropenyl acetate H_2SO_4	Δ^2-enol acetate	13

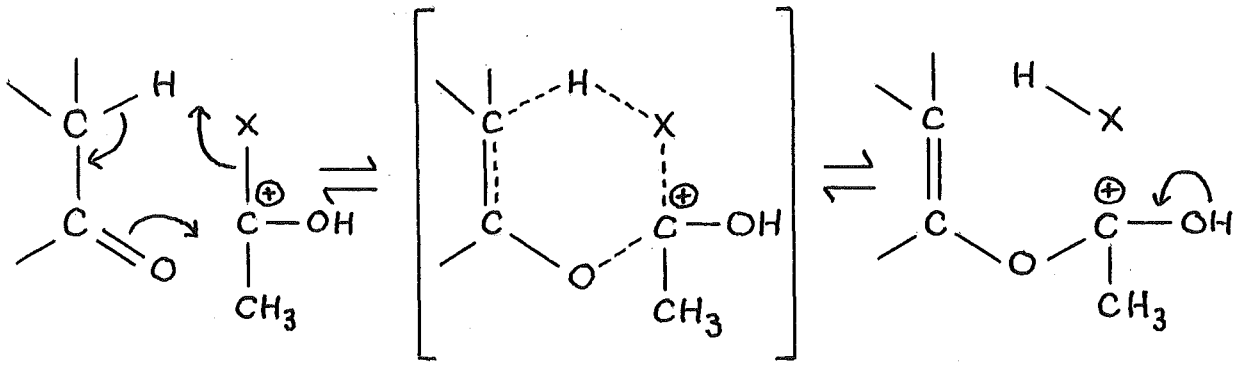
Position of keto-group	Compound	Conditions	Product	References
3-keto-(5α-H; 19-nor)	17β-acetoxy-19-nor-androstan-3-one	isopropenyl acetate TsOH	$\Delta^2:\Delta^3$ enol acetate (2:1)	10
3-keto-(5α-H; 19-nor)	2α-methyl-17β-acetoxy-19-nor-androstan-3-one	isopropenyl acetate TsOH	Δ^2-enol acetate	10
3-keto-(5β-H)	coprastan-3-one	isopropenyl acetate H_2SO_4	Δ^3-enol acetate	19
5-keto-	des-A-cholestan-5-one	acetic anhydride $CCl_4/HClO_4$	$\Delta^{5(10)}$-enol acetate	14
5-keto-	des-A-cholestan-5-one	acetic anhydride TsOH	$\Delta^5:\Delta^{5(10)}$-enol acetates (3:7)	14
5-keto-	des-A-cholestan-5-one	isopropenyl acetate TsOH	$\Delta^5:\Delta^{5(10)}$-enol acetates (7:3)	14
7-keto-(5α-H)	7-ketocholestanyl acetate	acetic anhydride TsOH	$\Delta^6:\Delta^7$-enol acetates (1:1)	18
7-keto-(5α-H)	7-ketocholestanyl acetate	isopropenyl acetate TsOH	Δ^6-enol acetate	18
11-keto-(5α-H)	3β-acetoxy-ergostan-11-one	acetic anhydride TsOH	$\Delta^{9(11)}$-enol acetate	6
11-keto-(5α-H)	methyl 3α-acetoxy-11-keto-etio cholanate	acetic anhydride TsOH	$\Delta^{9(11)}$ enol acetate	20
16-keto-	3β-hydroxy-5α-androstan-16-one	isopropenyl acetate H_2SO_4	$\Delta^{16}:\Delta^{15}$-enol acetates (30:1)	21
17a-keto-(18-nor-D-homo)	(±)18-nor-D-homo-estrone methyl ether	isopropenyl acetate H_2SO_4	$\Delta^{17(17a)}$-enol acetate	17

Position of keto-group	Compound	Conditions	Product	References
17a-keto-(18-nor-D-homo)	(±)18-nor-D-homo-estrone methyl ether	acetic anhydride H_2SO_4	$\Delta^{13(17a)}$- enol acetate	17
20-keto-	3β-acetoxyallo-pregnane-20-one	isopropenyl acetate H_2SO_4	Δ^{20}- enol acetate	4
20-keto-	3β-acetoxyallo-pregnane-20-one	acetic anhydride TsOH	$\Delta^{17(20)}$-enol acetate	4

Note: TsOH ≡ toluene-p-sulphonic acid

It is now pertinent to consider the proposals which have been made concerning the mechanism of enol acetylation. Marshall et.al. [2] found that the acid catalysed reaction of acetic anhydride with 20-keto steroids (A4), yielded an enol acetate which was proved to be the $\Delta^{17(20)}$ isomer (A5). However, a different enol acetate, the Δ^{20}- isomer (A6), was obtained [3,4] from the same ketone on treatment with isopropenyl acetate under acid conditions. On the basis of this, Cornforth [5] suggested that in enol acetylation, isopropenyl acetate is more susceptible to steric hindrance than acetic anhydride, and that the formation of an enol acetate is inhibited if the α-hydrogen atom to be removed is sterically hindered, viz. 17α- hydrogen is more hindered than the 21 - hydrogen atoms.

Crawshaw, Henbest and Jones [6] have proposed a mechanism for enol acetylations which involves a cyclic transition state for all acid catalysed reactions.



X = -OAc, $-O-\overset{\overset{C}{|}}{C} = C$, or halogen

Although these authors acknowledged Cornforth's suggestion that the accessibility of the hydrogen atom to be removed was of importance, they suggested that the formation of the $\Delta^{17(20)}$ enol acetate in the higher temperature acetic anhydride reaction was due to the greater thermodynamic stability of the $\Delta^{17(20)}$- isomer. In support of this statement, the Δ^{20}- enol acetate on heating under reflux with acetic anhydride in the presence of an acid catalyst gave the $\Delta^{17(20)}$ isomer.

However, Dauben *et.al.* [7], as a result of an examination of the reactions of $\Delta^{4,6}$- cholestadien-3-one, concluded that the acid catalysed isopropenyl acetate reaction took place by the mechanism above, but that the reaction with acetic anhydride under acid conditions proceeded by coordination of the $CH_3CO^{\oplus}$ group onto the ketone oxygen atom, and the proton loss

which followed would be governed by the requirement that the transition state received maximum stabilisation by hyper-conjugation [8].

The acid-catalysed reaction of $\Delta^{4,6}$-cholestadien-3-one (A1) with acetic anhydride yielded the $\Delta^{3,5,7}$-triene enol acetate (A2). Here the proton loss was at C-8, which while being more hindered than the hydrogen atoms at C-2, its loss proceeded <u>via</u> the transition state of lower energy.

Isopropenyl acetate, and pyridine-acetic anhydride conditions were reported to yield the $\Delta^{2,4,6}$- isomer (A3). This was attributed to the greater accessibility of the C-2 hydrogen atom as opposed to the C-8 hydrogen atom. However, while isopropenyl acetate under acid conditions gave a good yield of the enol acetate, (85%), no yields were quoted for the reaction with acetic anhydride-pyridine.

Enol acetylation of cholestan-2-one under all conditions gave the Δ^{2}- enol acetate (A7) [9]. Similarly, with 17β-acetoxy-androstan-3-one, all enol acetylation experiments yielded the Δ^{2}- isomer (A8) as the sole product [10].

The production of a Δ^{2}- enol acetate from both 2-keto and 3-keto (A/B trans) compounds may be attributed to the greater conformational stability of the Δ^{2}- double bond as opposed to the Δ^{1}- and Δ^{3}- double bonds which would be partially formed in the transition state of the enol acetylation reaction [11].

Some information concerning the stability of double bonds in various positions round the steroid nucleus may be obtained from the heats of hydrogenation of the cholestenes [12].

Double bond	$-\Delta H$ K cal/mole
Δ^1	27.3
Δ^2	25.85
Δ^3	27.97
Δ^5	25.85
Δ^6	27.36
Δ^{11}	28.93

The data given in the table above indicate that the Δ^2- double bond is considerably more stable than either Δ^1- or Δ^3-.

Reaction of 17β-acetoxy-2α-methyl-androstan-3-one with isopropenyl acetate under acid conditions [10] gave Δ^2- enol acetate (A9), which shows that the accessibility of the hydrogen atom to be removed is not the only factor that determines the direction of enolisation of steroid ketones, and that it may in fact be dominated by the directional effect arising from 'conformational strain' introduced into the transition state. Apart from the effect of conformational strain discussed above, the Δ^2- double bond is additionally stabilised by the inductive effect of the methyl group [11].

The reaction of acid catalysed isopropenyl acetate with 4α-methyl-cholestan-3-one yielded the Δ^2- enol acetate (A10)

as the sole product [13]. Here the accessibility of the hydrogen to be removed and the greater stability of the Δ^2-double bond oppose the inductive effect of the 4α-methyl group which would tend to stabilise the Δ^3- double bond; the overall effect favoured the Δ^2- enol acetate.

Djerassi et.al. [10] have investigated the effect of changing the angular substituent on C-10 on the enolisation of 3-keto compounds (A/B trans). 17β-Acetoxy-19-nor-androstan-3-one afforded a mixture of the Δ^2- and Δ^3- enol acetates (A11 and A12) in the ratio 2:1 when treated with acid catalysed isopropenyl acetate. Furthermore, although the crude product from the direct bromination of this ketone could not be resolved into its components, dehydrobromination of the crude material afforded a mixture which contained an appreciable quantity of the Δ^4- conjugated ketone. Thus the crude bromination product must have contained an appreciable amount of 4-bromo-ketones.

These results imply that the removal of the angular methyl group reduces the energy difference between the Δ^2- and Δ^3- enols by reducing the conformational strain introduced during the formation of a Δ^3- double bond.

The reaction of 2α-methyl-17β-acetoxy-19-nor-androstan-3-one with acid catalysed isopropenyl acetate gave the Δ^2- enol acetate (A13) as the sole product [10]. This suggests that the inductive effect of the 2α-methyl group dominates the directional factor due to the accessibility of the hydrogen atom.

The reaction of des-A-cholestan-5-one, which is analogous to 4α-methyl-19-nor-androstan-3-one, with isopropenyl acetate - toluene-p-sulphonic acid gave an enol acetate sample[14] in which the Δ^5 : $\Delta^{5(10)}$ (A14, A15) ratio was ca. 7:3, (analogous to a Δ^3 : Δ^2 ratio of 3:7 for the 4α-methyl-19-nor-3-ketone).

Thus for 3-ketones, the major factor in determining the direction of enolisation is the nature of the angular substituent, (C-10). Only when the difference in energy levels between the two possible enols due to conformational effects is small, (viz. in the 19-nor series) can the inductive effect of α-substituents and accessibility of the hydrogen atom have any effect on the direction of enol acetylation.

Angular methyl group present

Compound	Ratio Δ^2 : Δ^3
17β-acetoxy-androstan-3-one	100:0
2α-methyl-17β-acetoxy-androstan-3-one	100:0
4α-methyl-cholestan-3-one	100:0

19-Nor-series

Compound	Ratio Δ^2 : Δ^3
17β-acetoxy-19-nor-androstan-3-one	2:1
2α-methyl-17β-acetoxy-19-nor-androstan-3-one	100:0
des-A-cholestan-5-one (analagous to 4α-methyl-17β-acetoxy-19-nor-androstan-3-one)	7:3 ~~3:7~~

Des-A-cholestan-5-one when enol acetylated with acetic anhydride - toluene-p-sulphonic acid gave a mixture of $\Delta^{5(10)}$- and Δ^{5}- enol acetates [14] (ca. 7:3). However, when the enol acetylating system was acetic anhydride-perchloric acid-carbon tetrachloride, the enol acetate obtained was the pure $\Delta^{5(10)}$ isomer.

These results are similar to those obtained by Barton et.al. [15] in the 20-keto series, where it was found that acetic-anhydride-perchloric acid-carbon tetrachloride at room temperature afforded a better yield of the $\Delta^{17(20)}$ enol acetate than acetic anhydride-toluene-p-sulphonic acid at 140°. This is contrary to the suggestion put forward by earlier workers [6] who proposed that the formation of the $\Delta^{17(20)}$ enol acetate was due to the higher reaction temperature used.

House and Thompson [16], in the synthesis of octal-1-ones, studied the enol acetylation of decal-1-one (B1). Acid catalysed acetic anhydride conditions gave predominantly the $\Delta^{1(9)}$- enol acetate (B2), while isopropenyl acetate under acid conditions afforded a mixture (ca. 1:1) of the $\Delta^{1(9)}$ enol acetate, and the Δ^{1}- isomer (B3).

Somewhat analogous to this example is the enol acetylation of (±)-18-nor-D-homo-estrone methyl ether (B4) [17], in which the product composition was dependent upon the reaction conditions. Isopropenyl acetate with an acid catalyst afforded the $\Delta^{17(12a)}$- enol acetate (B6), whereas acetic anhydride gave the $\Delta^{13(17a)}$ isomer (B5).

7-Ketocholestanyl acetate (B7) [18], on enol acetylation with isopropenyl acetate, afforded the Δ^6- isomer (B8), but the use of acetic anhydride resulted in a mixture of Δ^6- and Δ^7- isomers (B8 and B9), the former predominating.

The examples given above lend support to the statement that, when the α-positions to the keto-group are sterically more hindered than for a 2-keto or 3-keto function, enol acetylation using isopropenyl acetate will give that enol acetate which is derived by the abstraction of the least hindered hydrogen atom. The reactions involving acetic anhydride will tend to give that isomer which would result by coordination of $CH_3CO^{\oplus}$ onto the oxygen atom of the keto function, followed by a proton loss which would be governed by the requirement that the transition state received maximum stabilisation by hyperconjugation. This would account for the isolation, from acetic anhydride reactions, of enol acetates with the highest possible degree of alkyl substitution.[11]

The monobromination of 6-ketocholestanyl acetate has been shown to give mainly the 5α-bromo-ketone [1], which suggests that the Δ^5- enol is inherently more stable than the Δ^6- enol. The greater stability of the Δ^5- as opposed to the Δ^6- double bond is further supported by heats of hydrogenation data obtained by Turner, viz., Δ^5 -25.85 ; Δ^6 -27.36 K.cals./mole.

Thus acid catalysed enol acetylation of the keto-acetate (B10), with acetic anhydride should give largely the Δ^5- enol acetate (B11). On the other hand, however, it is

difficult to predict whether (in the isopropenyl acetate reaction), the greater accessibility of the 7-hydrogen atoms as opposed to the 5-hydrogen atom would be sufficient to counteract the conformational effects which render the Δ^5- double bond thermodynamically more stable than the Δ^6- double bond.

DISCUSSION

(1) Enol Acetylation of the 6-Ketone

The enol acetylation of 6-ketocholestanyl acetate at room temperature with acetic anhydride-carbon tetrachloride in the presence of perchloric acid catalyst gave an oily crude product. Chromatography of the crude material on deactivated alumina allowed the separation of an enol acetate (m.p. 109°) from unchanged starting material.

Enol acetylation of the ketone with boiling acetic anhydride with sulphuric acid as a catalyst gave, after chromatographic separation, an enol acetate sample identical with that obtained from the perchloric acid catalysed reaction.

Earlier workers [22] studied the reaction of 3β-hydroxy-cholestan-6-one with a mixture of benzoyl chloride-benzoic anhydride and obtained as a product a compound which was described as 3β, 6-dibenzoyloxy-cholest-5-ene. The structure of this compound was proved by synthesis from 5α-chloro-3β, 6β-dibenzoyloxy-cholestane by pyrolytic dehydrochlorination.

The structure of the above enol acetate sample (m.p. 109°) was proved by bromination. Bromination in pyridine-acetic acid (1:10) [23] gave a good yield of a bromo-ketone which was identical with the known 3β-acetoxy-5α-bromo-cholestan-6-one. The absence of any 7α-bromo-ketone from the bromination product proved that the enol acetate sample was the pure Δ^5-isomer, i.e., 3β, 6-diacetoxy-cholest-5-ene (B11), and did not contain any Δ^6-isomer. Bromination of the enol acetate in carbon tetra-

chloride in the presence of either potassium carbonate [11] or propylene oxide [24] again gave pure 5α-bromo-ketone, but in slightly lower yield.

The formation of the Δ^5-enol acetate in acid-catalysed acetic anhydride reactions is consistent with the factors discussed previously in the introduction.

The reaction of the keto-acetate with boiling isopropenyl acetate using toluene-p-sulphonic acid as a catalyst, and subsequent chromatography on deactivated alumina, afforded an enol acetate (m.p. 70 - 71°) in low yield (20%), which had the characteristics (e.g. sharp m.p.) of a pure compound. The rotation of this enol acetate ($[\alpha]_D$ -47°) was similar to that of the Δ^5-enol acetate ($[\alpha]_D$-49°), but a mixture of the two samples melted over a wide range of temperature (ca. 85 - 95°).

The infrared spectra of the enol acetate samples differed slightly; the spectrum of the material (m.p. 70 - 71°) showed a band at 1157 cm.$^{-1}$, which was absent in the spectrum of the Δ^5-enol acetate. The 1157 cm.$^{-1}$ band may be attributed to the presence of a hydrogen atom attached to the carbon atom containing the double bond of the enol acetate. (cf. 3,5-cyclo-6-acetoxy-cholest-6-ene (C1), 1156 cm.$^{-1}$ [25]; des-A-5-acetoxy-cholest-5-ene (C2), 1155 cm.$^{-1}$ [11]; and 3β, 7-diacetoxy-cholest-6-ene (C3), 1157 cm.$^{-1}$ [11]). Thus it seemed probable that the enol acetate (m.p. 70 - 71°) was the Δ^6 -isomer (B12).

However, bromination of this enol acetate in pyridine-acetic acid (1:10), conditions which gave the best results for the bromination of the Δ^5-enol acetate, gave an oily solid as a product, which was difficult to crystallise, and melted over a wide range of temperature (123 - 130°). Bromine analysis of the sample indicated that it was a mono-bromo-ketone, and as there was no shift in the frequency of the carbonyl absorption in the infrared spectrum of the bromo-ketone [26], a mixture of 5α- and 7α- axial bromo-ketones was inferred.

The rotation of the bromo-ketone mixture was consistent with a 5α-:7α- ratio of *ca.* 1:1. Thus the enol acetate sample must have been a mixture of the Δ^5-:Δ^6- isomers in the ratio of 1:1.

In an endeavour to separate the enol acetate mixture into its components and to characterise the Δ^6- enol acetate, careful chromatography on deactivated alumina was employed on a sample (960 mg.). In spite of dividing the mixture into 28 fractions, no separation was achieved; infrared spectra and rotations of the fractions were identical with the original mixture. (*cf.* Jones and Wluka [18], in the study of the enol acetates of 7-ketocholestanyl acetate, who found the Δ^6- and Δ^7- isomers readily separable by chromatography on deactivated alumina).

A more accurate value for the ratio of enol acetate isomers formed in the reaction of acid-catalysed isopropenyl acetate with the keto-acetate was obtained by bromination of

the crude enol acetate without first crystallising, by which process the ratio of isomers in the mixture might have been changed.

Rotatory dispersion and rotation measurements on the crude bromo-ketone samples before and after filtration through silica gel are given in the experimental section (p.30). Comparison of the peak and trough heights of the rotatory dispersion curves of the bromo-ketone mixtures with the heights of the curves for authentic 5α- and 7α- bromo-cholestan-6-one enabled the ratio of 5α-:7α- bromo-ketones in the mixture, and thus the ratio of Δ^5-:Δ^6- enol acetates in the crude enol acetate mixture, to be determined. The ratio of isomers obtained by this method, and by rotation measurements, were identical; both methods giving a Δ^5-:Δ^6- enol acetate ratio of 55:45.

From these results, it can be seen that there is indeed some specificity of reaction in the enol acetylation of 6-ketocholestanyl acetate depending on the reaction conditions. Thus the Δ^5- isomer is formed readily under conditions in which the α-hydrogen atom accessibility is not important, i.e., in reactions involving acid catalysed reaction with acetic anhydride, but the Δ^6- enol acetate is formed in the reaction where hydrogen accessibility is important, i.e., in the acid catalysed isopropenyl acetate reaction. However, in the case of the isopropenyl acetate reaction which should give the Δ^6- isomer, the hydrogen accessibility effect (favouring Δ^6-) is opposed by the conformational effect (favouring Δ^5-), the result of

these two effects being a mixture of Δ^5- and Δ^6- enol acetates (*ca.* 1:1).

(2) Dehydrobromination of Bromo-ketones

The dehydrobromination of 5α-bromo-6-ketocholestanyl acetate was originally carried out in boiling pyridine [1]. Treatment of the bromo-ketone with a suspension of lithium carbonate in N,N-dimethyl formamide at 100° resulted in starting material being isolated. However, at 150° the same mixture gave the Δ^4- conjugated ketone in 70% yield.

Treatment of the 7α-bromo-ketone in the same manner afforded the Δ^7- conjugated ketone, which has recently been prepared by other routes [27]. The more successful of these methods was from 7-dehydrocholesteryl acetate by chromic acid oxidation to the 5α-hydroxy-Δ^7- conjugated ketone, and removal of the hydroxyl group with zinc and acetic acid.

Heilbron *et.al.* [1] originally studied the bromination of 6-ketocholestanyl acetate as a possible route to 7-dehydrocholesterol. This was to have been prepared by reduction of the Δ^7- conjugated ketone to the 6β-hydroxy compound, followed by elimination of water.

However, these authors were unsuccessful in their attempts to dehydrobrominate the 7α-bromo-ketone. Under the conditions they used (silver nitrate and boiling pyridine), only 3β-acetoxy-cholesta-6,7-dione (C4) was isolated, in low

yield (18% crude product), by crystallisation of the crude reaction product. This compound would be formed by hydrolysis of the bromo-ketone to the 7α-hydroxy compound, and oxidation of this to the dione by oxygen in the basic medium.

It was decided to repeat this experiment, and to separate the reaction products by chromatography on silica gel. By this method, two crystalline products were obtained from the reaction, and were characterised as the 6,7-dione (ca. 25%), and the Δ^7- conjugated ketone, (ca. 10%). It must be pointed out that the separation of the Δ^7- conjugated ketone from the crude reaction product by crystallisation (the method used by Heilbron et.al.[1]) would be difficult, if not impossible.

(3) Structure of the Enol Form of 3β-Acetoxy-cholesta-6,7-dione

Heilbron et.al.[1] have shown the 6,7-diketone to exist in the mono-enol form (C5 or C6), by the presence of one active hydrogen atom, and by the green-violet colour formed on reaction with alcoholic ferric chloride. The infrared spectrum of the compound has an absorption peak at 3424 $cm.^{-1}$ which may be assigned to the O-H stretching frequency of an intramolecular hydrogen bonded enol form of the diketone.

The possible configurations of the enol form of the diketone are either the Δ^5-7-ketone (C5) or the Δ^7-6-ketone (C6). It has been found that the rotatory dispersion curve of 6-acetoxy-3β-bromo-cholest-5-en-7-one (E2, C7)[5] is similar to the

curve obtained for 3β-acetoxy-cholest-5-en-7-one (E4, C8) [28]; the 6-acetoxy group having little or no effect on the rotatory dispersion curve. By analogy, it was hoped that the presence of either a Δ^5- or a Δ^7- double bond in the enol acetate of the dione (C9 or C10) might be revealed by comparison of the rotatory dispersion curve of the enol acetate with the curves of 3β-acetoxy-cholest-5-en-7-one and 3β-acetoxy-cholest-7-en-6-one.

The rotatory dispersion curve of the enol acetate of the dione (E1) is unlike that of the Δ^7-6-ketone (E3), but similar to the curve of the Δ^5-7-ketone (E4) in general shape. Thus it is probable that the enol acetate of the dione is 3β,6-diacetoxy-cholest-5-en-7-one (C9) and by inference the enol form of the dione is 3β-acetoxy-6-hydroxy-cholest-5-en-7-one (C5).

(4) Attempted Enol Acetylation of 7α-Bromo-6-ketocholestanyl Acetate

It has been found that 6-acetoxy-3β, 7α-dibromo-cholest-5-ene (D1) was resistant to further bromination [25]. In order to study the bromination of the corresponding 3β-acetoxy compound, enol acetylation of the 7α-bromo-ketone was attempted.

Enol acetylation employing acetic anhydride with toluene-p-sulphonic acid, and with carbon tetrachloride-

perchloric acid, gave unchanged bromo-ketone. However, prolonged heating under reflux with acetic anhydride using toluene-p-sulphonic acid as a catalyst, and removing the acetic acid formed in the reaction, partially affected enol acetylation (15%). Chromatography of the crude product on silica gel and elution with ether gave an oily fraction ($[\alpha]_D$ + 1°) which partially solidified on standing.

The infrared spectrum of this material indicated the presence of an enol acetate function, and no keto-function. This spectrum differs from that of 6-acetoxy-3β, 7α-dibromo-cholest-5-ene [25] by the higher frequency of the enol acetate carbonyl band, the presence of a strong C = C absorption band at 1650 $cm.^{-1}$, and the complex C - O bands of the enol acetate. On the basis of the above evidence, it is probable that the enol acetate product ($[\alpha]_D$ + 1°) is the Δ^6-isomer (D2), although no analytical data could be obtained.

In support of this, Rutherford and Stevens [29] have found that in enol acetylation of some α-halo-ketones, by treatment of the ketones with sodium methoxide and acetyl chloride, enolisation occurred towards the carbon atom carrying the halogen atom.

(5) Enol Acetylation of Δ^4-6-Ketocholestanyl Acetate

In an attempt to prepare the enol acetates of the Δ^4- conjugated ketone and to study the bromination products of

these compounds, enol acetylation experiments were carried out. Some examples of enol acetylations of conjugated ketones in the steroid series are given below.

Compound	Conditions	Product	References
cholest-4-en-3-one	isopropenyl acetate-sulphuric acid	$\Delta^{3,5}$-enol acetate	30
cholesta-4,6-dien-3-one	acetic anhydride-acetyl chloride	$\Delta^{3,5,7}$-enol acetate	7
cholesta-4,6-dien-3-one	isopropenyl acetate-TsOH	$\Delta^{2,4,6}$-enol acetate	7
3β-acetoxy-cholest-8-en-7-one	isopropenyl acetate-TsOH	$\Delta^{7,9(11)}$-enol acetate	31
3α, 20β-diacetoxy-5β-Δ^{8}-pregnen-11-one	acetic anhydride-TsOH	$\Delta^{7,9(11)}$-14α-H and 14β-H), + $\Delta^{8(14),9(11)}$-enol acetate	32

Note: TsOH ≡ toluene-p-sulphonic acid.

Enol acetylation of the Δ^{4}- conjugated ketone with boiling acetic anhydride and sodium acetate, acetic acid-carbon tetrachloride and perchloric acid, and with boiling acetic anhydride - toluene-p-sulphonic acid conditions each gave oily products, (A), (B), and (C) respectively, none of which could be crystallised. Chromatography of these products on deactivated alumina resulted in their decomposition, and in all cases no compound could be eluted. An attempt was made to purify product (C) by sublimation, but this too was unsuccessful.

In order to obtain information about the reaction product (C), a sample was hydrolysed under mild acid conditions

and the product chromatographed on deactivated alumina. Light petroleum-benzene (4:1) eluted a compound, the infrared (1695 cm.$^{-1}$) and ultra violet spectra (λmax. 2510 Å, ε -13,200) of which were those of a cross-conjugated dienone. Thus the conjugated ketone must be cholesta-4,7-dien-6-one (D3), which had previously not been prepared. No confirmation of this assignment could be made from rotatory dispersion measurements in view of the lack of compounds of analogous structure.

Elution with the same solvent gave a further compound which was characterised by m.p. 126° (lit. value 129 - 130°), infrared spectrum 1681 cm.$^{-1}$ (1686 cm.$^{-1}$) and ultra violet spectrum λmax. 3150 Å, ε -9,400 (λmax. 3140 Å, ε - 9,500) as cholesta-2,4-dien-6-one (D4) [33].

The isolation of the two conjugated ketones in which the 3β-acetoxy group is absent indicates that under the acid catalysed enol acetylation conditions, enol acetylation is accompanied by the loss of the 3β-acetoxy group. Analogous to this observation is the loss of the 3β-acetoxy group when 3β-acetoxy-cholest-5-en-7-one (D5) was heated under reflux in benzene in the presence of toluene-p-sulphonic acid to yield cholesta-3,5-dien-7-one (D6) [12].

Examination of infrared data obtained for the crude products (A, B, C) from the enol acetylation reactions, confirms that the 3β-acetoxy group is eliminated only under acid catalysed conditions. Thus reaction with sodium acetate and acetic anhydride, while yielding an enol acetate function,

the product still contains the 3β-acetate group.

Conditions	Enol Acetate	3β-Acetate
acetic anhydride-sodium acetate	1770, 1206, 1189 $cm.^{-1}$	1742, 1235 $cm.^{-1}$
acetic anhydride-carbon tetrachloride-perchloric acid	1767, 1205, 1188 $cm.^{-1}$	- - -
acetic anhydride-toluene-p-sulphonic acid	1767, 1200, 1190 $cm.^{-1}$	- - -

In spite of the fact that a more detailed examination of the enol acetylation reactions will have to be carried out before the enol acetates can be identified, it is still of interest to speculate about the identity of the reaction products (A, B, C).

In view of the infrared data, it seems likely that the major component of the sodium acetate - acetic anhydride reaction product will be 3β,6-diacetoxy-cholesta-4,6-diene (D7), even though the alternative $\Delta^{5,7}$- diene system (D8) may not be completely excluded.

Unless isomerisation of the double bonds occurs during the mild hydrolysis of crude product (C), which is unlikely, the two dienones, $\Delta^{2,4}$-6-ketone and $\Delta^{4,7}$-6-ketone must be derived from the $\Delta^{2,4,6}$- and $\Delta^{3,5,7}$- enol acetates (D9 and D10).

EXPERIMENTAL

Melting points are corrected. Specific rotations were measured in chloroform in a 1 dm. polarimeter tube at room temperature. Micro-analyses were carried out at the University of Otago. Infrared absorption measurements were in carbon disulphide solutions and were recorded with a Perkin-Elmer Model 221 double-beam instrument equipped with a sodium chloride prism. Ultraviolet absorption data were obtained with methanol solutions. Alumina used for chromatography was P. Spence Grade 'H'; deactivated alumina refers to grade 'H' to which 5% of 10% aqueous acetic acid has been added. Silica gel used for chromatography was Hopkin and Williams 'Material for Chromatography'. Light petroleum refers to the fraction of b.p. 50 - 70°

6-Nitrocholesteryl-nitrate.

A suspension of cholesterol (20g.) in acetic acid (80c.c.) was stirred with fuming nitric acid (1c.c.) at 20°. This was cooled to 0°, and fuming nitric acid (130c.c.) was added dropwise during 1 hr., and the mixture was stirred for a further 30 min. The solid obtained, after filtration and drying in air, was the product, 6-nitro-cholesteryl-nitrate (11.7g.), m.p. 128°. (Heilbron et.al. J.Chem.Soc., 1937, 801, quote m.p. 128°).

3β-Hydroxy-cholestan-6-one.

A solution of 6-nitro-cholesteryl nitrate (10g.) in acetic acid (140c.c.) and water (27c.c.) was heated with zinc powder (18g.) at 100° for 2 hr., and then heated under reflux for 10 hr. The solution was diluted with water (2l.) and the product extracted with ether (1l; 500c.c.). The etherial extract was washed successively with sodium bicarbonate, water, brine, and dried. Removal of the solvent at 20m.m. gave a colourless solid (9.6g.) as a residue. This solid (63g.) was heated under reflux with hydrochloric acid (190c.c.) and ethanol (675 c.c.) for 1½ hr. Dilution of the solution with water (2l.) gave a colourless solid m.p. 133-134°, which on crystallisation from ethanol afforded 3β-hydroxy-cholestan-6-one (28g.), as needles, m.p. 140-141°, $[\alpha]_D$ -2° (c=0.99), ν max. 3610cm.$^{-1}$ (OH), and 1718cm.$^{-1}$ (C=O). (Barton and Cox, J.Chem.Soc., 1948, 783, quote m.p. 140°, $[\alpha]_D$ -6°).

3β-Acetoxy-cholestan-6-one.

3β-Hydroxy-cholestan-6-one (38g.) was dissolved in the minimum amount of warm pyridine (ca. 100c.c.) and acetic anhydride (25c.c.) was added, and the solution left for 18 hr. at 20°. Removal of the solvent at 20m.m. and crystallisation from ethanol afforded 3β-acetoxy-cholestan-6-one (30.2g.) as needles, m.p. 129°, $[\alpha]_D$-24° (c=0.935), ν max. 1739 and 1236cm.$^{-1}$ (OAc), and 1721cm.$^{-1}$ (C=O). (Barton and Cox, J.Chem. Soc., 1948, 783, quote m.p. 129°, $[\alpha]_D$-16°).

3β-Acetoxy-5α-bromo-cholestan-6-one.

Bromine (0.40g. ; 1.1 mol.) in acetic acid (1.5c.c.) was added dropwise during 10 min. to a solution of 3β-acetoxy-cholestan-6-one (1.0g.) in dry ether (100c.c.) at 0°. The solution was stirred for 30 min., and isolation via ether and subsequent crystallisation from ether-light petroleum gave the bromo-ketone (607mg.), m.p. 164-165°, $[\alpha]_D$-134° (c=0.92), ν max. 1745 and 1236cm.$^{-1}$, (OAc), and 1724cm.$^{-1}$ (ax. bromo-ketone). (Heilbron et.al., J.Chem.Soc., 1937, 801, quote m.p. 162°, $[\alpha]_D$-133°).

3β-Acetoxy-7α-bromo-cholestan-6-one.

Bromine (1.1g. ; 1 mol.) in acetic acid (20c.c.) was added during 1 hr. to a stirred solution of 3β-acetoxy-cholestan-6-one (3.0g.) in ether (30c.c.) and acetic acid (7.0c.c.),

at 30°. The mixture was heated under reflux for 2 hr., and the oily solid (3.30g.), isolated *via* ether, was adsorbed on silica gel (100g.). Elution with light petroleum-benzene (1:1) and crystallisation from methanol-ether gave the bromo-ketone as needles (1.78g.), m.p. 146-147°, $[\alpha]_D$+44° (c=0.96), ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1724cm.$^{-1}$ (*ax.* bromo-ketone). (Heilbron *et.al.*, *J.Chem.Soc.*, 1937, 801, quote m.p. 145° $[\alpha]_D$+41°).

Isomerisation of 3β-Acetoxy-5α-bromo-cholestan-6-one.

A solution of the bromo-ketone (100mg.) in acetic acid-chloroform (10c.c. ; 1:1) containing aqueous hydrogen bromide (0.3c.c. ; 50%) was kept at 20° for 24 hr. Due to the dark colour of the solution, kinetic observations using the polarimeter were impossible, and the solution was worked up *via* ether to give a solid m.p. 125-130°, $[\alpha]_D$-68° (c=0.76), ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1721cm.$^{-1}$ (*ax.* bromo-ketone).

The rotation data indicate a mixture of bromo-ketones 5α-:7α-; 65:35.

Attempted Isomerisation of 3β-Acetoxy-7α-bromo-cholestan-6-one.

A solution of the bromo-ketone (100mg.) in chloroform-acetic acid (10c.c. ; 1:1) containing aqueous hydrogen bromide (0.3c.c. ; 50%) was kept at 20° for 24 hr. Isolation *via* ether and crystallisation from methanol yielded unchanged

bromo-ketone (78mg.) as needles, m.p. 146-147°, $[\alpha]_D$+43° (c=1.02), ν max. 1745 and 1236cm^{-1} (OAc), and 1721cm^{-1} (ax. bromo-ketone).

Enol Acetylation of 3β-Acetoxy-cholestan-6-one.

(a) A solution of 3β-acetoxy-cholestan-6-one (5g.) in carbon tetrachloride (130c.c.) was treated with acetic anhydride (7c.c.), and aqueous perchloric acid (0.5c.c.; 60%), and kept at 20° for 18 hr. The mixture was diluted with ether (1 l.) and washed successively with sodium bicarbonate solution, water, brine, and dried. Evaporation of solvent afforded an oil (5.73g.) which was adsorbed on deactivated alumina (500g.). Elution with light petroleum-benzene (100:35) gave solid 3β,6-diacetoxy-cholest-5-ene (3.74g.), and crystallisation from methanol-ether gave needles (2.7g.) m.p. 109°. Crystallisation from methanol gave needles m.p. 91-92°, $[\alpha]_D$-49° (c=0.98), (Found: C, 76.1; H, 10.2; O, 13.55. $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.3; O, 13.2%) ν max. 1761 and 1205cm^{-1} (enol acetate), 1745 and 1241cm^{-1} (3β-acetate), and 1701cm^{-1} (C=C). Elution with benzene afforded unchanged starting material (750mg.), identified by m.p. 129°, $[\alpha]_D$-24° (c=0.93), ν max. 1739 and 1236cm^{-1} (OAc), and 1721cm^{-1} (C=O).

(b) A solution of 3β-acetoxy-cholestan-6-one (451mg.) in acetic anhydride (8c.c.) and sulphuric acid (0.02c.c.) was heated under reflux for 1 hr. Isolation via ether afforded an oil (519 mg.) which was adsorbed on deactivated alumina (50g.)

Elution with light petroleum-benzene (10:3) and crystallisation from ether-methanol gave 3β,6-diacetoxy-cholest-5-ene (339mg.) as needles, m.p. 109°, $[\alpha]_D$-49° (c=0.98), ν max. 1761 and 1205cm.$^{-1}$ (enol acetate), 1745 and 1241cm.$^{-1}$ (3β-acetate), and 1701cm.$^{-1}$ (C=C).

(c) The solvent was fractionally distilled at 96° from a solution of 3β-acetoxy-cholestan-6-one (8.015g.) and toluene-p-sulphonic acid (1.27g.) in isopropenyl acetate (200c.c.). After 8 hr., during which time 50c.c. of solvent had distilled over, the remaining solvent was removed at 20m.m. pressure. The residue was worked up *via* ether in the usual manner, and afforded an oil (9.26g.) which was adsorbed on de-activated alumina (800g.). Elution with light petroleum-benzene (10:3), and crystallisation from methanol gave an *enol acetate* sample (1.58g.) as needles, m.p. 70-71°, $[\alpha]_D$-47° (c=1.07), (Found: C, 76.1; H, 10.1; O, 13.3. $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.3; O, 13.2%) ν max. 1761 and 1209cm.$^{-1}$ (enol acetate), 1742 and 1238cm.$^{-1}$ (3β-acetate), and 1701cm.$^{-1}$ C=C). Further elution with the same solvent followed by elution with benzene yielded unchanged starting material (5.28g.), m.p. 129°, $[\alpha]_D$-24° (c=0.85), ν max. 1739 and 1236cm.$^{-1}$ (3β-acetate), and 1721cm.$^{-1}$ (C=O).

Bromination of 3β,6-Diacetoxy-cholest-5-ene.

Bromine (250mg. ; 1.5 mol.) in acetic acid (1 c.c.) was added to a solution of the enol acetate (500mg.) in pyridine-acetic acid (4.5c.c. ; 1:10) at 20°. The uptake of the bromine by the enol acetate was rapid, and a precipitate of bromo-ketone formed, which was isolated *via* ether-chloroform (500c.c.; 20:1) and washed successively with aqueous sodium sulphite, hydrochloric acid (2N), aqueous sodium hydrogen carbonate, saturated brine and finally dried. Removal of solvent at 20mm. gave the crude product (553mg.), which was adsorbed on silica gel (50g.). Elution with light petroleum-benzene (1:1) and crystallisation from ether-light petroleum gave 3β-acetoxy-5α-bromo-cholestan-6-one (450mg.) as needles, m.p. 167-168°, $[\alpha]_D$-131° (c=0.96), ν max. 1745 and 1236cm.$^{-1}$, (3β-acetate), and 1724cm.$^{-1}$ (*ax.* bromo-ketone).

Bromination of the Enol Acetate mixture (m.p. 70-71°).

(a) Bromine (250mg. ; 1.5 mol.) in acetic acid (1.0c.c.) was added to a solution of the enol acetate (491mg.) in pyridine-acetic acid (4.5c.c. ; 1:10) at 20°. After 10 min. the excess bromine was destroyed by aqueous sodium sulphite and the steroidal material recovered *via* ether in the usual manner. Removal of the solvent at 20mm. gave a crude bromo-ketone mixture (511mg.), m.p. 115-125°, $[\alpha]_D$-50° (c=0.93), ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1721cm.$^{-1}$ (*ax.* bromo-ketone).

R.D. in methanol: [M] (3275Å), - 3600°; (3250Å), -4050°; (2800Å), + 5400°; (2760Å), + 5000.

Adsorption of the crude bromo-ketone mixture on silica gel (50g.) and subsequent elution with light petroleum-benzene (1:1) gave a mixed bromo-ketone sample (400mg.), $[\alpha]_D$-50° (c=0.99), ν max. 1745 and 1236cm^{-1} (OAc), and 1721cm^{-1} (ax. bromo-ketone). R.D. in methanol: [M] (3262Å), -4200°; (3225Å), -4500°; (2850Å), + 5970°; (2813Å), + 585°.

(b) Conditions as before (500 mg. enol acetate).

Crude reaction product (517 mg.) : $[\alpha]_D$-49° (c=1.04), R.D. in methanol: [M] (3300Å), -2800°; (2900Å) + 3950°.

Material after filtration through silica gel (425mg.): $[\alpha]_D$ -50° (c=0.87), R.D. in methanol: [M] (3350Å), -3200°; (2800Å), + 6480.

Rotations on the bromo-ketone mixtures both before and after filtration through silica gel indicate a ratio 5α : 7α roughly 55:45.

O.R.D. results and interpretations

Compound	Peak	5α:7α	Trough	5α:7α
5α-Bromo-cholestan-6-one	-13500		+18800	
7α-Bromo-cholestan-6-one	+7200		-9800	
Expt. (a) crude	-4050	55:45	+5400	55:45
Expt. (a) after filtration through silica gel	-4500	55:45	+5970	55:45
Expt. (b) crude	-2800	50:50	+3950	50:50
Expt. (b) after filtration through silica gel	-3200	50:50	+6480	55:45

Hydrolysis of 3β,6-Diacetoxy-cholest-5-ene.

3β,6-Diacetoxy-cholest-5-ene (400mg.) in methanol (20c.c.) was heated under reflux with aqueous potassium hydroxide (2c.c. ; 25%) for 30 min. Isolation in the usual manner afforded a solid which on crystallisation from methanol gave 3β-hydroxy-cholestan-6-one (306mg.) as fine needles, m.p. 140-141°, $[\alpha]_D$-2° (c=0.99), ν max. 3623cm.$^{-1}$ (OH), and 1721cm.$^{-1}$ (C=O).

Hydrolysis of Enol Acetate (m.p. 70-71°).

The enol acetate (120mg.) in methanol (6c.c.) was heated under reflux with aqueous potassium hydroxide (0.6c.c. ; 25%) for 30 min. Isolation *via* ether yielded a solid which on crystallisation from methanol gave 3β-hydroxy-cholestan-6-one (79mg.) as fine needles m.p. 140-141°, $[\alpha]_D$-2° (c=0.99), ν max. 3623cm.$^{-1}$ (OH), and 1721cm.$^{-1}$ (C=O).

Attempted preparation of 3β-Acetoxy-cholest-4-en-6-one.

3β-Acetoxy-5α-bromo-cholestan-6-one (1.0g.) and lithium carbonate (3.5g.) in N,N-dimethyl formamide (100c.c.) were kept at 100° for 2 hr. Isolation *via* ether, and washing successively with hydrochloric acid (2N), sodium bicarbonate, water, brine, and drying, yielded a solid, and crystallisation of this from ether-light petroleum gave unchanged bromo-ketone (833mg.) as needles m.p. 166-168°, $[\alpha]_D$-134° (c=0.92),

ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1721cm.$^{-1}$ (ax. bromo-ketone).

3β-Acetoxy-cholest-4-en-6-one.

3β-Acetoxy-5α-bromo-cholestan-6-one (950mg.) was added to a boiling suspension of lithium carbonate (3.5g.) in N,N-dimethyl formamide (100c.c.). The mixture was heated under reflux for 4 hr. and recovery of steroidal material *via* ether gave an oil (755mg.) which was adsorbed on deactivated alumina (750g.). Elution with light petroleum-benzene (2:1) gave the conjugated ketone (552mg.) which on crystallisation from methanol gave chunky needles, m.p. 111°, $[\alpha]_D$-49.5° (c=1.06), ν max. 1748 and 1230cm.$^{-1}$ (OAc), 1701cm.$^{-1}$ (C=C-C=O), and 1645cm.$^{-1}$ (C=C), λmax. 2360Å, (ε, 5,800). (Heilbron *et.al.*, *J.Chem.Soc.*, 1937, 801, quote m.p. 110°, $[\alpha]_D$-50.5, λ max. 2360Å (ε, 6,300)).

3β-Acetoxy-cholest-7-en-6-one.

3β-Acetoxy-7α-bromo-cholestan-6-one (250mg.) was added to a boiling suspension of lithium carbonate (900mg.) in N,N-dimethyl formamide (25 c.c.) under nitrogen. The suspension was heated under reflux for 3 hr., and working up *via* ether afforded an oil (216mg.) which was adsorbed on silica gel (30g.). Elution with benzene-ether (50:1) gave a solid (136mg.) which on crystallisation from methanol gave the conjugated ketone as needles, m.p. 152-153°, $[\alpha]_D$+1° (c=0.98), (Found: C, 78.6; H, 10.2; O, 10.9. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.5; O, 10.8%)

ν max. 1742 and 1236cm.$^{-1}$ (OAc), and 1684cm.$^{-1}$ (C=C-C=O), λ max. 2450 Å, (ε, 21,400). R.D. in methanol: [M] (5890Å), +800°; (5000Å), + 550°; (4000Å), + 1300°; (3450Å), + 6500; (3100Å), - 6000°. (Harvey and Bloch, Chem. and Ind., 1961, 595, quote m.p. 151-152° only).

Attempted Dehydrobromination of 3β-Acetoxy-7α-bromo-cholestan-6-one (cf. J.Chem.Soc. 1937, 801.)

The bromo-ketone (719mg.) was heated under reflux with pyridine (15c.c.) and silver nitrate (1.5g.) for 5 hr. After working up in the usual manner, a dark tar (520mg.) was obtained, and adsorbed on silica gel (50g.). Elution with light petroleum-benzene (1:2) and crystallisation from methanol, afforded 3β-acetoxy-cholestane-6,7-dione (147mg.) as needles, m.p. 162-163°, $[\alpha]_D$-115° (c=1.01), ν max. 3424 cm.$^{-1}$(OH), 1742 and 1233cm.$^{-1}$ (3β-acetate), 1680cm.$^{-1}$(C=C-C=O), and 1652cm.$^{-1}$ (C=C), λ max. 2740 Å, (ε, 11,700). R.D. in methanol: [M] (5890Å), -350°; (5000Å), -150°; (4000Å), -1150°; (3250Å), -5000°; (3000Å), -1500°; (2975Å), - 500°. (Heilbron et.al., J.Chem.Soc., 1937, 801, quote m.p. 156-157°, $[\alpha]_D$ -108°, λ max. 2745Å, (ε, 10,700)). Further elution with benzene-ether (50:1) gave 3β-acetoxy-cholest-7-en-6-one (75mg.) and crystallisation from methanol afforded needles, m.p. 152-153°, $[\alpha]_D$+1° (c=0.98), ν max. 1742 and 1236cm.$^{-1}$ (OAc), and 1684cm.$^{-1}$ (C=C-C=O), λ max. 2450Å, (ε, 21,400).

Acetylation of 3β-Acetoxy-cholestane-6,7-dione.

A solution of the diketone (90mg.) in pyridine (2c.c.) and acetic anhydride (0.2c.c.) was kept at 20° for 24 hr. Isolation via ether afforded a solid (108mg.) which on crystallisation from methanol gave the enol acetate (probably 3β,6-diacetoxy-cholest-5-en-7-one), m.p. 105-106°, $[\alpha]_D$-116° (c=0.99), (Found: C, 74.89; H, 9.55. $C_{31}H_{48}O_5$ requires C, 74.32; H, 9.67%) ν max. 1742 and 1233cm.$^{-1}$ (3β-acetate), 1767 and 1202cm.$^{-1}$ (enol acetate), 1695cm.$^{-1}$ (C=C-C=O), and 1650cm.$^{-1}$ (C=C), λ max. 2430Å, (ε max., 15100). (cf. 6-acetoxy-3β-bromo-cholest-5-en-7-one: λmax. 2430Å, (εmax., 14700) [25]). R.D. in methanol: [M] (5890Å), + 1800°; (5000Å), + 1500°; (4000Å), + 400°; (3375Å), - 850°; (3325Å), - 650°; (3300Å), - 1550°; (3275Å), - 700°; (2750Å), - 6100°.

Attempted Enol Acetylation of 3β-Acetoxy-7α-bromo-cholestan-6-one.

(a) A solution of the bromo-ketone (254mg.) and toluene-p-sulphonic acid (20mg.) in acetic anhydride (20c.c.) was heated under reflux for 1 hr. Isolation via ether gave unchanged starting material (251mg.) m.p. 140-142°, ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1724cm.$^{-1}$ (ax. bromo-ketone).

(b) The bromo-ketone (250mg.) in carbon tetrachloride (5.6c.c.), acetic anhydride (0.3c.c.), and perchloric acid (0.02c.c.) was kept at 20° for 18 hr. Isolation via ether afforded unchanged starting material (237mg.), m.p. 138-140°,

ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1724cm.$^{-1}$ (ax. bromo-ketone).

(c) The solvent was fractionally distilled at 140° from a solution of 3β-acetoxy-7α-bromo-cholestan-6-one (915mg.) and toluene-p-sulphonic acid (300mg.) in acetic anhydride 75c.c. After 7 hr., during which time 25c.c. of solvent had distilled over, the remaining solvent was evaporated at 20m.m., and the residue worked up *via* ether in the usual manner. Evaporation of solvent afforded an oily solid (1.04g.), which was adsorbed on silica gel (100g.). Light petroleum-benzene (1:2) eluted unchanged starting material (811mg.), which on crystallisation from methanol gave needles, m.p. 146-147°, $[\alpha]_D$ + 44° (c=0.96), ν max. 1745 and 1236cm.$^{-1}$ (OAc), and 1724cm.$^{-1}$ (ax. bromo-ketone). Elution with ether gave an oil (157mg.) which partially solidified on standing. Infra-red data indicated this oil to be an enol acetate, $[\alpha]_D$+1° (c=0.91) ν max. 1742, 1235, 1215 and 1133cm.$^{-1}$ (3β-acetate), 1789 and 1178cm.$^{-1}$ (enol acetate), and 1650cm.$^{-1}$. No analytical data could be obtained.

Enol Acetylation of 3β-Acetoxy-cholest-4-en-6-one.

(a) The conjugated ketone (315mg.) was heated under reflux with anhydrous sodium acetate (350mg.) and acetic anhydride (21c.c.) for 5 hr. Removal of the solvent at 20m.m. and isolation *via* ether afforded an oil (A) (346mg.), ν max. 1770, 1206 and 1189cm.$^{-1}$ (enol acetate), and 1742 and

1235cm.$^{-1}$ (3β-OAc).

(b) The conjugated ketone (350mg.) in carbon tetrachloride (9c.c.), acetic anhydride (0.5c.c.) and perchloric acid (0.02c.c.) was left at 20° for 18 hr. Isolation *via* ether gave an oil (B) (385mg.), ν max. 1767, 1205 and 1188cm.$^{-1}$ (enol acetate), 1661 (C=C). Chromatography on deactivated alumina was unsuccessful due to decomposition of this material on the column.

(c) A solution of 3β-acetoxy-cholest-4-en-6-one (494mg.) and toluene-*p*-sulphonic acid (18mg.) in acetic anhydride (25c.c.) was heated under reflux for 2 hr. Removal of the solvent at 20m.m. pressure followed by isolation in the usual manner afforded an oil (C) (498mg.), ν max. 1767, 1200 and 1190cm.$^{-1}$ (enol acetate), and 1658cm.$^{-1}$ (C=C).

Hydrolysis of the above Enol Acetate. (C)

A solution of the crude enol acetate (93mg.) from the acetic anhydride-toluene-*p*-sulphonic acid reaction, in methanol (10c.c.) and sulphuric acid (7N; 2c.c.) was heated under reflux for 1 hr. Isolation *via* ether yielded an oil (84mg.) which was adsorbed on deactivated alumina (8g.). Elution with light petroleum-benzene (4:1; 25 c.c.) gave a solid (29mg.) which on crystallisation from methanol afforded cholesta-4,7-dien-6-one as plates, m.p. 108-109°, $[\alpha]_D$+5° (c=1.13), (Found: C, 84.2; H, 10.7. $C_{27}H_{42}O$ requires

C, 84.7; H, 11.05%) ν max. 1695cm.$^{-1}$ (C=C-C=O), λ max. 2510Å, (εmax., 13220). R.D. in methanol: [M] (6000Å), - 650°; (5890Å), - 600°; (5000Å), - 250°; (4000Å), + 200°; (3650Å), + 230°; (3075Å), - 19200°; (2775Å), + 1900°; (2700Å), + 600°. Further elution with the same solvent (15c.c.) gave a solid (13mg.), cholesta-2,4-dien-6-one, m.p. 126°, ν max. 1681cm.$^{-1}$ (C=C-C=O). λ max. 3150Å (εmax., 9400). (Reich, Walker, and Collins, J.Org.Chem., 1951, 16, 1753, quote m.p. 129-130°, ν max. 1686cm.$^{-1}$, and λ max. 3140Å, (εmax., 9500)).

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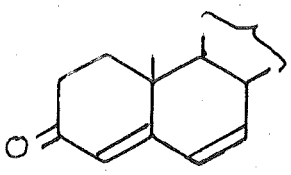

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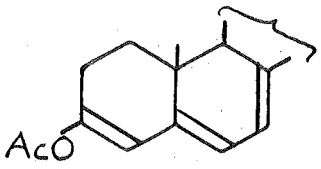

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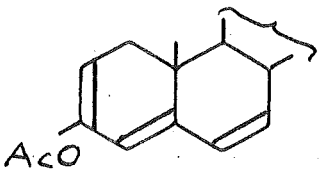

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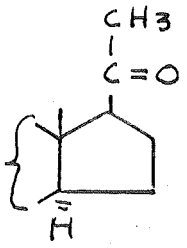

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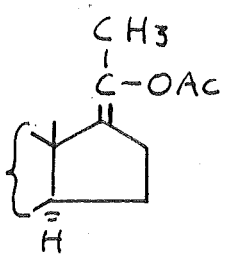

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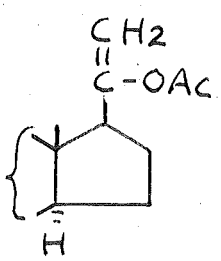

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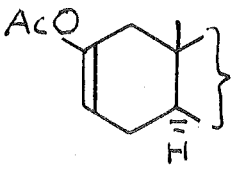

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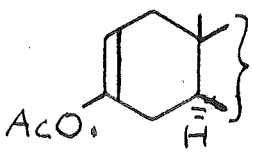

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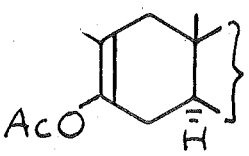

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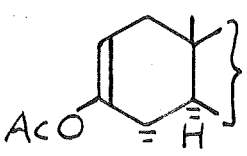

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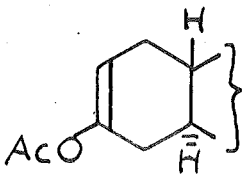

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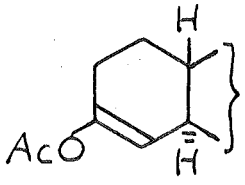

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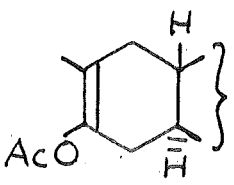

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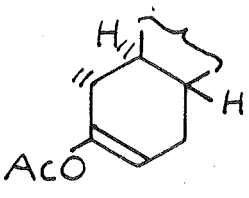

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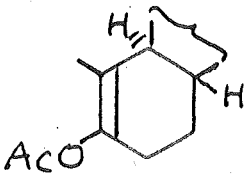

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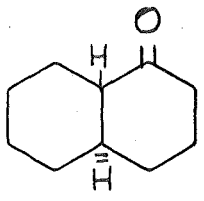

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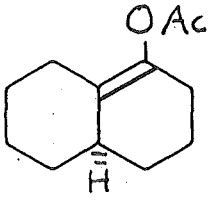

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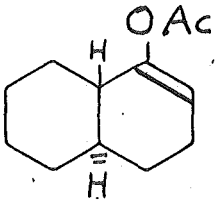

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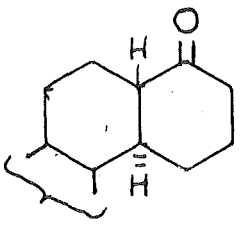

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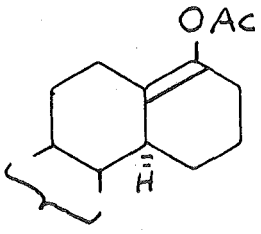

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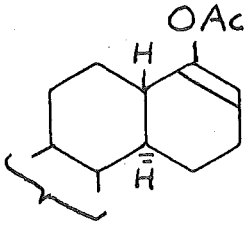

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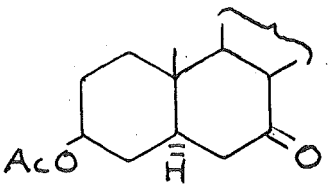

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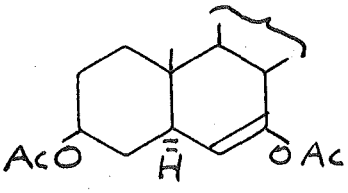

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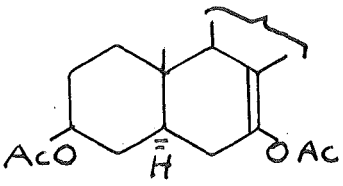

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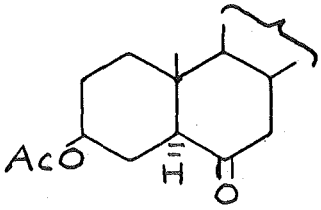

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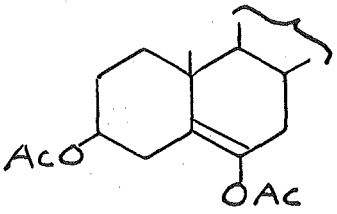

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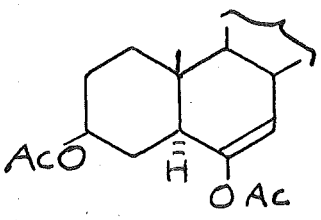

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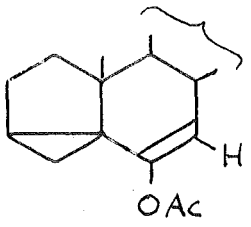

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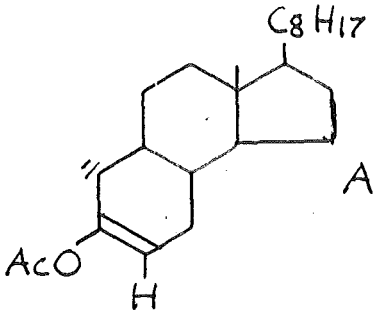

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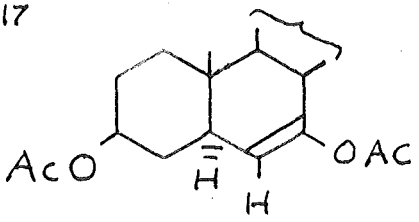

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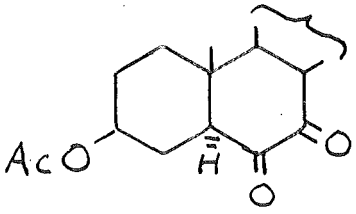

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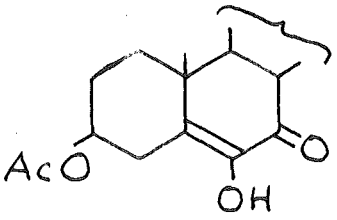

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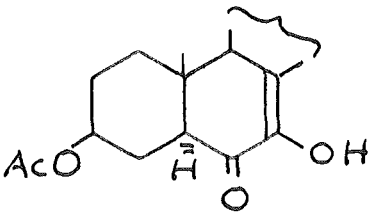

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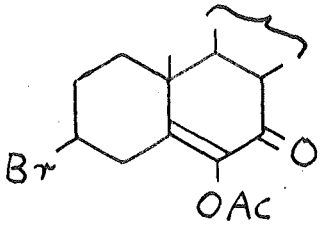

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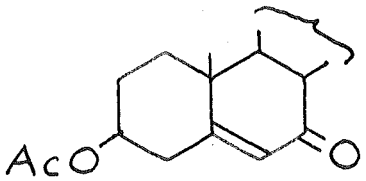

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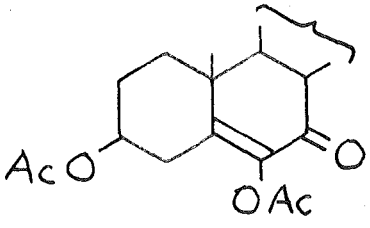

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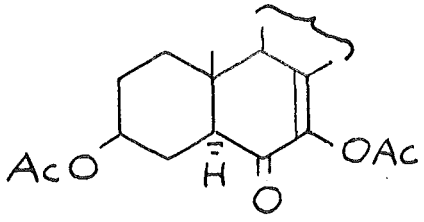

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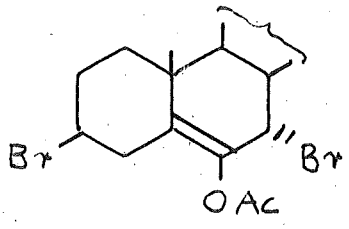

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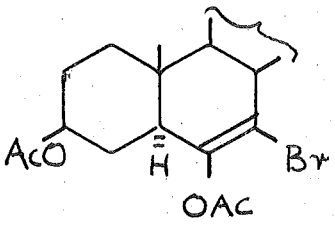

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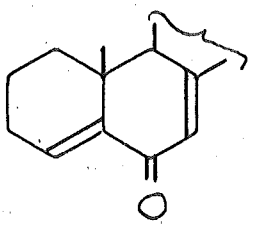

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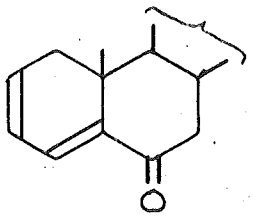

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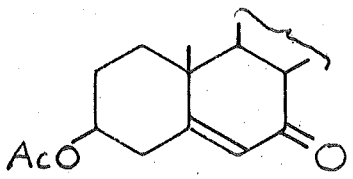

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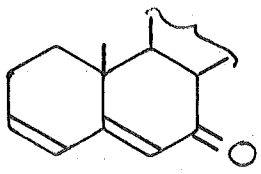

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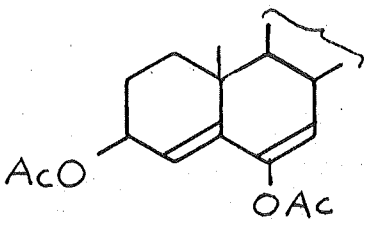

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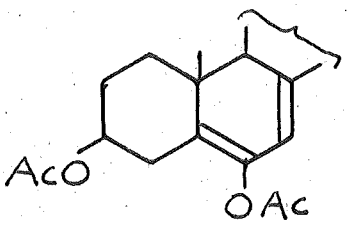

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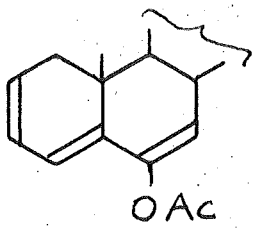

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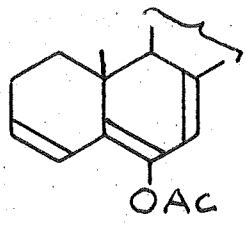

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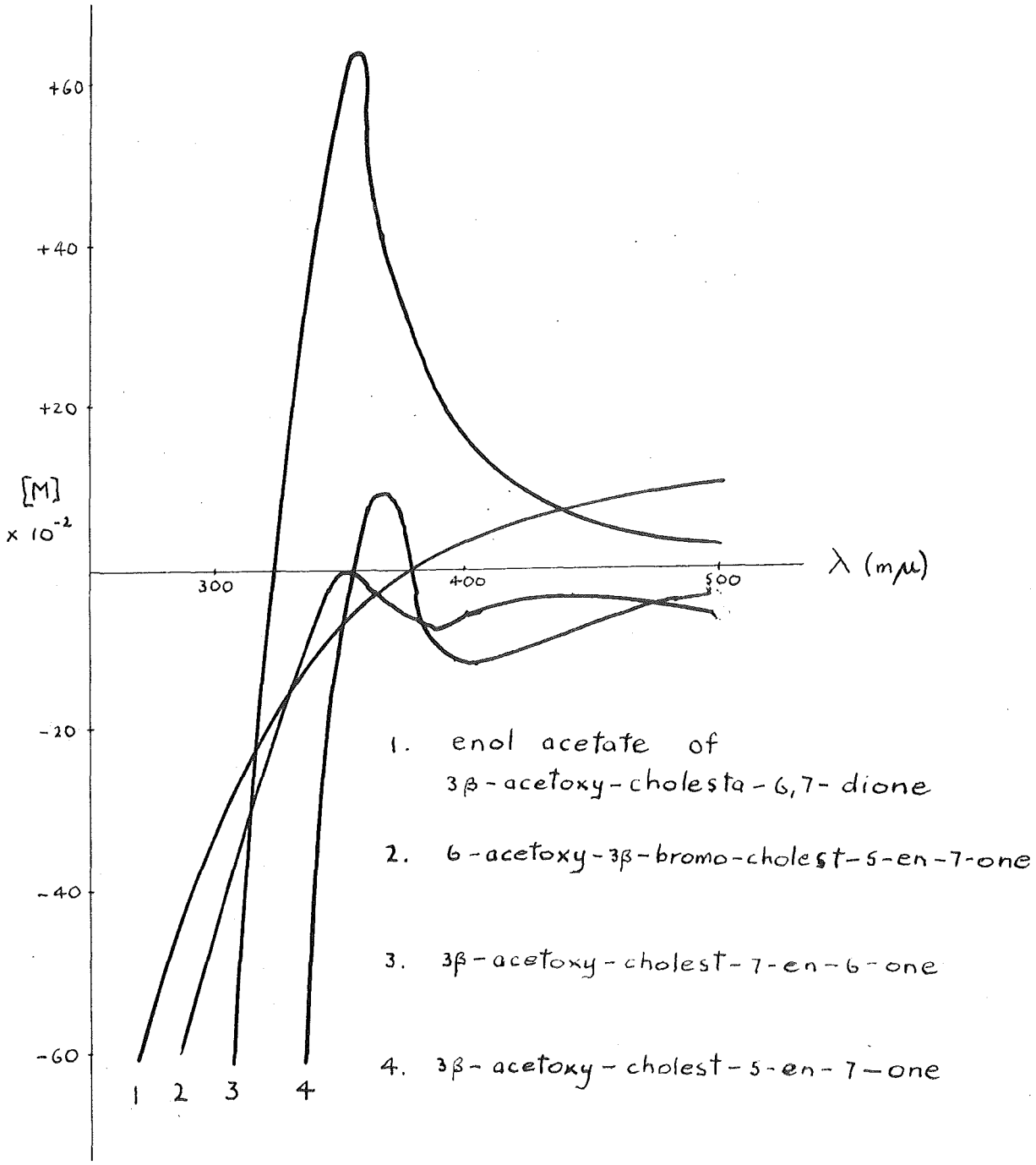

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3. 3β-acetoxy-cholest-7-en-6-one
4. 3β-acetoxy-cholest-5-en-7-one