1971

Studies Of Alpha-bromoketones And Alpha-acetoxyketones

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STUDIES OF α-BROMOKETONES AND α-ACETOXYKETONES

by

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Submitted in partial fulfillment

of the requirement for the degree of

Doctor of Philosophy

Faculty of Graduate Studies

The University of Western Ontario

London, Ontario, Canada

July 1971

ABSTRACT

The reactions of ring-A α-bromo and α-acetoxy ketosteroids of both 5α- and 5β-series with acetate ion were investigated in detail. By comparing the different amounts of α-acetoxyketones and α,β-unsaturated ketones formed at various temperatures in the two solvent systems studied, the following points have been established: (a) The mechanism of formation of α-acetoxyketone from α-bromoketone and acetate ion depends on the solvent system. In a polar solvent like acetic acid, a symmetric intermediate explains the results. In a less polar solvent like acetone, S_N2 displacement probably operates. (b) In acetic acid medium, α-acetoxyketone usually undergoes interchange of carbonyl and acetoxyl groups at temperatures higher than 135°, very probably via a cyclic ortho ester-like intermediate. (c) Around 200°, transfer of the acetoxyl group from the α- to the α'-position occurs. A symmetric intermediate with substantial charge separation satisfactorily explains the result. (d) Elimination of acetic acid to give α,β-unsaturated ketones occurs to a significant extent only when the resulting α,β-unsaturated

ketone is secondary-tertiary. As a result, the long-known h-Δ^1-cholestenone rearrangement is clarified through the successive operations of these four steps.

The reactions of monocyclic α-acetoxyketones with acetate ion in acetic acid were also investigated, using deuterium exchange and C-13 labelling. Besides confirming the results of steroid compounds, the degenerate rearrangements of monocyclic α-acetoxyketones were shown to be of preparative value for H- and C- labelling. Medium ring effects were observed in the seven-, eight- and nine-membered ring compounds.

ACKNOWLEDGEMENT

The author thanks Dr. E. W. Warnhoff for advice, guidance and forbearance during the course of this work. Thanks are also due to Drs. J. B. Stothers and M. Gordon for the ^{13}C-n.m.r. spectra and valuable discussions.

Contribution of the other members of the Chemistry Department is also gratefully acknowledged.

The author is indebted to the National Research Council of Canada for funds to carry out this work and for a Scholarship (1967-1970).

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CHAPTER I

INTRODUCTION

In the course of their investigation of the bromination of 3-ketosteroids, Butenandt and coworkers[1] noticed that the position of bromination was determined by the configuration at C-5 of the steroid skeleton. 3-Ketones of the 5β-series (A/B cis) were substituted at the 4-position, whereas the 5α-series (A/B trans) yielded 2-substitution products. 5β-Cholestan-3-one 1 and cholestan-3-one 2* were smoothly monobrominated exclusively at position 4 and 2 to give 4-bromo-5β-cholestan-3-one 3 and 2-bromocholestan-3-one 4,** respectively. Analogous reactions were also observed in 3-keto bile acids,[3] 3-keto pregnanes[4,5] and 3-keto androstanes.[6,7]

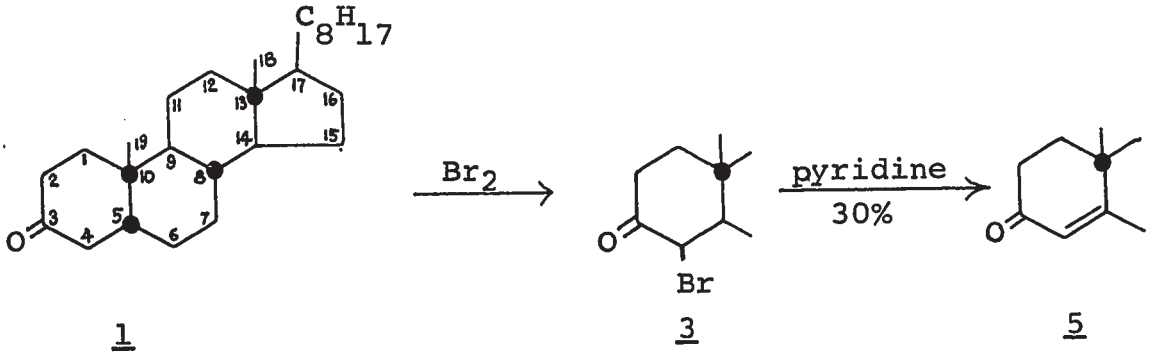
The 2-bromoketones and the 4-bromoketones behaved differently toward dehydrobrominating agents. 4-Bromo-5β-cholestan-3-one 3 reacted with boiling pyridine to give the

* In this thesis, 5α-cholestane derivatives are referred to as cholestane derivatives without the insertion of "5α-". Whenever the cis 5β-stereochemistry is meant, the "5β-" prefix is used.

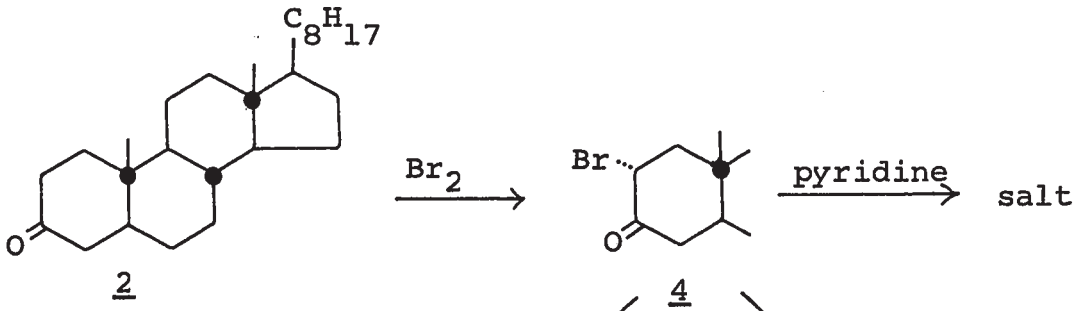
** The stereochemistry of bromine in the products was shown by later workers.[2]

expected product of dehydrobromination, Δ^4-cholesten-3-one 5, m.p. 79-80°, $[\alpha]_D$ +88°, which was a known compound at that time. The yield was rather low (30%), and a part of the bromoketone was converted into a sparingly soluble nitrogen-containing pyridinium salt. Under comparable conditions 2-bromocholestan-3-one 4 reacted with pyridine to give a similar salt in high yield, and no dehydrobromination occurred.[1] When more drastic conditions were tried, the products were uncrystallizable resins. When potassium acetate in acetic acid was used as dehydrobrominating agent, it was found that 2-bromocholestan-3-one 4 yielded an unsaturated ketone, m.p. 111-112°, $[\alpha]_D$ -32°, $\lambda_{max}^{CHCl_3}$ 240 nm. The years from 1934 to 1939 were the early stages of application of ultraviolet spectroscopy to organic chemistry, and the only characteristic known at that time about α,β-unsaturated ketones was that their absorption maxima were much longer than those of saturated or unconjugated ketones. Since the compound formed from 2-bromocholestan-3-one 4 and potassium acetate was different from Δ^4-cholesten-3-one 5 in physical properties and since its ultraviolet spectrum strongly indicated that it was an α,β-unsaturated ketone, Butenandt assigned the structure of Δ^1-cholesten-3-one 6 to this new compound.

Three years later, Ruzicka[8] isolated Δ^4-cholesten-3-one 5 from the thermal decomposition of the pyridinium salt



1 3 5



2 4

20% KOAc-HOAc 200°

γ-collidine

7 6

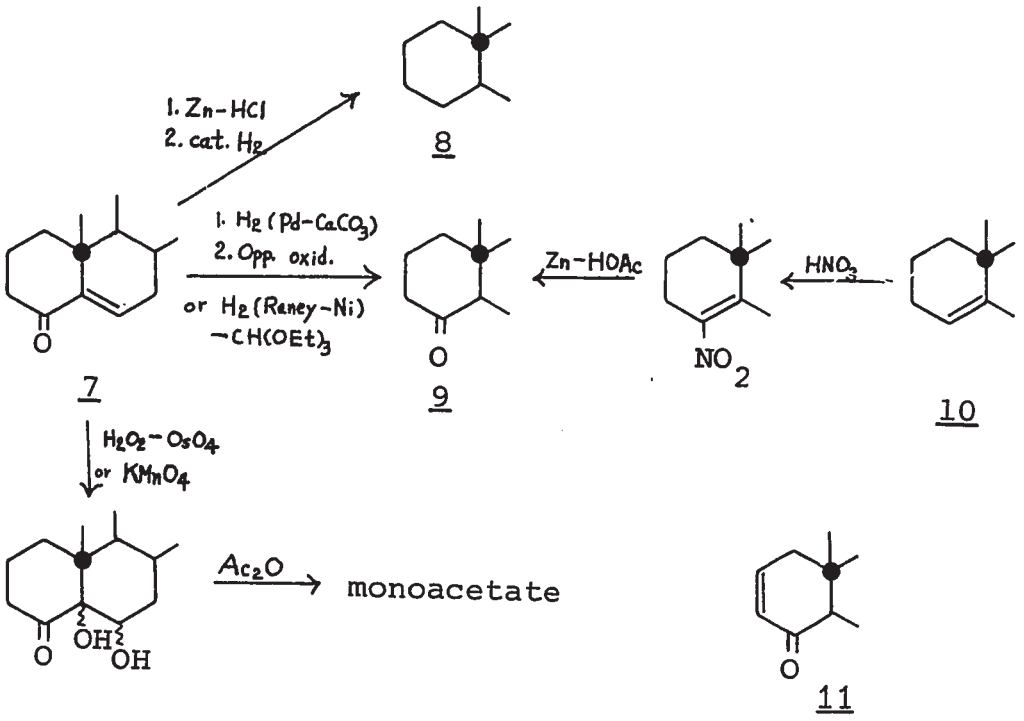
formed from 2-bromocholestan-3-one 4 and pyridine. With the hope of effecting direct dehydrobromination, Butenandt[9] investigated the reaction of 2-bromocholestan-3-one 4 with the sterically demanding base, γ-collidine. The reaction proceeded smoothly at reflux temperature and gave an unsaturated ketone, m.p. 95°, $[\alpha]_D$ +64°, λ_{max}^{EtOH} 230 nm (ε 10,800), in good yield. To his surprise, the compound was neither identical with Δ^4-cholesten-3-one 5 nor with the "Δ^1-cholesten-3-one" obtained from 2-bromocholestan-3-one 4 and potassium acetate in acetic acid, and therefore must be another α,β-unsaturated ketone. Because this compound yielded cholestan-3-one 2 on catalytic hydrogenation, Butenandt concluded that the γ-collidine-dehydrobrominated product was the true Δ^1-cholestan-3-one 6 and renamed the product from the potassium acetate-acetic acid reaction hetero-Δ^1-cholestenone (h-Δ^1-cholestenone).

By this time there were many more ultraviolet spectra of unsaturated ketosteroids available, and it was found that both the absorption maxima and the intensity of absorption at these maxima could be correlated with specific structural features.[10,11] Cyclohexenones whose conjugated double bond was di-secondary absorbed at ca. 230 nm. Substitution of an alkyl group or ring residue for hydrogen on the double

bond caused a bathochromic shift to ca. 240 nm. Moreover, for compounds with a transoid relationship of carbonyl group and carbon-carbon double bond, the extinction coefficients were around 9,000-12,000. For compounds with a cisoid relationship of carbonyl group and carbon-carbon double bond, the extinction coefficients were much lower (5,000-9,000).

Butenandt identified h-Δ^1-cholestenone as Δ^5-cholesten-4-one 7 by the following observations:[12] Clemmensen or Wolff-Kishner reduction of h-Δ^1-cholestenone and subsequent catalytic hydrogenation yielded cholestane 8. Therefore, the carbon skeleton is unchanged. Catalytic hydrogenation of h-Δ^1-cholestenone over palladium-calcium carbonate in alcoholic solution led to a mixture of alcohols which on Oppenauer oxidation gave cholestan-4-one 9. Hydrogenation over Raney-nickel in ethanol in the presence of ethyl orthoformate to protect the carbonyl group as the ketal and subsequent acid hydrolysis also gave cholestan-4-one 9. The latter compound had been prepared some years earlier from Δ^4-cholestene 10 by nitration and subsequent treatment with zinc dust in acetic acid.[13] Thus the carbonyl group in h-Δ^1-cholestenone must be at the 4-position. Since the ultraviolet data demand an α,β-unsaturated ketone,

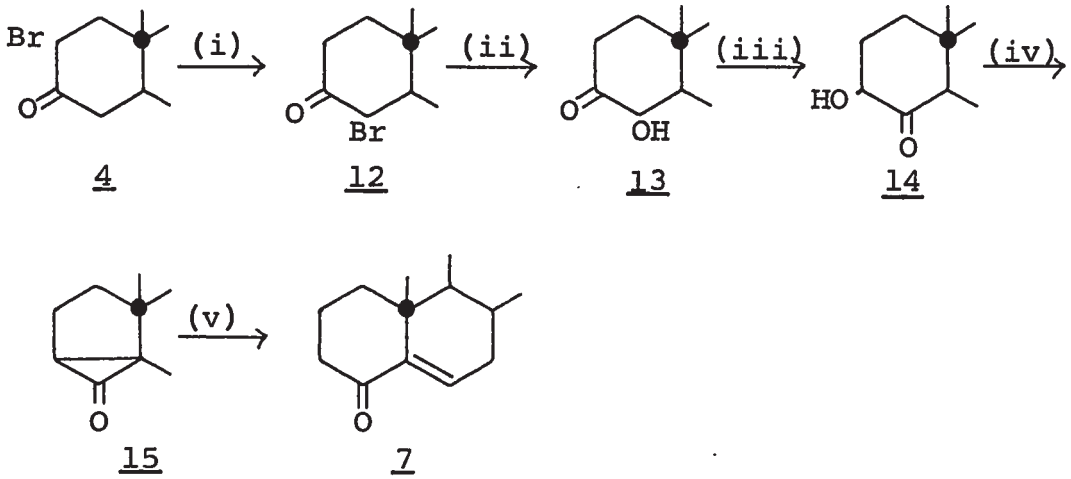
h-Δ^1-cholestenone can only be Δ^2-cholesten-4-one 11 or Δ^5-cholesten-4-one 7. The latter structure with its



secondary-tertiary double bond and the cisoid configuration of carbonyl and carbon-carbon double bond clearly fits the observed absorption maximum (240 nm) and extinction coefficient (7,000) much better than the alternative structure 11 with the double bond at the 2,3-position which would demand a shorter absorption maximum (< 230 nm) and higher extinction coefficient (9,000-10,000). The position of the double bond inferred from the ultraviolet data was also supported by chemical evidence. Hydroxylation of the

double bond either by hydrogen peroxide catalyzed by osmium tetroxide or by potassium permanganate gave a diol containing only one acetylatable hydroxyl group, presumably a secondary-tertiary diol. The alternative structure 11 would give rise to a di-secondary diol which should yield a diacetate on acetylation.

Butenandt postulated the following scheme for this unusual rearrangement.

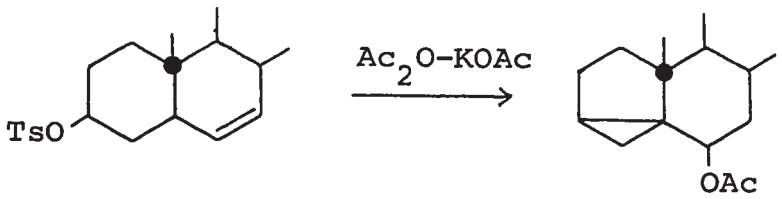


4 12 13 14

15 7

The first step is the transfer of bromine from the 2-position to the 4-position to give 4-bromocholestan-3-one 12. Although the same migration had been suggested by Richard[14] to explain the Favorskii product of some α-haloketones, no α'-bromoketones had ever been isolated from α-bromoketones on treatment with either potassium acetate-acetic acid or methoxide-methanol. The second step

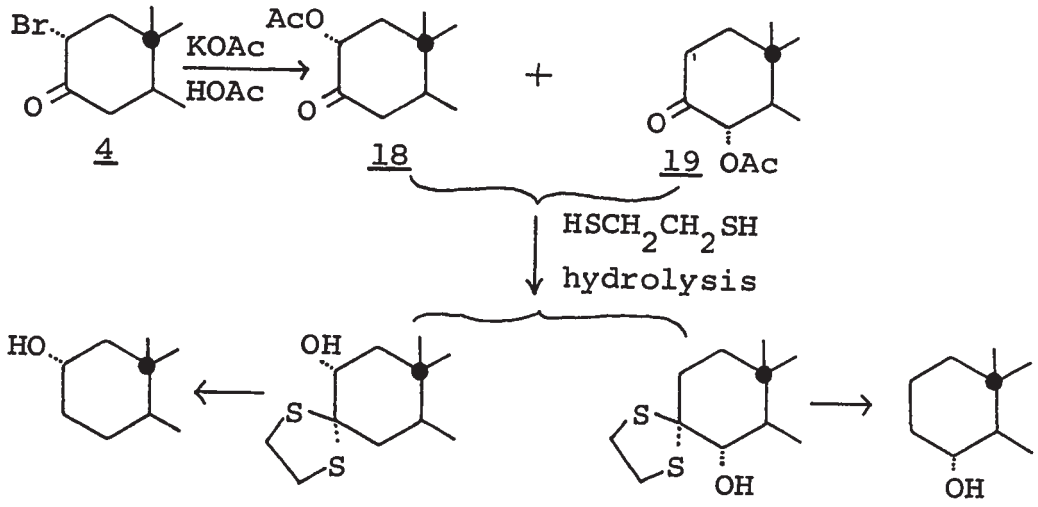
is conversion of bromoketone 12 to hydroxyketone 13, an unlikely reaction in a system without water or hydroxide ion. The third step is a simple acyloin rearrangement of 13 to 14. The fourth step is 1,3-elimination of water to give the cyclopropanone 15 which is also a type of intermediate suggested for Favorskii rearrangement of α-haloketones,[15] but without any supporting evidence. The final step is the rearrangement of the cyclopropanone 15 to the observed product 7. Butenandt pointed out the apparent similarity of the final step in his reaction scheme with the formation of i-cholesteryl acetate 17 from the reaction of cholesteryl tosylate 16 with potassium acetate in acetic anhydride,[16] conditions similar to those of his reaction.



16 17

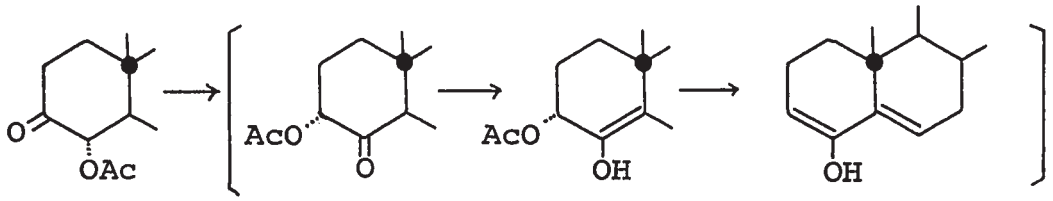
Almost ten years passed without any further work on this reaction before Fieser and Romero[17] reinvestigated the reaction at reflux temperature. An acetoxycholestanone, m.p. 147-149°, $[\alpha]_D$ +26°, was isolated in a yield (40%) about twice that reported for Δ^5-cholesten-4-one 7 by

Butenandt. Fieser and Romero showed the substance to be a complex composed of 2α-acetoxycholestan-3-one 18 and 4α-acetoxycholestan-3-one 19. The complex could not be resolved into its components by either chromatography or recrystallization. Condensation with ethanedithiol and saponification afforded a mixture of ethylenethioketal alcohols that were separable by chromatography. The two substances were characterized by the cholestanols that they afforded on desulfurization. One was identical with cholestan-2α-ol, the other identical with cholestan-4α-ol.

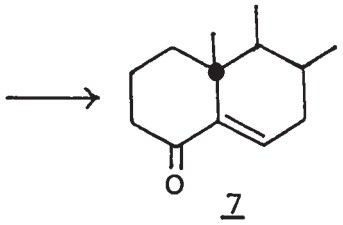


From the relative yields of acetoxycholestanones formed at reflux and Δ^5-cholesten-4-one 7 formed at 200°, Fieser and Romero suggested that both 2α- and 4α-acetoxycholestan-3-one 18 and 19 were the precursors of Δ^5-cholesten-4-one 7.

They formulated the rearrangement schemes as follows:



19 21



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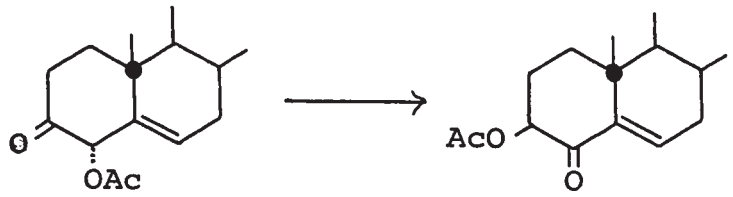
Fieser's scheme differs from Butenandt's in two main points. Firstly, based on experimental evidence, ketol acetates 19 and 21 instead of free ketols 13 and 14 were suggested as intermediates. The isomerization of 4α-acetoxycholestan-3-one 19 to 3α-acetoxycholestan-4-one 21, as Fieser pointed out, has analogy in the isomerization of Δ^5-cholestene-4α-ol-3-one acetate 22 to Δ^5-cholestene-3β-ol-4-one acetate 23 by acid-washed alumina.[18] Secondly, the formation of Δ^5-cholesten-4-one 7 was assumed to be the result of 1,4-allylic elimination of acetic acid from the enol of 21 to give the enol of the final product without involving any cyclopropanone-type intermediate such as 15.

The suggestion of ketol acetates instead of free ketols as intermediates to explain the introduction of the carbonyl



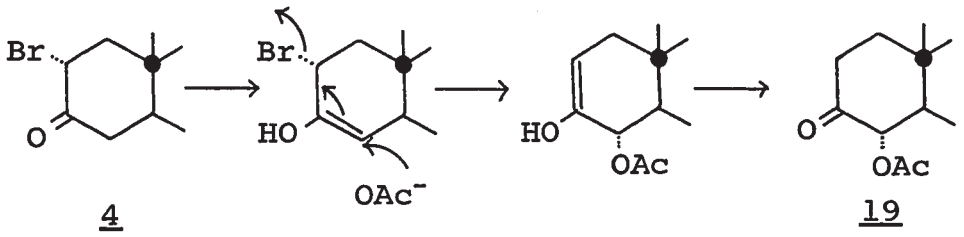
22 23

group at the 4-position is very reasonable. Ketol formation from either ketol acetates or bromoketones in the potassium acetate-acetic acid medium would not be expected to be a facile process since the only nucleophile available is acetate ion. However, a cyclopropanone-type intermediate such as 15 is not to be dismissed *a priori*, since present knowledge of the chemistry of cyclopropanones reveals that they do give ketol acetates with acetic acid.[19]

Although Fieser and Romero pointed out that both 2α-acetoxycholestan-3-one 18 and 4α-acetoxycholestan-3-one 19 might be the precursors of the final product 7, they did not specify how 18 might be transformed into 7.

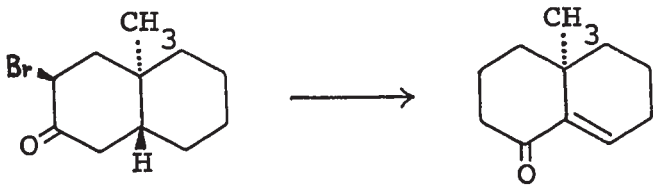
As to the formation of 4α-acetoxycholestan-3-one 19, Fieser and Romero assumed an α→α'-transfer of bromine to give 4α-bromocholestan-3-one 12, the first step in Butenandt's scheme, and subsequent displacement at C-4 by acetate ion. However, Eliel[20] suggested that the formation of 19 may be the result of an S_N2' attack of acetate ion on

the enol of 2α-bromocholestan-3-one 4 as indicated below:



4 19

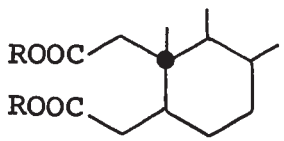
Fieser and Romero did no further work on the reaction and the problem lay dormant except for Djerassi's[21] work which showed that the rearrangement is apparently a general one for systems of this type by subjecting 2-bromo-trans-9-methyl-3-decalone 24 to Butenandt's conditions and isolating 9-methyl-$\Delta^{10(5)}$-4-octalone 25.



24 25

No further serious study was made of this reaction until Williamson and Johnson,[22] during their work on the application of nuclear magnetic resonance (n.m.r.) spectroscopy to stereochemical problems, synthesized ring-A α-acetoxy ketones in the cholestane series by unambiguous routes. Up to this time, most of the

ring-A α-acetoxy ketones reported in the literature had been prepared by displacement reactions on 2α-bromocholestan-3-one 4 or by acetylation of the acyloin condensation product of 2,3-secocholestane-2,3-dioic acid dimethyl ester 26 (R = CH_3).[8,17,23,24] The first reaction was always subject to abnormal displacement to give the 4-substituted compound and the second reaction was subject to the contamination by 3,4-secodiacid 27; therefore the α-acetoxy ketones obtained were usually mixtures of isomers and structural assignments



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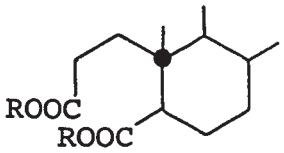

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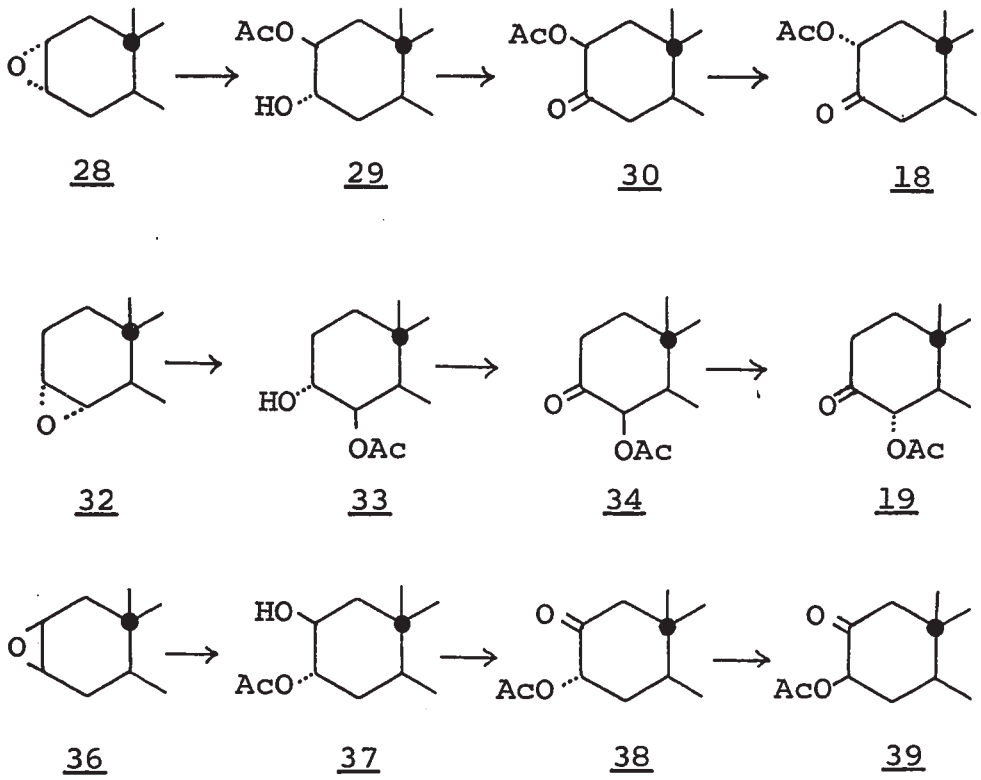
were in a rather confused state. Williamson and Johnson prepared the acetoxy ketone via diaxial hydroxy acetates obtained by acetolysis of the appropriate epoxides. Acetolysis of 2α,3α-oxidocholestane 28 gave 3α-hydroxy-2β-acetoxycholestane 29, which on Jones oxidation yielded the axial ketone 2β-acetoxycholestan-3-one 30. The acetoxy group in 30 was epimerized by acid to give the equatorial epimmer 2α-acetoxycholestan-3-one 18. 4α-Acetoxycholestan-3-one 19 and 3β-acetoxycholestan-2-one 39 were prepared in an analogous way from 3α,4α-oxidocholestane 32 and



28 29 30 18

32 33 34 19

36 37 38 39

2β,3β-oxidocholestane 36, respectively. Since the structures of the starting epoxides were well established, the structural assignments for the products 18, 19, 39 were unequivocal.

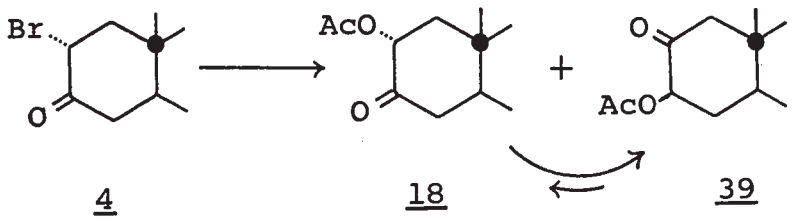
On mixing equal amounts of 2α-acetoxycholestan-3-one 18 and 4α-acetoxycholestan-3-one 19 and recrystallization from ethanol, Williamson and Johnson obtained in quantitative yield a complex, m.p. 149.0°-149.3°, $[\alpha]_D$ +27°, which was less soluble and higher melting than either of its components.

That the complex was formed from equal parts of its components followed from its synthesis, the average optical rotations for the components ($4\alpha = -4^{o}$, $2\alpha = +52^{o}$, av. $= +24^{o}$), and integration of the n.m.r. spectrum. Furthermore, it was shown to be identical with the complex, m.p. 147-149°, $[\alpha]_{D}$ $+26^{o}$, isolated by Fieser and Romero[17] on treating 2α-bromocholestan-3-one 4 with potassium acetate in refluxing acetic acid.

Williamson and Johnson proposed that 4α-acetoxycholestan-3-one 19 might be formed by $S_{N}2'$ attack on the enolic form of 2α-bromocholestan-3-one 4, as Eliel had suggested several years before. They also mentioned that 2α-acetoxycholestan-3-one 18 did not rearrange into 4α-acetoxycholestan-3-one 19 when treated with potassium acetate, but no experimental details were given.

With the authentic ring-A α-acetoxy ketones in hand, Williamson and Johnson proceeded further to investigate the related displacement of 2α-bromocholestan-3-one 4 with tetramethylammonium acetate in refluxing acetone. Crystalline 3β-acetoxycholestan-2-one 39 was isolated in 12% yield. The infrared (i.r.)spectra of the crude reaction mixture and the final product were very similar except for a band at 8.8 μ which appeared in the former and might be

attributed to 2α-acetoxycholestan-3-one 18, the expected product of normal displacement. A control experiment showed that 2α-acetoxycholestan-3-one 18 rearranged easily into 3β-acetoxycholestan-2-one 39 under the reaction conditions. The latter reaction is closely related to one of the steps (19→21) in Fieser's scheme for h-Δ^1-cholestenone formation.

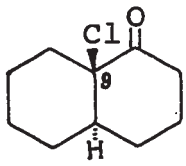


4 18 39

In contrast to 2α-bromocholestan-3-one 4, 4α-bromocholestan-3-one 12 on treatment with tetramethylammonium acetate in acetone gave a 20% yield of Δ^4-cholesten-3-one 5 and a 4% yield of the 1:1 complex of 2α-acetoxycholestan-3-one 18 and 4α-acetoxycholestan-3-one 19. A control experiment with 4α-acetoxycholestan-3-one 19 gave recovery of the starting material.[25] Thus abnormal displacement on the 4α-bromo-3-ketone 12 to give 2α-acetoxy-3-ketone 18 also occurs to some extent with tetramethylammonium acetate in acetone, if the 4α-bromo-3-ketone 12 used in the reaction was not contaminated with the 2α-bromo-3-ketone 4.

A related result was also reported in the decalone

system.[26] In the reaction of 9-chloro-trans-1-decalone 40 with potassium acetate in acetic acid, the abnormal displacement product, 2-acetoxy-1-decalone 41, was obtained in 47% yield along with some Δ^9-octalone-1 43. However, treatment with tetramethylammonium acetate in acetone gave only Δ^9-octalone-1 43 and 9-acetoxy-1-decalone 42, the normal displacement product.



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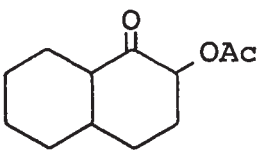

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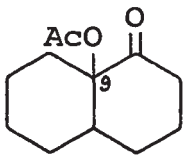

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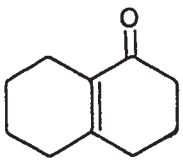

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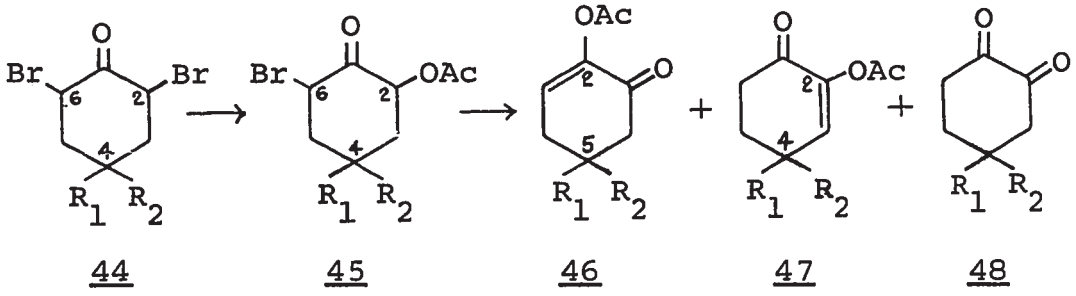
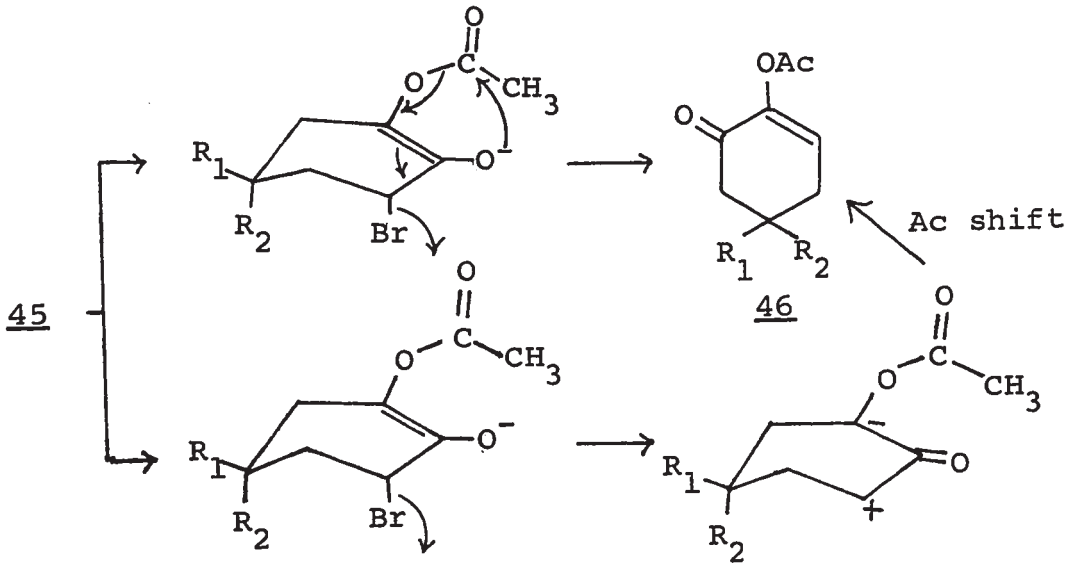
Williamson and Johnson's work dealt only with the postulated earlier stages of the h-Δ^1-cholestenone rearrangement, i.e., the bromoketone to acetoxyketone stage and the stage of interchange of carbonyl and acetoxyl groups of acetoxyketones. Bordwell's work on 4-substituted 2,6-dibromocyclohexanones 44 and 4-substituted 2-acetoxy-6-bromocyclohexanone 45 shed more light on the reaction of bromoketones with potassium acetate in acetic acid. Both 44 and 45 gave 5-substituted 2-acetoxycyclohex-2-enone 46, as the major product--an unsaturated ketone with the carbonyl group shifted to an adjacent position. 4-Substituted

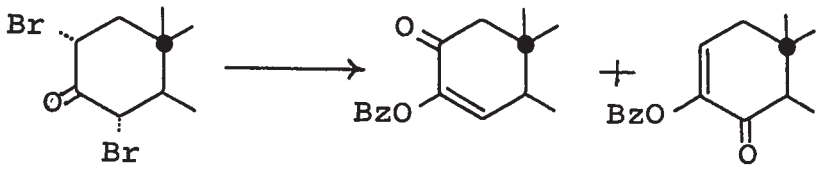
2-acetoxycyclohexan-2-enone 47 and the dione 48 were formed in minor amounts. The formation of 46 from 45 or 44 is very similar to the h-Δ^1-cholestenone rearrangement, since the latter involves the same migration of carbonyl group to an adjacent position and the formation of an α,β-unsaturated ketone as the final product, and since the two reactions were carried out under comparable conditions. Bordwell provided evidence to support the assumption that 45 was an intermediate in the reaction involving 44. The transformation of 45 into the final product 46 involved the





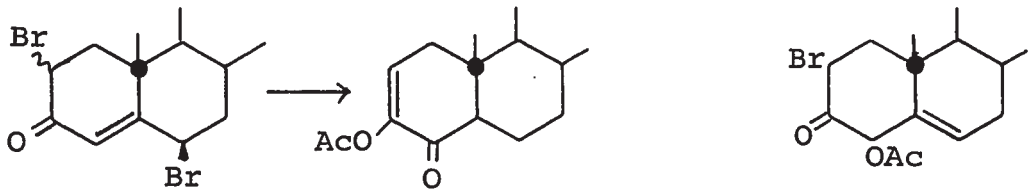
1,3-elimination of hydrogen bromide accompanied by acyl migration. Evidence was also presented to show that acyl migration does not precede the loss of bromide ion. The two mechanistic pathways suggested by Bordwell differ only in the order of bond breaking and bond making.

Bordwell also reinvestigated Inhoffen's work on 2α,4α-dibromocholestan-3-one 49 and proved by nuclear magnetic resonance spectroscopy that the products were 50 and 51, in agreement with his results in the cyclohexanone case.



49 50 51

Recent work by Julian[29] on the reaction of 2ξ,6β-dibromocholest-4-en-3-one 52 with potassium acetate in acetone is an extension of Bordwell's work on 49. The product, 3-acetoxycholesta-2,5-dien-4-one 53 can be easily explained by the intermediacy of 2-bromo-4-acetoxycholest-5-en-3-one 54, formed by initial S_N2' displacement of bromine at 6-position. An O^{18}-labelling result agreed with the mechanism proposed.



52 53 54

The foregoing introduction summarizes the state of knowledge of this unusual reaction when the present investigation of its detailed mechanism was started.

At the outset, we were faced with the following questions:

(i) Were both 2α- and 4α-acetoxycholestan-3-one 18 and 19 really precursors of Δ^5-cholesten-4-one 7? If so, did the 2α-isomer 18 isomerize to the 4α-isomer 19 first on its way to the final product?

(ii) How was the mixture of 2α- and 4α-acetoxycholestan-3-one 18 and 19 formed from 2α-bromocholestan-3-one 4 and potassium acetate in refluxing acetic acid? Is this a general reaction of bromoketones?

(iii) In view of Williamson and Johnson's differing results from reactions in acetone and in acetic acid, what was the effect of the medium on the course of reaction of bromoketones?

(iv) Was it possible to isolate intermediates other than 2α- and 4α-acetoxycholestan-3-one 18 and 19?

CHAPTER II

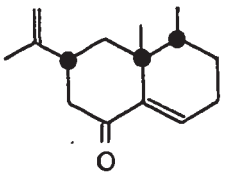
REARRANGEMENT OF α-BROMO KETOSTEROIDS AND α-ACETOXY KETOSTEROIDS

From the discussion in Chapter I, it is seen that although the so-called "h-Δ^1-cholestenone rearrangement" has been recognized as an unusual rearrangement for a long time,[12,17,21,22,27] not much attention has been paid to it since Butenandt's elucidation of the product as Δ^5-cholesten-4-one 7 and Fieser and Romero's isolation of acetolysis products at lower temperature. The lack of any detailed mechanistic study might be due to two causes, the poor yields of Δ^5-cholesten-4-one 7 reported by Butenandt[12] and by Djerassi[21] (20~27%), and the very confused state of the structural assignment for ring-A acetoxyketones, the most probable intermediates of this reaction.

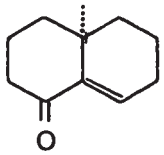
When we started our work in 1966, the structural assignment of acetoxyketones had already been clarified by Williamson and Johnson's unambiguous synthesis.[22] In addition, n.m.r. spectroscopy had been demonstrated to be a very powerful tool for the stereochemical study of

steroid acetoxyketones.[30]

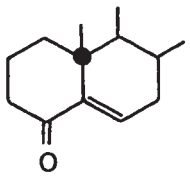
A clue to the cause of poor yield was provided by the observation that eremophilone 56 and 9-methyl-$\Delta^{10(5)}$-4-octalone 25, both of which possess the same chromophoric system as Δ^5-cholesten-4-one 7, were sensitive to air oxidation.[21,31] Therefore, it seemed worthwhile to reinvestigate the h-Δ^1-cholestenone rearrangement in the absence of air. When 2α-bromocholestan-3-one 4 was treated at 220-230° with potassium acetate and acetic acid in a sealed tube under a nitrogen atmosphere, Δ^5-cholesten-4-one 7 was formed in 80% yield based on thin layer chromatography (t.l.c.) and u.v. data, and crystalline material was isolated in 50% yield. A parallel reaction without the exclusion of air gave a more complex product as shown by t.l.c., and crystalline Δ^5-cholesten-4-one 7 was obtained in only 20% yield. In addition, it was found that even in the absence of oxygen, a minor amount (ca. 15%) of



56



25



7

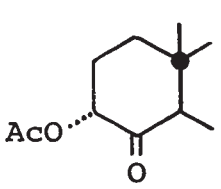
Δ^4-cholesten-3-one 5 and a trace of Δ^1-cholesten-3-one 6 were formed.

In the logical next step to follow Fieser's work the 1:1 complex of 2α-acetoxycholestan-3-one 18 and 4α-acetoxycholestan-3-one 19, free from any conjugated ketone, as shown by n.m.r., was treated with potassium acetate and acetic acid at 220-230°. The crude product contained at least 70% of Δ^5-cholesten-4-one 7 as estimated from u.v. and t.l.c. data. This result proved that Fieser's speculation,[17] that both 2α-acetoxy-3-ketone 18 and 4α-acetoxy-3-ketone 19 could serve as intermediate in the h-Δ^1-cholestenone rearrangement, was correct.

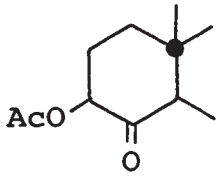
Since preliminary tests revealed that the h-Δ^1-cholestenone rearrangement could be made quite clean if run under a nitrogen atmosphere and that both 2α- and 4α-acetoxy-3-ketone 18 and 19 were indeed precursors of Δ^5-cholesten-4-one 7, a detailed study of the mechanism of this novel rearrangement looked promising.

The preparation of pure 2α-acetoxycholestan-3-one 18 and its 4α-isomer 19 for investigation of their inter-conversions and transformations to Δ^5-cholesten-4-one 7 would be an easy task in view of Williamson and Johnson's synthetic work.[22] According to Fieser's scheme for the

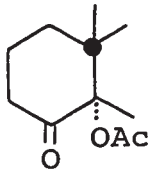
h-Δ^1-cholestenone rearrangement, the next reaction to investigate would be the interchange of acetoxyl and carbonyl groups in 4α-acetoxycholestan-3-one 19 to 3α- or 3β-acetoxycholestan-4-one 21 or 57, whichever is the more stable isomer. Although Fieser proposed direct formation of Δ^5-cholesten-4-one 7 from 21, other possibilities such as the involvement of 5α-acetoxycholestan-4-one 58 were also not unlikely and worth investigating. Detailed



21



57



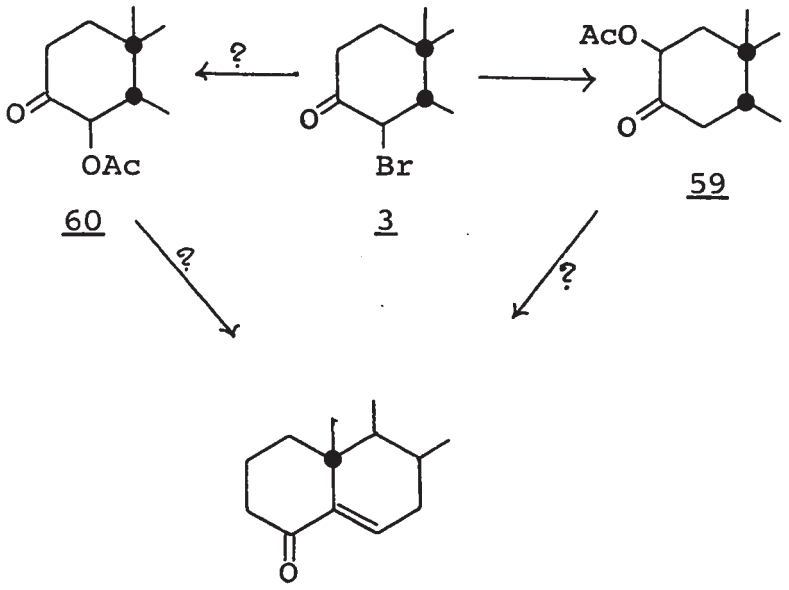
58

analysis of the reaction products of 2α-bromocholestan-3-one 4 and 4α-bromocholestan-3-one 12 with acetate ion in acetone as well as in acetic acid would give some insight into the structural influence and the solvent effect on the course of normal and abnormal displacements.

After our work in the 5α-cholestane series (A/B trans) had been started, Satoh[32] published his result in the closely related 5β-cholestane series (A/B cis). When 4β-bromo-5β-cholestan-3-one 3 was treated with potassium

acetate in refluxing acetic acid, the abnormal displacement product 2β-acetoxy-5β-cholestan-3-one 59 was isolated in good yield (68%).

However, Satoh's claim of the absence of the normal displacement product, 4β-acetoxy-5β-cholestan-3-one 60 was based only on the t.l.c. data, which, as shown by our later work, could not separate the 2β- and the 4β-isomers 59 and 60, at least in the two solvent systems used by us. No n.m.r. data of the crude product were given.



7

Satoh's result prompted the extension of our work into the 5β-cholestane series, since 2β- and 4β-acetoxy-5β-cholestan-3-one 59 and 60, the analogues of 2α- and 4α-acetoxycholestan-3-one 18 and 19 in the 5β-series, would be expected to rearrange into Δ^5-cholestan-4-one 7 under suitable conditions. Furthermore, comparisons of the acetolysis of the bromoketones in both series would shed light on the conformational influence in these reactions.

The results of the reactions of α-bromo ketosteroids and α-acetoxy ketosteroids with potassium acetate-acetic acid or with tetramethylammonium acetate-acetone are listed in Tables I-IV.(p. 30-33) To facilitate comparison, the reactions are grouped according to the type of reagents used. Also, discussion of the mechanistic significance of these results will not be closely parallel to the order in which the work was done.

Reactions were usually run until there was no bromoketone left. Since unsaturated ketones and acetoxy-ketones were the only products formed, the yields of various components were determined by spectroscopic analysis of the crude reaction mexture. In cases where only one unsaturated ketone was formed in significant amounts, the yield was estimated from the u.v. extinction coefficient of the crude product and should be accurate to ca. ±2% for

yields lower than 20%, and accurate to ±4% for yields higher than 50%. When more than one unsaturated ketone was formed, the total amount was estimated from u.v. data and the relative ratio estimated from the integration of vinylic protons in the n.m.r. spectrum. The yields of individual unsaturated ketones calculated in this way are estimated to be accurate to ca. ±5% for values greater than 30% and accurate to ca. ±2% for values smaller than 10%. The remainder of the crude product was taken as the yield of acetoxyketones. The relative amounts of isomeric ketones were roughly estimated by the height of the C-18 and C-19 methyls and the splitting pattern of the low field α-protons in the n.m.r. spectrum. The intensity of spots on t.l.c. plates was used as a check. Yields determined in this way are estimated to be subject to an error of ±5~10%. In one case, the specific rotation was used for estimating the yields of acetoxyketones, and the results are estimated to be accurate to ca. ±2%. If a compound was not detectable on t.l.c., its yield is reported as zero. If a compound failed to show up on n.m.r., but its absence was inconclusive from t.l.c., it is designated by "?" in the Tables. The purpose of reporting the composition of the crude products in percentage yields is merely to facilitate the comparison of the various reactions. It is

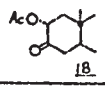
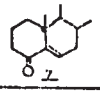
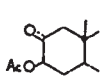
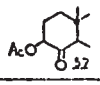
to be noted that the accuracy of the percentage yields does not affect the later discussion of the reaction of bromoketones and acetoxyketones.

In most cases, the crude product was separated by thin layer chromatography and the identity of the major components was checked by melting point and spectroscopic data of the purified components. Tables V and VI list the n.m.r. and u.v. data of the pure steroid bromoketones, acetoxyketones and conjugated ketones. Fig. 1 shows the low-field α-proton splitting patterns of the acetoxyketones. The t.l.c. data of steroid compounds are reported in the experimental section (Chapter V), Table VIII, p.136 .

The remainder of this chapter will be divided into five sections. Section (i) deals with the conversion of bromoketones into acetoxyketones in acetate-acetic acid or in acetate-acetone medium. Section (ii) deals with the interchange of carbonyl and acetoxyl groups of α-acetoxyketones. Section (iii) deals with the α→α' shift of acetoxyl group of α-acetoxyketones. Section (iv) concerns the elimination of acetic acid to give the final product, Δ^5-cholesten-4-one 7. In each section, possible mechanisms will be outlined first. Experimental results will then be discussed. Section (v) is a general conclusion for the mechanism of h-Δ^1-cholestenone rearrangement.

TABLE I

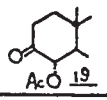
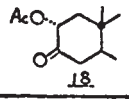
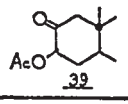
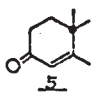
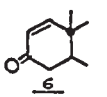
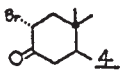
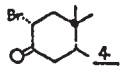
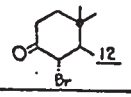
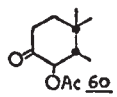
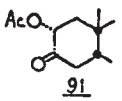
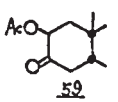
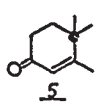
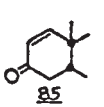
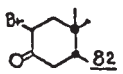
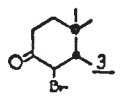
REACTION OF α-BROMO KETOSTEROIDS WITH POTASSIUM ACETATE IN ACETIC ACID

reaction	bromoketone	temperature	time (hr.)	% yield of products:  19	 18	 39	 7	 5	 6
1	 4	220-230°	5	0[a]	0[a]	0[a]	80[b]	15 ± 2[b]	5[c]
2	 4	97-103°	8	44 ± 2[d]	42 ± 2[d]	5 ± 2[b]	trace(?)[e]	6 ± 2[f]	trace(?)[e]
3	 4	133-135°	6	30 ± 5[b]	40 ± 5[b]	20 ± 5[b]	trace(?)[e]	7 ± 2[f]	trace(?)[e]
4	 4	200-210°	16			30 ± 5[b]	50 ± 5[f]	10 ± 2[f]	?[g]
5	 12	133-135°	3	40 ± 5[b]	40 ± 5[b]	10 ± 3[b]	trace(?)[e]	10 ± 5[b]	trace(?)[e]
6	 89	133-135°	3	no reaction					
7	 89	200-210°	14	?[g]	?[g]	45 ± 5[b]	30 ± 5[f]	5 ± 2[f]	?[g]
				 87	 39	unsaturated ketones			
8	 86	133-135°	3.5	25 ± 5[b]	75 ± 5[b]	trace[e]			
				 57	 58	 7	 11		
9	 88	133-135°	3.5	85 ± 5[b]	?[g]	15 ± 2[f]	?[g]		
				 59	 60	 7	 5	 85	
10	 82	133-135°	3.5	90 ± 5[b]	?[g]	trace(?)[e]	10 ± 5[b]	trace(?)[e]	
11	 3	133-135°	3.5	90 ± 5[b]	?[g]	trace(?)[e]	10 ± 5[b]	trace(?)[e]	

[a]Not visible in n.m.r. spectrum or t.l.c. [b]Estimated from n.m.r. and t.l.c. data [c]Estimated from the n.m.r. spectra of the mother liquor [d]Estimated from n.m.r., $[\alpha]_D$, and t.l.c. data [e]Not visible in the n.m.r. spectrum, but the presence of one of the enones was indicated by t.l.c. data [f]Estimated from n.m.r., t.l.c., and u.v. data [g]Not visible from the n.m.r. spectrum, but its absence is inconclusive from t.l.c. data

TABLE II

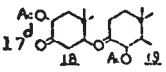
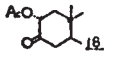
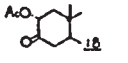
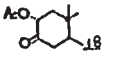
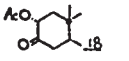
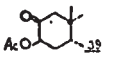
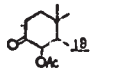
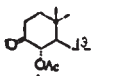
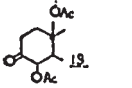
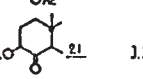
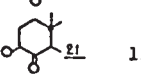
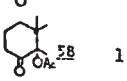
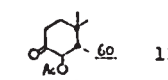
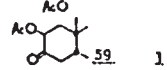
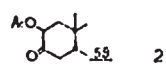
REACTIONS OF α-BROMO KETOSTEROIDS WITH TETRAMETHYLAMMONIUM ACETATE IN ACETONE

reaction	bromoketone	temperature	time (hr.)	% yield of products:  19	 18	 39	 5	 6
12	 4	r.t. reflux	40 2	?[d]	80 ± 5[b]	10 ± 5[b]	0[a]	8 ± 2[c]
13	 4	reflux	170	?[d]	60 ± 5[b]	30 ± 5[b]	0[a]	10 ± 5[b]
14	 12	r.t.	2.5		(4)[e]		(19)[e]	
				 OAc	 OAc 60	 91	 59	 5	 85
15	 82	r.t. reflux	12 2	?[d]	?[d]	27 ± 5[b]	27 ± 5[b]	0[a]	45 ± 2[c]
16	 3	r.t. reflux	20 1	?[d]	?[d]	25 ± 5[b]	25 ± 5[b]	45 ± 2[c]	6[f]

[a] Not visible in n.m.r. spectrum or t.l.c. [b] Estimated from n.m.r. and t.l.c. data [c] Estimated from n.m.r., t.l.c., and u.v. data [d] Not visible from the n.m.r. spectrum, but its absence is inconclusive from t.l.c. data [e] Williamson and Johnson's result[22] [f] Estimated after thick layer separation from the n.m.r. spectrum

TABLE III

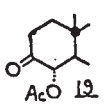
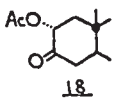
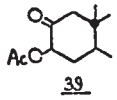
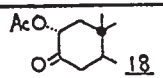
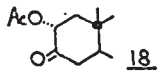
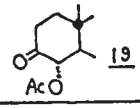
REACTIONS OF α-ACETOXY KETOSTEROIDS WITH POTASSIUM ACETATE IN ACETIC ACID

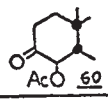
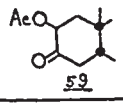
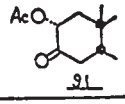
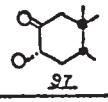
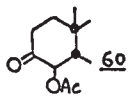
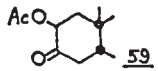
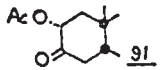
reaction	acetoxy-ketone	temperature	time	% yield of products							
				 19	 18	 39	 57	 58	 7	 5	 6
17[d]	 18 19	220-230°	4.5 hr.	0[a]	0[a]	0[a]	0[a]	0[a]	70 ± 10[f]	10 ± 5[f]	?[g]
18	 18	133-135°	4 hr.	?[g]	60 ± 10[b]	40 ± 10[b]	?[g]	?[g]	0[a]	0[a]	0[a]
19	 18	133-135°	3 days	?[g]	20 ± 5[b]	80 ± 10[b]	?[g]	?[g]	0[a]	0[a]	0[a]
20	 18	190-200°	2 hr.	0[c]	20 ± 5[b]	60 ± 10[b]	?[g]	?[g]	20 ± 2[f]	trace[e]	?[g]
21	 18	220-230°	5 hr.	0[a]	0[a]	?[g]	?[g]	0[a]	80 ± 5[f]	5 ± 2[f]	?[g]
22	 39	200-210°	16 hr.		10 ± 5[b]	40 ± 5[b]	?[g]	?[g]	45 ± 3[f]	5 ± 2[f]	?[g]
23	 18	133-135°	6 hr.	no reaction							
24	 19	170-180°	4 hr.			20 ± 5[b]			80 ± 5[f]	trace[e]	?[g]
25	 19	200-210°	16 hr.			5[b]			90[b]	trace[e]	?[g]
26	 21	133-135°	3 hr.	?[g]	?[g]	?[g]	>90[b]	trace[e]	<5[b]	0[a]	?[g]
27	 21	133-135°	12 hr.	?[g]	?[g]	?[g]	80 ± 5[b]	trace[e]	20 ± 2[f]	0[a]	?[g]
28	 58	133-135°	12 hr.	?[g]	?[g]	?[g]	80 ± 5[b]	trace[e]	20 ± 2[f]	0[a]	?[g]
				 60	 39	 39	 57	 58	 7	 5	 85
29	 60	133-135°	19 hr.	10 ± 5[b]	?[g]	?[g]	70 ± 10[b]	trace[e]	15 ± 5[b]	0[a]	?[g]
30	 59	133-135°	48 hr.	?[g]	50 ± 10[b]	50 ± 10[b]	?[g]	?[g]	0[a]	0[a]	0[a]
31	 59	220-230°	4 hr.						80 ± 10[f]	10 ± 5[f]	?[g]

[a] Not visible in n.m.r. spectrum or t.l.c. by m.p. of the recrystallization product [b] Estimated from n.m.r. and t.l.c. data [c] Absence shown [d] Without exclusion of air [e] Not visible in the n.m.r. spectrum, but its presence indicated by t.l.c. data [f] Estimated from n.m.r., t.l.c., and u.v. data [g] Not visible from the n.m.r. spectrum, but its absence is inconclusive from t.l.c. data

TABLE IV

REACTIONS OF α-ACETOXY KETOSTEROIDS WITH TETRAMETHYLAMMONIUM ACETATE IN ACETONE

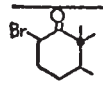
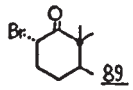
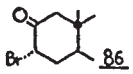
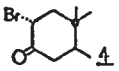
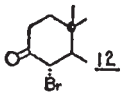
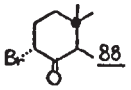
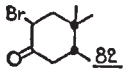
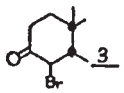
reaction	acetoxy-ketone	temperature	time	% yield of products:  19	 18	 39	unsat. ketone
32	 18	reflux	12 hr.	?[c]	70 ± 10[b]	30 ± 10[b]	0[a]
33	 18	reflux	4 days	?[c]	60 ± 10[b]	40 ± 10[b]	0[a]
34	 19	reflux	12 hr.		no reaction		

reaction	acetoxy-ketone	temperature	time	 60	 59	 91	 97	unsat. ketone
35	 60	reflux	2 days		no reaction			
36	 59	reflux	4 hr.	?[c]	>90	<5		0[a]
37	 91	reflux	4.5 hr.	?[c]	30 ± 10[d]	70 ± 10[d]	?[c]	0[a]

[a] Not visible in n.m.r. spectrum or t.l.c. [b] Estimated from n.m.r. and t.l.c. data
[c] Not visible from the n.m.r. spectrum, but its absence is inconclusive from t.l.c. data [d] t.l.c. data

TABLE V

N.M.R. DATA[a] OF STEROID BROMOKETONES, ACETOXYKETONES AND ENONES

compound	C-19 methyl	C-18 methyl	O=C-C(H)(Br)
	0.67	1.38	4.45 (d.d., J = 5.5 Hz.)
 89	0.67	1.17	5.10 (b.q., J = 7, 12 Hz.)
 86	0.67	0.73	4.33 (b.s., $w_{1/2}$ = 7 Hz.)
 4	0.67	1.10	4.72 (q., J = 6.5, 13.5 Hz.)
	0.67	1.12	4.46
 12	0.67	1.10	4.66 (d., J = 12.5 Hz.)
	0.67	1.28	4.16 (b.s., $w_{1/2}$ = 6 Hz.)
 88	0.67	0.73	4.30 (b.s., $w_{1/2}$ = 8 Hz.)
 82	0.68	1.05	4.70 (q., J = 5.5, 14 Hz.)
 3	0.68	1.08	4.88 (d., J = 11.5 Hz.)

[a] Figures in the table are δ values downfield from TMS (δ = 0.00). All spectra were taken in deuteriochloroform solutions.

Table V (continued)

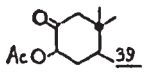
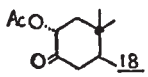
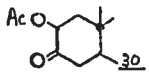
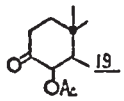
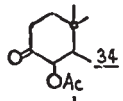
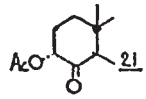
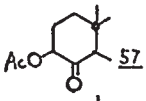
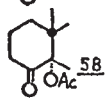
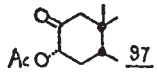
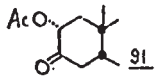
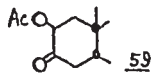
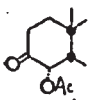
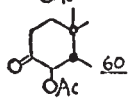
compound	C-18 methyl	C-19 methyl	CH_3COO-	$O=C-C\overset{H}{\underset{OAc}{}}$
 39	0.65	0.77	2.13	5.20 (m.)
 18	0.67	1.16	2.13	5.29 (q., J = 13, 6.5 Hz.)
 30	0.67	0.85	2.10	5.33 (q., J = 10, 7 Hz.)
 19	0.67	1.16	2.13	5.04 (d., J = 11.5 Hz.)
 34	0.67	1.12	2.08	4.92 (b.s., $w_{1/2}$ = 6 Hz.)
 21	0.65	0.75	2.10	4.83 (m.)
 57	0.65	0.75	2.13	5.20 (m.)
 58	0.66	0.82	2.13	
 97	0.65	1.09	2.15	5.25 (m.)
 91	0.69	1.17	2.15	5.35 (d.d., J = 8.5 Hz.)
 59	0.69	1.07	2.15	5.23 (q., J = 13.5, 6 Hz.)
	0.67	1.10	2.15	5.46 (d., J = 8 Hz.)
 60	0.69	1.07	2.15	5.55 (d., J = 12 Hz.)

Table V (continued)

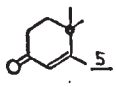
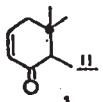
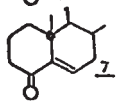
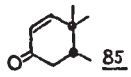
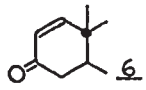
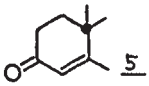
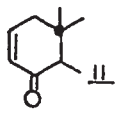
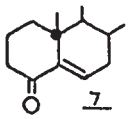
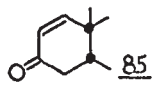
compound	C-18 methyl	C-19 methyl	O=C-C(H)=C-	O=C-C(H)=C-
 6	0.70	1.01	5.88 (d., J = 10.5 Hz.)	7.14 (d., J = 10.5 Hz.)
 5	0.72	1.17	5.70 (b.s., $w_{\frac{1}{2}}$ = 3 Hz.)	
 11	0.67	0.88	6.00 (d., J = 10 Hz.)	6.75 (m.)
 7	0.70	0.96		6.42 (m.)
 85	0.70	1.20	5.88 (d., J = 10.5 Hz.)	6.82 (d., J = 10.5 Hz.)

TABLE VI

U.V. SPECTRA OF STEROID α,β-UNSATURATED KETONES*

compound	alcohol λ_{max}	ϵ_{max}	ref.
 6	(230 nm)	(10,800)	9
 5	(241 nm)	(16,600)	11
 11	226 nm (239 nm)	7,830 (10,400)	86
 7	241 nm (241 nm)	6,610 (7,200)	9
 85	232 nm (232 nm)	8,050 (7,500)	93

*Figures in the parentheses are data reported in the literature.

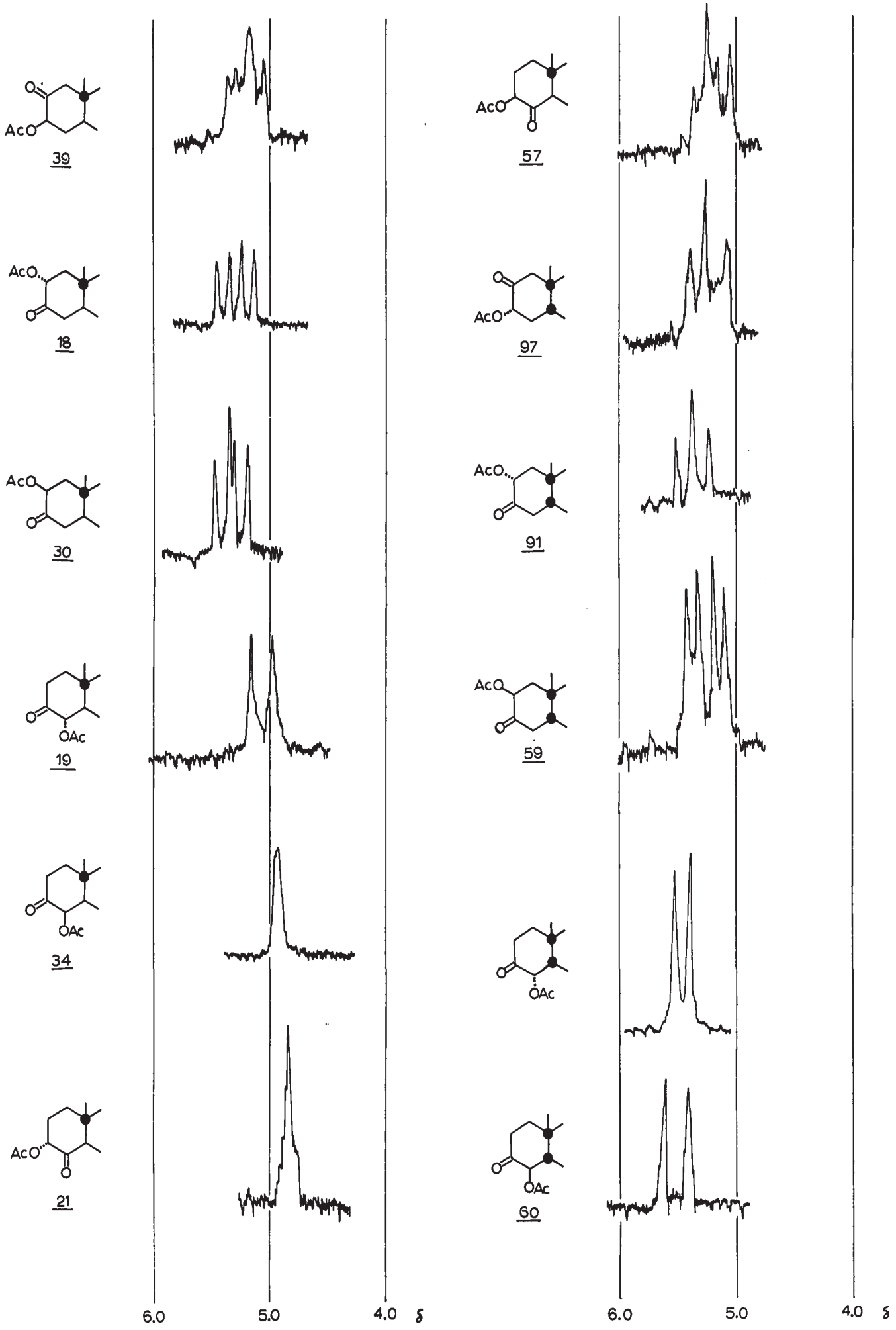
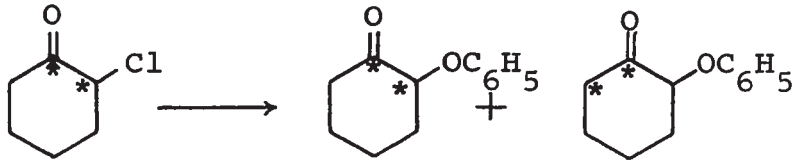

AcO
39
AcO
18
AcO
30
OAc
19
OAc
34
AcO
21
AcO
57
AcO
97
AcO
91
AcO
59
OAc
OAc
60
6.0
5.0
4.0
δ
6.0
5.0
4.0
δ

Fig. 1

(i) Conversion of Bromoketones into Acetoxyketones

As mentioned earlier, reactions of α-haloketones such as 2α-bromocholestan-3-one 4, 4α-bromocholestan-3-one 12,[17,22] 4β-bromo-5β-cholestan-3-one 3, and 9-chloro-trans-decalone-1 40 with acetate ion can form either normal or abnormal displacement products, depending on the structure of the haloketone and the solvent used. Smith and Gonzalez also observed both the normal and abnormal displacement products in the reaction of 2-chlorocyclohexanone with sodium phenoxide in petroleum ether,[33] although the reaction condition is quite different from the reaction with acetate ion in acetic acid or in acetone.



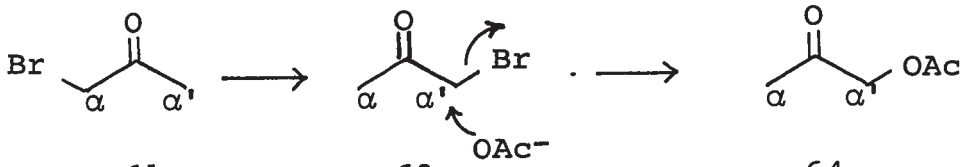
Fieser and Romero originally proposed that the normal product 62 came from direct displacement (mechanism A) while the abnormal product 64 arose from preliminary α→α'-shift of bromine in 61 to give the α'-bromoketone 63, followed by direct displacement (mechanism B). Mechanism B was not very convincing since α→α'-shift of halo-substituent has only been observed with α-haloketones in the presence of hydrogen bromide or chloride. Eliel,[20] Williamson and

Johnson,[22] and recently Satoh and coworkers[32] have all preferred the direct formation of α'-acetoxyketone 64 by

Mechanism A

61 62

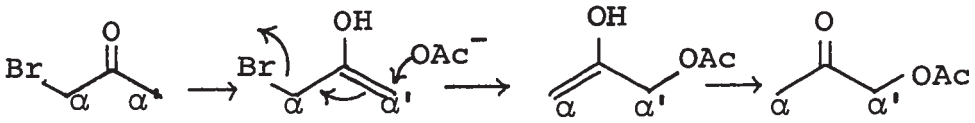
Mechanism B



61 63 64

S_N2' attack of acetate ion on the enol form 69 of the bromoketone (mechanism C), apparently by analogy with known

Mechanism C

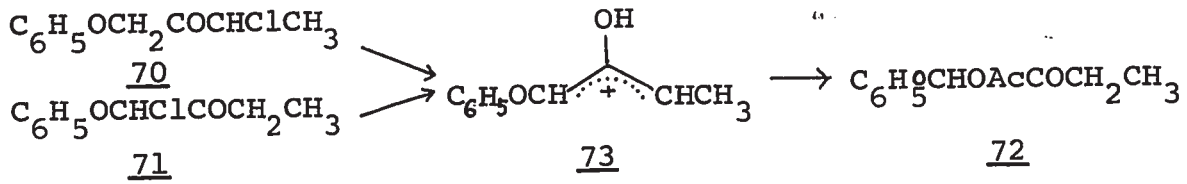


61 69 64

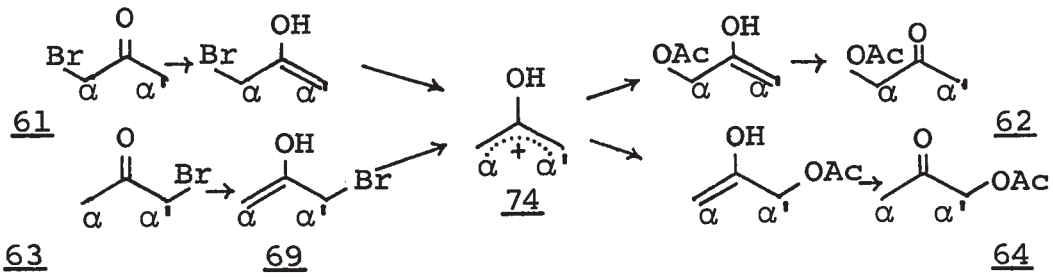
S_N2' displacements in allylic systems.[34] However, as Bordwell pointed out, this mechanism involves "the postulation of an unusual reaction path (S_N2') applied to an intermediate (the enol 69) present in small concentration." In addition, Bordwell's work on 2,6-dibromocyclohexanones 44, ruled out, at least in this case, S_N2' displacement as

an important pathway for the acetolysis of these bromoketones, and showed 1,3-elimination of hydrogen bromide to be the first step in the transformation of 45 into the major product 2-acetoxycyclohex-2-enones 46.

Rosnati and coworkers[35] demonstrated that isomeric chloroketones in the 1-phenoxypropanone series 70, 71 gave the same acetolysis product 72 on treatment with potassium acetate in acetic acid. A common symmetric intermediate 73 was proposed to explain the result. Put in general

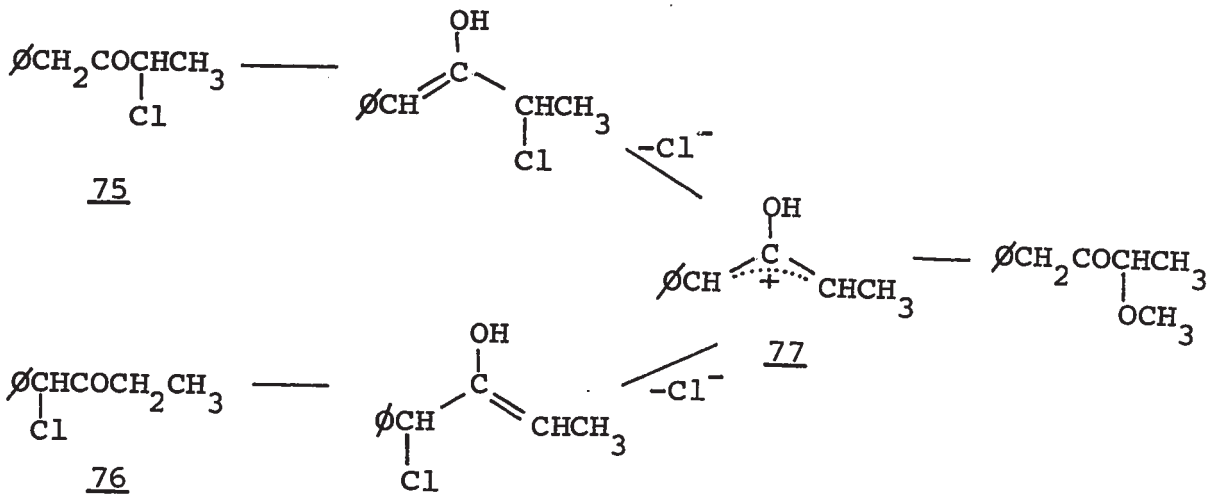


Mechanism D_1



terms, Rosnati and coworkers' mechanism involves ionization of the C-Br bond of the enol 69 aided by π-bond participation from the neighboring group to give the enolic carbonium ion 74, followed by nucleophilic attack by acetate ion at either the α- or the α'-position (mechanism D_1). Mechanism D_1 finds analogy in the mechanism for α-alkoxyketone formation from chloroketones such as 75 and 76. It was shown by

Bordwell and Carlson[36] that both the acid-catalyzed and the base-catalyzed solvolyses proceed by the same mechanism: solvolysis of an intermediate enol allylic chloride to the enolic carbonium 77 and subsequent attack by the solvent.

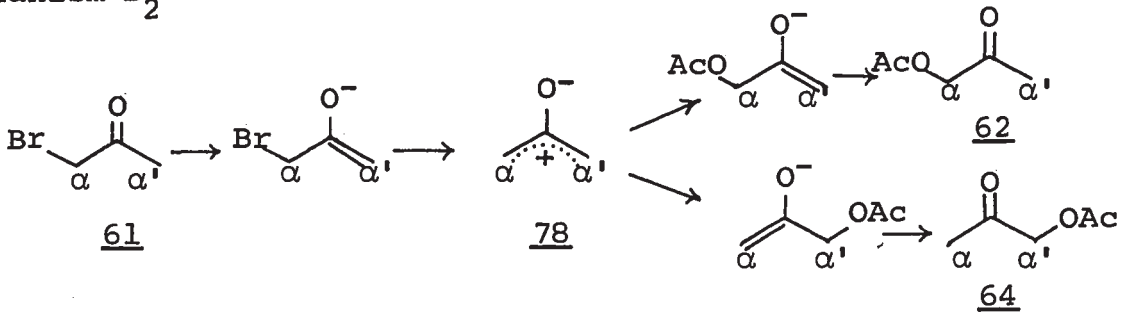


It is to be noted that this enolic carbonium ion mechanism for the acetolysis of bromoketones would account for the formation of normal and abnormal displacement products 62 and 64 at the same time and predicts that the same acetoxyketone mixtures would result from isomeric bromoketones 61 and 63.

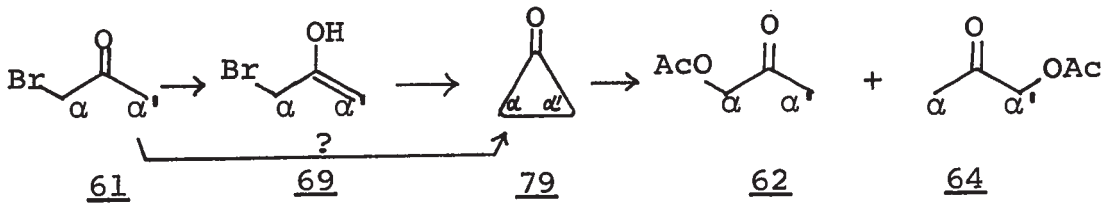
Other mechanisms involving a dipolar ion (zwitterion or oxyallyl) intermediate 78 or a cyclopropanone intermediate 79 are also possible (mechanisms D_2 and D_3).

Since it is difficult to distinguish between the last three mechanisms unambiguously, they will be grouped

Mechanism D_2



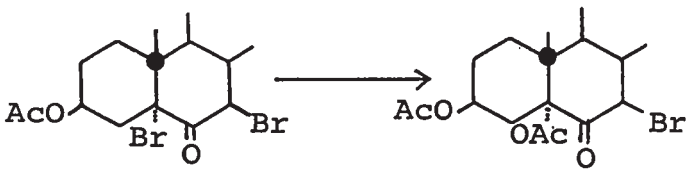
Mechanism D_3



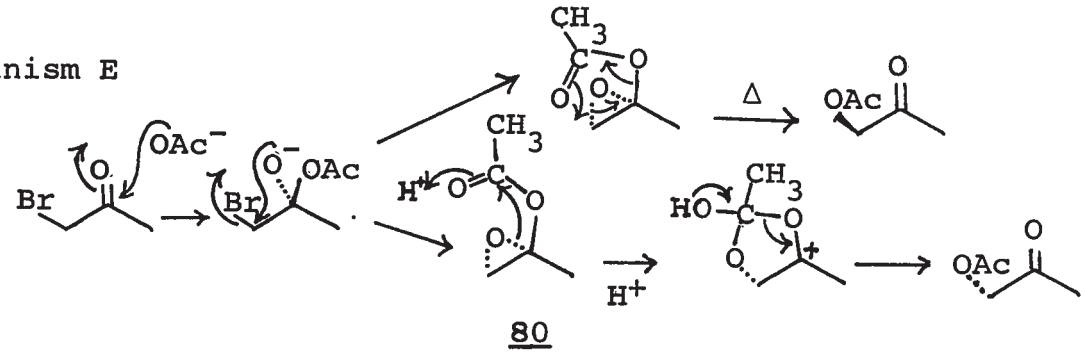
together and referred to as the symmetric intermediate mechanism or mechanism D. There are clearly some instances where this mechanism is not applicable, for example, in the reaction of bromoketones lacking α-protons.

There is one more alternative for formation of the normal displacement product 62. Instead of direct S_N2 displacement of bromine (mechanism A) or attack on the symmetric intermediate (mechanism D), the acetate ion could attack at the carbonyl group to give epoxy acetate 80, which could rearrange either thermally or catalytically into an acetoxyketone to give the normal displacement product (mechanism E). The formation of epoxy acetate

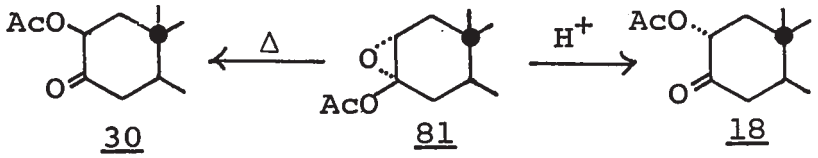
intermediate has been suggested by Cookson and coworkers[37] to explain the stereochemistry of the acetolysis of 3β-acetoxy-5α,7β-dibromocholestan-6-one.



Mechanism E



80



30 81 18

As to the stereochemistry of the mechanisms mentioned above, direct S_N2 displacement (mechanism A) must give inversion. The S_N2' mechanism (mechanism C) would give retention if Stork's result on his cyclohexyl allylic system[38] can be extended to the enol system. Since Williamson and coworkers[39] demonstrated that 3β-acetoxy-2α,3α-oxidocholestane 81 rearranged thermally to 2β-acetoxycholestan-3-one 30, but rearranged directly in acid to 2α-acetoxycholestan-3-one 18, the epoxy acetate route (mechanism E) would be expected to give retention

or inversion product, depending on whether the final step was thermal or catalytic. No stereochemical course could be predicted for mechanism B, since no $\alpha \rightarrow \alpha'$-shift of bromine has ever been observed in acetic acid or acetone. For the enolic carbonium ion mechanism or the zwitterionic mechanism (mechanism D_1 or D_2) attack from both sides and at both positions will be equally probable only if the intermediate has C_{2V} symmetry, otherwise steric and stereoelectronic effects will take place. For a cyclopropanone mechanism (mechanism D_3), no prediction could be made since the detailed mechanisms of both the formation of the cyclopropanone and the opening of the cyclopropanone ring are not yet well understood.[19]

Control experiments showed that the α-substituents in both bromoketones and acetoxyketones were easily epimerized in potassium acetate-acetic acid. Thus the configurations of the substituents of the products do not have much significance except that they represent the more stable ones. However, this is not the case with the tetramethylammonium acetate-acetone reagent, for although bromoketones are readily epimerized, the rate of epimerization of acetoxyketones is much slower, and occasionally the less stable epimer can be isolated.

When the reaction of 2α-bromocholestan-3-one 4 with

potassium acetate-acetic acid at 133-135° (reflux temperature)[17] was repeated (reaction 3), the crude product showed two acetoxyketone spots on a t.l.c. plate in a ratio of ca. 5:1, corresponding in Rf values to 2α-acetoxycholestan-3-one 18 (or 4α-acetoxycholestan-3-one 19) and 3β-acetoxycholestan-2-one 39. On lowering the reaction temperature to 97-103° and stopping the reaction as soon as all the bromoketone was consumed (reaction 2), the crude product was found to contain ca. 5% of the 3β-acetoxy-2-ketone 39. Thus the presence of 39 in the reaction at 133-135° was a result of further transformation of the 2α-acetoxy-3-ketone 18 formed during the reaction. This was confirmed by treating pure 2α-acetoxy-3-ketone 18 with potassium acetate-acetic acid at 133-135° for a longer time, whereupon the 3β-acetoxy-2-ketone 39 was formed in ca. 80% yield (reaction 19). Since control experiments showed that there was no interconversion between the 2α-acetoxy-3-ketone 18 (or the 3β-acetoxy-2-ketone 39) and the 4α-acetoxy-3-ketone 19 at 133-135° (reactions 18, 19, and 23), the ratio of the 2α-acetoxy-3-ketone 18 plus the 3β-acetoxy-2-ketone 39 to the 4α-acetoxy-3-ketone 19 formed in the reaction of 2α-bromo-3-ketone 4 with acetic acid-acetate mixture at temperatures lower than 133-135° represents the kinetically controlled formation of the

normal and abnormal displacement products.

As noted by previous workers,[12,22] the 2α-acetoxy-3-ketone 18 and the 4α-acetoxy-3-ketone 19 are not separable by recrystallization or column chromatography, and they have identical Rf values on t.l.c. and almost identical i.r. spectra. Thus resort has to be made to n.m.r. spectroscopy and optical rotations, but even in the n.m.r. spectra, the C-18 and C-19 methyl protons are identical, and the α-proton signals overlap partially. Quantitative estimation by α-proton integration is thus subject to some uncertainty.

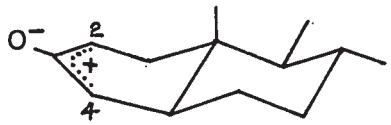
The difference in specific rotation (+52° for 18 and -4° for 19) is big enough for fairly accurate estimation. In this way, the ratio of C-2 to C-4 attack in the reaction of 2α-bromocholestan-3-one 4 with potassium acetate-acetic acid at 97-103° was estimated to be very close to 1:1 (reaction 2).

Reaction of 4α-bromocholestan-3-one 12 with potassium acetate-acetic acid at 133-135° also gave a mixture of isomeric acetoxyketones, the 2α-acetoxy-3-ketone 18, the 4α-acetoxy-3-ketone 19 and the 3β-acetoxy-2-ketone 39 (reaction 5). The ratio of C-2 to C-4 attack was estimated to be ca. 1:1 by n.m.r. integration of low field α-protons. The fact that, within experimental error,

2α-bromocholestan-3-one 4 and 4α-bromocholestan-3-one 12 gave the same acetolysis product is a strong indication for the common symmetric intermediate mechanism (mechanism D) for the reaction of bromoketones with potassium acetate in acetic acid. This inference was further supported by the acetoxyketones formed in the 5β-series. Both 2β-bromo-5β-cholestan-3-one 82 and 4β-bromo-5β-cholestan-3-one 3 gave only 2β-acetoxy-5β-cholestan-3-one 59 on treatment with potassium acetate-acetic acid. No trace of 4β-acetoxy-5β-cholestan-3-one 60 was detectable in the n.m.r. spectrum of the crude products (reactions 10 and 11).

The formation of both the 2- and the 4-substituted products in the 5α-series (reactions 2, 3 and 5) and the exclusive formation of the 2-substituted product in the 5β-series (reactions 10 and 11) can also be rationalized by the symmetric intermediate mechanism (mechanism D). The symmetric intermediate in the 5α-series 83 would be more susceptible to the C-4 attack than to the C-2 attack if the transition state comes after substantial change in the geometry of the planar intermediate (Δ^2-cholestene *v.s.* Δ^3-cholestene).[40] On steric grounds, if the attack is from the α-side, the chances should be equal for 2- and 4-position; if the attack is from the β-side, C-2 attack might be favored because of the presence of the extra 6β-H

interaction to hinder the C-4 attack. Thus it is not surprising that approximately equal amounts of C-2 attack and C-4 attack were observed.



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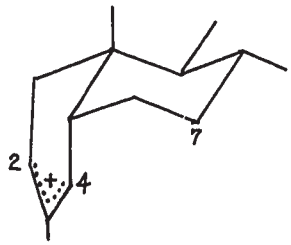
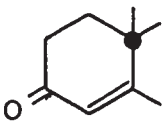


84

In the 5β-series, the symmetric intermediate should be more susceptible to C-2 attack than to C-4 attack if the geometry of the transition state has changed substantially from the planar form (Δ^3-5β-cholestene v.s. Δ^2-5β-cholestene). The steric environments are comparable for C-2 and C-4 if the attack is from β-side, but C-2 attack is strongly favorable if the attack is from α-side because of the presence of C-7 methylene group. Thus only the 2β-acetoxy-3-ketone 59 was formed from either the 2β-bromo-3-ketone 82 or the 4β-bromo-3-ketone 3.

Beside the acetoxyketones discussed above, minor amounts of unsaturated ketones were also observed during the acetolysis with potassium acetate-acetic acid. The unsaturated ketones formed from 2α-bromocholestan-3-one 4, 4α-bromocholestan-3-one 12, 2β-bromo-5β-cholestan-3-one 82 and 4β-bromo-5β-cholestan-3-one 3 were all mainly

Δ^4-cholestan-3-one 5. Not much Δ^1-3-ketone (Δ^1-cholesten-3-one 6 or Δ^1-5β-cholestan-3-one 85) was observed.



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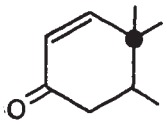

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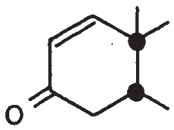


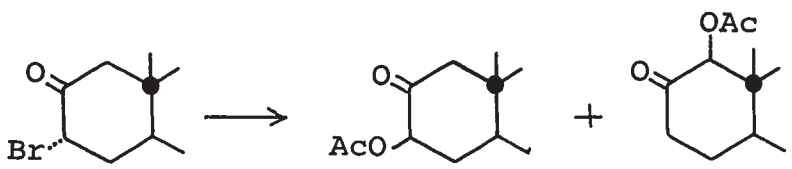
85

Speculation on the mechanism of their formation will be presented after the discussion of the reaction of bromoketones with tetramethylammonium acetate in acetone.

With the intention of getting more support for the symmetric intermediate mechanism D for the acetolysis of bromoketones with potassium acetate-acetic acid, three more ring-A bromoketones were prepared and treated with potassium acetate-acetic acid.

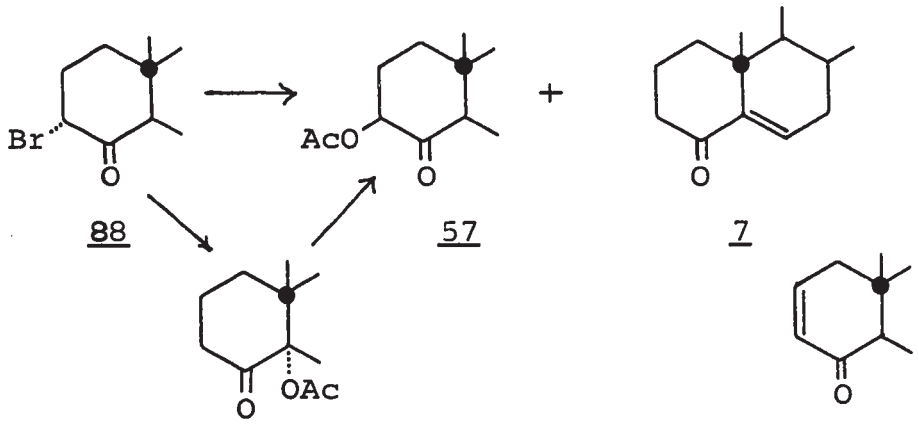
Two acetoxyketones were formed in a ratio of about 1:3 from 3α-bromocholestan-2-one 86, the major one being 3β-acetoxycholestan-2-one 39, the normal displacement product (reaction 8). Although no attempt was made to isolate the minor isomer, the n.m.r. spectrum of the crude product was consistent with its being 1β-acetoxy-cholestan-2-one 87 because of the presence of a singlet ($w_{½}$ = 3 Hz.) at δ 4.70 for the C-1 proton.

3β-Acetoxycholestan-4-one 57 was the only acetoxyketone formed from 3α-bromocholestan-4-one 88 (reaction 9). Only



86 39 87

a trace of the abnormal substitution product, 5α-acetoxycholestan-4-one 58, was detected. However, since a control experiment revealed that the 5α-acetoxy-4-ketone 58 was readily isomerized into the 3β-acetoxy-4-ketone

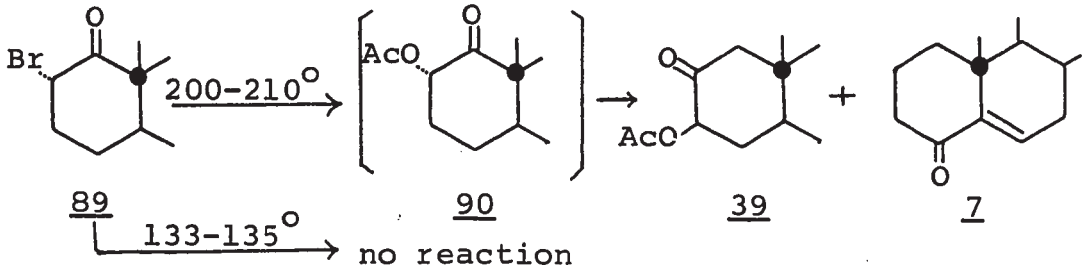


88 57 7 58 11

57 by potassium acetate-acetic acid at 133-135° (reaction 28), the absence of the 5α-acetoxy-4-ketone 58 has no mechanistic significance. In addition to the acetoxyketone 57, the crude acetolysis product from 3α-bromocholestan-4-one 88 (reaction 9) contained ca. 15% of Δ^5-cholesten-4-one 7. Since 3α-acetoxy-cholestan-4-one 21 gave a much lower yield (ca. 6%) of Δ^5-cholesten-4-one 7 under comparable conditions

(reaction 26), at least part of the Δ^5-cholesten-4-one 7 was formed directly from the 3α-bromo-4-ketone 88. Analogous to the reactions of 2α-bromocholestan-3-one 4 and 2β-bromo-5β-cholestan-3-one 82 (reactions 2 and 10), no significant amount of the normal elimination product, Δ^2-cholesten-4-one 11 was formed in the acetolysis of the 3α-bromo-4-ketone 88 (reaction 9). Discussion of unsaturated ketone formation will also be deferred.

The most interesting acetolysis reaction of a bromoketone with potassium acetate in acetic acid was that of 2α-bromocholestan-1-one 89. Reaction at 133-135° gave quantitative recovery of the starting material (reaction 6). The inertness of the 2α-bromo-1-ketone 89 is expected if acetolysis in acetic acid prefers to go through a symmetric intermediate mechanism D since there is no α'-proton in 89. Comparison of the reactions of 2α-bromocholestan-3-one 4 and 2α-bromocholestan-1-one 89 (reactions 2, 3, and 6) indicates that direct S_N2 displacement (mechanism A) can not be a major route for the formation of the normal displacement product, since it is difficult to rationalize why the shift of carbonyl function from C-3 to C-1 should alter the reactivity of the bromo-substituent to such a great extent. However, an epoxy acetate pathway (mechanism E) is also consistent with the inertness of 2α-bromo-1-ketone



89. Because of the well-known steric congestion around the C-1 position, the sluggishness toward acetate ion attack on the carbonyl group of 2α-bromocholestan-1-one 89 is expected.

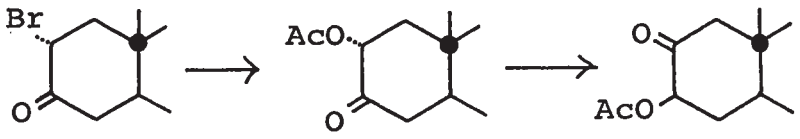
The same argument[41] has been used to explain the failure of 89 to undergo the quasi-Favorskii rearrangement since the symmetric intermediate mechanism and the epoxy acetate mechanism (mechanisms D and E) have the same structural requirement as the cyclopropanone and semi-benzilic mechanisms respectively, for the Favorskii rearrangement.

When the 2α-bromo-1-ketone 89 was treated with potassium acetate-acetic acid at 200-210°, the product was a mixture of 3β-acetoxycholestan-2-one 39 and Δ^5-cholesten-4-one 7 (reaction 7). From the discussion of the acetoxyketone rearrangement to be presented later in this chapter, 2α-acetoxycholestan-1-one 90 is the most reasonable intermediate for the formation of both the 3β-acetoxy-2-ketone 39 and Δ^5-cholesten-4-one 7. Thus either the

direct displacement or the epoxy acetate pathway (mechanism A or E) must operate at higher temperature to give the acetolysis product even though these mechanisms are not important at 133-135°.

When the reaction of 2α-bromocholestan-3-one 4 with tetramethylammonium acetate was repeated according to the procedure of Williamson and Johnson,[22] to our surprise, n.m.r. and t.l.c. examination of the crude product showed that the major component was 2α-acetoxycholestan-3-one 18, and not the 3β-acetoxy-2-ketone 39. The amount of the latter was less than 10% (reaction 12). Only after reflux for five days was there an appreciable amount of the 3β-acetoxy-2-ketone 39 formed (reaction 13). The difference between our result and that of Williamson and Johnson[22] can be explained by slight differences in the reaction medium since it was found later that the rate of reaction of bromoketones or acetoxyketones with this reagent was not easily reproducible and seemed to depend on the pH and the minute amount of water in the system, probably introduced mainly with the tetramethylammonium acetate. The reaction of 2α-bromocholestan-3-one 4 with tetramethylammonium acetate-acetone can therefore be formulated as follows: (see p. 55)

The second step was confirmed by treating pure 2α-acetoxycholestan-3-one 18 with tetramethylammonium



4 18 39

+ unsaturated ketone

acetate-acetone (reaction 32, 33). Thus if the reaction conditions are chosen properly, the most convenient way to prepare the 2α-acetoxy-3-ketone 18 is the reaction of 2α-bromocholestan-3-one 4 with acetate ion in acetone.

Comparison of the acetoxyketone distributions from the reaction of 2α-bromocholestan-3-one 4 with acetate ion in acetic acid and in acetone (reactions 2 and 12) supports the suggestion made earlier that acetolysis in acetic acid proceeds mainly by the symmetric intermediate mechanism D. If the formation of the 2α-acetoxy-3-ketone 18 and the 4α-acetoxy-3-ketone 19 in acetic acid is a result of S_N2 displacement (mechanism A) and/or epoxy acetate rearrangement (mechanism E) in competition with S_N2' displacement (mechanism C), it is difficult to rationalize why the change of solvent from acetic acid to acetone should suppress S_N2' displacement so completely as to give the 2α-acetoxy-3-ketone 18 as the sole product. On the other hand, the symmetric intermediate mechanism can not be an important route in acetone, since there is no obvious reason why

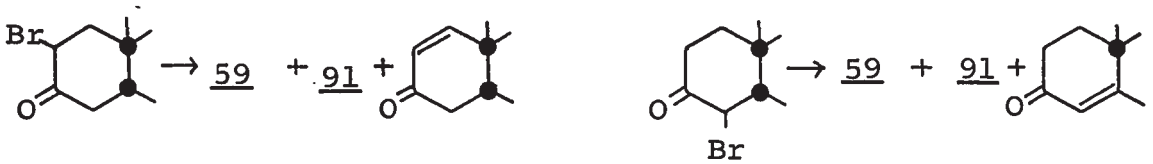
attack of acetate ion on the intermediate 83 should occur at both C-2 and C-4 in acetic acid, but exclusively at C-2 in acetone. The conclusion that acetolysis in acetic acid proceeds mainly by the symmetric intermediate (probably the enolic carbonium ion or zwitterionic intermediate i.e. mechanism D_1 or D_2) and reaction in acetone proceeds mainly by direct S_N2 displacement and/or epoxy acetate intermediate (mechanism A and/or E) is in agreement with the high Grunwald-Winstein Y-value of acetic acid (-1.68) compared to that of acetone (approx. -4.1*).[42]

Although a control experiment on 3β-acetoxy-2α,3α-oxidocholestane 81 in tetramethylammonium acetate-acetone gave complete recovery of the starting material, we still feel reluctant to exclude the epoxy acetate mechanism (mechanism E) because of the stereochemical influence (i.e. 3β-acetoxy-2α, 3α-oxidocholestane 81 v.s. 3α-acetoxy-2β,3β-oxidocholestane) that might be important and because of the unreproducibility of the rate of reaction in acetone.

The 5β-series gave entirely different results. Reaction of both 2β-bromo-5β-cholestan-3-one 82 and 4β-bromo-5β-cholestan-3-one 3 with acetate-acetone gave only the 2-substituted products, 2β-acetoxy-5β-cholestan-3-one 59 and 2α-acetoxy-5β-cholestan-3-one 91 in addition to unsaturated ketones (reactions 15, 16). The complete

*Extrapolated value

change from normal displacement in the case of the 2β-bromo-3-ketone 82 to abnormal displacement in the case of the 4β-bromo-3-ketone 3 can be rationalized in two ways. If a symmetric intermediate is involved (mechanism D), exclusive formation of 2-substituted products in acetone can be explained in the same way as the acetolysis in acetic acid. However, by analogy to the 5α-series, and in view of the different unsaturated ketone formed from each bromoketone (see later), a symmetric intermediate is not very likely and one is forced to conclude that the 2β-bromo-3-one 82 undergoes direct S_N2 displacement or the epoxy acetate route (mechanism A or E) to give the normal product, whereas the 4β-bromo-3-ketone 3 undergoes S_N2' (mechanism C) exclusively to give the abnormal products, contrary to Bordwell's objection to S_N2' displacement being an important route for the reaction. A full understanding awaits the



82 85 3 5

investigation of the reaction of some more bromoketones with acetate ion in acetone, e.g., reinvestigation of the reaction of pure 4α-bromocholestan-3-one 12 with acetate ion in acetone.

A control experiment revealed that pure 2α-acetoxy-5β-cholestan-3-one 91 isomerized into the 2β-isomer 59 at about the same rate (reaction 37) as the reaction of the 2β-bromo-3-ketone 82 or the 4β-bromo-3-ketone 3 with acetate-acetone (reaction 15, 16). Therefore, reaction in acetone, in contrast to that in acetic acid, afforded the kinetically controlled product, 2α-acetoxy-5β-cholestan-3-one 91, in appreciable amount. A more sensitive technique such as optical rotation is required to ascertain whether part of the 2β-acetoxy-5β-cholestan-3-one 59 formed directly from the bromoketones.

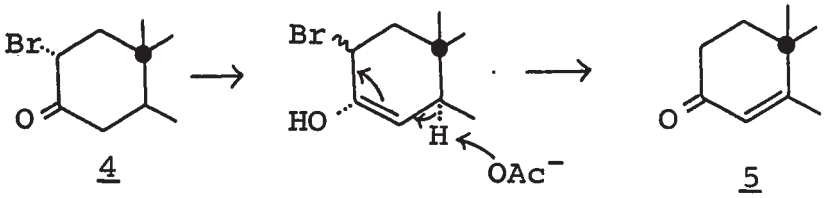
The appreciable amount of α-attack observed in the two bromo-5β-cholestanone cases is unexpected. In the case of 2β-bromo-5β-cholestan-3-one 82, it might result from the direct S_N2 attack on the 2-position with inversion of configuration. In the case of 4β-bromo-5β-cholestan-3-one 3, it is difficult to see why the acetate ion does not approach the 2-position of the Δ^2-enol of 3 from the β-side which is more favored on steric ground.

Comparison of the unsaturated ketones formed in the reaction of 2α- and 4α-bromocholestan-3-one 4 and 12 and 2β- and 4β-bromo-5β-cholestan-3-one 82 and 3 in both acetic acid and acetone gives very interesting results. For reactions in acetic acid (reactions 2, 5, 10, and 11), the

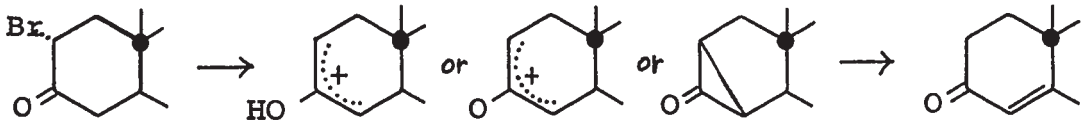
major unsaturated ketone is always the more stable one, i.e. Δ^4-cholesten-3-one 5, no matter whether the bromine substituent is at the 2- or the 4-position. But for reactions in acetone (reactions 12, 14, 15, and 16), the major unsaturated ketone is the one expected from normal 1,2-elimination of hydrogen bromide without rearrangement, i.e. Δ^4-cholesten-3-one 5 from 4α-bromocholestan-3-one 12 and 4β-bromo-5β-cholestan-3-one 3, but Δ^1-cholesten-3-one 6 and Δ^1-5β-cholesten-3-one 85 from 2α-bromocholestan-3-one 4 and 2β-bromo-5β-cholestan-3-one 82 respectively.

The formation of Δ^4-cholesten-3-one 5 as well as Δ^1-cholesten-3-one 6 in the dehydrobromination of 2α-bromocholestan-3-one 4 by pyridine bases or by lithium salts in dimethylformamide has been known for a long time.[43] Possible mechanisms for the formation of the rearranged elimination product, Δ^4-cholesten-3-one 5, have been suggested. The possibility of debromination and rebromination to give 4α-bromocholestan-3-one 12, i.e. the first step in mechanism B, followed by normal 1,2-elimination has been ruled out at least for the pyridine bases by the work of Marshall and Warnhoff.[44] Two other possibilities are 1,4-elimination of hydrogen bromide from the Δ^3-enol of 2α-bromocholestan-3-one 4, and the formation of a symmetric intermediate such as 83 with subsequent proton shift. It is to be noted that

these two mechanisms involve the same intermediates as the



4 5



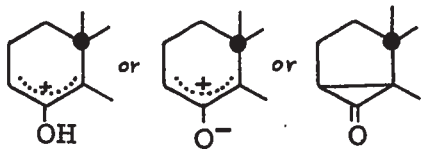
4 83 5

S_N2' displacement and symmetric intermediate mechanisms C and D respectively, proposed earlier for acetolysis of bromoketones.

The different dehydrobromination behavior in the potassium acetate-acetic acid and tetramethylammonium acetate-acetone systems can be easily explained if the symmetric intermediate mechanism is assumed to be responsible for the rearranged elimination product. As mentioned earlier, a solvent like acetic acid with a higher Grunwald-Winstein Y-value facilitates the formation of symmetric intermediates such as 83 and 84, both of which can undergo proton loss to the more stable product Δ^4-cholesten-3-one 5. Therefore, in addition to displacement product, the major unsaturated ketone formed during the acetolysis of α-bromo

3-ketosteroids in acetic acid is Δ^4-cholesten-3-one 5 whether the bromo-substituent is on C-2 or C-4. On the other hand, formation of symmetric intermediates such as 83 and 84 in acetone is suppressed because of the low ionizing power of the medium, and direct E2 elimination is the only pathway operating to give the observed unrearranged product. However, if 1,4-elimination were responsible for the rearranged product in acetic acid, one would expect that it would also operate in acetone, and no difference in dehydrobromination behaviors should be observed in these two media.

The formation of Δ^5-cholesten-4-one 7, and not Δ^2-cholesten-4-one 11 during the acetolysis of 3α-bromocholestan-4-one 88 in acetic acid (reaction 9) and the minute amount of unsaturated ketone formation during the acetolysis of 3α-bromocholestan-2-one 86 (reaction 8) agree with the rationalization delineated above. In the first case, Δ^5-cholesten-4-one 7, the more stable of the two possible isomers was formed from the symmetric intermediate 92. In the second case, since all the α- and β-positions of 93 are secondary or quaternary, acetate ion attack predominates over proton loss and acetoxyketones are the only products observed.



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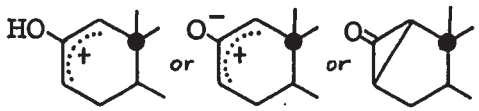


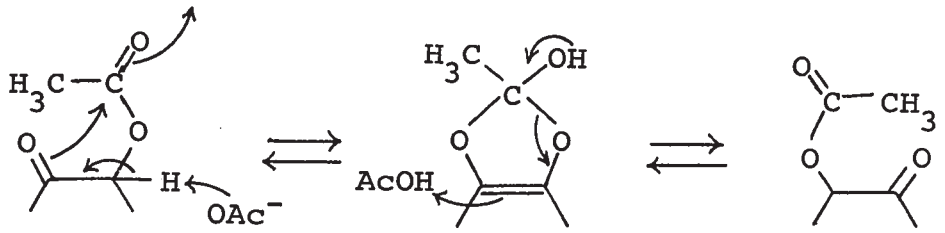
93

The difference in the amounts of unsaturated ketone formed in the acetolysis of 2α-bromocholestan-3-one 4, and 2β-bromo-5β-cholestan-3-one 82 in acetone (reactions 12 and 15) was unexpected. One possible explanation depends on the observed faster rate of acetoxyketone formation from 2α-bromocholestan-3-one 4 than that of 2β-bromo-5β-cholestan-3-one 82. The slowness of conversion of 82 into acetoxyketones might result in a larger amount of elimination product. However, since the rates of the reaction of bromoketones with tetramethylammonium acetate-acetone are not easily reproducible, the difference in the rates observed for single runs may not be real.

In conclusion, the mechanism of conversion of bromoketones into acetoxyketones depends drastically on the reaction medium. In acetate-acetic acid, symmetric intermediate mechanism D is the major pathway. In acetate-acetone, direct displacement mechanism A and/or epoxyacetate mechanism E predominate. The minor amount of unsaturated ketones formed also fits into this scheme.

(ii) Interchange of Carbonyl and Acetoxyl Groups of Acetoxyketones

The first step in Fieser's scheme for the transformation of 4α-acetoxycholestan-3-one 19 into Δ^5-cholesten-4-one 7 is the interchange of functional groups to give 3α- or 3β-acetoxycholestan-4-one 21 or 57. Our observations of the rearrangement of 2α-acetoxycholestan-3-one 18 into 3β-acetoxycholestan-2-one 39 by acetate ion in refluxing acetic acid or in refluxing acetone (reactions 18,19,32, and 33) provides more exact analogy than that mentioned by Fieser.[17] The mechanism generally accepted for the interchange reaction proceeds through a cyclic ortho ester intermediate such as 96.[18]

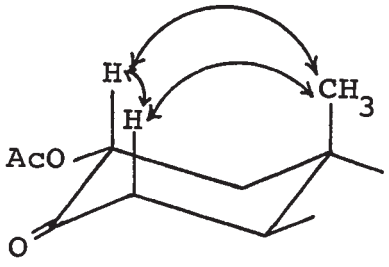


96

When 2α-acetoxycholestan-3-one 18 was treated with potassium acetate-propionic acid at 133-135° for two days the crude product was a 7:3 mixture of 2α-acetoxycholestan-3-one 18 and 3β-acetoxycholestan-2-one 39, no trace of propionoxyl group was incorporated into the organic moiety. Thus the interchange of functional groups of

acetoxyketones, at least in carboxylic acid at 133-135°, is intramolecular. This result is strong support for the mechanism mentioned above. Further observation that the 2α-acetoxy-3-ketone 18 was rearranged into the 3β-acetoxy-2-ketone 39 by γ-collidine, although at somewhat higher temperature (215°) is additional evidence for the intramolecularity of the rearrangement.

The greater thermodynamic stability of the 3β-acetoxy-2-ketone 39 relative to the 2α-acetoxy-3-ketone 18 as observed in the above reactions can be attributed to the difference between the two CH_3-H repulsive interactions in 18 and a single CH_3-H interaction plus one less repulsive H-H interaction in 39.



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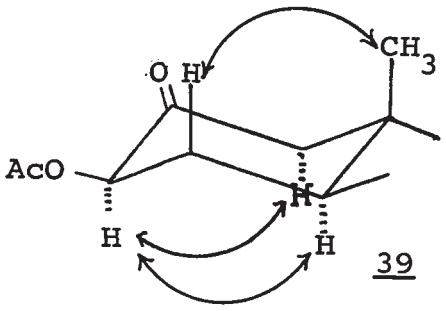

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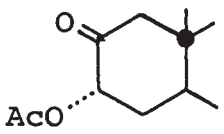
In contrast to the 2α-acetoxy-3-ketone 18, the 4α-acetoxy-3-ketone 19 did not undergo the interchange reaction in refluxing potassium acetate-acetic acid or in refluxing tetramethylammonium acetate-acetone (reactions 23 and 34). It was also recovered unchanged on treatment with

γ-collidine at 215°. The difference between 18 and 19 can be rationalized by the fact that a 2,3-double bond is much more stable and more readily introduced than a 3,4-double bond in the 5α-series.[40] Since the mechanism suggested for the interchange reaction involves enolization, the 2α-acetoxy-3-ketone 18 is expected to react faster than the 4α-isomer 19. Raising the reaction temperature of the 4α-isomer 19 to 170-180° resulted in conversion into the final product Δ^5-cholesten-4-one 7 (reaction 24), indicating that the interchange reaction of the 4α-acetoxy-3-ketone 19 into the 3β-acetoxy-4-ketone 57 began to take place at 170-180°, followed by more rapid conversion of the latter into Δ^5-cholesten-4-one 7. Control experiment starting with pure 3α-acetoxy-4-ketone 21 confirmed the above assumption (reactions 26 and 27).

Analogous derivatives of the 5β-series behaved somewhat differently. Both 2β-acetoxy-5β-cholestan-3-one 59 and 4β-acetoxy-5β-cholestan-3-one 60 undergo interchange of functional groups in refluxing potassium acetate-acetic acid to give 3α-acetoxy-5β-cholestan-2-one 97 and 3β-acetoxycholestan-4-one 57 respectively (reactions 30 and 29). In refluxing tetramethylammonium acetate-acetate, both the 4β-acetoxy-3-ketone 60 and the 2β-acetoxy-3-ketone 59 are recovered unchanged in almost quantitative yield

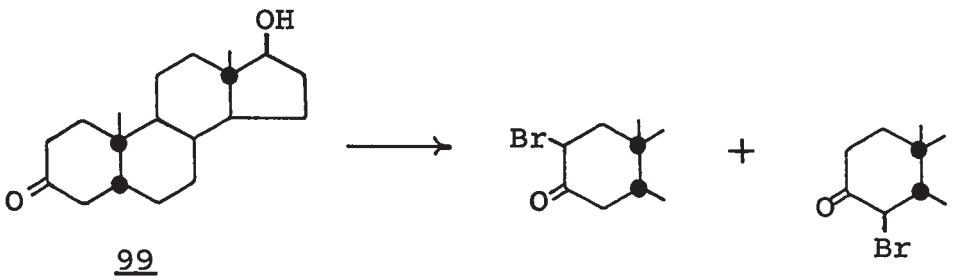
(reactions 35 and 36). Bullucci has suggested that in the



97

5β-series the direction of enolization might not be as unequivocal as in 5α-series since dehydrochlorinations of 3β-chloro-5β-cholestane 98 gave a mixture of Δ^2-5β-cholestene and Δ^3-5β-cholestene in a ratio of 55:45[45] and bromination of 17β-hydroxy-5β-androstan-3-one 99 gave a mixture of the 2-bromoketone and the 4-bromoketone in a ratio of 1:4.[46] Our observations of the different behavior of acetoxyketones in 5α- and 5β-series toward interchange reactions agrees with Bullucci's suggestion.

98



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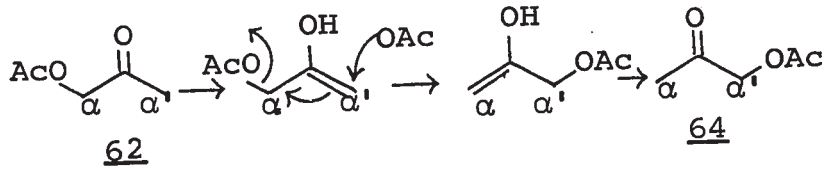
(iii) α→α'-Shift of Acetoxyl Group of α-Acetoxyketones

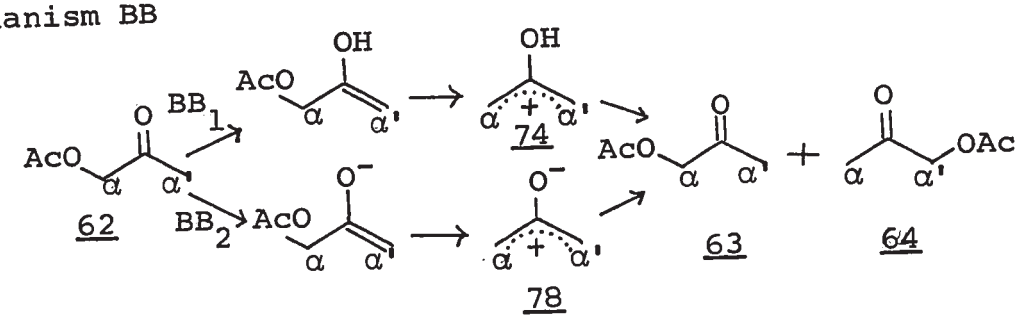
As mentioned earlier, both 2α-acetoxycholestan-3-one 18

and 4α-acetoxycholestan-3-one 19 were found to be intermediates in the h-Δ^1-cholestenone rearrangement by the conversion of 1:1 complex of 18 and 19 into Δ^5-cholesten-4-one 7 at 220-230° (reaction 17). The most reasonable first step for the transformation of the 2α-acetoxy-3-ketone 18 into Δ^5-cholesten-4-one 7 is α→α'-transfer of the acetoxyl group from C-2 to C-4 to give 4α-acetoxycholestan-3-one 19. At least four mechanisms can be proposed for this transformation.

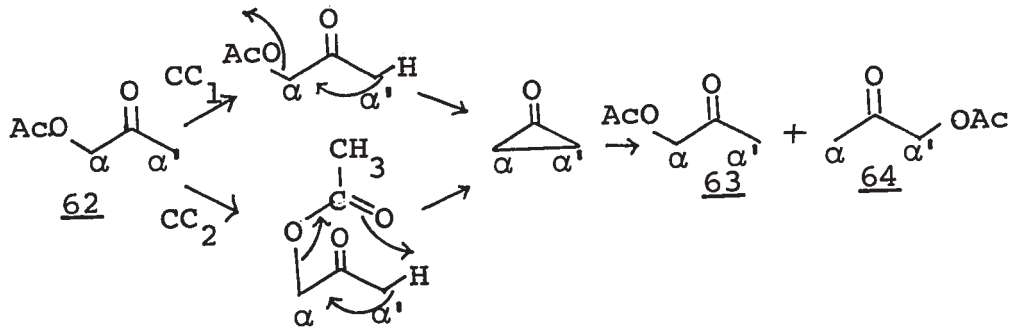
Mechanism AA



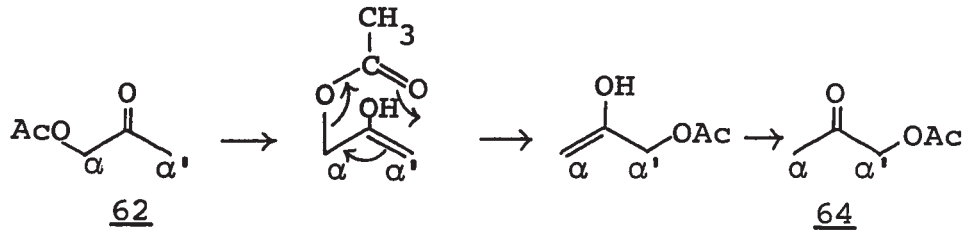
Mechanism BB



Mechanism CC

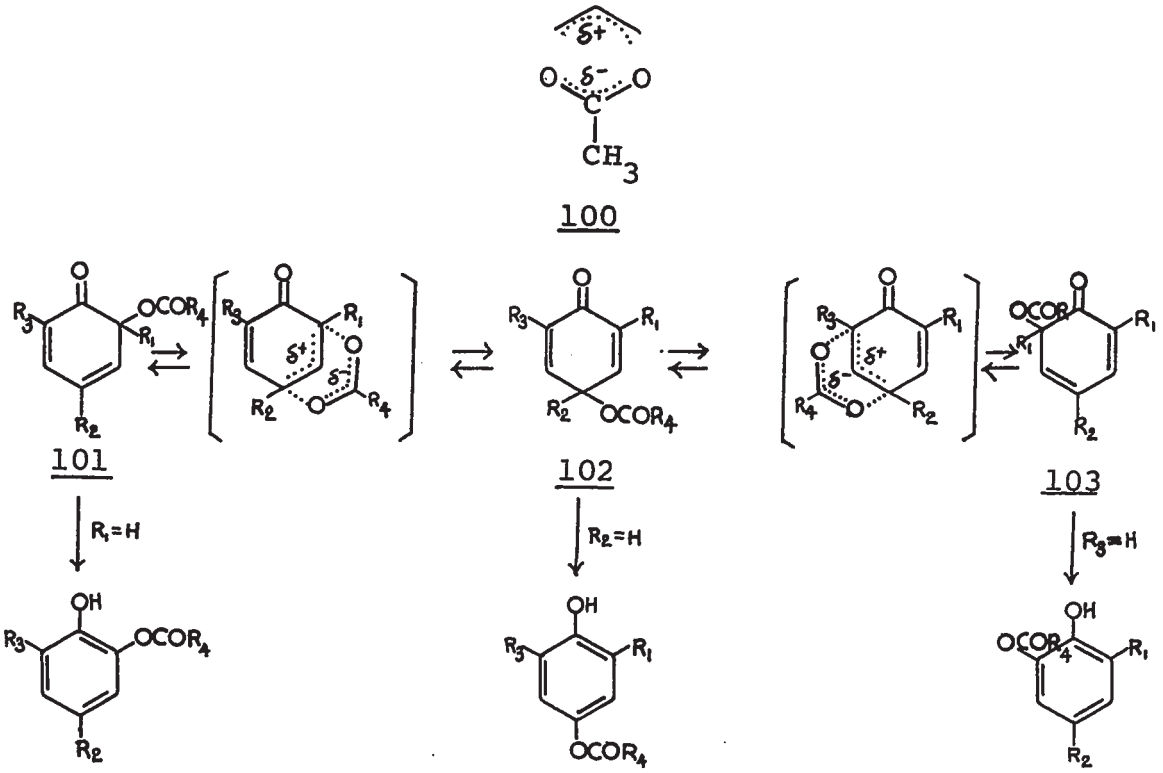


Mechanism DD



62 64

Mechanism AA is S_N2' attack by acetate ion on the enol form of the acetoxyketone. Mechanism BB_1 and BB_2 are loss of acetate ion from the enol and the enolate respectively, to give the enolic carbonium ion 74 and the zwitterion 78 respectively, followed by acetate ion attack on either α- or α'-position. Mechanism CC_1 and CC_2 involve formation of cyclopropanone 79 by intermolecular and intramolecular 1,3-elimination of acetic acid. Mechanism DD is intramolecular acetoxyl group transfer in the enol of α-acetoxyketone 62 to give the enol of α'-acetoxyketone 64. Analogy is provided by the allylic rearrangement of allyl esters in gas phase or in solution.[47] A transition state with substantial charge separation but with a structure resembling that of a Cope rearrangement, such as 100 has been proposed.[47] Similar intermediates have been recently proposed for the thermal rearrangement of 6-acyloxycyclohexane-2,4-dione 101 into 102 and 103.[48] Of all the mechanisms proposed above, mechanism DD is unique in that the acetoxyl group transfer is intramolecular.



100

101 102 103

It should be pointed out that although S_N2' displacement seems to be a less probable pathway for the formation of the rearranged acetoxyketones from bromoketones with potassium acetate-acetic acid, this mechanism should not be ruled out <u>a priori</u> for the α→α'-transfer in acetoxyketones under more drastic condition and with this much poorer leaving group.

As mentioned before, the interconversion between the 2α-acetoxy-3-ketone <u>18</u> and the 4α-acetoxy-3-ketone <u>19</u> does not take place in refluxing acetic acid-acetate mixture (reactions 18,19 and 23). At higher temperature (190-200°),

reaction of the 2α-acetoxy-3-ketone 18 resulted in partial conversion into Δ^5-cholesten-4-one 7, the acetoxyketone in the crude product was mainly the interchange product, 3β-acetoxycholestan-2-one 39, plus some starting material. No trace of the α→α'-transfer product, 4α-acetoxy-3-ketone 19, was detectable (reaction 20). This behavior can be interpreted in two ways, a slow rate-determining rearrangement of the 2α-acetoxy-3-ketone 18 to the 4α-acetoxy-3-ketone 19, followed by a fast conversion of 19 into Δ^5-cholesten-4-one 7; or direct rearrangement of the 2α-acetoxy-3-ketone 18 to Δ^5-cholesten-4-one 7 without the intervention of the 4α-acetoxy-3-ketone 19. The latter possibility is completely unreasonable and thus must be ruled out.

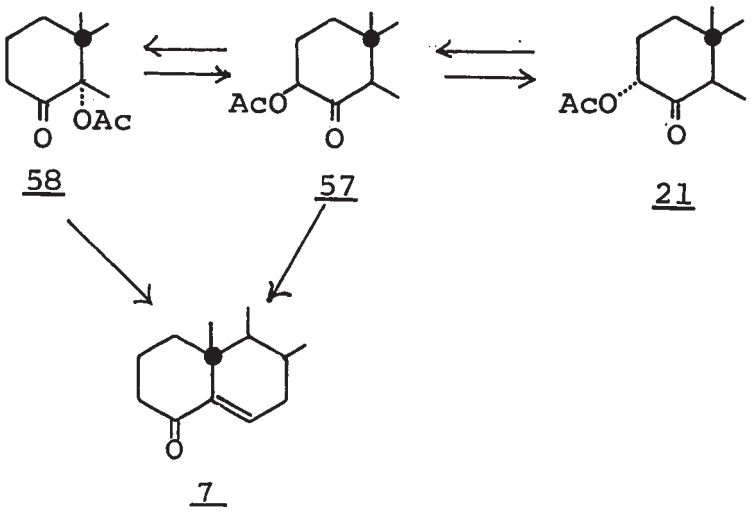
Comparison of the amount of Δ^5-cholesten-4-one 7 formed from the 2α-acetoxy-3-ketone 18, the 3β-acetoxy-2-ketone 39, the 4α-acetoxy-3-ketone 19 and the 2α-bromo-3-ketone 4 under comparable conditions (reactions 20, 22, 25, and 4) demonstrated that the 4α-acetoxy-3-ketone 19 is transformed into Δ^5-cholesten-4-one 7 much faster than the 2α-isomer 18, consistent with the above assumption that the rate-determining step is the α→α'-transfer of the acetoxyl group (18 → 19).

Acetoxyketones in the 5β-series showed very similar

behavior. α→α'-Transfer of the acetoxyl group does not take place in the refluxing acetic acid-acetate mixture. Only interchange reactions were observed with 4β- and 2β-acetoxy-5β-cholestan-3-one 60 and 59 (reactions 29 and 30). Raising the temperature of the reaction of 2β-acetoxy-5β-cholestan-3-one 59 to 220-230° resulted in complete conversion into the final product, Δ^5-cholesten-4-one 7 (reaction 31), indicating that α→α'-transfer does occur at higher temperature.

Investigation of the reaction of 4α-acetoxycholestan-3-one 19 at 170-180° indicated that the initial interchange reaction is the rate-determining step for its final conversion into Δ^5-cholesten-4-one 7. Therefore the next reaction to be investigated was the interconversion of 3β-acetoxycholestan-4-one 57 and 5α-acetoxycholestan-4-one 58 and their transformation into the final product, Δ^5-cholesten-4-one 7.

When the 3α-acetoxy-4-one 21 and the 5α-acetoxy-4-one 58 were treated with acetic acid-acetate at 133-135°, a mixture of 3β-acetoxycholestan-4-one 57 and Δ^5-cholesten-4-one 7 in a ratio of ca. 4:1 and traces of 5α-acetoxycholestan-4-one 58 was obtained in both cases (reactions 27 and 28). The conversion of 5α-acetoxycholestan-4-one 58 into 3β-acetoxycholestan-4-one 57 was the first case studied

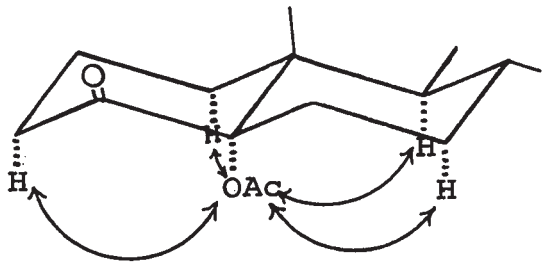


58 57 21

7

thus far in which α→α'-transfer was demonstrated to operate by isolation of the α'-acetoxyketone. The greater thermodynamic stability of 3β-acetoxycholestan-4-one 57 compared to 5α-acetoxycholestan-4-one 58 can be rationalized as follows: 5α-acetoxycholestan-4-one 58 has four repulsive AcO-H interactions because of the axial orientation of its 5α-acetoxyl group, whereas 3β-acetoxycholestan-4-one 57 with its 3β-acetoxyl group in an equatorial position, has only four H-H interactions.

The ease of α→α'-transfer of the acetoxyl group in 5α-acetoxycholestan-4-one 58 (perhaps also in 3α- and 3β-acetoxycholestan-4-one 21 and 57 as will be shown later) compared to that in 2α-acetoxy-3-ketone 18 and the



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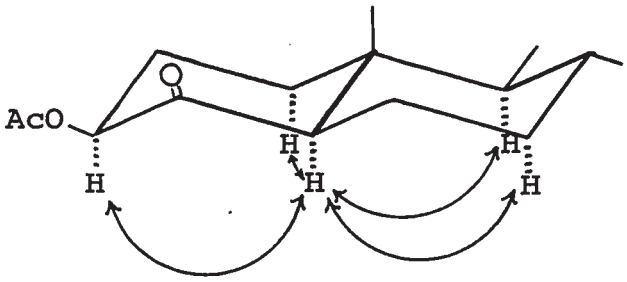

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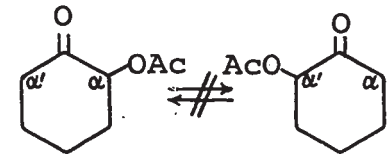
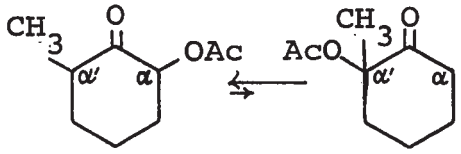
4α-acetoxy-3-ketone 19 is probably due to the presence of an additional alkyl substituent at α- or α'-position to stabilize the partial carbonium ion character in the transition state. All of the four mechamisms proposed above for α→α'-transfer of the acetoxyl group are consistent with this rationalization, especially the enolic carbonium ion mechanism BB_1 and the zwitterionic mechanism BB_2, in both of which substantial cationic character is developed in the transition state. The same difference was observed in a monocyclic case. Whereas 2-acetoxycyclohexanone 104(6) only gave interchange product on treatment with potassium acetate in refluxing acetic acid, 2-acetoxy-6-methyl-cyclohexanone 105 readily underwent α→α'-transfer of the acetoxyl group at 133-135° to give a mixture of 105 and 2-acetoxy-2-methylcyclohexanone 106 in a ratio of ca. 4:1.

It should be mentioned here that the same structural

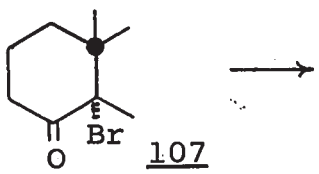


104(6)



105 106

influence has been observed in the isomerization of 5α-bromocholestan-4-one 107 into 3β-bromocholestan-4-one 88 by hydrogen bromide.[49] No similar α→α'-transfer has been



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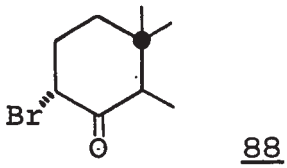
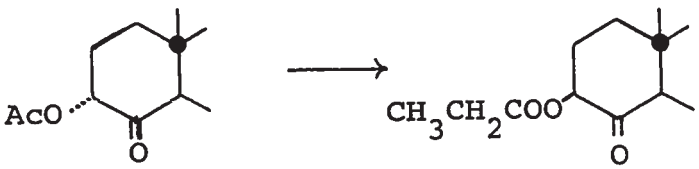


88

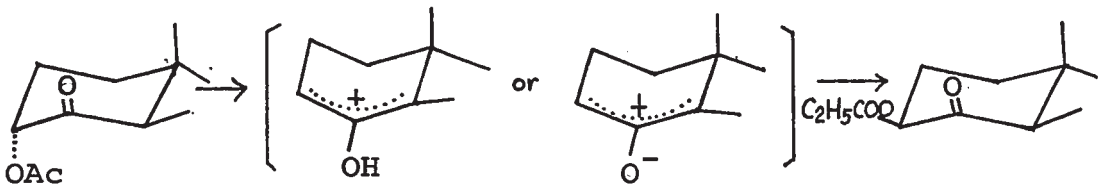
observed in 2α- or 4α-bromocholestan-3-one 4 or 12. The question of whether this rearrangement is a bromide or a bromonium ion shift is unknown.

Reaction of 3α-acetoxycholestan-4-one 21 with potassium acetate-propionic acid at 133-135° gave mainly 3β-propionoxycholestan-4-one 108, the product of incorporation of external carboxylate.



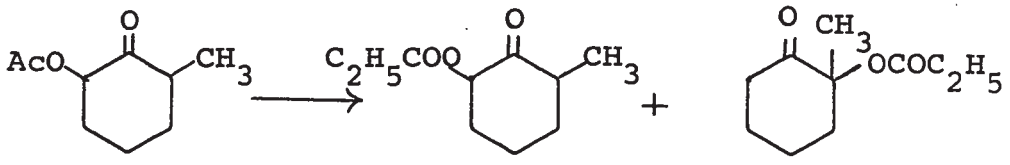
21 108

Of the several mechanisms that could account for the incorporation, the most reasonable one would seem to proceed by a symmetric intermediate mechanism BB and subsequent solvent attack. One additional substituent at the α'-position is assumed to be responsible for the more



21 92 108

facile formation of the symmetric intermediate which has cationic character on the enolic part, in exactly the same way that one additional substituent was proposed to be responsible for the facile conversion of 5α-acetoxycholestan-4-one 58 into 3β-acetoxycholestan-4-one 57. 2-Acetoxy-6-methylcyclohexanone 105, the monocyclic analogue of 3α- or 3β-acetoxycholestan-4-one 21 or 57, behaves in the same way. External carboxylate incorporates readily at 133-135°.



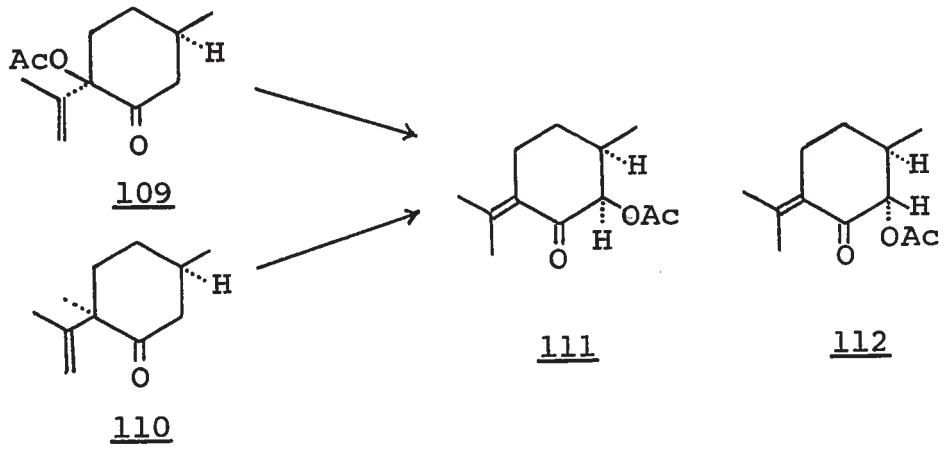
105

It should be pointed out that although the symmetric intermediate mechanisms BB give a very satisfactory

explanation for the external carboxylate incorporation, it does not exclude the possibility that other mechanisms operate at the same time. The thermal stability of 5α-acetoxycholestan-4-one 58 up to 210° does not exclude the intramolecular acetoxyl group transfer, since enol formation might be hindered by the absence of acetic acid and acetate ion. Treatment of the 5α-acetoxy-4-ketone 58 with γ-collidine at 215° for 18 hours gave 10% of 3β-acetoxycholestan-4-one 57, the α→α'-transfer product. However, since the elimination product, Δ^5-cholesten-4-one 7 was also formed in 18% yield, thus introducing acetate ion into the medium, it is not certain whether the α→α'-transfer is intramolecular or intermolecular.

Sheehan[50] has recently observed a similar reaction in his work on acetoxyisopulegone. Both trans- and cis-4-acetoxyisopulegone 109 and 110 were found to isomerize thermally into cis- and trans-2-acetoxypulegone 111 and 112. Since the isomerization occurred readily at 200° without any solvent, it was concluded that the rearrangement should be intramolecular and proceeded by a cyclic transition state (i.e. mechanism DD).

Therefore, symmetric intermediate with substantial carbonium ion character (mechanism BB) explains in a very

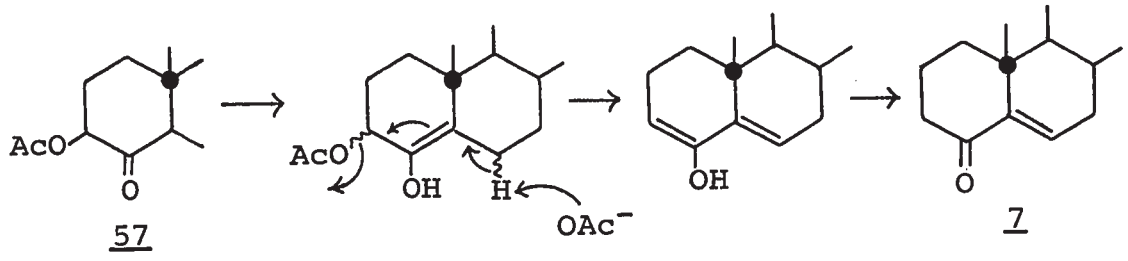


109 110 111 112

satisfactory way the reactivities of various acetoxyketones toward α→α'-transfer and toward external carboxylate ion incorporation. However, none of the other three mechanisms mentioned above can be ruled out. More work on the closely related 2-acetoxycyclohexanone 104(6) might give a better understanding of α→α'-transfer of acetoxyl group (see Chapter III).

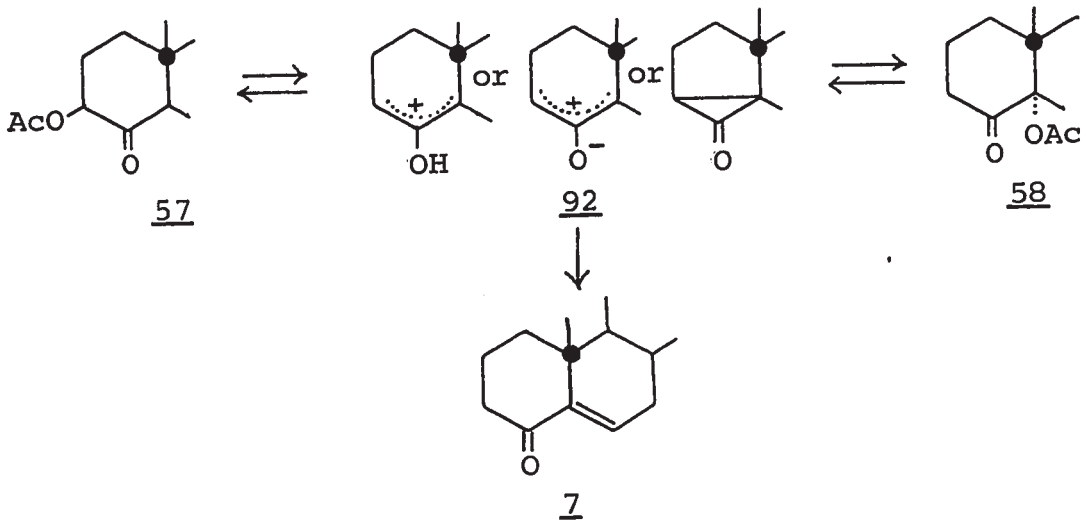
(iv) Formation of Δ^5-Cholesten-4-one 7

Several mechanisms can be proposed for the last stage of the rearrangement. The first possibility is 1,4-elimination of acetic acid from the enol form of 3β-acetoxycholestan-4-one 57, originally suggested by Fieser.[17] The second possibility is rapid reversible formation of symmetric intermediate (cf. mechanism BB or CC) and slow leakage into the more stable unsaturated ketone



57 7

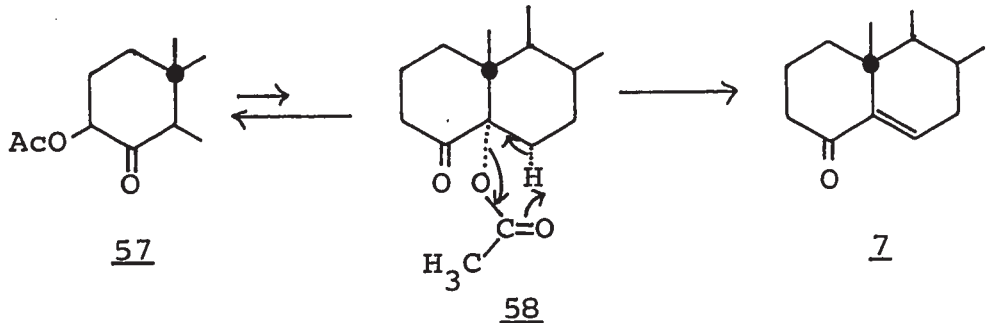
Δ^5-cholesten-4-one 7 by proton loss.



57 92 58

7

A third possibility is less likely but still must be considered. It involves 1,2-elimination of acetic acid from 5α-acetoxycholestan-4-one 58 to give the final product 7.

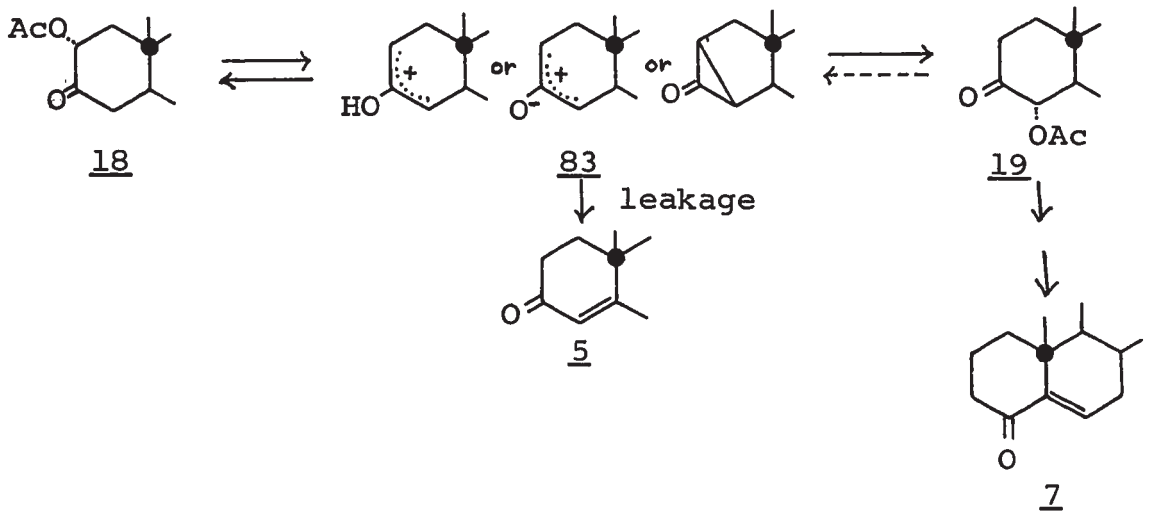


57 58 7

Distinction among these three mechanisms is difficult, since the 3β-acetoxy-4-ketone 57 is in rapid equilibrium with the 5α-acetoxy-4-ketone 58. Considering the high ionizing power of acetic acid and the mechanism of abnormal elimination of α-bromoketones, the second mechanism is certainly the most probable one.

It is also of some interest to consider the origin of the minor amounts of unsaturated ketones other than Δ^5-cholesten-4-one 7 in the acetoxyketone rearrangements. Comparison of the reaction of 2α-acetoxycholestan-3-one 18, 3β-acetoxycholestan-2-one 39 and 4α-acetoxycholestan-3-one 19 at 200-230° revealed that there is definitely more Δ^4-cholesten-3-one 5 formed in the reactions starting with the 2α-acetoxy-3-ketone 18 or the 3β-acetoxy-2-ketone 39 than in those starting with the 4α-acetoxy-3-ketone 19 (reactions 17, 21, 22, 24, and 25). This observation is consistent with the picture that transformation of the 2α-acetoxy-3-ketone 18 into the 4α-acetoxy-3-ketone 19 proceeds, at least in part, by the symmetric intermediate mechanism (mechanism BB or CC) and the intermediate 83 partly leaks into Δ^4-cholesten-3-one 5, the more stable one of the two possible unsaturated ketones. For reactions starting with the 4α-acetoxy-3-ketone 19, the compound is converted almost exclusively into Δ^5-cholesten-4-one 7 by

the more facile interchange and elimination processes before it gets a chance to form the symmetric intermediate 83. The



5β-series gave similar results. Much more Δ^4-cholesten-3-one 5 was formed in the reaction of 2β-acetoxy-5β-cholestan-3-one 59 than that of 4β-acetoxy-5β-cholestan-3-one 60 (reactions 31 and 29).

Therefore the Δ^4-cholesten-3-one 5 formed in the h-Δ^1-cholestenone rearrangement (reactions 1 and 4) can be concluded to arise by three distinct paths, partly during the acetolysis of the 2α-bromo-3-ketone 4, partly during the α→α'-transfer of the 2α-acetoxy-3-ketone 18, and partly during the solvolysis of the 4α-acetoxy-3-ketone 19. In all the reactions of α-bromo and α-acetoxy ketosteroids in acetic acid studied, Δ^1-cholesten-3-one 6, Δ^1-5β-cholesten-3-one 85 or Δ^2-cholesten-4-one 11 has never been detected

in the n.m.r. spectra of the crude products. From the t.l.c. data, these cannot be present in >5% yield.

Thus the formation of unsaturated ketones from bromoketones and acetoxyketones can be generalized as follows: in acetic acid, the major product is always the more stable (more substituted) of the two possible α,β-unsaturated ketones no matter whether the bromo or the acetoxy substituent is at the α- or α'-position; in acetone, direct 1,2-elimination is responsible for unsaturated ketone formation from bromoketones, and there is no evidence of unsaturated ketones arising from direct E2-elimination of acetoxyketones.

(v) Conclusion

From the foregoing discussion of the reactions of bromoketones and acetoxyketones in acetic acid-acetate at various temperatures, the probable detailed mechanism of h-Δ^1-cholestenone rearrangement has been established as follows: (also see Fig. 2).

(a) Acetolysis of 2α-bromocholestan-3-one 4 or its 4α-isomer 12 occurs around 100° and proceeds by the symmetric intermediate 83 to give a mixture of 2α- and 4α-acetoxycholestan-3-one 18 and 19 in approximately equal amounts. Both 18 and 19 were shown to be the precursors of Δ^5-cholesten-4-one 7.

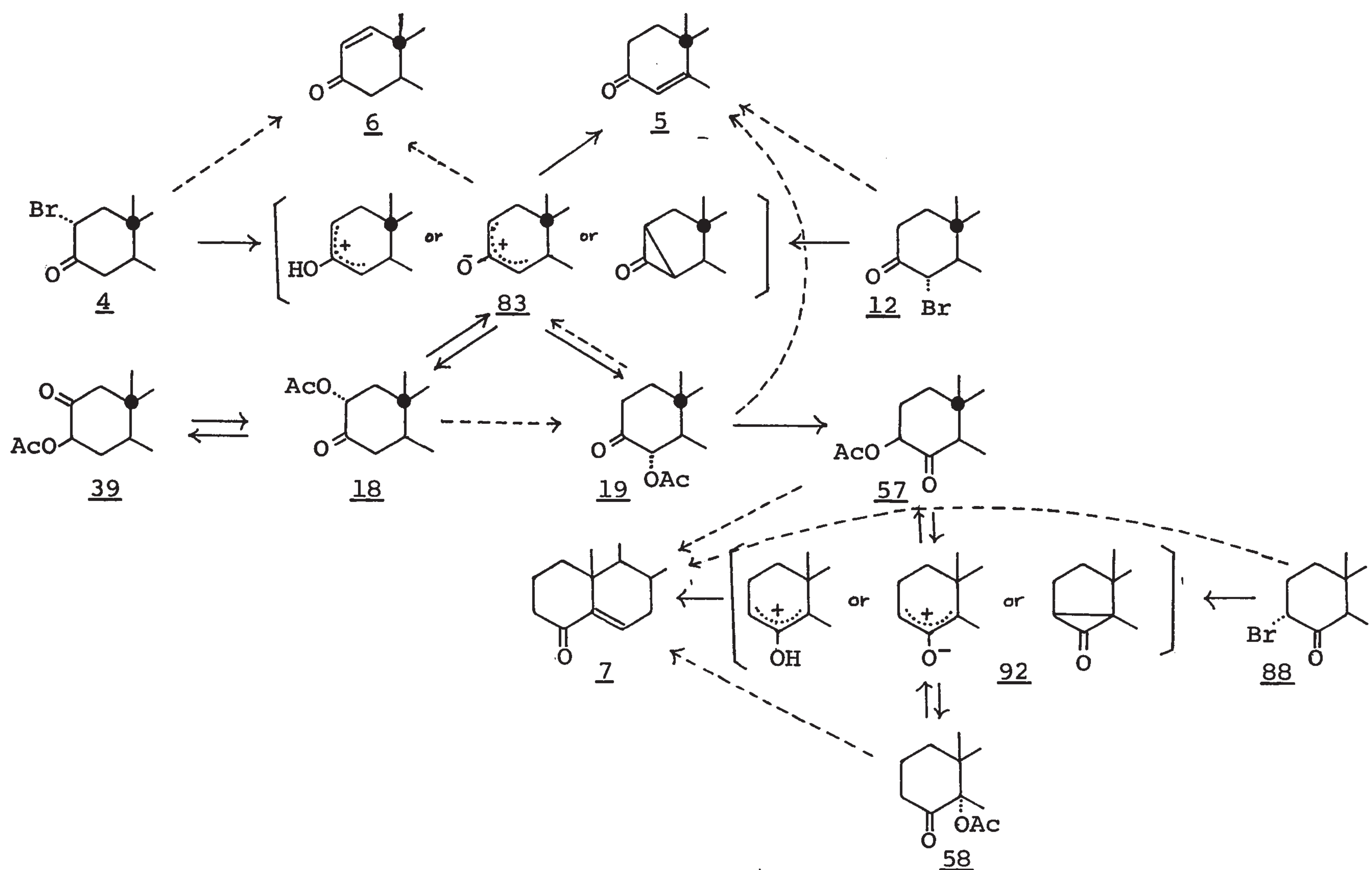


Fig. 2

(b) For the conversion of 2α-acetoxycholestan-3-one 18 into Δ^5-cholesten-4-one 7, the transformation of 18 into its 4α-isomer 19 by α→α'-transfer of the acetoxyl group is the rate determining step. The transfer reaction is not operative until the temperature is ca. 200°.

(c) Interchange of functional groups in 4α-acetoxycholestan-3-one 19 takes place at 170°. Once 3β-acetoxycholestan-4-one 57 is formed, it converts readily into Δ^5-cholesten-4-one 7 at 170°.

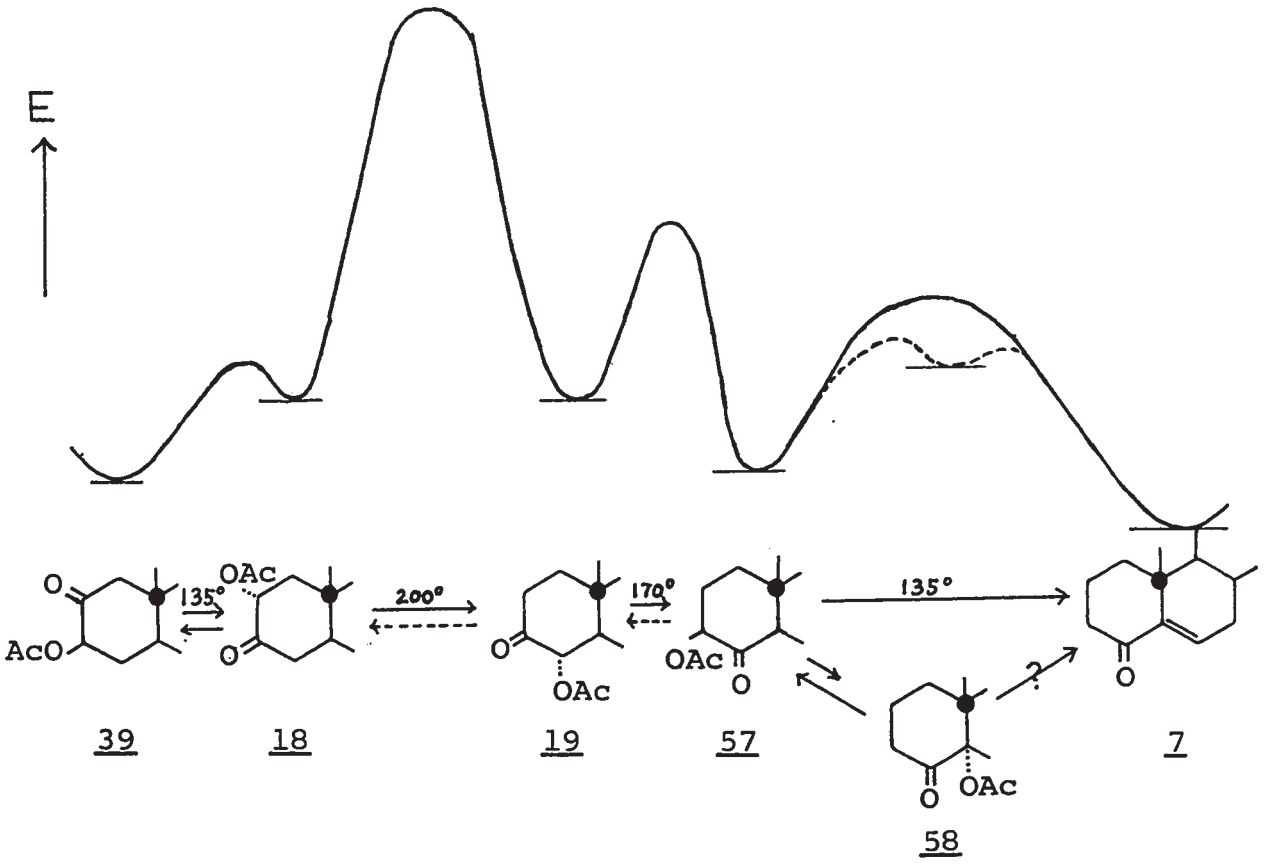
(d) At temperature as low as 135°, 3β-acetoxycholestan-4-one 57 is in rapid equilibrium with 5α-acetoxycholestan-4-one 58, and converts slowly into the final product 7. The formation of Δ^5-cholesten-4-one 7 from 57 or 58 probably proceeds by the symmetric intermediate 92 although other pathways such as direct 1,4-elimination of acetic acid from the enol form of the 3β-acetoxy-4-ketone 57 and ester pyrolysis of the 5α-acetoxy-4-ketone 58 are also possible.

(e) Reversible conversion of 2α-acetoxycholestan-3-one 18 into 3β-acetoxycholestan-2-one 39 occurs readily around 135°. Because of the greater thermodynamic stability of the 3β-acetoxy-2-ketone 39, it serves as a reservoir for the 2α-acetoxy-3-ketone 18. This interchange reaction has

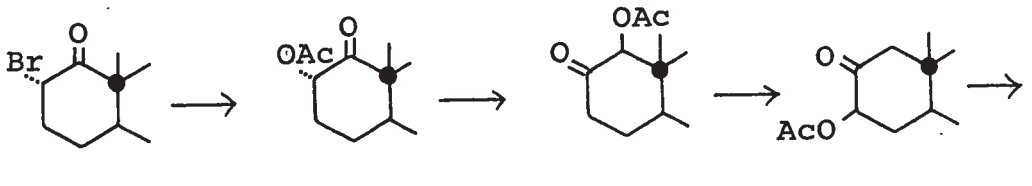
no net effect on the h-Δ^1-cholestenone rearrangement.

(f) The symmetric intermediate 83 formed during the acetolysis of 2α- or 4α-bromo-3-ketone 4 or 12 and during the interconversion between 2α- and 4α-acetoxy-3-ketone 18 and 19 partly leaks into the unsaturated ketones Δ^4-cholesten-3-one 5 and Δ^1-cholesten-3-one 6. Δ^4-Cholesten-3-one 5 is formed in much larger amount since it is more substituted than Δ^1-cholesten-3-one 6.

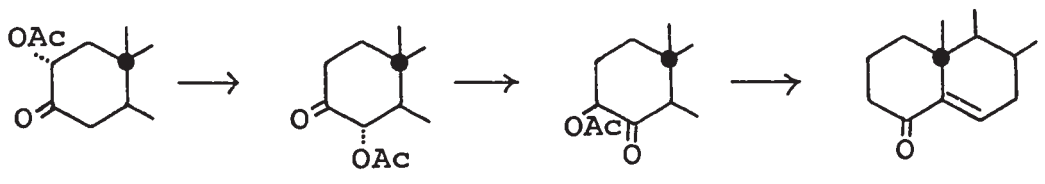
The present knowledge of the h-Δ^1-cholestenone rearrangement can be summarized in the following energy profile. A similar diagram can be drawn for compounds in the 5β-series.



With the intermediates of the h-Δ^1-cholestenone rearrangement convincingly established at this point, one would predict that all ring-A α-bromoketones and α-acetoxyketones in both the 5α- and 5β-series should yield Δ^5-cholesten-4-one 7 on treatment with potassium acetate-acetic acid at the appropriate temperature. This is indeed the case as shown by Table I to Table IV. The most dramatic result is that of 2α-bromocholestan-1-one 89. Although this compound resisted acetolysis in refluxing acetic acid-acetate, at 200-210° it gave Δ^5-cholesten-4-one 7 in good yield. Thus the functional groups did move around the ring from the 1- and 2-positions to the 4- and 5-positions by successive interchanges and α→α'-transfers! The only acetoxyketone detected in the reaction mixture was



89 90 87 39



18 19 57 7

3β-acetoxycholestan-3-one 39, just as one would have predicted from the evidence presented above that the rate-determining step of the h-Δ^1-cholestenone rearrangement is conversion of the 2α-acetoxy-3-ketone 18 into the 4α-acetoxy-3-ketone 19 and that 3β-acetoxy-2-ketone 39 serves as a reservoir for the 2α-acetoxy-3-ketone 18 because of the relative thermodynamic stability.

CHAPTER III

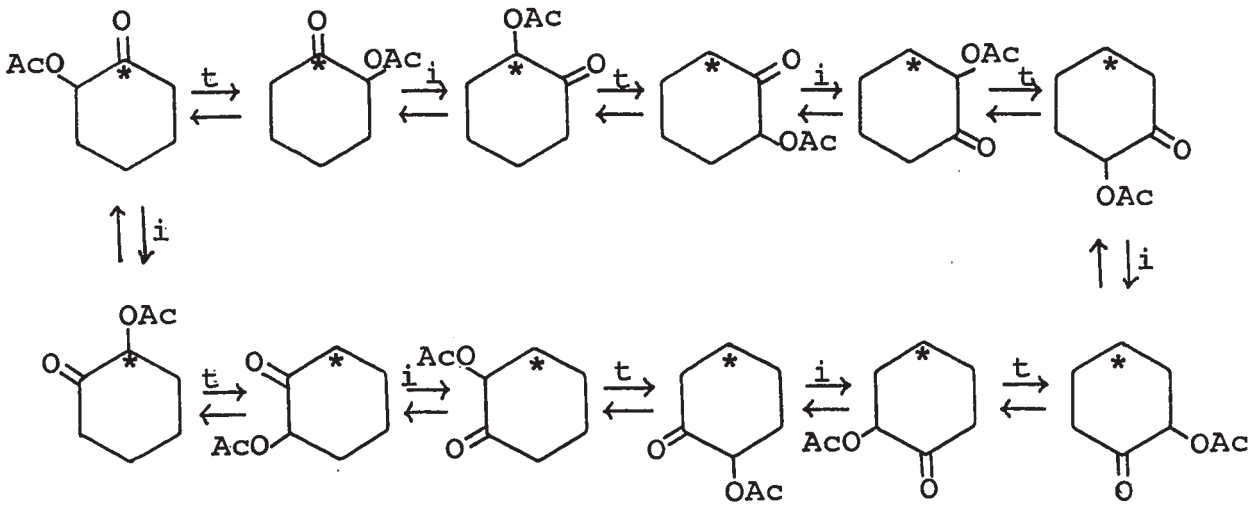
DEGENERATE REARRANGEMENT OF 2-ACYLOXYCYCLANONES

From the discussion in Chapter II, it is seen that interchange of the functional groups and α→α'-transfer of the acetoxyl group in acetoxyketones are the essential steps in the transformation of ring-A α-acetoxyketosteroids into Δ^5-cholesten-4-one 7. The interchange step was clearly demonstrated to operate in 2α-acetoxycholestan-3-one 18, 4β-acetoxy-5β-cholestan-3-one 60, and 2β-acetoxy-5β-cholestan-3-one 59 on treatment with refluxing acetic acid-potassium acetate mixture. However, α→α'-transfer reaction was demonstrated unambiguously only in one case, 3β-acetoxycholestan-4-one 57 and 5α-acetoxycholestan-4-one 58 in refluxing acetic acid-acetate medium. For all other acetoxyketones studied, no α→α'-transfer product was actually isolated. As mentioned in the last chapter, the 3β-acetoxy-4-ketone 57 and the 5α-acetoxy-4-ketone 58 have the special structural feature of the α- and α'-positions being secondary and tertiary, in contrast to the secondary-secondary nature of all of the other acetoxyketones.

Since α→α'-transfer of halogen of α-haloketones has only been demonstrated in the presence of hydrogen bromide or chloride, it was of interest to investigate in detail the related α→α'-transfer of the acetoxyl group of α-acetoxyketones in acetic acid-acetate medium.

The failure to detect the α→α'-transfer product from most α-acetoxyketosteroids must be attributed to the drastic conditions required for the transfer reaction and the faster rates of subsequent steps. For example, once the 2α-acetoxy-3-ketone 18 was transformed into the 4α-acetoxy-3-ketone 19 by α→α'-transfer at ca. 200°, the latter readily underwent a further interchange reaction and irreversible elimination of acetic acid to give the final product Δ^5-cholesten-4-one 7 because of the tertiary nature of the 5-position. A good choice for the study of the interchange and the transfer reactions of α-acetoxyketones without the complication by elimination would be 2-acetoxycyclanones 104(n) with all of the carbon atoms being secondary. Although both the interchange and the transfer reactions are degenerate in unsubstituted 2-acetoxycyclanones 104(n), the simultaneous operation of these two reactions should cause the carbonyl and acetoxyl groups to pirouette around the ring in a rearrangement which is easily revealed by deuterium exchange or carbon-label scrambling. If the

reaction is carried out in deuterated acetic acid-acetate medium, every ring hydrogen will be labilized after successive rearrangement and the molecule will be perdeuterated. If the reaction is started with acetoxycyclanone 104(n) labelled at one specific carbon atom of the ring, the probability of finding the label at every carbon atom of the ring will be equal.



On the other hand, if neither the interchange nor the transfer process occurs, three deuterium atoms, at most, would be incorporated into the ring and the carbon label would remain at the original place. If only the interchange process takes place, a maximum of five deuterium atoms can be incorporated into the ring and only two carbon atoms would be labelled.

Deuterium exchange experiments were carried out first since it did not require the preparation of carbon-labelled acetoxyketones and could be done with acetic acid-d_4 and potassium acetate-d_3.

The relative intensity of the C-H and C-D stretching modes in the i.r. spectrum of the acetoxyketones (2930, 2860 cm^{-1} for C-H; 2210, 2110 cm^{-1} for C-D) is useful for qualitative estimation of the extent of deuteration, especially since non-α C-D stretching is found to be stronger than α C-D stretching.

Since all of the ring protons except that at the 2-position of the acetoxycyclanones 104(n) have similar chemical shifts and are strongly coupled to adjacent protons, the n.m.r. spectrum can be used for quantitative estimation of deuterium exchange in these compounds only by comparison with an added calibration standard. Besides, the value obtained in this way is only the average number of deuterium atoms incorporated into the molecule. Accurate quantitative calculation of deuterium incorporation was made by mass spectroscopy. The molecular ion peak of most acetoxycyclanones 104(n) is very weak because the molecule loses the acetyl group (CH_3CO-) very readily on electron bombardment to give the M-CH_3CO^+ (M-43) peak of moderate intensity. Fortunately, there are no peaks just lower than

$M-CH_3CO^+$ and no peaks between the $M-CH_3CO^+$ and the molecular ion peaks to complicate the analysis, and therefore calculations based on the $M-CH_3CO^+$ ion signal should give the extent of ring deuteration accurately. In confirmation, for 2-acetoxycyclohexanone 104(6), in which the molecular ion peak is fairly strong, calculations based on both the M^+ peak and the $M-CH_3CO^+$ peak give identical results for ring deuteration. One great advantage of mass spectroscopic analysis over n.m.r. analysis is that the former gives not only the deuterium content but also the relative distribution of deuterated species.

The first reaction examined was the deuterium exchange of 2-acetoxycyclohexanone 104(6) since it has the same ring as the steroid acetoxyketones and has been reported to be stable to 180° in the absence of activated carbon.[51] For reaction at 140°, partially deuterated 2-acetoxycyclohexanone 104(6) was obtained in 22% yield after purification. Mass spectroscopic analysis showed that the ring was mainly tri- and penta-deuterated (reaction 40). No significant amount of more highly deuterated species was observed. Therefore only the interchange of functional groups occurs at 140°, consistent with the result in the steroid series.

Treatment of 2-acetoxycyclohexanone 104(6) with potassium acetate-d_3 in acetic acid-d_4 at 220° gave a 13%

TABLE VII

DEUTERIUM EXCHANGE OF ACYLOXYCYCLANONES

reaction	compound	temperature	time (hr.)	yield	extent of ring deuteration $d_{no.D.}$ (%)
38		133-135°	6	4[a]	d_0 (2.6), d_1 (6.8), d_2 (29.3), d_3 (52.7), d_4 (2.9), d_5 (4.1)
39		220°	15	0[b]	
40		140°	12	34[c], 22[d]	d_2 (12.8), d_3 (44.5), d_4 (12.0), d_5 (29.7)
41		220°	14	17[c], 13[d]	d_5 (1.6), d_6 (6.1), d_7 (21.9), d_8 (37.8), d_9 (32.1)
42[e]		215°	48	8[c], 7[d]	d_3 (2.4), d_4 (9.1), d_5 (16.8), d_6 (22.1), d_7 (26.3) d_8 (10.2), d_9 (13.1)
43		240°	20	10[a], 5[f]	d_3 (4.7), d_4 (18.2), d_5 (31.3), d_6 (13.1), d_7 (16.3), d_8 (6.5), d_9 (4.9), d_{10} (2.6), d_{11} (1.4)
44		240°	40	14[a]	d_3 (7), d_4 (27), d_5 (50), d_6 (3), d_7 (5)
45		240°	40	22[a]	d_0 (3.3), d_1 (1.6), d_2 (1.6), d_3 (2.7), d_4 (5.3), d_5 (12.5), d_6 (14.2), d_7 (25.7), d_8 (9.8), d_9 (13.5), d_{10} (3.4), d_{11} (3.8), d_{12} (1.1), d_{13} (1.0)
46		240°	57	29[g]	d_{10} (1.4), d_{11} (2.4), d_{12} (3.7), d_{13} (5.7), d_{14} (6.7), d_{15} (8.3), d_{16} (7.9), d_{17} (10.8), d_{18} (10.8), d_{19} (15.4), d_{20} (15.7), d_{21} (10.4)
47		150°	40	65[h]	d_2 (3.8), d_3 (24.2), d_4 (14.0), d_5 (58)
48		170°	43	26[h]	d_3 (2.1), d_4 (19.2), d_5 (78.7)
49		180-185°	43	1.5[h]	mainly d_5

[a]After bulb-to-bulb distillation [b]By g.l.p.c. analysis [c]After purification by thick layer [d]After purification by thick layer and bulb-to-bulb distillation [e]In acetic acid-d_4 only [f]After purification by bulb-to-bulb distillation and preparative g.l.p.c. [g]After purification by sublimation [h]After recrystallization, m.p. 84-85.5°

yield of deuterated compound after purification (reaction 41). The mass spectrum revealed that there was complete equilibration among the ring protons and external deuterium, consistent with the expectation that α→α'-transfer of the acetoxyl group would occur around 220°.

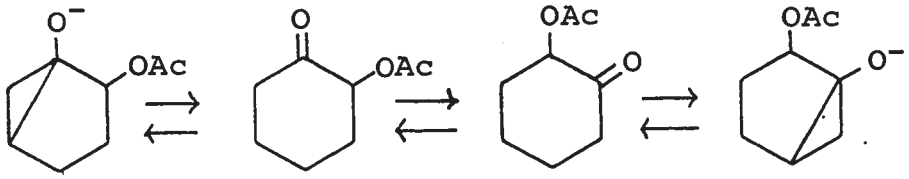
In parallel runs where potassium acetate in acetic acid was used instead of potassium acetate-d_3 in acetic acid-d_4, 2-acetoxycyclohexanone 104(6) was recovered in much higher yield (77% for 140° reaction, 22% for the 220° reaction). The reason for such a big difference in yields is unclear, but might be attributed to some small amount of impurity in either the acetic acid-d_4 or the potassium acetate-d_3.

It should be pointed out that potassium acetate is not essential for the complete deuteration of the ring. A control experiment with 2-acetoxycyclohexanone 104(6) in acetic acid-d_4 alone at 215° also gave the perdeuterated product, although in a somewhat lower yield and at a slower rate (reaction 42).

The reaction of 2-acetoxycyclohexanone 104(6) with potassium acetate in propionic acid gave tne same result as obtained from the steroid compounds 2α-acetoxycholestan-3-one 18 and 3α-acetoxycholestan-4-one 21. No incorporation of propionoxyl group was observed at 140°, a condition under which the interchange of functional groups occurs readily

as shown by the deuterium exchange experiment, thus confirming that the interchange reaction was intramolecular. At 220°, there was complete equilibration between acetoxyl and propionoxyl groups, consistent with the α→α'-transfer being intermolecular, but in no way excluding its being intramolecular.*

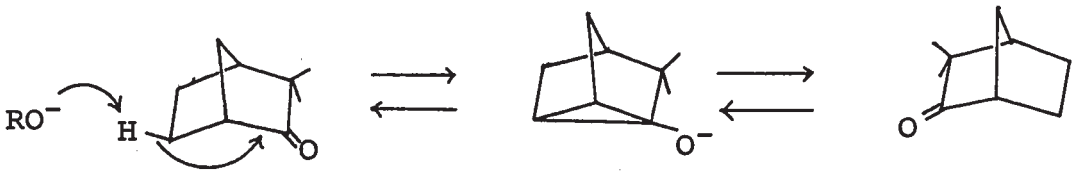
Although complete deuteration of the ring is an indication that both the interchange and the α→α'-transfer reactions of acetoxyketone occur at 220°, there are other conceivable ways to explain the result. One obvious alternative is homoenolization of the ketone. Combined with the interchange process, it could give rise to complete deuterium exchange.



Homoenolate ion 114 has been advanced by Nickon and coworkers[52] to account for the racemization and deuterium incorporation of camphenilone 113 with potassium t-butoxide in t-butyl alcohol at 185°. Compared to the acetic

*Preliminary results by Warnhoff and Ouchi indicate that intramolecular α→α'-transfer is a possible pathway, since ^{13}C-acetoxycyclohexanone is almost completely scrambled when heated in toluene at 250°.

acid-acetate reagent used in our study, Nickon's reagent is undoubtedly much stronger for proton abstraction. Besides, the rigid ring system of camphenilone 113 is ideally constructed for 6-exo-proton abstraction to form the homoenolate, whereas the more flexible 2-acetoxycyclohexanone 104(6) has to sacrifice a certain amount of entropy to attain the required geometry.



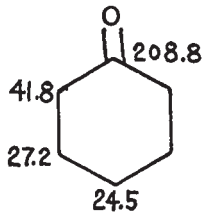
113 114 113

The easiest way to distinguish between a homoenolate pathway and an α→α'-transfer pathway is by carbon atom labelling. If homoenolate formation alone were responsible for exchange of ring protons, the carbon label would be distributed only between two positions.

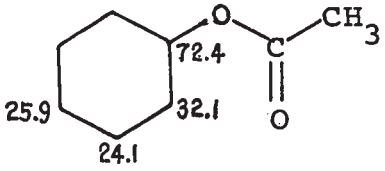
Between ^{13}C- and ^{14}C-labels, we chose the former for two main reasons. Firstly, it is well known[54] that ^{13}C-n.m.r. spectroscopy can be used to locate the ^{13}C-label at each position of the ring without having to do preliminary degradative work; whereas with ^{14}C-label, the known degradative schemes do not distinguish between C-1 and C-2, C-3 and C-6, C-4 and C-5.[53] Secondly, ^{13}C-n.m.r. spectroscopy

is available in our department. Moreover, with the 60% ^{13}C enrichment to be used in our study, carbon-label scrambling can be qualitatively followed by i.r. at the same time, since the $^{12}C{=}O$ and $^{13}C{=}O$ stretching modes are well separated (1730 and 1690 cm^{-1} respectively).

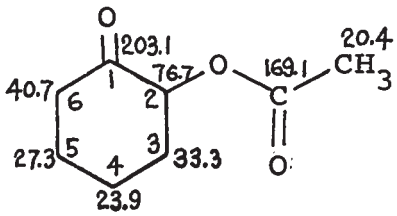
All ^{13}C-n.m.r. spectra were determined by Dr. J. B. Stothers and Dr. M. Gordon in this Department. The spectra were run in benzene solution with double irradiation to remove proton coupling effects. The eight carbon atoms of 2-acetoxycyclohexanone 104(6) with ^{13}C in natural abundance give rise to well-separated signals (Fig. 3). With reference to the chemical shifts of cyclohexanone 115(6) and cyclohexyl acetate 116, the eight peaks of 2-acetoxycyclohexanone 104(6) were tentatively assigned as follows:



115(6)

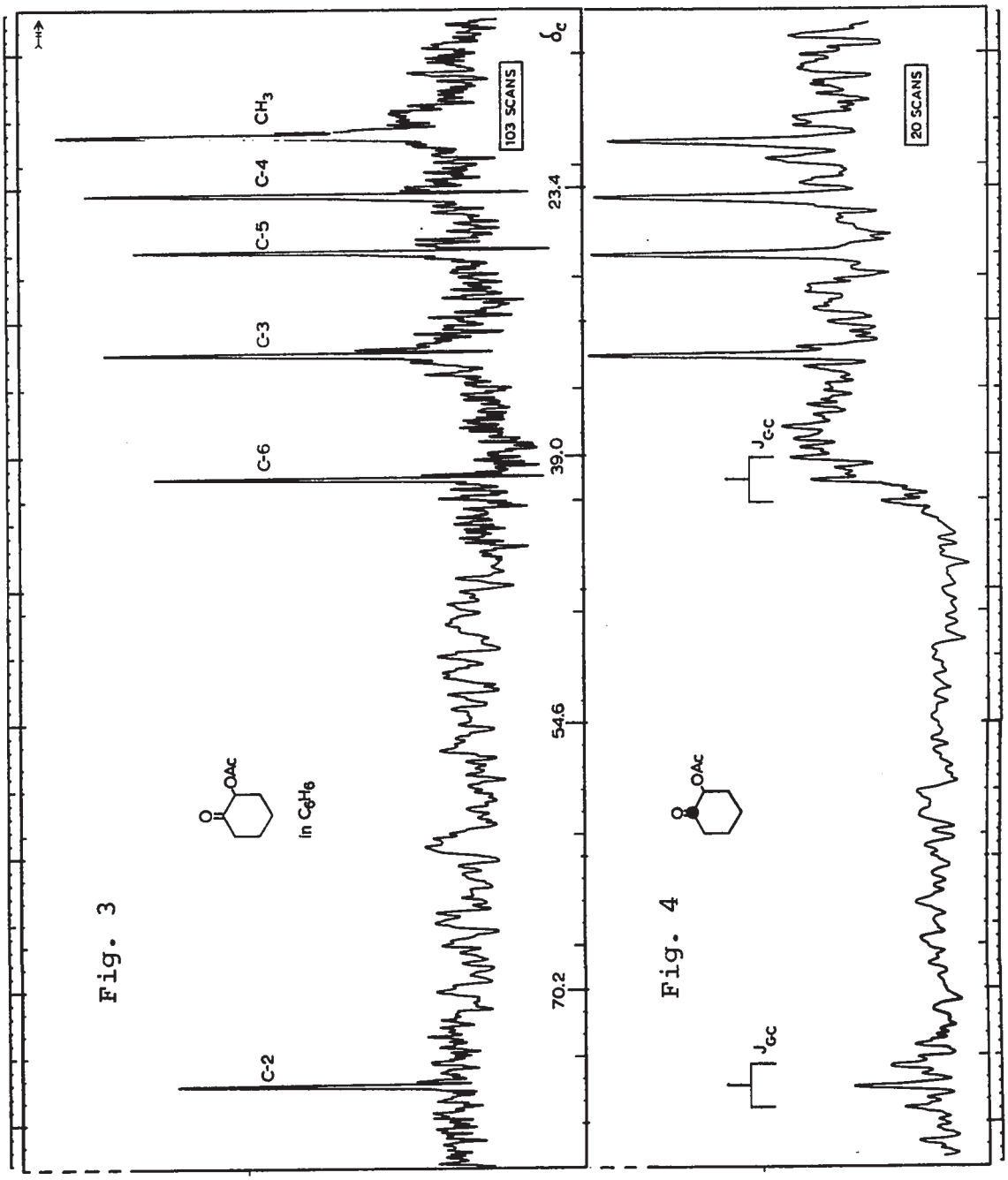


116



104(6)

The figures in the formula are chemical shifts in ppm from TMS. The assignments for all positions except C-4 and C-5 were confirmed by the spectra of the partially deuterated


C-2
C-6
C-3
C-5
C-4
CH3
103 SCANS
70.2
54.6
39.0
23.4
δc
OAc
in C6H6
Fig. 3
20 SCANS
JCC
JCC
OAc
Fig. 4

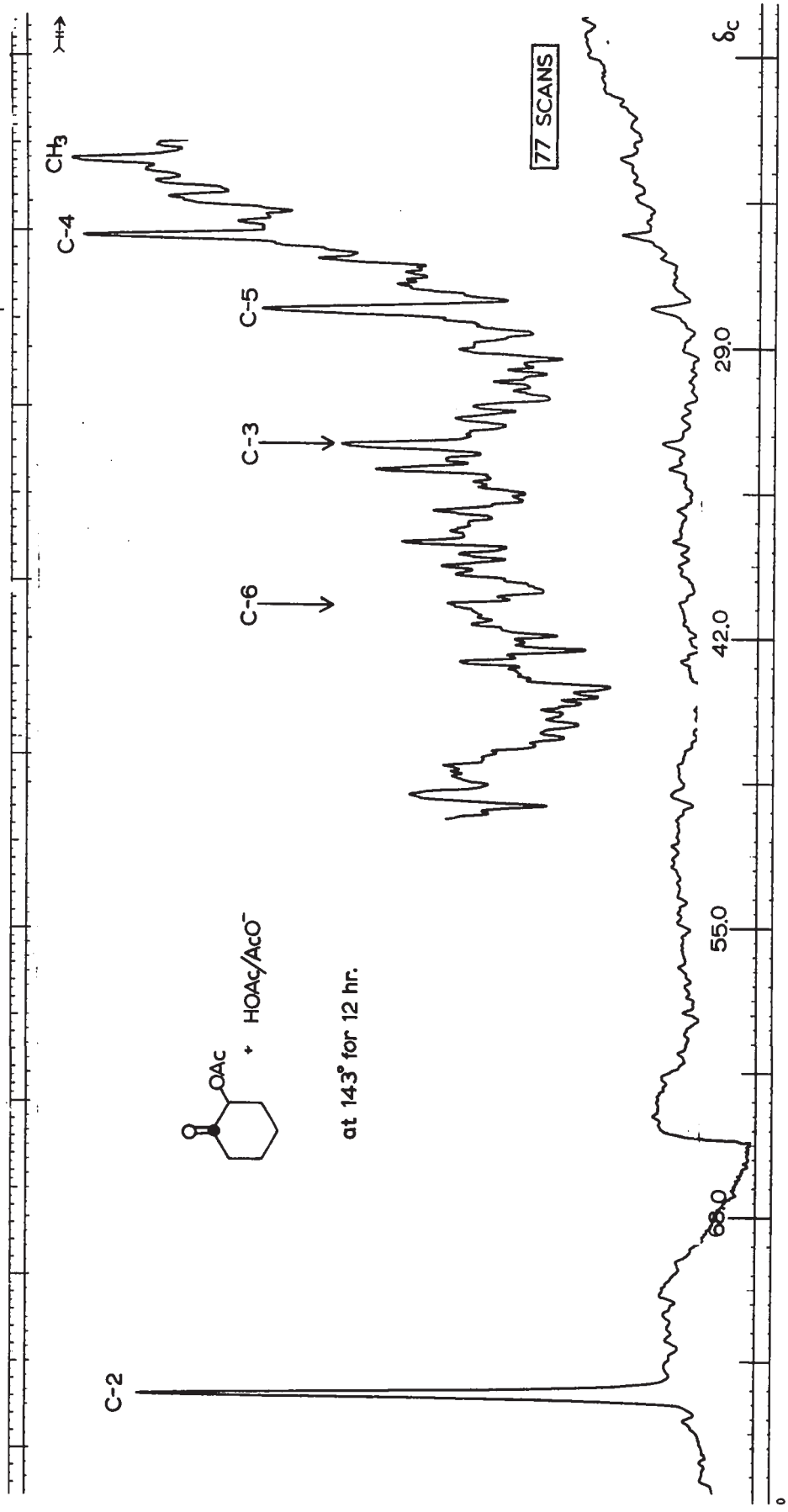

C-2
C-4
CH3
C-5
C-3
C-6
OAc
+ HOAc/AcO⁻
at 143° for 12 hr.
77 SCANS
δc
68.0
55.0
42.0
29.0

Fig. 5

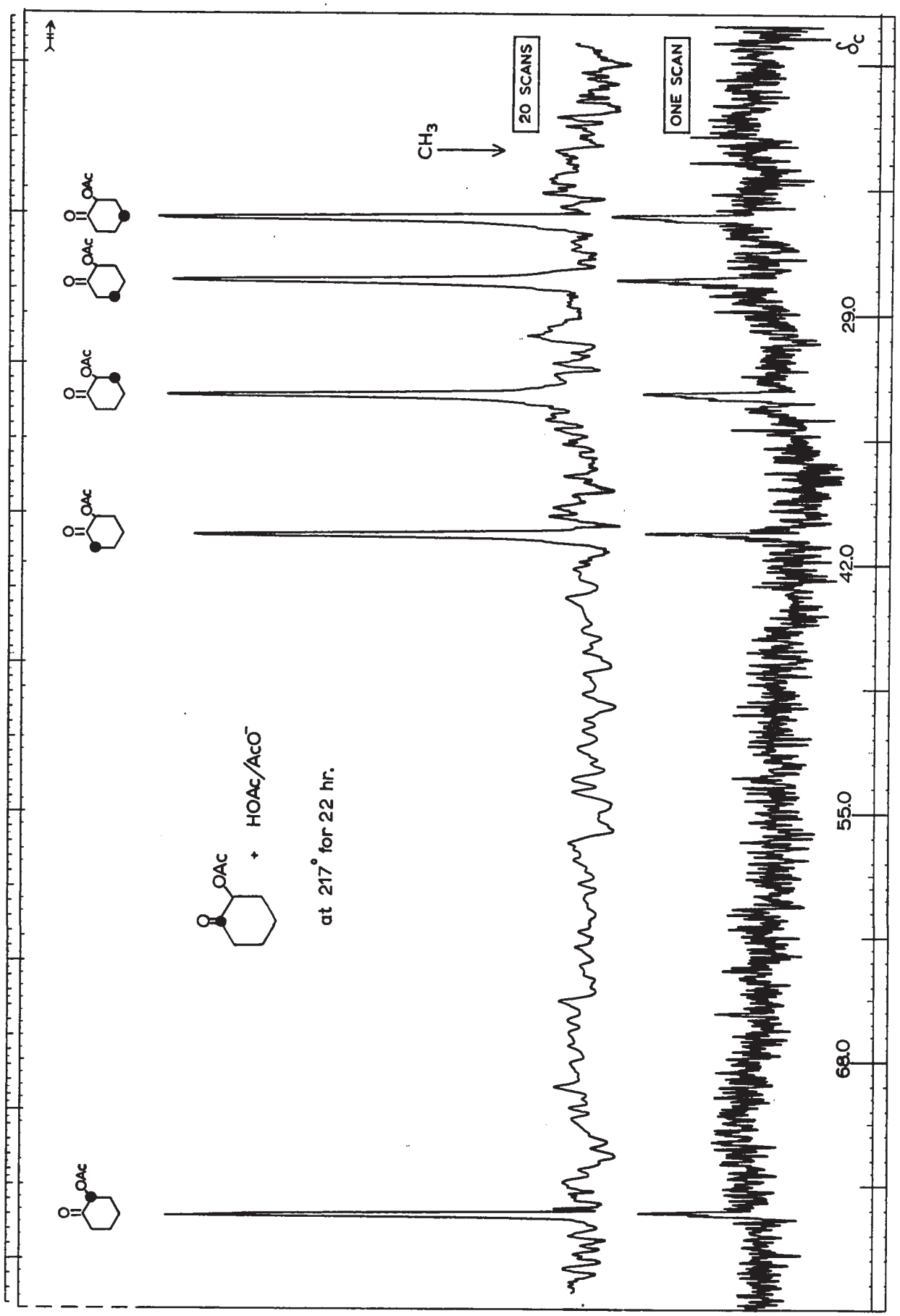

OAc
+ HOAc/AcO⁻
at 217° for 22 hr.
CH3
20 SCANS
ONE SCAN
68.0
55.0
42.0
29.0
δc

Fig. 6

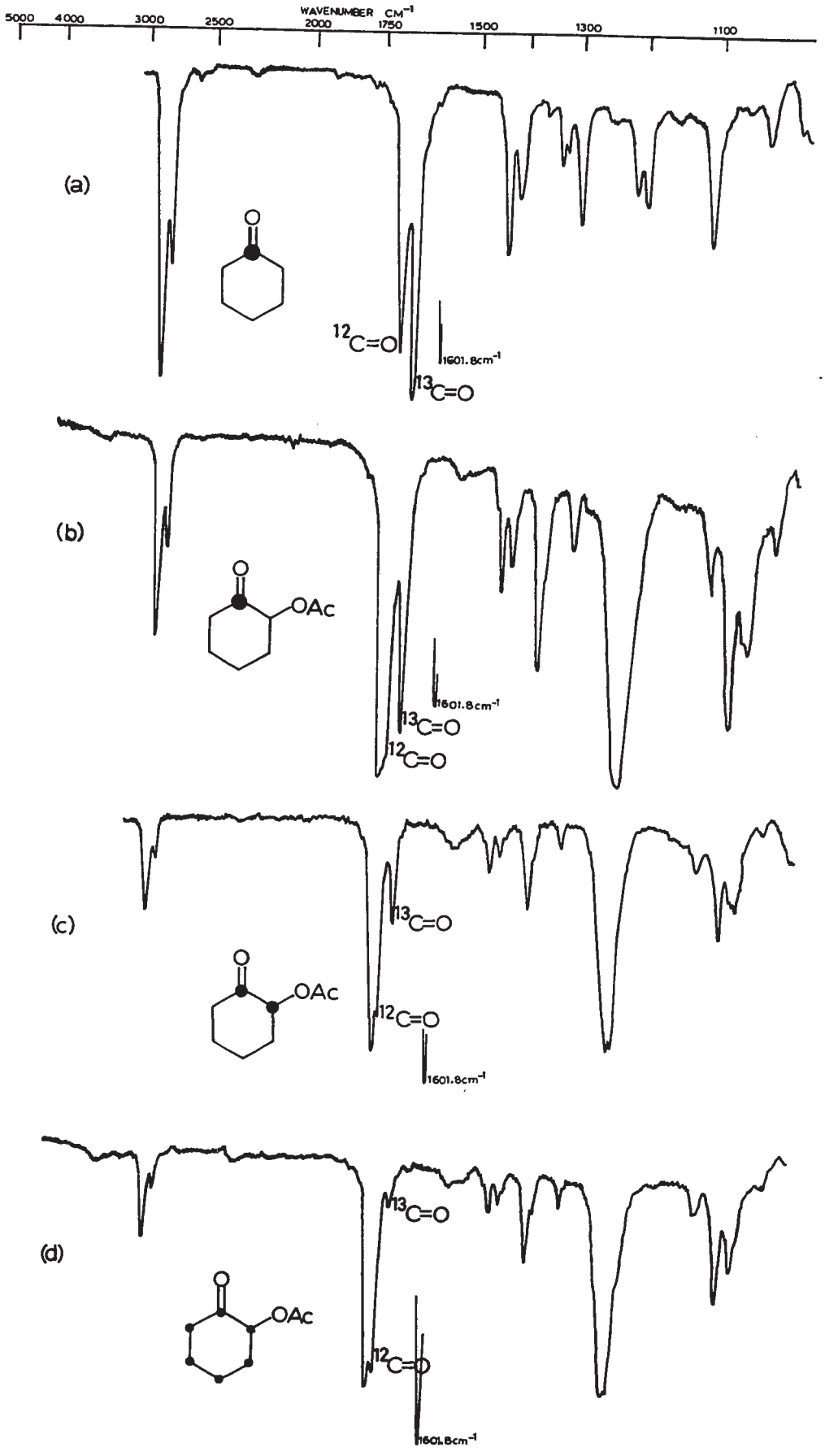

WAVENUMBER CM⁻¹
5000 4000 3000 2500 2000 1750 1500 1300 1100
(a)
12C=O
1601.8cm⁻¹
13C=O
(b)
OAc
1601.8cm⁻¹
13C=O
12C=O
(c)
13C=O
OAc
12C=O
1601.8cm⁻¹
(d)
13C=O
OAc
12C=O
1601.8cm⁻¹

Fig. 7

and the carbon-labelled compounds to be described later.

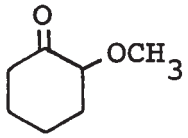
^{13}C-Enriched 2-acetoxycyclohexanone 104(6) was prepared by epoxidation and thermal rearrangement of the enol acetate of cyclohexanone 115(6) with 60% ^{13}C enrichment at the carbonyl carbon. In the n.m.r. spectrum of the enriched 2-acetoxycyclohexanone, only the peak of δ_C 203.1 was enhanced. The C-2 and C-6 signals clearly showed ^{13}C-^{13}C coupling (Fig. 4). Thus the carbon label was exclusively located at the C-1 position and this compound is unambiguously 2-acetoxycyclohexanone-1-^{13}C (60%) 104(6)-1-^{13}C (60%).

When this 2-acetoxycyclohexanone-1-^{13}C (60%) was treated with potassium acetate-acetic acid at 142-144^{o} for 12 hours, a 77% yield of crystalline material was recovered after purification. In the n.m.r. spectrum of this sample, the peaks at δ_C 203.1 (C-1) and 76.7 (C-2) were both enhanced (Fig. 5). Moreover, the relative intensity of ^{13}C=O to ^{12}C=O stretching modes in the i.r. spectrum of this sample was diminished to about one half of that of the starting material (Figs. 7b and 7c). The distribution of carbon label between C-1 and C-2 positions confirms the conclusion deduced from deuterium exchange work that at 140^{o} only interchange of functional groups occurs.

When 2-acetoxycyclohexanone-1-^{13}C (60%) with no detectable enrichment at other carbons was treated with potassium acetate-acetic acid at 220^{o} for 22 hours,

crystalline material was recovered in 22% yield. The ^{13}C-n.m.r. spectrum of the sample revealed that the carbon-label was distributed around the six carbon atoms of the ring (Fig. 6). I.r. spectrum also showed a big decrease in the ratio of $^{13}C{=}O$ to $^{12}C{=}O$ stretching intensity (Fig. 7b and 7d). To our mind, $\alpha \rightarrow \alpha'$-transfer of the acetoxyl group combined with the interchange process is the only credible explanation compatible with complete scrambling of carbon label around the ring.

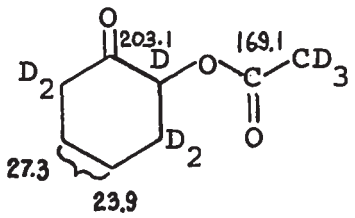
Therefore homoenolate formation was ruled out as the only pathway responsible for complete deuteration of the ring. Positive exclusion of homoenolization in acetic acid-acetate medium could be tested on a suitably substituted cyclohexanone derivative such as 2-methoxycyclohexanone 117.



117

With both the deuterated and carbon-labelled samples available, the ^{13}C-n.m.r. assignment of 2-acetoxycyclohexanone 104(6) can be discussed in more detail. Because the ^{13}C-n.m.r. spectrum was obtained only with complete proton decoupling, the partially deuterated compound, 2-trideuteroacetoxycyclohexanone-2,3,3,6,6-d_5 obtained from

deuterium exchange at 140°, is very useful for analysis of ^{13}C-n.m.r. spectra. Only four sharp peaks at δ_c 23.9,27.3, 169.1 and 203.1 were observed. Since C-2, C-3, C-6 and the methyl carbon in the acetoxyl group are coupled with deuterium ($J_{^{13}C-D} \sim$ 20Hz.) and since the ketone carbonyl absorbs at lower field than the ester carbonyl, the absorptions at 203.1 and 169.1 ppm arise from C-1 and the acetoxyl carbonyl respectively, as expected from the model compounds 115(6) and 116, and the absorptions at 23.9 and 27.3 should belong to C-4 and C-5. The assignment of the 203.1 absorption to C-1 was further confirmed by the spectrum of 2-acetoxycyclohexanone-1-^{13}C (60%) 104(6)-1-^{13}C-(60%) (Fig. 4). In addition to the peak at δ_c 203.1 being enhanced, patterns at 40.7 and 76.7 each appear as an overlapping doublet and singlet instead of the simple sharp



singlets in the spectrum of the compound with ^{13}C in natural abundance. Since the doublets with coupling constants 40 Hz., clearly are due to ^{13}C-^{13}C coupling because of the 60% enrichment of ^{13}C at the C_1-position, absorptions at 76.7 and 40.7 must come from C-2 and C-6. The 76.7 peak

was shown to belong to C-2 by the spectrum of the mixture of 2-acetoxycyclohexanone-1-^{13}C and 2-acetoxycyclohexanone-2-^{13}C obtained from the interchange reaction at 142-144^{o} (Fig. 5). Peaks at δ_c 203.1 and 76.7 were enhanced and peaks at 40.7 and 33.3 ppm were split. Therefore the peaks centered at 40.7 come from C-6 and those at 33.3 from C-3. The highest field peak at 20.4 must arise from the methyl carbon of the acetoxyl group. The only uncertainty remaining is the distinction between C-4 and C-5 at 23.9 and 27.3 ppm.

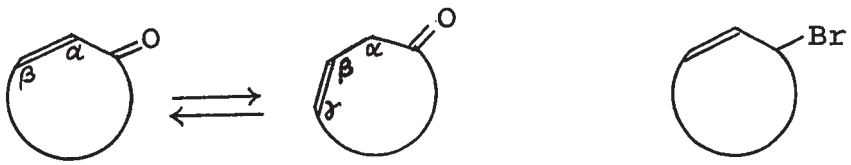
Besides mechanistic interest, the acetoxyketone rearrangement, especially in the monocyclic series, could prove useful in the preparation of deuterium and carbon-labelled compounds since there are not many known reactions that give complete deuteration or carbon-scrambling of cycloalkane derivatives.[55] With this possibility in mind, 2-acetoxycyclanones 104(n) of other ring sizes (n=5,7,8,9,12) were prepared and their deuterium exchange reaction examined.

Table VII summarizes the deuterium exchange results of 2-acyloxcyclanones. Except for 2-acetoxycyclopentanone 104(5), acetoxycyclanones 104(n) of other ring sizes studied (i.e. n=6,7,8,9,12) undergo pentadueteration in the ring at reflux temperature of acetic acid-acetate mixture,

indicating that keto acetate interchange takes place in all of these compounds. When 2-acetoxycyclododecanone 104(12) was treated with deuterated acetic acid-acetate at 240° for 57 hours, the acetoxyketone was recovered in 22% yield. Mass spectroscopic analysis revealed that there was complete equilibration between ring protons and the external deuterium source (reaction 46). Thus the α-acetoxyketone grouping did migrate all the way around the annular periphery to introduce twenty-one deuterium atoms into the ring! However, for acetoxycyclanones 104(n) of medium size (n=7,8,9), the ring size plays a major role in the extent of further incorporation of deuterium atoms beyond pentadeuteration (reactions 43, 44 and 45). All of the four mechanisms proposed for the α→α'-transfer process require three adjacent carbon atoms of the ring (α-C, C=O, α'-C) to approach trigonal hydridization at the transition state. Comparison of reactions of 2-acetoxycyclanones 104(n) of various ring sizes revealed that the ease of deuteration (6>7>8<9<12) correlates generally with the ease of introduction of three adjacent trigonal centers into carbocycles as judged by other reactions in which this phenomenon can be observed.

Heap and Whitham[56] have shown that the equilibrium constants for medium-ring α,β- and β,γ-unsaturated ketones

118 and 119 depend on the ring size. An increase in ring size from six to nine progressively favors the β,γ-unsaturated ketone 119, and it is the more stable isomer in the eight- and nine-membered rings. Hydrolysis of the 1-bromocycloalk-2-enes 120 also indicated that the rate decreased with increase in ring size from seven to nine. Heap and Whitham rationalized these two observations by the torsional effects and non-bonded interactions generated in medium-size rings when three adjacent carbon atoms are forced into trigonal hydridization state. However, since the yield of the recovered acetoxycyclanones 104(n) for n=7,8,9 are rather poor (reactions 43, 44 and 45), the



118 119 120

question of whether the correlation results solely from the changing rate of the α→α'-transfer reaction, or whether the acetoxyketone 104(n) is drained off into side products is not yet answered. The extremely slow rate of deuteration and the poor yield observed for 2-acetoxycyclopentanone 104(5) (reaction 38) have no satisfactory explanation.

In summary, deuterium exchange experiments of acetoxycyclanones 104(n) indicated that the acetoxyketone

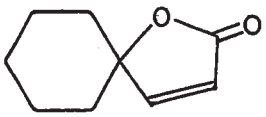
rearrangement can be utilized for the preparation of deuterated or carbon-labelled cycloalkane derivatives in fairly good yields for ring sizes of six and twelve, and probably larger, but only in low yields for ring sizes seven and nine, and cannot be used in eight- or five-membered ring compounds.

The side products for most of the reactions of 2-acetoxycyclanones 104 are either volatile or else non-distillable, since pure 2-acetoxycyclanones 104 were usually obtained by bulb-to-bulb distillation of the crude reaction product. One exception is the seven-membered ring case, g.l.p.c. analysis of the crude product of the reaction of 2-acetoxycycloheptanone 104(7) revealed the presence of two side products A and B in addition to the starting material.

The structures of A and B were elucidated for two reasons: firstly, to find whether they are condensation products; secondly, once their structures are known, insight might be provided into a way to avoid their formation, thus improving the yield in the deuterium exchange reactions.

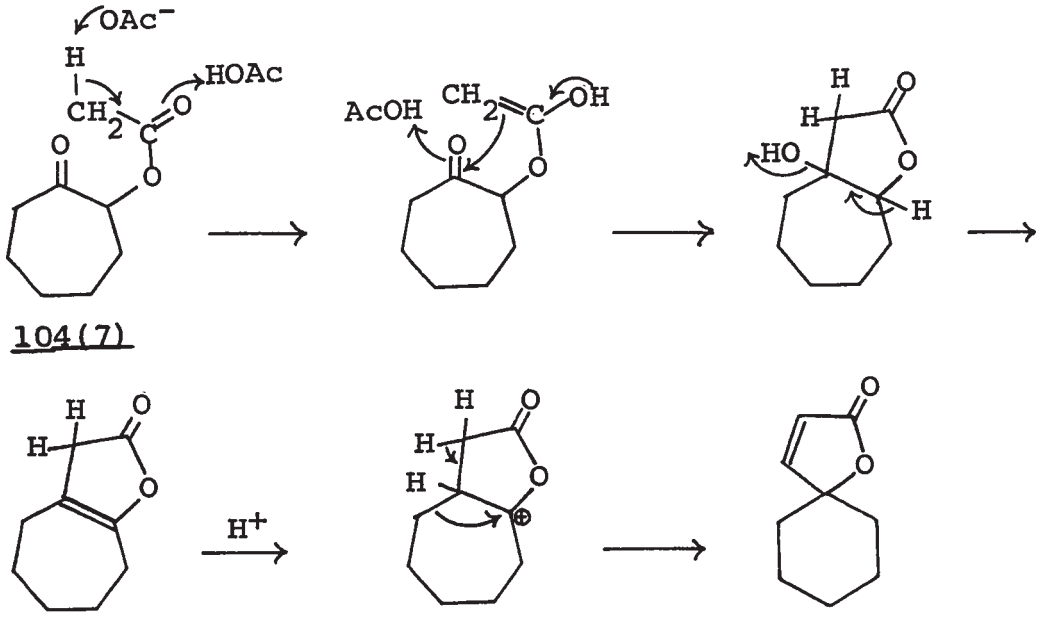
Treatment of 2-acetoxycycloheptanone 104(7) with acetic acid-acetate at 250^{o} for 2 days gave a 23% yield of distillable material, which was found to contain ca. 40% of A and 30% of B by g.l.p.c. and n.m.r. analysis.

Separation by fractional distillation and column chromatography gave A (95% pure) in 2.6% overall yield and crystalline B in 2.8% overall yield. Although compound A has not been obtained completely pure, its spectroscopic data are consistent with the structure 121. Both u.v. [λmax 215 nm (ϵ 10,700)] and i.r. spectra (νmax 1760 cm^{-1})



121

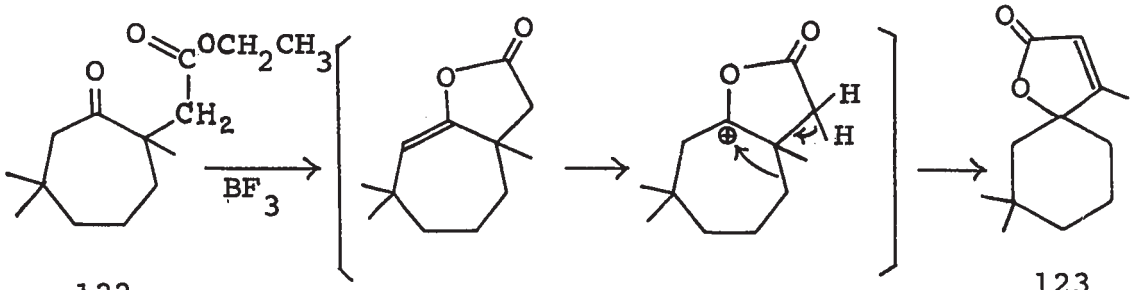
indicated the presence of an α,β-unsaturated γ-lactone grouping. The molecular weight was determined by mass



104(7)

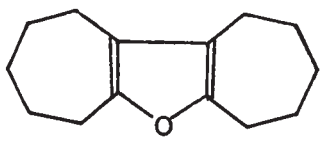
121

spectroscopy to be 152. N.m.r. spectrum(Fig. 8) has doublets at δ 5.99 and 7.45, indicating the presence of two vinylic protons. The formation of 121 from acetoxycycloheptanone 104(7) can be formulated as on p.108 and has the precedent in the recently published transformation of 122 into 123 by acid catalysis.[57]



122 123

Structure 124 was assigned to compound B from its spectroscopic data and elemental analysis. Both the u.v. [λmax 227 nm (ϵ 7,700)] and i.r. spectra (νmax 1445 cm^{-1}) are consistent with the furan structure. Mass spectroscopy revealed the molecular weight to be 204. The tetra-substituted nature of the furan ring was confirmed by the three humps in its n.m.r. spectrum at δ 1.71, 2.31,



124

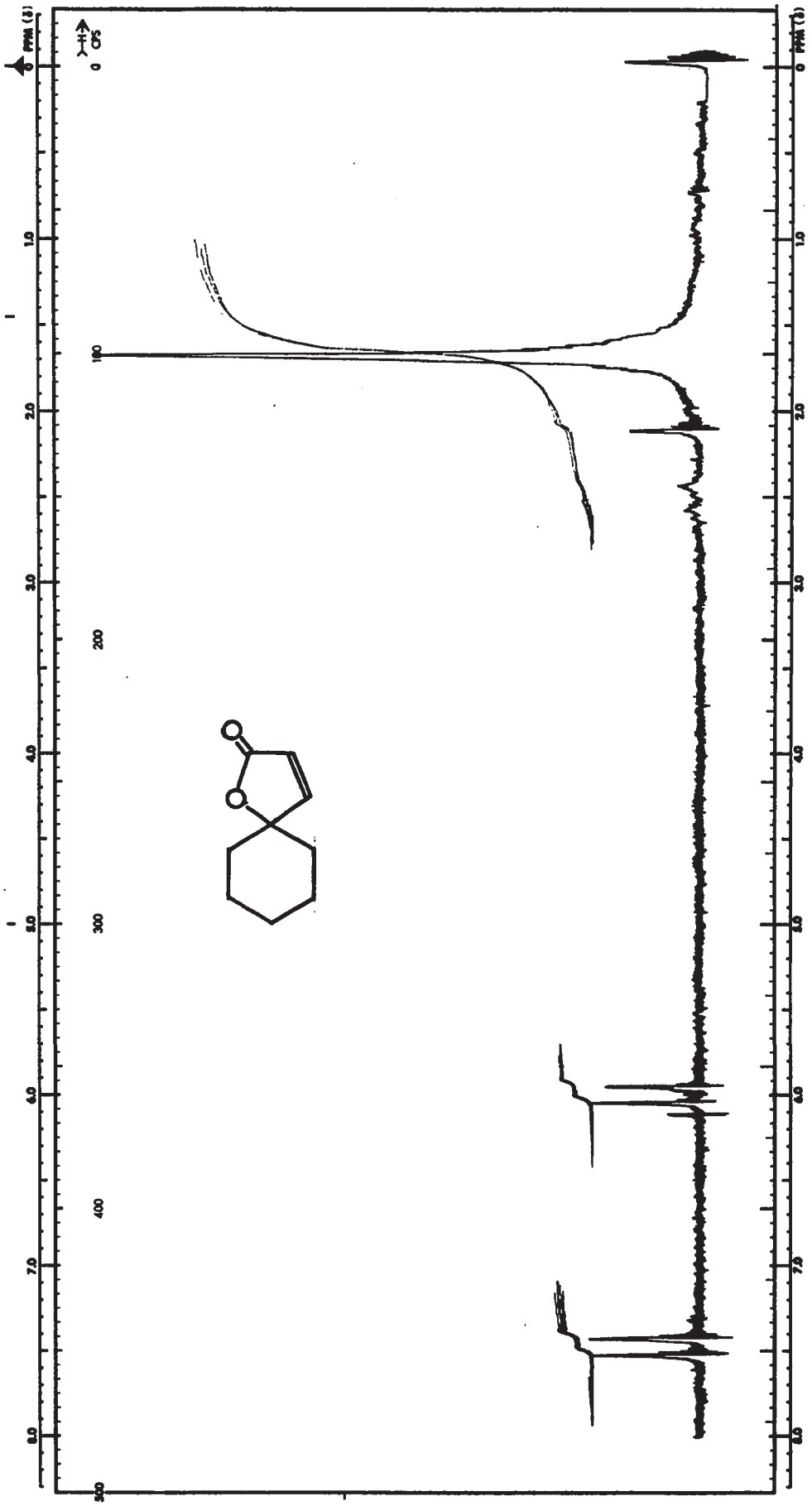
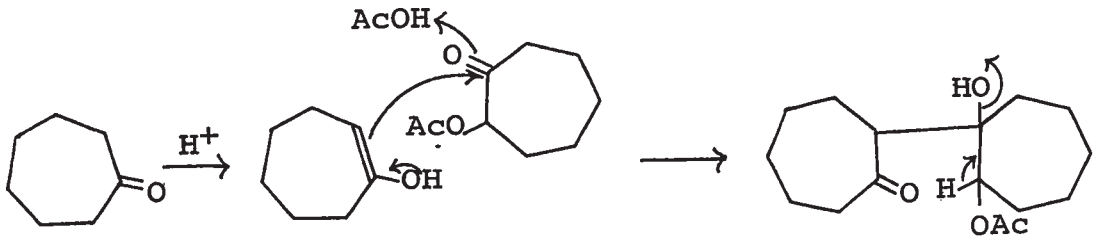


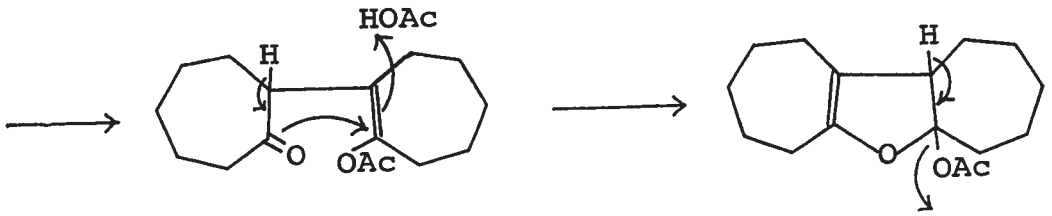
Fig. 8

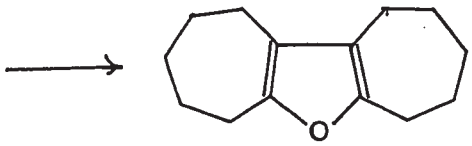
and 2.68 ppm in a ratio of 3:1:1 and the absence of low field absorptions.

The furan 124 can be rationalized as a condensation product between cycloheptanone 115(7) and 2-acetoxycycloheptanone 104(7) as follows:



115(7)





124

Since 124 was formed in ca. 7% crude yield, the cycloheptanone 115(7) required in the condensation scheme can be easily explained by the 5% contamination of cycloheptanone 115(7) known to be present in the starting material, 2-acetoxycycloheptanone 104(7).

We have no knowledge of the structure of other products in the reaction of 2-acetoxycycloheptanone 104(7) and the

way they are formed, but if these are further transformation products of compound A 121, one obvious way to improve the yield in the exchange reaction would be to use trimethylacetates, isobutyrates or benzoates instead of acetate, since the formation of 121 involves ester condensation as the first step.

In view of the greater tendency of the benzoyloxyl group than acetoxyl group to serve as a leaving group in pyrolytic reactions, and the lack of α-hydrogen in the benzoyloxyl group, 2-benzoyloxycyclohexanone 125 was expected to undergo more facile degenerate rearrangement and to be subject to fewer side reactions if α→α'-transfer of acyl groups is an intramolecular allylic shift (mechanism DD).

Treatment of 2-benzoyloxycyclohexanone 125 with deuterated acetic acid-acetate at 150° gave a 65% recovery of the benzoyloxyketone 125 which was mainly pentadeuterated (reaction 47). Raising the temperature to 170° and 185° decreased the recovered yield to 26% and 1.5% respectively, and the amount of 2-acetoxycyclohexanone 104(6) increased correspondingly, but no more than five deuterium atoms were incorporated into the recovered benzoyloxyketone 125. The results indicated that the interchange reaction of 2-benzoyloxycyclohexanone 125

occurred readily at 150° and was intramolecular, but α→α'-transfer of benzoyloxyl group was not much faster than that of the acetoxyl group and proceeded at a rate comparable with the intermolecular carboxyl group exchange.

Rearrangement of benzoyloxyketone 125 with potassium benzoate in benzoic acid would be difficult to follow by deuterium exchange. Resort has to be made to carbon-label scrambling work on 2-benzoyloxycyclohexanone-1-^{13}C 125-1-^{13}C which could be readily made from 2-acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C.

CHAPTER IV

PREPARATION OF COMPOUNDS

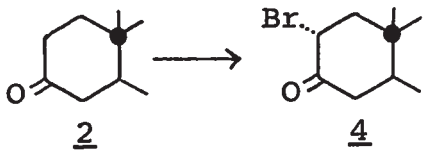
(i) Steroid Compounds

The α-bromo and α-acetoxy ketosteroids used in the present study were all prepared by well-established procedures. Chart I and Chart II outline the synthetic scheme for α-bromo and α-acetoxy ketosteroids respectively. Comments in this section are mainly confined to improvements discovered in the course of our work.

Cholestanones

5β-Cholestan-3-one 1. It has been known for a long time that presence of acid or base has a big effect on the stereochemical course of hydrogenation of α,β-unsaturated ketones.[58] Hydrogenation of Δ^4-cholesten-3-one 5 in ethyl acetate in the presence of palladium on charcoal gave 5β-cholestan-3-one 1 and cholestan-3-one 2 in a ratio of *ca.* 4:1. With Nishimura's[59] modification, acetic acid containing small amount of hydrobromic acid was used as solvent, 5β-cholestan-3-one 1 was obtained in 95% purity and the product was readily recrystallizable.

Chart I



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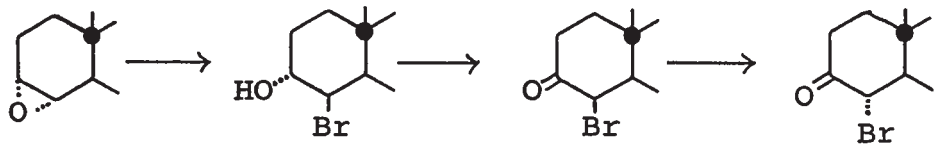

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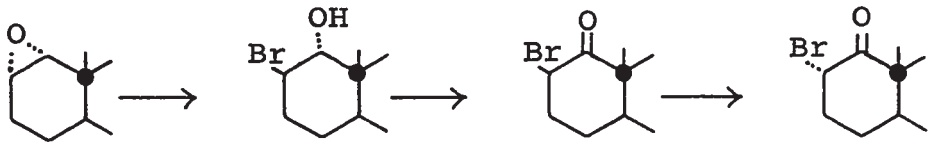

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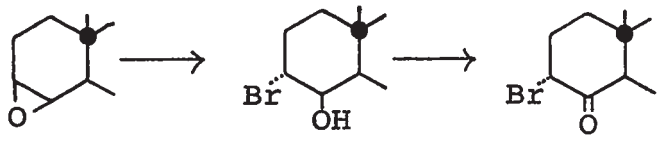

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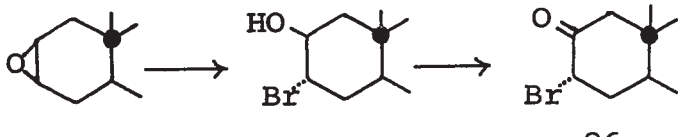

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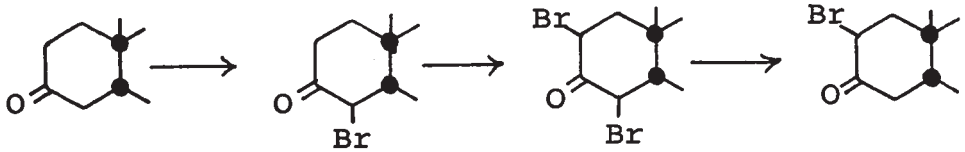
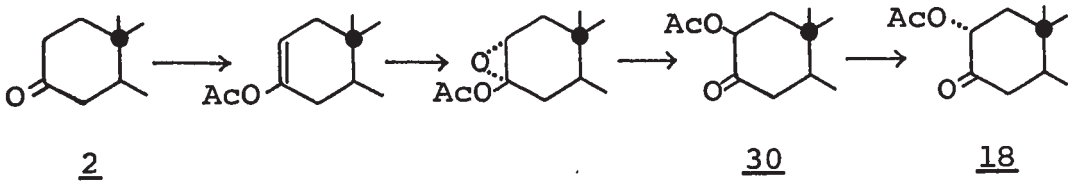


1 3 82

Chart II



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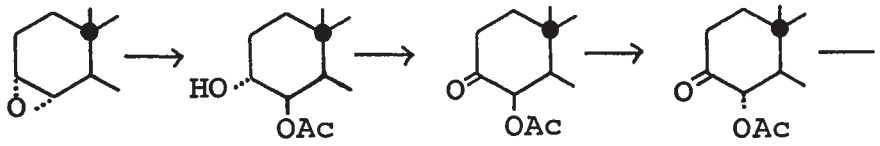

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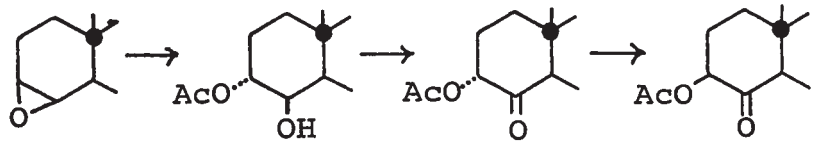

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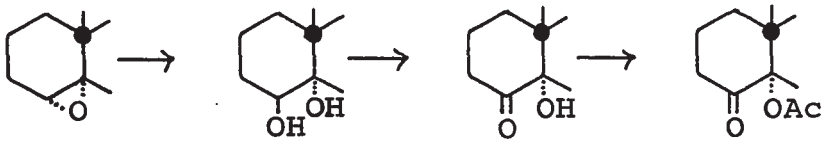

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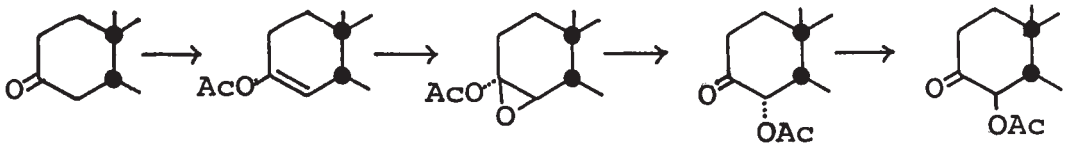

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Cholestenones

Δ^1-Cholesten-3-one 6. Crystalline Δ^1-cholesten-3-one 6, m.p. 96-99°, has been prepared by Green and Long[60] in 82% yield on treating 2α-bromo-cholestan-3-one 4 with calcium carbonate in boiling dimethylacetamide. However, in our hands, the crude product was shown by n.m.r. to be a mixture of ca. 30% of Δ^4-cholesten-3-one 5 and 70% of Δ^1-cholesten-3-one 6. Three recrystallizations gave Δ^1-cholesten-3-one 6 which is free from Δ^4-cholesten-3-one 5 in 42% yield.

Cholestenes

Δ^1-Cholestene. A sample prepared from the lithium aluminum hydride-aluminum chloride reduction of Δ^1-cholesten-3-one 6[61] was contaminated by ca. 30% of Δ^2-cholestene as revealed by n.m.r. and t.l.c. data. Since neither chromatography on alumina nor recrystallization gave much fractionation, it was used as such in the epoxidation reaction. In an attempted preparation of Δ^1-olefin, Striebel and Tamm found that treatment of the thiolethylene ketal of Δ^1-cholesten-3-one 6 with Raney-nickel gave Δ^2-cholestene as the only isolable product.[62]

Δ^3-Cholestene. Preparation of Δ^3-cholestene from

Δ^4-cholesten-3-one 5 by hydroboration-elimination[63] is much more convenient than by zinc-dust reduction of this conjugated ketone,[64] especially on a large scale. Δ^3-Cholestene was obtained in higher yield and purity by the first method. The main side-product in both reactions is Δ^3-5β-cholestene, arising from initial β-attack at C-5.

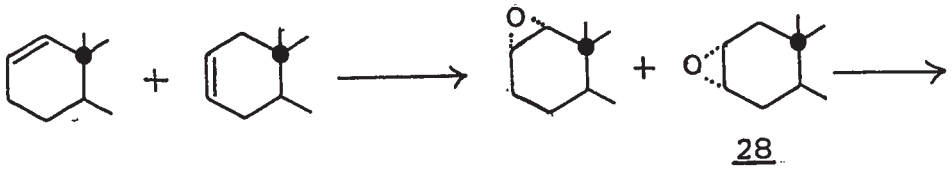
Δ^4-Cholestene 10. Lithium aluminum hydride-aluminum chloride reduction of Δ^4-cholesten-3-one 5 gave Δ^4-cholestene, which was contaminated by ca. 10% of Δ^3-5β-cholestene. The crude product was easily purified by recrystallization.

Epoxides

1α,2α-Oxidocholestane. The mixture of 1α,2α-oxidocholestane and 2α,3α-oxidocholestane 28 obtained by epoxidation of impure Δ^1-cholestene cannot be separated by recrystallization. A pure sample was obtainable in low yield by separation on thick layer. The melting point of the pure sample (94-95°) was higher than that reported in the literature (89-90°).[61]

A better way for separating the above mixture was found during preparation of bromohydrins from the epoxides. It was found that 2β-bromocholestan-1α-ol was more readily converted into epoxide on silica gel than 2β-bromocholestan-3α-ol. Thus the mixture of bromohydrins prepared from crude 1α,2α-oxidocholestane was readily separated by thick layer

chromatography into pure 1α,2α-oxidocholestane and 2β-bromocholestan-3α-ol in quantitative yields.



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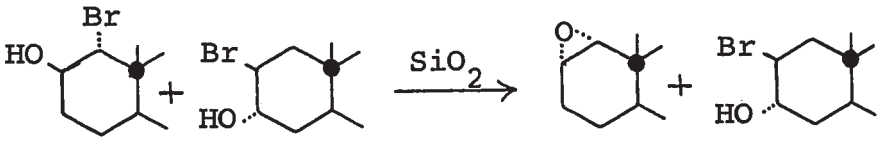


4α,5α-Oxidocholestane. Because of the special location of the double bond, Δ^4-cholestene is subject to β-side attack as well as α-side attack, in contrast to Δ^1-, Δ^2-, Δ^3-, Δ^5-cholestenes, which are approached predominately from the α-side.[65] The ratio of α-side attack to β-side attack was found to be subject to subtle changes in the medium. When Δ^4-cholestene was epoxidized in chloroform according to the procedure of Heilbron,[66] the crude product was a mixture of 4α,5α-oxidocholestane and 4β,5β-oxidocholestane in a ratio of ca. 7:3. However, change of chloroform to carbon tetrachloride altered the ratio to ca. 9:1, and isomerically pure 4α,5α-oxidocholestane was obtained in 70% yield after one recrystallization.

Enol Acetates and Oxido Acetates

3-Acetoxycholest-2-ene (cholestan-3-one Δ^2-enol acetate) and 3-acetoxy-5β-cholest-3-ene (5β-cholestan-3-one Δ^3-enol acetate). Although it has been well established that cholestan-3-one 2 prefers Δ^2-enolization and 5β-cholestan-3-one 1 prefers Δ^3-enolization, the enol acetates prepared from 2 and 1 by treatment with isopropenyl acetate in the presence of sulfuric acid catalysis are not pure: 3-acetoxycholest-2-ene is contaminated by ca. 10% of 3-acetoxycholest-3-ene; 3-acetoxy-5β-cholest-3-ene is contaminated by ca. 10% of 3-acetoxy-5β-cholest-2-ene. Moreover, the isomers are not separable by recrystallization.

Since we were interested only in the acetoxyketones, impure enol acetate was used for the next epoxidation step. The oxido acetate mixtures were easily separable by recrystallization.

Bromoketones

2α-Bromocholestan-3-one 4. 2α-Bromocholestan-3-one 4 prepared from cholestan-3-one 2 by bromination in acetic acid is always contaminated by 10~20% of the parent ketone even if more than one equivalent of bromine was added.[67] The main trouble arises from the co-precipitation of cholestan-3-one 2 with 2α-bromocholestan-3-one 4 during the reaction. When carbon tetrachloride was used as the solvent

and a little more than one equivalent of bromine was added, the crude reaction mixture was mainly 2α-bromocholestan-3-one 4 plus a small amount of 2α,4α-dibromocholestan-3-one. No trace of the parent ketone was detectable from t.l.c. The small amount of dibromoketone was easily separated by recrystallization.

2β-Bromo-5β-cholestan-3-one 82. The simplest way to prepare this compound from the parent ketone 5β-cholestan-3-one 1 is the dibromination-debromination scheme, which has been used successfully by Williamson and Johnson[22] to prepare the 4α-bromocholestan-3-one 12 in almost quantitative yield from cholestan-3-one 2. By using a large excess of chromous acetate for a short period of time for the debromination step, 2β-bromo-5β-cholestan-3-one 82 was prepared from 5β-cholestan-3-one 1 in 60% yield.

Acetoxyketones

3β-Acetoxycholestan-4-one 57. In contrast to other acetoxyketones, for which the axial-equatorial isomerization was cleanly effected by hydrochloric acid in acetic acid, treatment of 3α-acetoxycholestan-4-one 21 with hydrochloric acid in acetic acid gave a very complex product mixture, probably due to the tertiary nature of C-5. However,

3α-acetoxycholestan-4-one 21 was converted by refluxing acetic acid-acetate into the equatorial isomer, 3β-acetoxycholestan-3-one 57 in good yield, the only detectable side-products being Δ^5-cholesten-4-one 7 and minute amount of 5α-acetoxycholestan-4-one 58.

(ii) Acyloxycyclanones

All acyloxycyclanones used in the present work were prepared from the hydroxycyclanones or the parent cyclic ketones. In the case of 2-acetoxycyclohexanone 104(6), 2-acetoxycyclononanone 104(9) and 2-benzoyloxycyclohexanone 125 where the corresponding hydroxyketones were readily available, direct acylation with acetic anhydride or benzoyl chloride gave the desired products in high yields.

In cases where the parent cyclic ketones were the starting material, there were three routes to the acetoxyketones.

(a) Acetoxylation with lead tetra-acetate: Treatment of symmetric cyclic ketones with one molar equivalent of lead tetra-acetate gave a mixture of α-acetoxyketone, α,α'-diacetoxyketone and starting material, which were usually easily separated by fractional distillation. This is the simplest of the three routes and is the method of choice if the starting ketone is readily available. The

only disadvantage is the fact that there is always some diacetoxyketone formed and it is tedious to recycle the unreacted ketone. Yields after purification without recycling usually range from 20% to 30% except for the very poor yield (6%) from cyclopentanone 115(5).

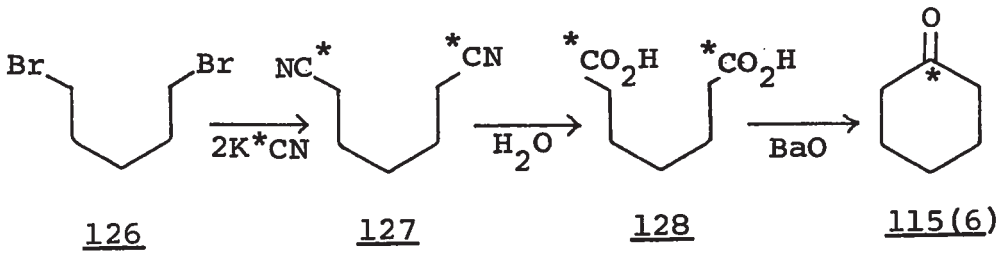
(b) Via enol acetate and oxido acetate: Enol acetates were prepared from the parent ketone by acid-catalyzed reaction with isopropenyl acetate in 85~90% yield. Epoxidation and subsequent thermal rearrangement afforded the desired acetoxyketone in 60~70% yield. This is certainly the preferred route when the starting ketone is the limiting factor, e.g., with carbon-labelled compounds.

(c) Via chloroketone: For unsymmetric ketones such as 2-methylcyclohexanone, chlorination with sulfuryl chloride, followed by treatment with potassium acetate in acetic acid gave mainly the thermodynamically more stable isomer of the two possible α-acetoxyketones, whereas lead tetra-acetate acetoxylation described above gave approximately equal amounts of the two possible isomers. For symmetric ketones, route (a) and (b) are the methods of choice since the chloroketone pathway is a two step synthesis and the first step is subject to dichlorination.

(iii) Cyclohexanone-1-^{13}C 115(6)-1-^{13}C

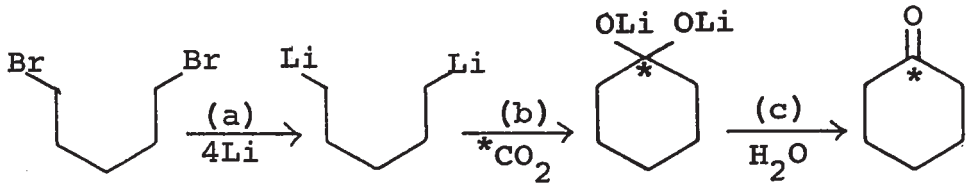
After an extensive survey of the literature, two routes, both starting with 1,5-dibromopentane 126 seemed to be most suitable for the synthesis of cyclohexanone labelled at C-1. Reaction of 1,5-dibromopentane 126 with labelled potassium

Route A



126 127 128 115(6)

Route B



126 129 130 115(6)

cyanide, hydrolysis of the resulting dinitrile 127 and subsequent pyrolysis of the barium salt of the diacid 128 give cyclohexanone 115(6) (route A). Preparation of 1,5-dilithiopentane 129 and treatment with labelled carbon dioxide give cyclohexanone 115(6)directly upon hydrolysis (route B).

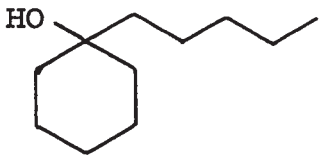
Route B is the method of choice for ^{13}C-labelled compound although most of the cyclohexanone-1-^{14}C

115(6)-1-^{14}C reported in the literature has been synthesized by route A. The major disadvantages of route A are the requirement of two moles of labelled cyanide per mole of cyclohexanone and the high cost of ^{13}C-labelled potassium cyanide ($1,000 per gram of ^{13}C, 60% enrichment). For route B, only one mole of carbon dioxide is used up for one mole of cyclohexanone produced, and labelled carbon dioxide can be easily generated from the much cheaper ^{13}C-labelled barium carbonate ($300 per gram of ^{13}C, 60% enrichment).

Preparation of cyclohexanone 115(6) in ca. 20% yield by route B was originally discovered by West and Rochow.[68] Because of the cost of ^{13}C-labelled carbon, yield was also of importance in our synthesis of cyclohexanone-1-^{13}C 115(6)-1-^{13}C. In an extensive investigation of the reaction, the side reactions were diminished to achieve a reproducible 50% yield of cyclohexanone 115(6) based on barium carbonate.

The side products of the reaction by route B were mainly a less volatile compound X and some nondistillable material. Compound X had a retention time about four times longer than that of cyclohexanone 115(6) in g.l.p.c. The mass spectrum of X showed a molecular ion at m/e 170 and a fragment ion at 152 ($M-18^{+}$). There is a weak O-H

absorption at 3500 cm^{-1} in its i.r. spectrum but no carbonyl absorption. Thus compound X is consistent with the tertiary alcohol structure 131, and probably comes from



131

$$---(CH_2)_5CO\ (CH_2)_5CO(CH_2)_5CO---$$

132

the reaction of cyclohexanone 115(6) with one end of the dilithiopentane 129. The nondistillable material was an amorphous solid, and was only slightly soluble in ether. Its i.r. spectrum showed moderately strong C=O absorption around 1720 cm^{-1}. Thus the nondistillable material must be polymeric ketones 132 arising from intermolecular condensation.

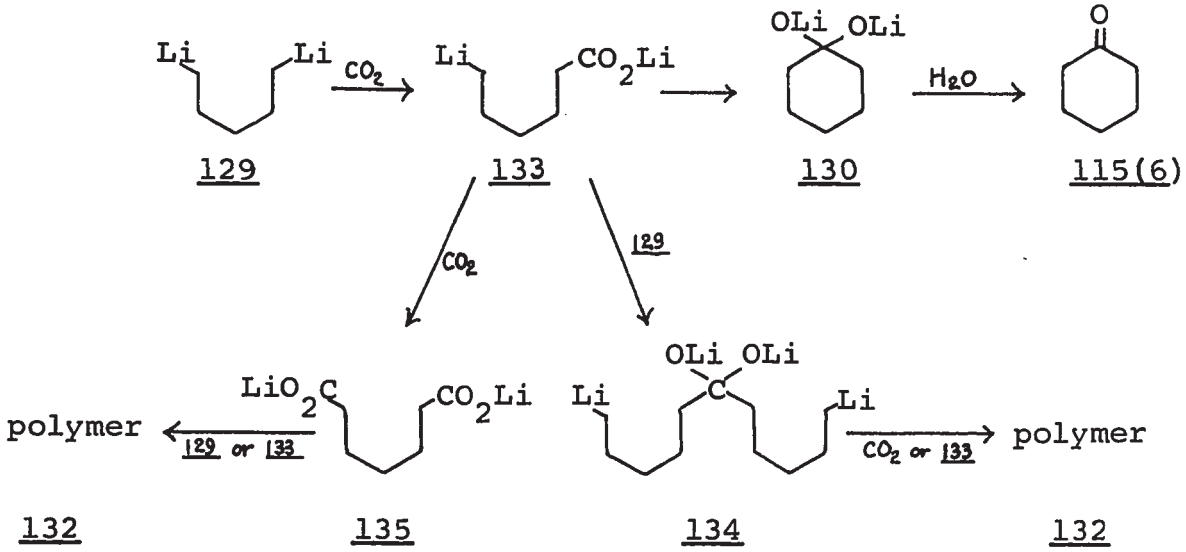
The formation of the tertiary alcohol 131 and the polymeric ketone 132 will be discussed in detail along with the three steps of route B.

(a) 1,5-Dilithiopentane 129. The preparation of 1,5-dilithiopentane 129 from 1,5-dibromopentane 126 and lithium sand in 60-80% yield has been reported by several workers.[68,69] However, in our hands, the reaction of 126 with lithium sand (prepared from BDH 98% or 99.5% lithium rod, or from Foote Mineral Co. high purity lithium ribbon) or lithium dispersion (Lithium Corp. of America) gave

unreproducible low yields (0~20%) of organolithium compound. The main side reaction seemed to be Wurtz-type coupling because the titration value for bromide ion after hydrolysis of the reaction mixture was always quantitative. Since the intermolecular Wurtz-type coupling product would consume some of the carbon dioxide at the carbonation stage and give rise to polymeric material, a high yield of 1,5-dilithiopentane 129 from the dibromide 126 was essential to optimize the yield of cyclohexanone. The problem was solved by adding 2.5% sodium metal to the molten lithium when the sand was made. The same effect of sodium has been observed earlier in the preparation of n-butyllithium and phenyllithium.[70] The reaction of 1,5-dibromopentane 126 with lithium sand containing 2.5% sodium went smoothly at -20° to give 1,5-dilithiopentane 129 in 75~85% yields. The yields were determined by titration with sec-butyl alcohol, using 1,10-phenanthroline as an indicator.[71]

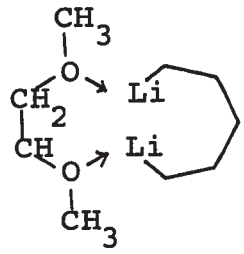
(b) Carbonation of 1,5-dilithiopentane 129 to the gem-dialkoxide 130. Since barium carbonate was used as the ^{13}C source, 129 was allowed to react with gaseous carbon dioxide to form the gem-dialkoxide 129, which is inert to further attack by alkyllithium. Carbon dioxide was generated gradually in the reaction system in ca. 80-90% yield by the

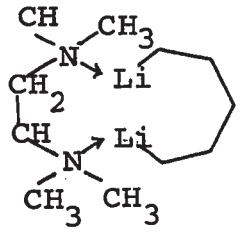
action of concentrated sulfuric acid on barium carbonate. Most of the unwanted polymeric ketone 132 was formed during the carbonation step, and its formation can be rationalized as follows. Once one end of 1,5-dilithiopentane 129 reacts with carbon dioxide to form 133, there is a competition between intra- and intermolecular reactions. Intramolecular cyclization gives arise to the gem-dialkoxide 130, which yields the desired product cyclohexanone 115(6) on hydrolysis. There are at least two possible intermolecular processes which will lead to polymer formation. Firstly, 133 could react with a new molecule of 1,5-dilithiopentane 129 to give the dimeric species 134, which after further reaction with carbon dioxide or 133, would lead to polymeric material. As far as entropy is concerned,



intramolecular cyclization is preferred to intermolecular reaction for the formation of six-membered rings, i.e., 130 should be formed much faster than 134. Moreover, this intermolecular reaction between 133 and 1,5-dilithiopentane 129 could be suppressed further by working at high dilution of 129. The second intermolecular process is the reaction of 133 with one more molecule of carbon dioxide to form the dicarboxylate 135. Once 135 is formed, it is destined to give rise to polymeric material since there is no intermolecular pathway possible for the dicarboxylate 135 and it will wander around till it reacts with 1,5-dilithiopentane 129 or 133 present in the system no matter how dilute the solution of 129 is. Since a three-body collision is very unlikely, the dicarboxylate 135 has to come from 133, the only way to suppress the formation of 135 is slow passage of carbon dioxide and efficient mixing of the gaseous and liquid phases, i.e., working at high dilution of carbon dioxide. However, even with the efficient stirring device described in the Experimental Section and in a fairly dilute solution (0.17M) of 1,5-dilithiopentane 129, maximum amount of intramolecular reaction is 50%. The persistence of intermolecular reaction might be attributed to the well-known polymeric nature of organolithium compound.[72] Since there are

always other molecules of 1,5-dilithiopentane 129 present after carbon dioxide had reacted with one end of 129 to form 133, the intermolecular process between 133 and 129 within the same cluster would be a facile one. A possible way to solve this problem might be to use a suitable bidentate ligand such as ethyleneglycol dimethyl ether (glyme) or N,N,N',N'-tetramethylethylenediamine (TMEDA) to chelate 1,5-dilithiopentane 129 in the monomeric form. Since chelation decreases the stability of organometallic

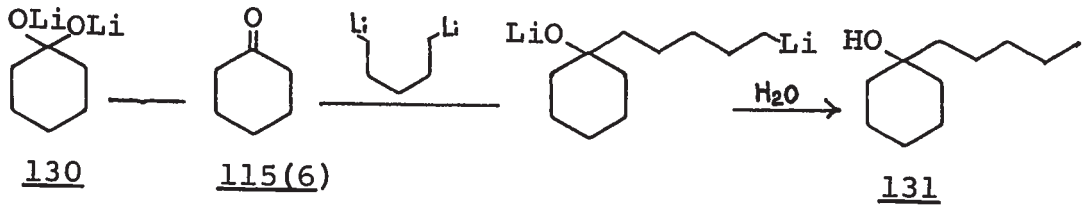




compounds in ether,[82] thus necessitating modification of the carbonation temperature, we have not investigated the use of glyme or TMEDA extensively.

(c) Hydrolysis of the gem-dialkoxide 130. Because carbon dioxide is the limiting agent in the present case, excess 1,5-dilithiopentane 129 is deliberately maintained to the end of the reaction. As pointed out by Jorgenson in a review,[73] excess organolithium compound can cause the formation of tertiary alcohol. Since the gem-dialkoxide 130 and 1,5-dilithiopentane 129 hydrolyze at comparable rates,

cyclohexanone liberated from 130 may be taken up by the remaining 1,5-dilithiopentane 129 to give the tertiary alcohol 131. Following Jorgenson's procedure, instead of



130 115(6) 131

adding water to the crude reaction mixture, it was hydrolyzed by pouring into a well-stirred solution of dilute hydrochloric acid. In this way the formation of the tertiary alcohol 131 was substantially decreased, but never completely suppressed. In view of the suggestion that the excess organolithium compound could be destroyed after completion of carbonation but before the hydrolytic work-up,[73] methyl iodide was added to consume the excess 1,5-dilithiopentane 129 and it was found that tertiary alcohol formation during the work-up was completely suppressed.

With all the precautions mentioned above, cyclohexanone 115(6) was prepared from 1,5-dibromopentane 126 and carbon dioxide in 50% yield based on barium carbonate.

CHAPTER V

EXPERIMENTAL

General

Melting points were taken on a Reichert-Kofler microscope hotstage. Optical rotations were measured with chloroform solutions, in a 1-dm. tube on a Rudolph Model 80 Polarimeter. Optical rotatory dispersions (O.R.D.) were recorded with chloroform solutions in a 1-cm. quartz cell on a Durrum-Jasco ORD/UV-5 Spectropolarimeter. Infrared spectra were recorded on a Beckman IR-5A or IR-10 Spectrophotometer in carbon tetrachloride solutions. Ultraviolet spectra were taken on a Cary Model 14 Spectrophotometer in 95% ethanol solution. Proton nuclear magnetic resonance spectra (n.m.r.) were determined with deuteriochloroform solutions on a Varian A-60 or T-60 or HA-100 instrument with tetramethylsilane (TMS) as internal reference. Chemical shifts were reported as δ values in ppm downfield from TMS ($\delta = 0.00$). ^{13}C nuclear magnetic resonance spectra were determined with benzene solutions in a 12-mm. tube on a Varian HA-60 instrument operating at 15.1 MHz. internally locked on benzene with proton

noise decoupling. Chemical shifts were reported as δ_c values in ppm downfield from TMS (δ_c = 0.0) using $\delta_{c\ benzene}$ = 128.7 ppm. Mass spectra were run on Varian M-66 in the department or on Hitachi RMV-6 instruments by Morgan-Schaffer Co., Montreal, Canada.

Gas liquid partition chromatography (g.l.p.c.) was carried out on a Glowall Model 400, fitted with 1.8 m. x 3.4 mm. spiral wound glass column for analysis and a 1.8 m. x 10 mm. column for preparative work. A hydrogen flame detector was used, and in the preparative work, in conjunction with a 50:1 stainless steel splitter. The column packing was 5% diethylene glycol succinate (DEGS) on nonacid-washed 60-80 mesh Chromosorb P.

Fractional distillations were done on a Nestor and Faust 8" micro spinning band or on a Nestor and Faust 18" semi-micro spinning band.

Solutions in organic solvents were dried by washing them with saturated sodium chloride solution and then allowing to stand over anhydrous magnesium sulfate before filtration. Removal of organic solvent was effected on a rotary evaporator under the reduced pressure provided by a water aspirator, with the flask heated by a water bath (40-60^{o}). Petroleum ether refers to the fraction boiling at 60-80^{o} unless otherwise specified.

Microanalyses were carried out in the laboratories of A. B. Gygli, Toronto, Canada or in the laboratories of J. F. Alicino, Metuchen, N.J., U.S.A.

Sealed tube reactions were heated in a Fischer HI-TEMP oil bath or in Hans Hosli furnace.

For reactions of steroid compounds with potassium acetate in acetic acid, "work-up" means removal of acetic acid on the rotary evaporator, dilution with water, and extraction with ether, followed by washing the ether layer with 5% aqueous sodium bicarbonate solution until pH>8, drying over magnesium sulfate and removal of ether on the rotary evaporator. For reactions of steroid compounds with tetramethylammonium acetate in acetone, "work-up" means removal of acetone on rotary evaporator, extraction with ether, followed by washing the ether layer with water and saturated sodium chloride solution, drying over magnesium sulfate and removal of ether on the rotary evaporator.

For reactions of monocyclic compounds with potassium acetate in acetic acid, "work-up" means dilution of the crude reaction mixture with water, extraction with ether, followed by washing the ether layer with 5% aqueous sodium bicarbonate solution until pH>8, drying over magnesium sulfate and removal of ether by simple distillation at atmospheric pressure.

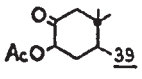
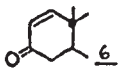
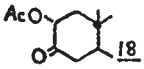
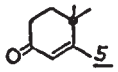
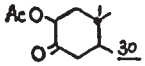
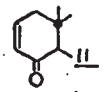
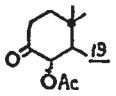
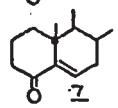
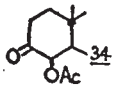
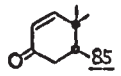
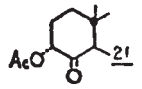
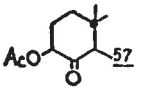
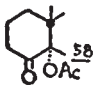
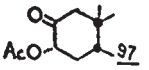
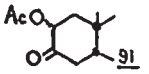
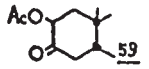
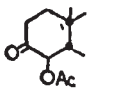
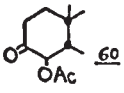
Camag DF-5 silica gel with calcium sulfate binder was used for thin layer chromatography (t.l.c.) and for thick layer chromatography (20 g. per 20 x 20 cm. plate). Benzene-ethyl acetate 90:10 (solvent A) or petroleum ether (b.p. 60-80°)-ethyl acetate 85:15 (solvent B) was used for development. A GE G15T8 lamp was used to detect u.v.-absorbing spots and then a 30% sulfuric acid solution was used for charring of t.l.c. plates. The bands of thick layer chromatography were detected with the help of u.v.-light and ordinary transmitted light. The bands cut from the thick layer were extracted with ether.

Silica gel-silver nitrate thin layer was prepared by spreading a slurry of 30 g. of Camag DF-5 silica gel in a solution of 7.5 g. of silver nitrate in 60 ml. of water on six 20 x 20 cm. glass plates. All t.l.c. on silica gel-silver nitrate were developed with petroleum ether.

Table VIII lists the Rf values of steroid α-acetoxyketones and α,β-unsaturated ketones.

TABLE VIII

Rf VALUES OF STEROID α-ACETOXYKETONES AND ENONES

compound	solvent A	solvent B	compound	solvent A	solvent B
 39	0.48	0.26	 6	0.44	0.30
 18	0.40	0.21	 5	0.30	0.19
 30	0.40	0.21	 11	0.46	
 19	0.40	0.21	 7	0.46	0.35
 34	0.35		 85	0.48	0.34
 21	0.46	0.26			
 57	0.48	0.26			
 58	0.40	0.20			
 97	0.40	0.21			
 91		0.21			
 59	0.48	0.26			
	0.40				
 60	0.48	0.26			

Δ^1-Cholesten-3-one 6

The method of Green and Long[60] was followed. 2α-Bromocholestan-3-one 4 (30.0 g., m.p. 169-170°, free from cholestan-3-one 2, prepared as described on p. 149) was dehydrobrominated with calcium carbonate in boiling dimethylacetamide. Crude Δ^1-cholesten-3-one 6 was obtained in 92% yield. U.v., n.m.r. and t.l.c. data showed the presence of ca. 30% of Δ^4-cholesten-3-one 5. Three recrystallizations from methanol-ether gave 10.0 g. (41%) of Δ^1-cholesten-3-one 6 m.p. 94-98° (lit.[60] m.p. 98°) which was free from Δ^4-cholesten-3-one 5 as judged from t.l.c. and n.m.r. data. Concentration of the mother liquors and repeated recrystallizations gave a further 2.0 g. (8%) of colorless crystals, m.p. 81-93°.

I.r. spectrum: νmax 1680 cm^{-1} (C=O).

N.m.r. spectrum: δ 0.70 (3H, s., C-18 methyl), 1.01 (3H, s., C-19 methyl), 5.88 (1H, d., J=10.5 Hz., C-2 H), 7.14 ppm (1H, d., J=10.5 Hz., C-1 H)

Δ^4-Cholesten-3-one 5

Δ^4-Cholesten-3-one 5 was prepared by the Oppenauer oxidation of cholesterol, according to the procedure of Organic Syntheses.[74] On hundred gram scale, it was obtained in 70% yield, m.p. 75-80° (lit.[74] m.p. 79.5-80.5°).

I.r. spectrum: νmax 1675 (C=O) and 1620 cm^{-1} (conj. C=C).
N.m.r. spectrum: δ 0.72 (3H, s., C-18 methyl), 1.17 (3H, s., C-19 methyl), 5.70 ppm (1H, b.s., $w_{\frac{1}{2}}$=3 Hz., C-4 H)

5β-Cholestan-3-one 1

The procedure of Nishimura and coworkers[59] was followed. Δ^4-Cholesten-3-one 5 (4.0 g., m.p. 75-80°, single spot on t.l.c.) dissolved in acetic acid was hydrogenated in the presence of palladium-on-charcoal in a Parr Model 3910 hydrogenator. Hydrogen uptake was complete within one day. Work up gave 3.2 g. (80%) of crude 5β-cholestan-3-one 1. T.l.c. (solvent A) of the crude product showed that it was contaminated by less than 5% of cholestan-3-one 2. One recrystallization from ether-95% ethanol gave 2.0 g. (50%) of colorless plates, m.p. 59-61° (lit.[59] m.p. 59-61°).
N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.00 ppm (3H, s., C-19 methyl)

Δ^1-Cholestene

The following procedure was essentially that of Djerassi and coworkers.[61]

A solution of 9.8 g. of Δ^1-cholesten-3-one 6 (m.p. 94-98°, free from Δ^4-cholesten-3-one 5) in 150 ml. of anhydrous ether was added to a solution of lithium

aluminum hydride (2.0 g.) and aluminum chloride (12.0 g.) in 250 ml. of anhydrous ether. The mixture was refluxed for 2 hr. Ethyl acetate was added to destroy the excess hydride, and the mixture was washed with 20% aqueous sulfuric acid solution and dried. After the removal of solvent, the 9.3 g. (99%) of residue left was chromatographed in petroleum ether (b.p. 30-60°) on 130 g. of neutral alumina (Woelm, activity IV). The petroleum ether eluate (ca. 300 ml.) gave 3.7 g. (39%) of Δ^1-cholestene. T.l.c. on silica gel-silver nitrate (solvent A) and the n.m.r. spectrum showed that it was contaminated by ca. 30% of Δ^2-cholestene. Two recrystallizations from methanol-ethyl acetate gave 2.0 g. (21%) of long needles, m.p. 67-68° (lit.[61] m.p. 70-71°). Concentration of the mother liquors gave a further 1.2 g. (13%) of crystals, m.p. 60.5-65°. T.l.c. on silica gel-silver nitrate showed there was not much fractionation of Δ^1-cholestene and Δ^2-cholestene on recrystallization. N.m.r. spectra: δ 0.67 (3H, s., C-18 methyl), 0.81 (3H, s., C-19 methyl), 5.50 (1H, b.d., J=11 Hz., C-2 H), 5.88 ppm (1H, b.d., J=11 Hz., C-1 H)

Δ^2-Cholestene

Cholestan-3β-ol[75] (10.0 g., m.p. 140-142°, free from cholesterol) was converted via the toluene-p-sulfonate

ester into Δ^2-cholestene according to the procedure of Douglas and coworkers.[76] One recrystallization of the crude product from acetone gave 6.3 g. (63%) of pure Δ^2-cholestene, m.p. 71-73° (lit.[76] m.p. 74-75°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.75 (3H, s., C-19 methyl), 5.60 ppm (2H, b.s., $w_{1/2}$=6 Hz., C-2 H and C-3 H)

Δ^3-Cholestene

(a) By hydroboration and 1,2-elimination of Δ^4-cholesten-3-one 5. The procedure of Caglioti and coworkers[63] was followed with slight modification. A stream of diborane (generated from 38 g. of sodium borohydride and 330 g. of boron trifluoride etherate) was bubbled through a solution of 40 g. of Δ^4-cholesten-3-one 5, m.p. 75-80°, in 80 ml. of diethylene glycol dimethyl ether (diglyme) at room temperature for 1 hr. After standing at room temperature for another 1 hr., the reaction mixture was treated with 400 ml. of acetic anhydride at 120° for 2 hr.* When the reaction mixture had cooled to room temperature, the diglyme was distilled off under vacuum, and the residue was diluted with water and extracted with ether. The combined ether extracts were washed four times with 10% aqueous sodium hydroxide solution and dried. Removal of

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*Treatment with acetic anhydride at temperatures lower than reflux temperature seemed to give a higher yield of cholestenes.

ether left 38.6 g. of dark brown residue which was chromatographed in petroleum ether (b.p. 30-60°) on 500 g. of neutral alumina (Woelm, activity I). The petroleum ether (b.p. 30-60°) eluate (ca. 4 l.) gave 19.6 g. (49%) of semicrystalline Δ^3-cholestene, whose n.m.r. spectrum showed that it was contaminated by ca. 20% of Δ^3-5β-cholestene (vinylic protons at δ 5.34, b.d., J=11 Hz., 5.70, b.d., J=11 Hz.). Two recrystallizations from acetone gave 12.0 g. (30%) of Δ^3-cholestene, m.p. 74.5-75°, (lit. m.p. 78-79°,[63] 74-75°[64]) which was free from Δ^3-5β-cholestene according to the n.m.r. spectrum.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.78 (3H, s., C-19 methyl), 5.29 (1H, b.d., J=10 Hz., C-3 H or C-4 H), 5.55 ppm (1H, b.d., J=10 Hz., C-4 H or C-3 H)

(b) By zinc-dust reduction of Δ^4-cholesten-3-one 5. Δ^4-Cholesten-3-one 5 (2.0 g., m.p. 80-80.5°), in 750 ml. of acetic acid was reduced by 400 g. of zinc dust at room temperature according to the procedure of McKenna and coworkers.[64] A mixture of approximately equal amounts of Δ^3-cholestene and Δ^3-5β-cholestene was obtained in 60% yield. Repeated recrystallization from acetone gave 0.6 g. (13%) of Δ^3-cholestene, m.p. 70-74.5°, $[\alpha]_D$ +61° (c, 2.25) [lit.[64] m.p. 74-75°, $[\alpha]_D$ +58° (c, 0.70)]. The n.m.r. spectrum was identical with that obtained in (a).

Δ^4-Cholestene 10

Δ^4-Cholestene 10 was prepared from Δ^4-cholesten-3-one 5 following the procedure of Djerassi and coworkers[61] for the preparation of Δ^1-cholestene from Δ^1-cholesten-3-one 6.

A solution of 80 g. of Δ^4-cholesten-3-one 5, m.p. 77.5-80°, in 1.4 l. anhydrous ether was added to a solution of lithium aluminum hydride (15 g.) and aluminum chloride (100 g.) in 2.0 l. of anhydrous ether. The mixture was refluxed for 2 hr. Ethyl acetate was added to destroy the excess hydride, and the mixture was washed with 20% aqueous sulfuric acid solution and dried. After the removal of solvent, there was left 60 g. (78%) of crude Δ^4-cholestene 10. The n.m.r. spectrum and t.l.c. behavior (silica gel-silver nitrate) showed that the crude product was contaminated by ca. 10% of Δ^3-5β-cholestene, but was free from Δ^3-cholestene. Two recrystallizations from ether-acetone gave 38 g. (50%) of long needles, m.p. 74-78°, which was free from Δ^3-5β-cholestene. Two more recrystallizations raised the melting point to 78-80.5° (lit. m.p. 82.5°,[77] 79-80°[78]).

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.01 (3H, s., C-19 methyl), 5.30 ppm (1H, b.s., $w_{½}$=8 Hz., C-4 H)

1α,2α-Oxidocholestane

Δ^1-Cholestene (2.0 g., 5.4 mmol., m.p. 67-68°,

containing ca. 20% of the Δ^2-isomer) in 10 ml. of chloroform was epoxidized with 6.7 mmol. of perbenzoic acid in 15 ml. of chloroform at -10°, according to the method of Fürst and Plattner[79] for epoxidation of Δ^2-cholestene. The crude product was obtained in quantitative yield. The n.m.r. spectrum showed that it was a mixture of ca. 80% of 1α,2α-oxidocholestane and ca. 20% of 2α,3α-oxidocholestane 28. One recrystallization from acetone gave 1.6 g. (80%) of colorless prisms, m.p. 77-93°. Two more recrystallizations of a small amount of the sample raised the melting point to 90-95°, but the n.m.r. spectrum revealed that there was no fractionation of 1α,2α-oxidocholestane from its 2α,3α-isomer 28 on recrystallization. Purification of 150 mg. of the sample of m.p. 77-93° on one thick layer (solvent A) and one recrystallization gave 45 mg. of colorless prisms, m.p. 94-95° (lit.[61] m.p. 89-90°). The n.m.r. spectrum showed that it was free from the 2α,3α-isomer.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.91 (3H, s., C-19 methyl), 3.05 ppm (2H, m., C-1 H and C-2 H)

2α,3α-Oxidocholestane 28

The method of Fürst and Plattner[79] was followed. A solution of 4.0 g. (10.8 mmol.) of Δ^2-cholestene, m.p.

71-72.5°, in 20 ml. of chloroform was epoxidized with 12.2 mmol. of perbenzoic acid in 25 ml. of chloroform. Crude product was obtained in quantitative yield. One recrystallization from ether-95% ethanol gave 3.6 g. (88%) of 2α,3α-oxidocholestane 28, m.p. 103-106° (lit.[79] m.p. 105°).

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.75 (3H, s., C-19 methyl), 3.09 ppm (2H, m., C-2 H and C-3 H)

3α,4α-Oxidocholestane 32

The method of Fürst and Plattner[79] for the epoxidation of Δ^2-cholestene was followed. A solution of 11.0 g. (29.7 mmol.) of Δ^3-cholestene, m.p. 74-74.5° in 50 ml. of chloroform was epoxidized with 32.4 mmol. of perbenzoic acid in 70 ml. of chloroform. Crude 3α,4α-oxidocholestane 32 was obtained in quantitative yield. Two recrystallizations from ether-95% ethanol gave 10.3 g. (82%) of colorless plates, m.p. 116.5-118° (lit.[80,81] m.p. 117-118°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.77 (3H, s., C-19 methyl), 2.69 (1H, d., J=4 Hz., C-4 H), 3.15 ppm (1H, b.s., $w_{½}$=8 Hz., C-3 H)

4α,5α-Oxidocholestane

The method of Heilbron and coworkers[66] was followed with slight modification.

(a) Epoxidation with m-chlorobenzoic acid in carbon tetrachloride. To 2.0 g. (5.4 mmol.) of Δ^4-cholestene 10, m.p. 78-80.5°, dissolved in 50 ml of carbon tetrachloride and cooled to -10°C, was added 1.8 g. (5.6 mmol.) of 54% m-chlorobenzoic acid (Aldrich Chem. Co.) in 100 ml. of carbon tetrochloride. After 12 hr. at -10°, the mixture was filtered to remove m-chlorobenzoic acid. The carbon tetrachloride solution was washed with 5% aqueous sodium sulfite solution, 5% aqueous sodium bicarbonate solution and dried. Removal of ether gave a quantitative yield of crude crystalline product. The n.m.r. sepctrum showed that there was less than 10% contamination by 4β,5β-oxidocholestane. One recrystallization from acetone gave 1.4 g. (70%) of colorless plates, m.p. 93-98°, which were free from 4β,5β-oxidocholestane. Two more recrystallizations raised the melting point to 100-102° (lit.[66] m.p. 100-101°).

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.05 (3H, s., C-19 methyl), 2.90 ppm (1H, b.s., $w_{\frac{1}{2}}$=7 Hz., C-4 H).

(b) Epoxidation with m-chloroperbenzoic acid in other organic solvents. Δ^4-Cholestene 10, m.p. 78-80.5°, was epoxidized with m-chloroperbenzoic acid in the same manner as described in part (a) except that carbon tetrachloride was replaced by methylene chloride, or ether, or benzene.

In all three cases, crude products were obtained in quantitative yield. The n.m.r. spectrum of the crude product showed that ca. 30%, 20%, 10% of 4β,5β-oxidocholestane was present when the reaction was carried out in methylene chloride, ether and benzene respectively. Two to three recrystallizations were required to get rid of this contaminant.

(c) Epoxidation by perbenzoic acid in chloroform. The procedure of Heilborn was followed.[66] The n.m.r. spectrum of the crude product showed the presence of ca. 30% 4β,5β-oxidocholestane.

3β,4β-Oxidocholestane

3α-Hydroxy-4β-acetoxycholestane (4.0 g., m.p. 158-160°) was converted to 3β,4β-oxidocholestane via 3α-mesyloxy-4β-acetoxycholestane according to the procedure of Fürst and Scotoni.[80] Crude 3β,4β-oxidocholestane was obtained in 82% yield. Recrystallization from methanol-ether gave a first crop of 2.3 g. (65%), m.p. 97-100°, a second crop of 0.35 g. (10%), m.p. 94-99° (lit.[80] m.p. 98-99°).
N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.95 (3H, s., C-19 methyl), 3.00 ppm (2H, m., C-3 H and C-4 H)

3-Acetoxycholest-2-ene (cholestan-3-one Δ^2-enol acetate)

The method of Dauben and coworkers[83] was followed.

The reaction of 2.0 g. of cholestan-3-one 2, m.p. 120-129°, and 2.5 ml. of isopropenyl acetate under acidic catalysis gave quantitative yield of crude 3-acetoxycholest-2-ene. One recrystallization from methanol-chloroform gave 2.1 g. (93%) of cream-colored crystals, m.p. 83-87°. Repeated recrystallizations raised the melting point to 87-89° (lit.[83] m.p. 90-90.5°), but the n.m.r. spectrum of this material showed that there was always some contamination (ca. 10%) by 3-acetoxycholest-3-ene. (vinylic proton at 5.00, b.s., $w_{½}$=2.5 Hz.).

I.r. spectrum: νmax 1750 (C=O) and 1680 cm^{-1} (C=C)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.83 (3H, s., C-19 methyl), 2.12 (3H, s., CH_3COO-) 5.25 ppm (1H, b.s., $w_{½}$=10 Hz., C-2 H)

3-Acetoxy-5β-cholest-3-ene (5β-cholestan-3-one Δ^3-enol acetate)

The method of Dauben and coworkers[83] was followed. 3-Acetoxy-5β-cholest-3-ene, m.p. 82-88° (lit.[83] m.p. 83.1-83.6°), was obtained in 60% yield from 5.3 g. of 5β-cholestan-3-one 1, m.p. 59-61°. A small amount of this sample was repeatedly recrystallized to raise the melting point to 86-90°, but its n.m.r. spectrum revealed that there was always some contamination by 3-acetoxy-5β-choles-2-ene (vinylic proton at δ 5.25, m.).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.97 (3H, s., C-19 methyl), 2.10 (3H, s., CH_3COO-), 5.09 ppm (1H, b.s., $w_{\frac{1}{2}}$=4 Hz., C-4 H)

2α,3α-Oxido-3β-acetoxycholestane 81

3-Acetoxycholest-2-ene (8.6 g., m.p. 85-90°, containing ca. 10% of 3-acetoxycholest-3-ene) was epoxidized with perbenzoic acid according to the procedure of Williamson and Johnson.[22] Crude 2α,3α-oxido-3β-acetoxycholestane 81 was obtained in quantitative yield. The n.m.r. spectrum of the crude product revealed the presence of ca. 10% of 3α,4α-oxido-3β-acetoxycholestane (C-4 H at δ 2.87, b.s., $w_{\frac{1}{2}}$=2.5 Hz.). Two recrystallizations from ethyl acetate gave 5.2 g. (59%) of prisms, m.p. 124-130° (lit.[22] m.p. 133-134.5°). The n.m.r. spectrum showed that it was free from 3α,4α-oxido-3β-acetoxycholestane.

I.r. spectrum: νmax 1745 cm^{-1} (C=O)

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.95 (3H, s., C-19 methyl), 3.30 ppm (1H, b.d., J=5.5 Hz., C-2 H)

3β,4β-Oxido-3α-acetoxy-5β-cholestane

The procedure of Williamson and Johnson[22] for epoxidizing cholestanone enol acetate was followed.

To 2.2 g. (5.14 mmol.) of 3-acetoxy-5β-cholest-3-ene (m.p. 86-89°, containing ca. 10% of 3-acetoxy-5β-cholest-2-ene)

cooled to -10°, was added 10.1 mmol. of perbenzoic acid in 45 ml. of chloroform, also cooled to -10°. After 3 days at -10°, t.l.c. showed that there was no starting material left. The reaction mixture was poured into a cold 10% aqueous sodium carbonate solution, shaken for 5 min., and then extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated to leave 2.5 g. of crystalline solid which was shown by n.m.r. to contain a small amount of 2β,3β-oxido-3α-acetoxy-5β-cholestane (C-2 H at δ 3.20, m.). One recrystallization from ether-95% ethanol separated it completely from the contaminant and gave 1.16 g. (51%) of colorless prisms, m.p. 130-138°. Two more recrystallizations raised the melting point to 134-139°.

I.r. spectrum: ν max 1745 cm^{-1} (ester C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.87 (3H, s., C-19 methyl), 2.07 (3H, s., CH_3COO-), 3.09 ppm (1H, s., C-4 H)

2α-Bromocholestan-3-one 4

A modification of the procedure of Fieser and coworkers[67] was used.

A solution of 25 g. (0.156 mole) of bromine and 2 ml. of 48% hydrobromic acid in 60 ml. of acetic acid was added

from a dropping funnel to a well-stirred solution of 60 g. (0.156 mole) of cholestan-3-one 2,[84] m.p. 127-129°, in 1.5 l. of carbon tetrachloride in a 3-l. round-bottomed flask. The addition was completed in 30 min., and the stirring was continued for another 1 hr. The reaction mixture was washed with water, 5% aqueous sodium sulfite solution, water, and dried. Removal of carbon tetrachloride and two recrystallizations from petroleum ether-carbon tetrachloride gave 39 g. (54%) of 2α-bromocholestan-3-one 4, m.p. 167-169° (lit.[67] m.p. 168-169°). Concentration of the mother liquors gave a second crop of 3.5 g. (5%), m.p. 164-168°. T.l.c. showed that both crops were free from cholestan-3-one 2.

I.r. spectrum: ν max 1730 cm^{-1} (C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.10 (3H, s., C-19 methyl), 4.72 ppm (1H, q., J=6.5, 13.5 Hz., C-2 H)

2α-Bromocholestan-1-one 89

The procedure of Djerassi and coworkers[61] was followed with modifications.

1α,2α-Oxidocholestane (700 mg., 18.2 mmol., m.p. 77-93°, containing ca. 20% of 2α,3α-oxidocholestane 28) in 40 ml. of chloroform was treated with 15.0 ml. of 48% hydrobromic acid for 10 min. Washing with 5% aqueous

sodium sulfite solution and then with water and evaporation in vacuuo after drying gave 855 mg. of oil, which showed two spots on t.l.c. (solvent A). The n.m.r. spectrum showed that it was a mixture of 2β-bromocholestan-1α-ol and 2β-bromocholestan-3α-ol.* The mixture was separated on four thick plates. Extraction of the combined upper bands (major component) gave 368 mg. of partially crystalline material which was found by n.m.r. to be a mixture of 2β-bromocholestan-1α-ol and 1α,2α-oxidocholestane uncontaminated by any 2,3-isomers. Retreatment of this mixture with 48% hydrobromic acid and work up as described above gave 440 mg. (52%) of oil which was shown by n.m.r. to be pure 2β-bromocholestan-1α-ol. Attempts to crystallize the oily material from ether-methanol failed. N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.20 (3H, s., C-19 methyl), 3.95 (1H, b.s., $w_{\frac{1}{2}}$=6 Hz., C-1 H), 4.39 ppm (1H, b.s., $w_{\frac{1}{2}}$=9 Hz., C-2 H)

The crude oily 2β-bromocholestan-1α-ol (300 mg., 0.78 mmol. after thick layer chromatography) was dissolved in 20 ml. of acetic acid and treated with 80 mg. of chromium trioxide in 0.5 ml. of water. The solution was kept at room temperature overnight, diluted with water and

*N.m.r. spectrum of 2β-bromocholestan-3α-ol: δ 0.67 (3H, s., C-18 methyl), 4.25 ppm (2H, b.s., $w_{\frac{1}{2}}$=10 Hz., C-2 H and C-3 H)

extracted with ether. The combined ether extracts were washed with 5% aqueous sodium bicarbonate solution, and then dried. Removal of ether gave 290 mg. (90%) of partially crystalline solid whose n.m.r. spectrum was consistent with the structure of 2β-bromocholestan-1-one.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.38 (3H, s., C-19 methyl), 4.55 ppm (1H, d.d., J=5.5 Hz., C-2 H)

The crude 2β-bromocholestan-1-one (290 mg.) obtained as above was dissolved in 5 ml. of chloroform and treated with gaseous hyd gen bromide for 5 min. at 70°. The chloroform was removed under reduced pressure to leave 290 mg. of crude 2α-bromocholestan-1-one 89. Purification on two thick layer plates developed in solvent A gave 186 mg. (64%) of colorless oil. Two recrystallizations from 95% ethanol gave 162 mg. (56%) of colorless plates, m.p. 150-154° with a transition at 117° (lit.[61] m.p. 154-156°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.17 (3H, s., C-19 methyl), 5.10 ppm (1H, b.q., J=7,12 Hz., C-2 H)

3α-Bromocholestan-4-one 88

(a) From 3β,4β-oxidocholestane via 3α-bromocholestan-4β-ol. The usual procedure for preparation of bromohydrin from epoxide was followed.[61,85] 3β,4β-Oxidocholestane (430 mg., 1.05 mmol., m.p. 94-99°) in

25 ml. of chloroform was shaken with 48% aqueous hydrobromic acid (8 ml.) at room temperature for 10 min. The chloroform layer was washed with 5% aqueous sodium sulfite solution, water, and then dried. Evaporation of chloroform left 420 mg. (86%) of crude 3α-bromocholestan-4β-ol. Recrystallization from methanol-ether gave 241 mg. (49%) of colorless plates, m.p. 173.5-180°. A second crop from the mother liquor yielded 122 mg. (25%) of material, m.p. 160-178.5°.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.02 (3H, s., C-19 methyl), 1.80 (1H, s., O-H), 3.88 (1H, b.s., $w_{\frac{1}{2}}$=7 Hz., C-4 or C-3 H), 4.37 ppm (1H, unresolved doublet with further coupling, $w_{\frac{1}{2}}$=8 Hz., C-3 or C-4 H)

3α-Bromocholestan-4β-ol (360 mg., 0.77 mmol., m.p. 160-178.5°) dissolved in 20 ml. of acetic acid was oxidized with 80 mg. of chromium trioxide in 0.5 ml. of water. The solution was kept at room temperature overnight, diluted with water and extracted with ether. The combined ether extracts were washed with 5% aqueous sodium bicarbonate solution, and then dried. Removal of ether left 312 mg. (87%) of crude 3α-bromocholestan-4-one 88. One recrystallization from acetone-95% ethanol gave 207 mg. (58%) of colorless crystals, m.p. 125.5-127.5° (lit.[86] m.p. 120-121°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.73 (3H, s., C-19 methyl), 4.30 ppm (1H, b.s., $w_{½}$=8 Hz., C-3 H)

(b) From 5α-hydroxycholestan-4-one. Following the method of Shoppee and coworkers,[86] 5α-hydroxycholestan-4-one (120 mg., 0.30 mmol., m.p. 150-159°) was converted in quantitative yield into 3α-bromocholestan-4-one 88. Two recrystallizations from acetone-95% ethanol gave 88 mg. (58%) of crystalline material, m.p. 97-121°. Two more recrystallizations raised the melting point to 116-124°. The n.m.r. spectrum was identical with those obtained in part (a).

3α-Bromocholestan-2-one 86

The procedure of Barton and Alt[85] was followed. 2β,3β-Oxidocholestane 36 (1.50 g., m.p. 84-86°) was converted via 3α-bromocholestan-2β-ol into 0.91 g. (50% overall yield) of 3α-bromocholestan-2-one 86 m.p. 151-154°, once recrystallized from chloroform-methanol (lit.[85] m.p. 151-153°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.73 (3H, s., C-19 methyl), 4.33 ppm (1H, b.s., $w_{½}$=7 Hz., C-3 H)

4α-Bromocholestan-3-one 12

4α-Bromocholestan-3-one 12 was prepared from 3α,4α-oxidocholestanone 32 according to the reaction scheme

of Sorm and coworkers.[81]

3α,4α-Oxidocholestane 32 (424 mg., m.p. 115-117.5°) was converted by treatment with 48% aqueous hydrobromic acid into 406 mg. (79%) of 4β-bromocholestan-3α-ol, m.p. 160-162°).

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 1.08 (3H, s., C-19 methyl), 2.10 (1H, s., O-H), 4.10 (1H, b.s., $w_{½}$=6 Hz., C-3 or C-4 H), 4.25 ppm (1H, unresolved doublet with further coupling, $w_{½}$=6 Hz., C-4 or C-3 H)

4β-Bromocholestan-3α-ol (243 mg., m.p. 136-141.5°) was oxidized with chromic trioxide in acetic acid in quantitative yield to crude 4β-bromocholestan-3-one.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.28 (3H, s., C-19 methyl), 4.16 ppm (1H, b.s., $w_{½}$=6 Hz., C-4 H)

The crude 4β-bromocholestan-3-one was epimerized with hydrogen bromide in acetic acid to 4α-bromocholestan-3-one 12. Purification on thick layer (solvent A) and two recrystallizations from ethyl acetate-95% ethanol gave 85 mg. (35%) of colorless needles, m.p. 143-147° (lit.[81] m.p. 152-154°).

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.10 (3H, s., C-19 methyl), 4.66 ppm (1H, d., J=12.5 Hz., C-4 H)

4β-Bromo-5β-cholestan-3-one 3

5β-Cholestan-3-one 1 (1.29 g., 3.34 mmol., m.p. 58-61°) in 40 ml. of acetic acid was treated with 3.70 mmol. of bromine in 5 ml. of acetic acid according to the procedure of Butenandt and Wolff.[1] Crude oily 4β-bromo-5β-cholestan-3-one 3 was obtained in quantitative yield. Attempted recrystallization from acetone or 95% ethanol failed. Purification of a 400-mg. portion on two thick-layers (solvent A) gave 395 mg. of colorless semicrystalline solid. Attempted recrystallization from various solvents also failed. A 0.90-g. portion of the crude material was chromatographed on 20 g. of silica gel. Elution with ether (ca. 300 ml.) afforded 0.52 g. of semicrystalline material, which after two recrystallizations from acetone-95% ethanol yielded 210 mg. (23%) of colorless needles, m.p. 110-114° (lit.[1] m.p. 110-111°).

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.08 (3H, s., C-19 methyl), 4.88 ppm (1H, d., J=11.5 Hz., C-4 H)

2β-Bromo-5β-cholestan-3-one 82

The procedure of Williamson and Johnson[22] for the preparation of 4α-bromocholestan-3-one 12 was followed.

Chromous acetate was prepared under a nitrogen atmosphere by passing an aqueous solution of 0.53 g.

(2.0 mmol.) of chromium trichloride hexahydrate through a Jones reductor into a 50-ml. three-necked flask and then precipitating the acetate with aqueous sodium acetate solution. The brick red precipitate of chromous acetate was washed with deoxygenated water, 95% ethanol, anhydrous ether, and finally dried by a rapid passage of dry deoxygenated nitrogen through the flask.

To this dry powder was added, with stirring, 267 mg. (0.482 mmol.) of 2β,4β-bromo-5β-cholestan-3-one, m.p. 129.5-136.5°,[87] in 3 ml. of chloroform and 5 ml. of acetic acid. Stirring was continued for 10 min. Air was then blown through the solution to oxidize the excess chromous ion. The dark green slurry was taken up in 20 ml. of ether and washed with water, dilute sodium bicarbonate solution and dried. The removal of ether gave 198 mg. (88%) of colorless solid. T.l.c. showed two spots, the minor one corresponding in Rf value to 5β-cholestan-3-one 1, and no starting material was left. The crude product was purified on two 20 x 20 cm. thick layer plates, and the major band gave 144 mg. (63%) of solid which showed a single spot on t.l.c. One recrystallization from methanol-acetone gave 70 mg. of 2β-bromo-5β-cholestan-3-one 82, m.p. 135-137°.

I.r. spectrum: ν max 1730 cm^{-1} (C=O)

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.05 (3H, s., C-19 methyl), 4.70 ppm (1H, q., J=5.5,14 Hz., C-2 H)

O.R.D.: $[\alpha]_{589}$-9°, $[\alpha]_{310}$-430° (trough), $[\alpha]_{269}$+650°(peak) (c = 0.530)

Analysis: Cald. for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74

Found : C, 68.88; H, 9.23

Cholestan-4β,5α-diol

Collins' procedure[88] for mild acid hydrolysis of the epoxide was followed.

A solution of 1.5 g. of 4α,5α-oxidocholestane, m.p. 100-102°, in 350 ml. of acetone and 35 ml. of water containing 3.0 ml. of 2N sulfuric acid was kept at room temperature for 2 days. After removal of acetone at room temperature under reduced pressure, water was added and the product was extracted with ether. The ether extracts were washed with water, 5% sodium bicarbonate solution, and dried. Removal of ether left 1.5 g. of crude cholestan-4β,5α-diol. One recrystallization from acetone gave 1.0 g. (67%) of colorless crystals, m.p. 169-170° with transition at 158° (lit.[89] m.p. 171-172°).

N.m.r. spectrum: δ pyridine 0.72 (3H, s., C-18 methyl), 1.55 (3H, s., C-19 methyl), 4.00 (1H, b.s., $w_{½}$=8 Hz., C-4 H), 5.10 ppm (2H, b.s., $w_{½}$=20 Hz., O-H)

5α-Hydroxycholestan-4-one

5α-Hydroxycholestan-4-one was prepared according to the method of Eastham and coworkers.[90] Cholestane-4β,5α-diol (1.0 g., m.p. 166-172°) was oxidized with chromic trioxide in pyridine to 5α-hydroxycholestan-4-one. The crude product was obtained in quantitative yield. One recrystallization from methanol yielded 0.56 g. (56%) of colorless plates, m.p. 156-158° (lit.[90] m.p. 157-158°).

I.r. spectrum: νmax 3580, 3400 (O-H) and 1720 cm^{-1} (C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.80 ppm (3H, s., C-19 methyl)

2β-Acetoxycholestan-3-one 30

2α,3α-Oxido-3β-acetoxycholestane 81 (0.93 g., m.p. 124-130°) was thermally isomerized into 2β-acetoxycholestan-3-one 30 according to the procedure of Williamson and Johnson.[22] One recrystallization from 95% ethanol yielded 0.68 g. (72%) of colorless prisms, m.p. 139-147° (lit.[22] m.p. 147.5-147.9°).

I.r. spectrum: νmax 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.85 (3H, s., C-19 methyl), 2.10 (3H, s., CH_3COO-), 5.33 ppm (1H, q., J=10,7 Hz., C-2 H)

2α-Acetoxycholestan-3-one 18

2β-Acetoxycholestan-3-one 30 (3.28 g., m.p. 139-147°) in 70 ml. of acetic acid was treated with 0.5 ml. of 36% aqueous hydrochloric acid according to the procedure of Williamson and Johnson.[22] Work up and two recrystallizations from 95% ethanol yielded 2.87 g. (89%) of 2α-acetoxycholestan-3-one 18 as colorless needles, m.p. 122-124°, $[\alpha]_D$+57° (c 1.96) [lit.[22] m.p. 124.7-125.2°, $[\alpha]_D$+51.55 (c 1.67)].

I.r. spectrum: νmax 1750 (ester C=O) and 1735 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.16 (3H, s., C-19 methyl), 2.13 (3H, s., CH_3COO-), 5.29 ppm (1H, q., J=13,6.5 Hz., C-2 H)

3β-Acetoxycholestan-2-one 39

3β-Acetoxycholestan-2-one 39 was prepared from 2α-acetoxycholestan-3-one 18 according to the method of Williamson and Johnson.[22]

2α-Acetoxycholestan-3-one 18 (500 mg., m.p. 122-124°) was treated with 570 mg. of tetramethylammonium acetate in 35 ml. of acetone at reflux for four days. T.l.c. revealed 60% conversion into 3β-acetoxycholestan-2-one 39. One recrystallization gave 204 mg. (40%) of

3β-acetoxycholestan-2-one, m.p. 141-144.5°. A small portion was recrystallized once more to raise the m.p. to 144-145° (lit.[22] m.p. 145.5-146.1°).

I.r. spectrum: νmax 1745 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.77 (3H, s., C-19 methyl), 5.20 ppm (1H, m., C-3 H)

4β-Acetoxycholestan-3-one 34

4β-Acetoxycholestan-3α-ol 33, m.p. 158-160°, was prepared from 4.0 g. of 3α,4α-oxidocholestane 32 according to the method of Fürst and Scotoni[80] in 56% overall yield.

4β-Acetoxycholestan-3α-ol 33 (0.81 g., m.p. 158-160°) was treated with Jones reagent according to the procedure of Williamson and Johnson.[22] The crude product, obtained in quantitative yield, was almost pure 4β-acetoxycholestan-3-one 34 as shown by the n.m.r. and t.l.c. data. Two recrystallizations from 95% ethanol of a 40-mg. portion of the crude product yielded 7 mg. of colorless needles, m.p. 130-134° (lit.[22] m.p. 133.7-134.4°).

I.r. spectrum: νmax 1750 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.12 (3H, s., C-19 methyl), 2.08 (3H, s., CH_3COO-), 4.92 ppm (1H, b.s.,

$w_{½}$=6 Hz., C-4 H)

4α-Acetoxycholestan-3-one 19

The method of Williamson and Johnson[22] was used.

Crude 4β-acetoxycholestan-3-one 34 (0.82 g., obtained from oxidation of 4β-acetoxycholestan-3α-ol) in 25 ml. of acetic acid containing three drops of 36.6% hydrochloric acid was allowed to stand at room temperature overnight. Evaporation of solvent gave 0.80 g. (98%) of solid. Two recrystallizations from 95% ethanol gave 0.61 g. (75%) of colorless needles, m.p. 135.5-142.5°. One more recrystallization raised the melting point to 143.5-144° (lit.[22] m.p. 144-145°).

I.r. spectrum: νmax 1750 (ester C=O) and 1735 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.16 (3H, s., C-19 methyl), 2.13 (3H, s., CH_3COO-), 5.04 ppm (1H, d., J=11.5 Hz., C-4 H)

3α-Acetoxycholestan-4-one 21

Williamson and Johnson's procedure[22] for the oxidation of diaxial hydroxy acetates to axial acetoxyketones was followed.

To 1.30 g. (2.91 mmol.) of 3α-acetoxycholestan-4β-ol (m.p. 170-178°, prepared from 3α,4α-oxidocholestane

according to the procedure of Fürst and Scotoni[80]) dissolved in 130 ml. of acetone (distilled from a mixture of Drierite and potassium permanganate) was added dropwise 1.0 ml. (7.96 meq.) of standard chromic acid solution* over a 5-min. period with rapid stirring of the solution. After an additional 1 min., the reaction was quenched in 5% aqueous potassium acetate solution and extracted with ether. The ether extract was washed with water and dried. Evaporation of ether gave 1.27 g. (90%) of 3α-acetoxycholestan-4-one 21. Two recrystallizations from methanol-acetone give material of m.p. 93-94.5°.

I.r. spectrum: νmax 1745 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.75 (3H, s., C-19 methyl), 2.10 (3H, s., CH_3COO-), 4.83 ppm (1H, unresolved triplet due to further coupling, $w_{½}$=5 Hz., C-3 H)

O.R.D.: $[\alpha]_{589}$+24°, $[\alpha]_{320}$-510° (trough), $[\alpha]_{270}$+1110° (peak) (c, 0.620)

Analysis: Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88

Found : C, 78.85; H, 10.43

* The standard chromic acid solution was prepared by dissolving 26.75 g. of chromium trioxide in 23 ml. of conc. sulfuric acid and diluting the mixture to 100 ml. with water.

3β-Acetoxycholest-5-en-4-one 23

3β-Acetoxycholest-5-en-4β-ol was prepared by selenium dioxide oxidation of cholesteryl acetate according to the method of Petrow and coworkers.[91] Colorless crystals of m.p. 177-189° (lit.[91] 192-193°) and showing a single spot on t.l.c. was obtained in 10% yield from 30 g. of cholesteryl acetate.

3β-Acetoxycholest-5-en-4β-ol (2.1 g., m.p. 177-189°) in 20 ml. of carbon tetrachloride was oxidized at room temperature with 15 ml. of dimethylsulfoxide and 10 ml. of acetic anhydride. After standing at room temperature for 2 days, the reaction mixture was stirred for 6 hr. with 100 ml. of water to hydrolyze excess acetic anhydride, and then extracted with ether. The combined ether extracts were washed with water, 5% aqueous potassium bicarbonate solution and dried. Removal of ether gave 2.1 g. (100%) of solid. Two recrystallizations from methanol gave 1.49 g. (71%) of 3β-acetoxycholest-5-en-4-one, m.p. 97-115° (lit.[18] m.p. 120-121°). A 200-mg. portion was purified by thick layer chromatography (solvent A) followed by one recrystallization to yield 130 mg. of colorless plates, m.p. 117-121°.

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 0.99 (3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.20 (1H, d.d.,

J=8 Hz., C-3 H), 6.40 ppm (1H, unresolved quartet due to further coupling, $w_{½}$=10 Hz., C-6 H)

3β-Acetoxycholestan-4-one 57

(a) By basic isomerization of 3α-acetoxycholestan-4-one 21. A solution of 140 mg. of 3α-acetoxycholestan-4-one 21, m.p. 93-94.5°, and 0.9 g. of potassium acetate in 4.5 ml. of acetic acid was refluxed under nitrogen at 135° for 3 hr. After removal of acetic acid under reduced pressure, water was added to the resulting residue and the product extracted with ether. The ether extract was washed with water, 5% aqueous sodium bicarbonate solution, water, and then dried. Removal of ether gave 130 mg. (93%) of crystalline solid. Two recrystallizations from 95% ethanol gave 70 mg. of 3β-acetoxycholestan-4-one 57, m.p. 107-118.5° (lit.[92] m.p. 117-118°).

I.r. spectrum: νmax 1745 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.75 (3H, s., C-19 methyl), 2.13 (3H, s., CH_3COO-), 5.20 ppm (1H, unresolved quartet due to further coupling, C-3 H)

(b) By catalytic hydrogenation of 3β-acetoxycholest-5-en-4-one 23. 3β-Acetoxycholest-5-en-4-one 23 (410 mg., m.p. 97-115°) in 40 ml. of ethyl acetate was hydrogenated at room temperature in the presence of 200 mg. of 5%

palladium-on-carbon for 24 hr. After removal of the solid catalyst, the evaporation of ethyl acetate left 338 mg. of slightly yellow oil. T.l.c. of the crude product showed that there were two major components present in a ratio of 6:4. Separation of the crude product on two thick layers (solvent A) gave 50 mg. of semicrystalline 3β-acetoxycholestan-4-one 57. One recrystallization from 95% ethanol gave 27 mg. of colorless crystals, m.p. 114-118°, whose infrared and n.m.r. spectra were identical with those obtained in (a). The other component was identified by m.p., m.m.p. (98-99°), i.r. and n.m.r. data to be cholestan-4-one 9 resulting from hydrogenation and hydrogenolysis of the 3-acetoxyl group.

(c) By acidic isomerization of 3α-acetoxycholestan-4-one 21. 3α-Acetoxycholestan-4-one 21 (95 mg., crude product from Jones' oxidation of 3α-acetoxycholestan-4β-ol) in 2.5 ml. of acetic acid was treated with a drop of 36% aqueous hydrochloric acid at room temperature for 12 hr. T.l.c. of the crude reaction mixture indicated that there were at least three major components.

5α-Acetoxycholestan-4-one 58

A mixture of 0.86 g. of 5α-hydroxycholestan-4-one, m.p. 150-159°, 12.0 ml. of acetyl chloride and 8.0 ml. of

freshly distilled dimethylaniline in 50 ml. of chloroform was refluxed for one day. Water was added to hydrolyze excess acetyl chloride. After standing at room temperature for one day, the chloroform layer was washed with 5% aqueous sodium bicarbonate solution, dilute hydrochloric acid solution, and dried. The removal of solvent left 1.06 g. of oil. T.l.c. showed that there was still some starting material left. Purification of the crude product on six 20 x 20 cm. thick layer gave 0.62 g. (67%) of solid which after two recrystallizations from methanol-ether gave 0.50 g. (55%) of 5α-acetoxycholestan-4-one 58, m.p. 147-148.5°.

I.r. spectrum: νmax 1740 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.66 (3H, s., C-18 methyl), 0.82 (3H, s., C-19 methyl), 2.13 ppm (3H, s., CH_3COO-)

O.R.D.: $[\alpha]_{589}$+31°, $[\alpha]_{308}$-1140 (trough), $[\alpha]_{273}$+2120 (peak) (c, 0.916)

4α-Acetoxy-5β-cholestan-3-one

The procedure of Williamson and Johnson[22] for thermal rearrangement of 2α,3α-oxido-3β-acetoxycholestane was followed.

A 1.16-g. sample of 3β,4β-oxido-3α-acetoxy-5β-cholestane, m.p. 130-138°, was placed in a 15-ml. centrifuge

tube which was immersed for 5 min. in an oil bath maintained at 160°. On cooling, the product remained an oil. The n.m.r. spectrum was consistent with the structure of 4α-acetoxy-5β-cholestan-3-one. No attempt was made to crystallize the compound.

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 1.10 (3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.46 ppm (1H, d., J=8 Hz., C-4 H)

4β-Acetoxy-5β-cholestan-3-one 60

4α-Acetoxy-5β-cholestan-3-one (1.16 g., crude product, see previous experiment) in 20 ml. of acetic acid was treated with three drops of 48% hydrobromic acid at room temperature for 8 hr. The solvent was removed at room temperature and reduced pressure to give 1.10 g. of slightly brown oil. Attempted crystallization from 95% ethanol failed. Purification of the crude product on four thick plates followed by one recrystallization from 95% ethanol gave 0.75 g. (65%) of colorless prisms, m.p. 104-107°. One more recrystallization raised the melting point to 106-108°.

I.r. spectrum: νmax 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.69 (3H, s., C-18 methyl), 1.07

(3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.55 ppm (1H, d., J=12 Hz., C-4 H)

Analysis: Calc. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88

Found : C, 77.90; H, 10.28

Reaction of 2α-Bromocholestan-3-one 4 with Potassium Acetate in Acetic Acid at 220-230° (Reaction 1)*

2α-Bromocholestan-3-one 4 (500 mg., m.p. 167-169°) and 3.00 g. of potassium acetate (both dried separately at 80° under 0.4 Torr for 3 hr.) in 14.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220-230° (furnace temperature reading) for 5 hr. After being cooled to room temperature, the tube was opened and the reaction mixture was worked up to give 394 mg. (95%) of a brown oil, which solidified on standing at room temperature. Recrystallization from acetone gave 208 mg. (49%) of Δ^5-cholesten-4-one 7, m.p. 93-105°. Purification on a thick layer (solvent B) followed by two recrystallizations from acetone gave 97 mg. of colorless plates, m.p. 110-112° (lit.[12] m.p. 111-112°).
U.v. spectrum: λmax 241 nm (ϵ 6,610) [lit.[12] 241 nm (ϵ 7,200)]
I.r. spectrum: νmax 1685 (C=O) and 1625 cm^{-1} (conj. C=C)
N.m.r. spectrum: δ 0.70 (3H, s., C-18 methyl), 0.96 (3H, s., C-19 methyl), 6.42 ppm (1H, unresolved quartet due to further coupling, $w_{1/2}$=7.5 Hz., C-6 H)

The amount of this unsaturated ketone in the crude product as estimated from t.l.c. and n.m.r. data was

*The number for the reaction refers to that listed in Tables I-IV and Table VII.

ca. 80%. The n.m.r. spectrum of the crude product also revealed the presence of ca. 15% of Δ^4-cholesten-3-one 5 (vinylic proton at δ 5.70, b.s., $w_{\frac{1}{2}}$=3 Hz.). No vinylic proton absorptions due to Δ^1-cholesten-3-one 6 was visible in the n.m.r. spectrum of the crude product. However, after the mother liquor was separated on a thick layer (solvent A), the upper unsaturated ketone band (Rf 0.46) was shown by n.m.r. integration of vinylic protons to be a mixture of Δ^5-cholesten-4-one 7 and Δ^1-cholesten-3-one 6 in a ratio of ca. 5:1. Therefore, the amount of Δ^1-cholesten-3-one 6 formed in the h-Δ^1-cholestenone rearrangement was estimated to be ca. 5%.

A parallel reaction without the exclusion of air gave a more complex product mixture, which showed at least seven spots of moderate intensity on the t.l.c. (solvent A), whereas the crude product of the reaction under a nitrogen atmosphere showed only two major spots on t.l.c., corresponding in Rf values to Δ^5-cholesten-4-one 7 and Δ^4-cholesten-3-one 5. Crystalline material of m.p. 90-105° was isolated in 20% yield in the reaction without the exclusion of air.

Reaction of 2α-Bromocholestan-3-one 4 with Potassium Acetate Alone at 220-230°

2α-Bromocholestan-3-one 4 (100 mg., m.p. 168-172°)

and 0.60 g. of dried potassium acetate* were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220-230° (furnace temperature reading) for 5 hr. The reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with water and dried. Removal of ether left 80 mg. of a brown oil. T.l.c. (solvent A) and i.r. data indicated that the crude product was a mixture of acetoxyketones. The amount of unsaturated ketone as judged from the t.l.c. data was less than 5%.

Reaction of 2α-Bromocholestan-3-one 4 with Potassium Acetate in Acetic Acid at 97-103° (Reaction 2)

2α-Bromocholestan-3-one 4 (288 mg., m.p. 168-170°) and 1.70 g. of dried potassium acetate in 9.5 ml. of acetic acid was warmed in an oil bath (bath temperature 105-110°, solution temperature 97-103°) until no starting material was left as judged from the t.l.c. data. Work up gave 250 mg. (91%) of slightly brown oil, λmax 239 nm (ϵ 990, based on the molecular weight of 430). Analysis by a combination of u.v., t.l.c. (solvent A), and n.m.r. data, which is described in detail below, indicated that the

*Potassium acetate was dried at 0.5 Torr for 3 hr. at 80° and stored in a flask with ground glass stopper.

crude product was composed of 3β-acetoxycholestan-2-one 39 (5%, Rf 0.49), Δ^1-cholesten-3-one 6 and/or Δ^5-cholesten-4-one 7 (trace*, Rf 0.44), 2α- and/or 4α-acetoxycholestan-3-one 18 and/or 19 (86%, Rf 0.40), Δ^4-cholesten-3-one 5 (6%, Rf 0.30). Purification of 163 mg. of the crude product on a thick layer (solvent A) and isolation of the major acetoxyketone band (Rf 0.40) gave 139 mg. (85%) of colorless solid, $[\alpha]_D$+28° (c, 2.00), single spot (Rf 0.40) on t.l.c. (solvent A). From the specific rotation, it was concluded that 2α- and 4α-acetoxycholestan-3-one 18 and 19 were formed in a ratio of 1:0.97. Recrystallization from 95% ethanol gave 111 mg. of the 1:1 complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19, m.p. 145-147° (lit.[22] m.p. 149-149.3°).

I.r. spectrum: νmax 1750 (ester C=O) and 1735 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.68 (3H, s., C-18 methyl), 1.16 (3H, s., C-19 methyl), 2.12 (3H, s., CH_3COO-), 5.15 ppm (1H, m., C-2 H or C-4 H)

Attempts to separate C-19 methyls and α-protons in n.m.r. spectra of the 1:1 complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19 by varying the solvent

*When a compound failed to show up on n.m.r. but was detectable from t.l.c., it is reported as trace.

(carbon tetrachloride, benzene, pyridine) were unsuccessful.

Analysis of the Crude Product of the Previous Reaction

N.m.r. spectrum revealed that the crude product was mainly 2α- and 4α-acetoxycholestan-3-one 18 and 19 (δ 0.68 for C-18 methyl, 1.16 for C-19 methyl, 5.15, m., for α-protons) plus minor amounts of 3β-acetoxycholestan-2-one 39 (δ 0.65 for C-18 methyl, 0.77 for C-19 methyl) and Δ^4-cholesten-3-one 5 (δ 5.70, b.s., $w_{½}$=3 Hz., for vinylic proton). No peaks due to Δ^1-cholesten-3-one 6 and Δ^5-cholesten-4-one 7 (δ 5.88, d., and 7.14, d., for vinylic protons of 6; 6.42, unresolved quartet, for vinylic proton of 7) were visible in the low field region. T.l.c. (solvent A) showed four spots, Rf 0.48 (39, minor), 0.46 (6 or 7, trace), 0.40 (18 or 19, major), 0.30 (5, minor). Therefore the amount of Δ^4-cholesten-3-one 5 in the crude product was calculated from the u.v. data [λ_{max} 239 nm (ε 990)] to be ca. 6% based on ε 16,500 for the pure compound, and the amount of Δ^1-cholesten-3-one 6 and/or Δ^5-cholesten-4-one 7 were reported as "trace".

Comparison of the relative peak heights of the C-18 and C-19 methyls in the n.m.r. spectrum and the intensity of spots on the t.l.c. plate indicated that 3β-acetoxycholestan-2-one 39 was present in ca. 5%. The

rest of the crude product was taken as the percentage of 2α- and 4α-acetoxycholestan-3-one 18 and 19. The low field α-proton pattern in n.m.r. spectrum indicated 18 and 19 were present in a ratio of 1:0.9.

Reaction of 2α-Bromocholestan-3-one 4 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 3)

2α-Bromocholestan-3-one 4 (1.00 g., m.p. 167-169°) and 7.00 g. of dried potassium acetate in 35 ml. of acetic acid was refluxed at 133-135° (solution temperature) under a nitrogen atmosphere for 6 hr. Work up gave 828 mg. (87%) of crystalline material, λ max 239 nm (ϵ 1130, based on the estimated molecular weight of 430). Analysis by a combination of u.v., n.m.r., and t.l.c. (solvent A) data indicated that the crude product was a mixture of 3β-acetoxycholestan-2-one 39 (20%, Rf 0.49), Δ^1-cholesten-3-one 6 and/or Δ^5-cholesten-4-one 7 (trace, Rf 0.44), 2α- and 4α-acetoxycholestan-3-one 18 and 19 (70%, Rf 0.40), Δ^4-cholesten-3-one 5 (10%, Rf 0.30). The ratio of 18 to 19 was estimated from the splitting patternof the low field protons to be close to 1:0.8. One recrystallization from 95% ethanol gave 400 mg. of crystalline material, m.p. 119-140°. A 300-mg. portion was purified on a thick layer (solvent A). The major band (Rf 0.40) gave 164 mg. of

crystalline material which after three recrystallizations from 95% ethanol amounted to 72 mg. of the 1:1 complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19, m.p. 145-147°.

Reaction of 2α-Bromocholestan-3-one 4 with Potassium Acetate in Acetic Acid at 200-210° (Reaction 4)

2α-Bromocholestan-3-one 4 (180 mg., m.p. 166-169°) and 1.10 of dried potassium acetate in 6.8 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated in an oil bath at 200-210° for 16 hr. Work up gave 158 mg. (100%) of a brown oil, λmax 239 nm (ϵ 4250, based on the estimated molecular weight of 403). T.l.c. (solvent A) showed three spots, Rf 0.48 (7 or 39 or 6, major), 0.40 (18 or 19, minor), 0.30 (5, minor). T.l.c. (solvent B) showed three spots, Rf 0.35 (7 or 6, major), 0.26 (39, major), 0.19 (18 or 19 or 5, minor). Analysis by a combination of u.v., t.l.c., and n.m.r. data showed that the crude product was Δ^5-cholesten-4-one 7 (50%), 3β-acetoxycholestan-2-one 39 (30%), 2α- and/or 4α-acetoxycholestan-3-one 18 and/or 19 (10%), and Δ^4-cholesten-3-one 5 (10%). The crude product was separated on a thick layer (solvent B) into three bands. Band 1 (Rf 0.35) on work up gave 60 mg. of crude Δ^5-cholesten-4-one 7, which after three recrystallizations from acetone yielded

15 mg. of colorless prisms, m.p. 108-112°. Band 2 (Rf 0.26) on work up gave 36 mg. of acetoxycholestanone mixture, which after two recrystallizations from 95% ethanol afforded 28 mg. of 3β-acetoxycholestan-2-one 39, t.l.c. single spot, m.p. and m.m.p. 143-145°. On admixture with the 1:1 complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19, the m.p. was depressed to 115-141°. Band 3 (Rf 0.19) consisted mainly of Δ^4-cholesten-3-one 5, but no attempt was made to isolate it.

Reaction of 4α-Bromocholestan-3-one 12 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 5)

4α-Bromocholestan-3-one 12 (70 mg., m.p. 153.5-160.5°) and 0.51 g. of dried potassium acetate in 3.0 ml. of acetic acid were refluxed under a nitrogen atmosphere (solution temperature 133-135°) until t.l.c. showed the complete absence of starting material (3 hr.). Work up gave 60 mg. (90%) of a brown oil. A combination of t.l.c. (solvent A) and n.m.r. data indicate that the crude product was composed of 3β-acetoxycholestan-2-one 39 (10%, Rf 0.49), Δ^1-cholesten-3-one 6 and/or Δ^5-cholesten-4-one 7 (trace, Rf 0.44), 2α-acetoxycholestan-3-one 18 (40%, Rf 0.40), 4α-acetoxycholestan-3-one 19 (40%, Rf 0.40) and Δ^4-cholesten-3-one 5 (10%, Rf 0.30). Three

recrystallizations of the crude product from 95% ethanol gave 16 mg. of the 1:1 complex of 2α- and 4α-acetoxycholestan-3-ones 18 and 19, m.p. and m.m.p. 145-147°. On admixture with 4α-acetoxycholestan-3-one 19, the m.p. was depressed to 134-147°. On admixture with 3β-acetoxycholestan-2-one 39, the m.p. was depressed to 120-145°.

Reaction of 2α-Bromocholestan-1-one 89 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 6)

2α-Bromocholestan-1-one 89 (130 mg., m.p. 150-154°) and 1.50 g. of dried potassium acetate in 10.0 ml. of acetic acid was refluxed at 133-135° (solution temperature) under a nitrogen atmosphere for 3 hr. Work up gave 119 mg. (92%) of solid, which was shown by n.m.r. and t.l.c. data to be mainly starting material.

Reaction of 2α-Bromocholestan-1-one 89 with Potassium Acetate in Acetic Acid at 200-210° (Reaction 7)

2α-Bromocholestan-1-one 89 (119 mg., recovered material from the previous experiment) and 0.70 g. of potassium acetate in 4.5 ml. of acetic acid was sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated in an oil bath at 200-210° for 14 hr. Work up gave 106 mg. (100%) of

a brown oil, λmax 230 nm (ε 3080, based on the estimated molecular weight 414), four spots on t.l.c. (solvent B). The composition of the crude product was estimated by a combination of n.m.r., u.v., and t.l.c. data to be Δ^5-cholesten-4-one 7 (30%, Rf 0.35), 3β-acetoxycholestan-2-one 39 (45%, Rf 0.26), Δ^4-cholesten-3-one 5 (5%, Rf 0.19) and an unknown compound (20%, Rf 0.60). No trace of starting material was detectable on the t.l.c. plate. The crude product was separated on a thick layer (solvent B) into three bands. Band 1 (Rf 0.35) on extraction gave 25 mg. of crude Δ^5-cholesten-4-one 7, which after two recrystallizations from acetone gave 14 mg. of colorless plates, m.p. and m.m.p. 109-112°. Band 2 (Rf 0.26) on extraction yielded 19 mg. of crude 3β-acetoxycholestan-2-one 39, which after two recrystallizations from 95% ethanol yielded 10 mg. of colorless plates, m.p. and m.m.p. 143-145°. Band 3 was mainly Δ^4-cholesten-3-one 5, but no attempt was made to isolate it.

Reaction of 3α-Bromocholestan-2-one 86 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 8)

3α-Bromocholestan-2-one 86 (80 mg., m.p. 151-154°) and 0.55 g. of dried potassium acetate in 3.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a

nitrogen atmosphere for 3.5 hr. Work up gave 75 mg. of slightly brown solid. A combination of t.l.c. (solvent A) and n.m.r. data indicated that the crude product was composed of 3β-acetoxycholestan-2-one 39 (75%, Rf 0.48) an unknown acetoxyketone (25%, Rf 0.40) and trace amounts of unsaturated ketones (Rf 0.40, 0.30). The n.m.r. spectrum of the crude product was consistent with the unknown acetoxyketone (Rf 0.40) being 1β-acetoxycholestan-2-one 87 (δ 0.65 for C-18 methyl, 0.92 or C-19 methyl, 2.12 for CH_3COO-, 4.70 for C-1 H). Two recrystallizations of the crude product from 95% ethanol gave 14 mg. of 3β-acetoxycholestan-2-one 39, m.p. and m.m.p. 143-145°. No attempt was made to isolate the other acetoxyketone.

Reaction of 3α-Bromocholestan-4-one 88 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 9)

3α-Bromocholestan-4-one 88 (140 mg., m.p. 125.5-127.5°) and 1.30 g. of dried potassium acetate in 6.0 ml. of acetic acid was refluxed at 133-135° (solution temperature) under a nitrogen atmosphere for 3.5 hr. Work up gave 129 mg. of brown oil, λmax 230 nm (ε 1190). A combination of u.v., t.l.c. (solvent B) and n.m.r. data indicated that the crude product was Δ^5-cholesten-4-one 7 (15%, Rf 0.35), 3β-acetoxycholestan-4-one 57 (85%, Rf 0.25) and

5α-acetoxycholestan-4-one 58 (trace, Rf 0.20). The crude product was separated on a thick layer (solvent B) into two bands. Band 1 on work up gave 28 mg. of crude Δ^5-cholesten-4-one 7, which after two recrystallizations gave 10 mg. of colorless plates, m.p. and m.m.p. 109-112°. Band 2 on work up gave 64 mg. of crude 3β-acetoxycholestan-4-one 57, which after two recrystallizations from 95% ethanol afforded 42 mg. of colorless plates, m.p. 108-118°, whose n.m.r. spectrum and Rf value were identical with those of the sample prepared from isomerization of 3α-acetoxycholestan-4-one 21.

Reaction of 2β-Bromo-5β-cholestan-3-one 82 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 10)

2β-Bromo-5β-cholestan-3-one 82 (200 mg., m.p. 133-135.5°) and 1.3 g. of dried potassium acetate in 7.0 ml. of acetic acid were refluxed at 133-135° (solution temperature) under a nitrogen atmosphere for 3.5 hr. Work up gave 184 mg. (97%) of solid. Analysis by a combination of n.m.r., and t.l.c. (solvent B) data indicated that the crude product was Δ^1-5β-cholesten-3-one 85 and/or Δ^5-cholesten-4-one 7 (trace, Rf 0.34), 2β-acetoxy-5β-cholestan-3-one 59 (90%, Rf 0.26) and Δ^4-cholesten-3-one 5 (10%, Rf 0.21). One recrystallization from 95% ethanol afforded 120 mg. (64%)

of 2β-acetoxy-5β-cholestan-3-one 59, m.p. 139-148°. Two more recrystallizations from 95% ethanol yielded 91 mg. of colorless needles, m.p. 146-150°, m.m.p. with the authentic sample obtained from 4β-bromo-5β-cholestan-3-one 3 (see next experiment), 146-150°.

Reaction of 4β-Bromo-5β-cholestan-3-one 3 with Potassium Acetate in Acetic Acid (Reaction 11)

4β-Bromo-5β-cholestan-3-one 3 (145 mg., m.p. 110-140°) and 1.0 g. of dried potassium acetate in 5.0 ml. of acetic acid were refluxed at 133-135° (solution temperature) for 3.5 hr. Work up gave 138 mg. (100%) of slightly brown solid. Analysis by a combination of n.m.r. and t.l.c. (solvent A) data indicated that the crude product was Δ^1-5β-cholesten-3-one 85 and/or Δ^5-cholesten-4-one 7 (trace, Rf 0.48), 2β-acetoxy-5β-cholestan-3-one 59 (90%, Rf 0.48), Δ^4-cholesten-3-one 5 (10%, Rf 0.30). The splitting pattern of the low field α-proton revealed the absence of 4β-acetoxy-5β-cholestan-3-one 60. One recrystallization from 95% ethanol gave 101 mg. (73%) of crystalline 2β-acetoxy-5β-cholestan-3-one 59, m.p. 129-140°. A 10 mg. portion was recrystallized twice from 95% ethanol to give 5 mg. of colorless needles, m.p. 148-149.5° (lit.[32] m.p. 149-151°).

I.r. spectrum: νmax 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.69 (3H, s., C-18 methyl), 1.07 (3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.23 ppm (1H, q., J=13.5,6 Hz., C-2 H)

Reaction of 2α-Bromocholestan-3-one 4 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 12)

2α-Bromocholestan-3-one 4 (506 mg., m.p. 166-170°) and 620 mg. of tetramethylammonium acetate in 35 ml. of dried acetone* were stirred at room temperature for 40 hr. T.l.c. (solvent A) revealed that there was ca. 80% reaction. The mixture was then refluxed on steam bath for 2 hr. Work up gave 427 mg. (89%) of crystalline solid, λmax 227 nm (ϵ 867, based on the estimated molecular weight of 438). Analysis by a combination of u.v., n.m.r., and t.l.c. data estimated the crude product to be 3β-acetoxycholestan-2-one 39 (10%, Rf 0.48), Δ^1-cholesten-3-one 6 (8%, Rf 0.44), and 2α-acetoxycholestan-3-one 18 (80%, Rf 0.40). No trace of Δ^4-cholesten-3-one 7 (Rf 0.30) was detected by t.l.c. One

*Tetramethylammonium acetate was prepared by acidifying a 10% solution of tetramethylammonium hydroxide with acetic acid to a litmus paper end point and then evaporating to dryness at 0.5 Torr at 150° on an oil bath. The dry, flaky foam was used without further purification. Acetone was dried by distilling from Drierite.

recrystallization from 95% ethanol gave 245 mg. (51%) of 2α-acetoxycholestan-3-one 18 as colorless plates, m.p. and m.m.p. 120-122°. From the mother liquor a second crop of 70 mg. (15%) of 2α-acetoxycholestan-3-one 18, m.p. 117-122°, was obtained, bringing the total yield up to 66%.

Reaction of 2α-Bromocholestan-3-one 4 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 13)

2α-Bromocholestan-3-one 4 (2.0 g., m.p. 167-169°) and 2.40 g. of tetramethylammonium acetate in 140 ml. of dried acetone was refluxed on steam bath for seven days. Work up gave 1.71 g. (88%) of an oil, which slowly solidified on standing at room temperature. T.l.c. (solvent A) and n.m.r. data revealed that the crude product was 3β-acetoxycholestan-2-one 39 (30%, Rf 0.48), Δ^1-cholesten-3-one 6 (10%, Rf 0.44), and 2α-acetoxycholestan-3-one 18 (60%, Rf 0.40). No trace of Δ^4-cholesten-3-one 5 was detectable by t.l.c.

Reaction of 2β-Bromo-5β-cholestan-3-one 82 with Tetramethylammonium Acetate in Acetone (Reaction 15)

2β-Bromo-5β-cholestan-3-one 82 (200 mg., m.p. 133-135.5°) and 240 mg. of tetramethylammonium acetate in 16 ml. of dried acetone were stirred at room temperature for 12 hr. T.l.c. showed that there was ca. 20% of starting material

left. The reaction was completed by refluxing on a steam bath for 2 hr. Work up gave 184 mg. (97%) of slightly brown oil, λ max 233 nm (ϵ 3160, based on the estimated molecular weight of 416). Analysis by a combination of u.v., n.m.r., and t.l.c. (solvent B) indicated that the crude product was composed of Δ^1-5β-cholesten-3-one 85 (45%, Rf 0.34), 2β-acetoxy-5β-cholestan-3-one 59 (27%, Rf 0.26), and 2α-acetoxy-5β-cholestan-3-one 91 (27%, Rf 0.21). No trace of Δ^4-cholesten-3-one 5 was detectable on the t.l.c. plate. Separation on thick layer (solvent B) yielded three bands. Band 1 (Rf 0.34) on extraction gave 45 mg. of crystalline solid, which after one recrystallization from methanol-acetone gave 36 mg. of Δ^1-5β-cholesten-3-one 85, m.p. 102-105° (lit.[93] m.p. 104°).

U.v. spectrum: λ_{max} 232 nm (ϵ 8,030) [lit.[93] 232 nm (ϵ 7,500)]

I.r. spectrum: ν_{max} 1680 cm^{-1} (C=O)

N.m.r. spectrum: δ 0.70 (3H, s., C-18 methyl), 1.20 (3H, s., C-19 methyl), 5.88 (1H, d., J=10.5 Hz., C-2 H), 6.82 ppm (1H, d., J=10.5 Hz., C-1 H)

Band 2 (Rf 0.26) on extraction yielded 31 mg. of crystalline solid, which after one recrystallization from 95% ethanol gave 26 mg. of 2β-acetoxy-5β-cholestan-3-one 59, m.p. 140-147°.

Band 3 (Rf 0.21) on extraction yielded 44 mg. of

crystalline solid, which after one recrystallization from 95% ethanol gave 27 mg. of 2α-acetoxy-5β-cholestan-3-one 91, m.p. 139-140° (lit. 138-139°,[32] 137-138° [45]).

I.r. spectrum: ν_{max} 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.69 (3H, s., C-18 methyl), 1.17 (3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.35 ppm (1H, d.d., J=8.5 Hz., C-2 H)*

Reaction of 4β-Bromo-5β-cholestan-3-one 3 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 16)

4β-Bromo-5β-cholestan-3-one 3 (334 mg., crude bromination product after purification by thick layer, single t.l.c. spot, i.e. free from 2β,4β-dibromo-5β-cholestan-3-one and 5β-cholestan-3-one 1) and 400 mg. of tetramethylammonium acetate in 25 ml. of dried acetone were stirred magnetically for 20 hr. at room temperature. T.l.c. (solvent A) showed that there was ca. 20% of starting material left. The reaction was completed by refluxing on a steam bath for one hour. Work up gave 282 mg. (95%) of slightly brown oil, λmax 240 nm (ε 8250, based on the

*Peaks at δ 5.35 ppm appears as a quartet at 100 MHz. with J=9.5, 7 Hz.

estimated molecular weight of 414). From t.l.c. (solvent A), u.v., and n.m.r. data the crude product was estimated to be composed of Δ^1-5β-cholesten-3-one 85 (trace, Rf. 0.48), 2β-acetoxy-5β-cholestan-3-one 59 (25%, Rf 0.48), 2α-acetoxy-5β-cholestan-3-one 91 (25%, Rf 0.40), and Δ^4-cholesten-3-one 5 (45%, Rf 0.30). Separation on a thick layer (solvent A) gave three bands. Band 1 (Rf 0.48) on extraction gave 54 mg. of oil, which was shown by n.m.r. to be mainly 2β-acetoxy-5β-cholestan-3-one 59, contaminated by ca. 25% of Δ^1-5β-cholesten-3-one 85. The amount of Δ^1-5β-cholesten-3-one 85 present in the crude product was estimated therefore to be ca. 6%. Band 2 (Rf 0.40) on extraction gave 52 mg. of crystalline solid, which was shown by n.m.r. to be practically pure 2α-acetoxy-5β-cholestan-3-one 91. Band 3 (Rf 0.30) was mainly Δ^4-cholesten-3-one 5.

Reaction of 1:1 Complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19 with Potassium Acetate in Acetic Acid at 220-230°

(Reaction 17)

1:1 Complex of 2α- and 4α-acetoxycholestan-3-one 18 and 19 (200 mg., m.p. 119-140°, contaminated by ca. 5% of 3β-acetoxycholestan-2-one 39, but free from any unsaturated ketone as revealed by n.m.r.) and 1.20 g. of dried potassium acetate in 5.0 ml. of acetic acid were sealed in a thick-walled

Pyrex tube and heated at 220-230° (furnace temperature reading) for 4.5 hr. Work up gave 135 mg. (82%) of brown oil, λmax 241 nm (ε 5700, based on molecular weight 384). T.l.c. (solvent A) showed three spots, Rf 0.70 (unknown, minor), 0.46 (7, major), 0.30 (5, minor). Both t.l.c. and u.v. data indicated that the crude product contained ca. 70% of Δ^5-cholesten-4-one 7 (Rf 0.46) and ca. 10% of Δ^4-cholesten-3-one 5 (Rf 0.30) and some unknown compound (Rf 0.70). Purification on a thick layer (solvent B) gave 54 mg. of a colorless oil which after two recrystallizations from acetone gave 16 mg. of Δ^5-cholesten-4-one 7, m.p. and m.m.p. 109-110°.

Reaction of 2α-Acetoxycholestan-3-one 18 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 18 and 19)

2α-Acetoxycholestan-3-one 18 (270 mg., m.p. 120-123°) and 1.40 g. of dried potassium acetate in 7.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 4 hr. Work up gave 235 mg. (87%) of solid. T.l.c. (solvent A) and n.m.r. revealed that the crude product was a mixture of 3β-acetoxycholestan-2-one 39 (40%, Rf 0.48) and 2α-acetoxycholestan-3-one 18 (60%, Rf 0.40). Retreatment of the crude product with potassium acetate in acetic acid at reflux for 3 days gave 180 mg. (66%) of

solid, λmax 271 nm (ϵ 343, based on molecular weight of 444). T.l.c. (solvent A) and n.m.r. revealed that the conversion into 3β-acetoxycholestan-2-one 39 was ca. 80%. Both t.l.c. and u.v. data showed the complete absence of α,β-unsaturated ketone. One recrystallization from 95% ethanol gave 84 mg. of 3β-acetoxycholestan-2-one 39, m.p. 115-142°, single t.l.c. spot. Three more recrystallizations gave 40 mg. of colorless plates, m.p. and m.m.p. 144-145°.

Reaction of 2α-Acetoxycholestan-3-one 18 with Potassium Acetate in Propionic Acid

2α-Acetoxycholestan-3-one 18 (100 mg., m.p. 122-124°) and 0.60 g. of dried potassium acetate in 3.0 ml. of propionic acid was heated under a nitrogen atmosphere at 133-135° (solution temperature) for 2 days. Work up gave 100 mg. of brown oil. The n.m.r. spectrum of the crude product showed the complete absence of propionoxyl group. T.l.c. (solvent A) revealed two spots (Rf 0.48 and 0.40) in a ratio of 7:3. Separation on a thick layer (solvent A) and extraction of the upper band afforded 41 mg. of crystalline material whose n.m.r. spectrum was identical with that of authentic 3β-acetoxycholestan-2-one 39. Two recrystallizations from 95% ethanol yielded 34 mg. of colorless plates, m.p. and m.m.p. 142-145°.

Mass spectrum: m/e 444 (M^+), no ion in the m/e 458 region

Reaction of 2α-Acetoxycholestan-3-one 18 with Potassium Acetate in Acetic Acid at 190-200° (Reaction 20)

2α-Acetoxycholestan-3-one 18 (140 mg., m.p. 120-123°) and 1.10 g. of dried potassium acetate in 6.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 190-200° (furnace temperature reading) for 2 hr. Work up gave 135 mg. of brown oil, λmax 241 nm (ϵ 1300, based on the estimated molecular weight of 432). A combination of u.v., n.m.r., and t.l.c. (solvent A) indicated that the crude product was composed of 3β-acetoxycholestan-2-one 39 (60%, Rf 0.48), 2α- and 4α-acetoxycholestan-3-one 18 and/or 19 (20%, Rf 0.40), Δ^5-cholesten-4-one 7 (20%, Rf 0.40), Δ^4-cholesten-3-one 5 (trace, Rf 3.0). Recrystallization of the crude product from 95% ethanol gave 57 mg. of crude 3β-acetoxycholestan-3-one 39, m.p., 111-140°, single t.l.c. spot. Two more recrystallizations gave 20 mg. of colorless plates, m.p. and m.m.p. 141-145°.

The mother liquor of the first recrystallization was separated on a thick layer (solvent A). Extraction of the band (Rf 0.40) just below the major unsaturated ketone band gave 17 mg. of crystalline material, single t.l.c. spot. One recrystallization from 95% ethanol afforded 8 mg. of

2α-acetoxycholestan-3-one 18, m.p. and m.m.p. 120-123°.

Reaction of 2α-Acetoxycholestan-3-one 18 with Potassium Acetate in Acetic Acid at 220-230° (Reaction 21)

2α-Acetoxycholestan-3-one 18 (200 mg., m.p. 120-123°) and 1.20 g. of dried potassium acetate in 7.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220-230° (furnace temperature reading). Work up gave 148 mg. (90%) of brown oil, λ max 240 nm (ϵ 6210, based on molecular weight of 384). A combination of n.m.r., u.v., and t.l.c. (solvent A) data indicated that the crude product contained Δ^5-cholesten-4-one 7 (80%, Rf 0.48) and Δ^4-cholesten-3-one 5 (5%, Rf 0.30). No trace of starting material was detectable from t.l.c. or n.m.r. data. Purification of the crude product on a thick layer gave 50 mg. of crude Δ^5-cholesten-4-one 7, which after three recrystallizations from acetone afforded 12 mg. of colorless prisms, m.p. and m.m.p. 110-112°.

Reaction of 3β-Acetoxycholestan-2-one 39 with Potassium Acetate in Acetic Acid at 200-210° (Reaction 22)

3β-Acetoxycholestan-2-one 39 (100 mg., m.p. 140-145°) and 0.60 g. of dried potassium acetate in 4.0 ml. of acetic

acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated in an oil bath at 200-210° for 16 hr. Work up gave 90 mg. (96%) of brown oil, λmax 238 nm (ε 3530, based on the estimated molecular weight of 414). A combination of t.l.c. (solvent A), u.v., and n.m.r. data indicated that the crude product was composed of 3β-acetoxycholestan-2-one 39 (40%, Rf 0.48), Δ^5-cholesten-4-one 7 (45%, Rf 0.46), 2α- and 4α-acetoxy-cholestan-3-one 18 and/or 19 (10%, Rf 0.40), Δ^4-cholesten-3-one 5 (5%, Rf 0.30).

Reaction of 4α-Acetoxycholestan-3-one 19 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 23)

4α-Acetoxycholestan-3-one 19 (200 mg., m.p. 136-143°) and 1.40 g. of potassium acetate in 7.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 6 hr. Work up gave 190 mg. (95%) of brown oil. Both t.l.c. and n.m.r. data showed the crude product was mainly the starting material, no trace of unsaturated ketone was detected.

Reaction of 4α-Acetoxycholestan-3-one 19 with Potassium Acetate in Acetic Acid at 170-180° (Reaction 24)

4α-Acetoxycholestan-3-one 19 (184 mg., m.p. 136-143°)

and 1.40 g. of dried potassium acetate in 7.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 170-180° (furnace temperature reading) for 4 hr. Work up gave 174 mg. (100%) of brown oil, λmax 240 nm (ϵ 5,700 based on the estimated molecular weight of 396). A combination of u.v., n.m.r., and t.l.c. (solvent A) data showed that the crude product was composed of Δ^5-cholesten-4-one 7 (80%, Rf 0.40), acetoxyketone mixture (20%, Rf 0.40) and Δ^4-cholesten-3-one 5 (trace, Rf 0.30). The crude product was separated on a thick layer (solvent B). Band 1 (Rf 0.35) on work up afforded 74 mg. of crude Δ^5-cholesten-4-one 7, which after three recrystallizations from acetone gave 55 mg. of colorless plates, m.p. and m.m.p. 110-112°. Band 2 (Rf 0.30) on extraction afforded 49 mg. of a mixture of Δ^5-cholesten-4-one 7 and acetoxyketones. Band 3 (Rf 0.26) on extraction afforded 16 mg. of acetoxyketones, which was shown by the n.m.r. spectrum to be a mixture of 2α- and/or 4α-acetoxycholestan-3-one 18 and/or 19 and 3β-acetoxycholestan-2-one 39 and/or 3β-acetoxycholestan-4-one 57.

Reaction of 4α-Acetoxycholestan-3-one 19 with Potassium Acetate in Acetic Acid at 200-210° (Reaction 25)

4α-Acetoxycholestan-3-one 19 (100 mg., m.p. 136-143°) and 0.60 g. of dried potassium acetate in 4.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 200-210° in an oil bath for 16 hr. Work up gave 90 mg. (100%) of brown oil. N.m.r. and t.l.c. (solvent A) revealed that Δ^5-cholesten-4-one 7 was the main product and the amount of acetoxyketones was less than 5%. The t.l.c. data revealed that Δ^4-cholesten-3-one 5 was present in very small amount, if at all.

Reaction of 3α-Acetoxycholestan-4-one 21 with Potassium Acetate in Acetic Acid at 133-135°(Reaction 26)

3α-Acetoxycholestan-4-one 21 (140 mg., m.p. 93-94.5°) and 0.90 g. of dried potassium acetate in 4.5 ml. of acetic acid was refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 3 hr. Work up gave 130 mg. (93%) of crude oil. T.l.c. (solvent A) and n.m.r. revealed that the crude product was mainly (>90%) 3β-acetoxycholestan-4-one 57 (Rf 0.48), ca. 5% of Δ^5-cholesten-4-one 7 (Rf 0.44) and trace amount of 5α-acetoxycholestan-4-one 58

(Rf 0.40). Two recrystallizations from 95% ethanol gave 70 mg. of 3β-acetoxycholestan-4-one 57 m.p. 107-118.5°.

Reaction of 3α-Acetoxycholestan-4-one 21 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 27)

3α-Acetoxycholestan-4-one 21 (100 mg., m.p. 93-94.5°) and 0.70 g. of dried potassium acetate in 4.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 12 hr. Work up gave 97 mg. (100%) of solid, λmax 241 nm (ϵ 1,270, based on the estimated molecular weight of 432). A combination of u.v., n.m.r., and t.l.c. (solvent B) data indicated that the crude product was composed of 3β-acetoxycholestan-4-one 57 (80%, Rf 0.35), Δ^5-cholesten-4-one 7 (20%, Rf 0.26) and 5α-acetoxycholestan-4-one 58 (trace, Rf 0.21). The crude product was separated on a thick layer (solvent B) into two bands. Band 1 (Rf 0.35) on extraction yielded 15 mg. of Δ^5-cholesten-4-one 7 which after two recrystallizations from acetone gave 8 mg. of colorless plates, m.p. and m.m.p. 109-112°. Band 2 (Rf 0.26) on extraction yielded 40 mg. of 3β-acetoxycholestan-4-one 57, which after two recrystallizations from 95% ethanol gave 30 mg. of colorless plates, m.p. 102-119°.

Reaction of 3α-Acetoxycholestan-4-one 21 with Potassium Acetate in Propionic Acid

3α-Acetoxycholestan-4-one 21 (100 mg., m.p. 93-94.5°) and 0.70 g. of dried potassium acetate in 5.0 ml. of propionic acid were heated at 130° (solution temperature) under a nitrogen atmosphere for 5 hr. Work up gave 95 mg. (92%) of oil, λmax 241 nm (ϵ 440, based on molecular weight of 458). The n.m.r. spectrum indicated the presence of propionoxyl group (δ 1.19, t., J=7 Hz., 2.35, q., J=7 Hz.). From the u.v. and n.m.r. data, the crude product was estimated to be composed of 3β-propionoxycholestan-4-one 108 (90%, Rf 0.49), Δ^5-cholesten-4-one 7, (7%, Rf 0.44) and an unknown acyloxyketone (trace, Rf 0.40). Purification of the crude product on a thick layer (solvent A) gave 43 mg. of crystalline solid, which after three recrystallizations from 95% ethanol gave 3 mg. of 3β-propionoxycholestan-4-one 108, m.p. 109-111°.

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 0.75 (3H, s., C-19 methyl), 1.19 (t., overlapping with methylene envelope, J=7 Hz., $C\underline{H}_3CH_2COO$-), 2.35 (q., partly overlapping with methylene envelope, J=7 Hz., $CH_3C\underline{H}_2COO$-), 5.20 ppm (1H, m., very similar to those of 3β-acetoxycholestan-4-one 57, C-3 H).

Mass spectrum: m/e 458 (M^+)

Reaction of 5α-Acetoxycholestan-4-one 58 with Potassium Acetate in Acetic Acid at 133-135°. (Reaction 28)

5α-Acetoxycholestan-4-one 58 (100 mg., m.p. 147-148.5°) and 0.70 g. of dried potassium acetate in 4.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 12 hr. Work up gave 96 mg. (99%) of brown solid, λmax 240 nm (ϵ 1,360 based on the estimated molecular weight of 432). A combination of t.l.c. (solvent B), n.m.r. and u.v. data indicated that the crude product was composed of 3β-acetoxycholestan-4-one 57 (80%, Rf 0.35), Δ^5-cholesten-4-one 7 (20%, Rf 0.26) and 5α-acetoxycholestan-4-one 58 (trace, Rf 0.21). The crude product was separated on a thick layer (solvent B) into two bands. Band 1 on (Rf 0.35) extraction yielded 12 mg. of Δ^5-cholesten-4-one 7, which after two recrystallizations from acetone gave 5 mg. of colorless plates, m.p. and m.m.p. 109-112°. Band 2 (Rf 0.26) on extraction gave 37 mg. of 3β-acetoxycholestan-4-one 57, which after one recyrstallization from 95% ethanol gave 30 mg. of colorless plates, m.p. 106.5-117.5°.

Pyrolysis of 5α-Acetoxycholestan-4-one 58

5α-Acetoxycholestan-4-one 58 (100 mg., m.p. 147-148.5°) was heated under a nitrogen atmosphere on an oil bath at 200-210° for 2 hr. T.l.c. (solvent A), i.r. and n.m.r.

showed the product was essentially pure starting material. When the pyrolysis was done under 0.1 Torr at 200-210°, most of the sample sublimed up away from the heat source in 0.5 hr.

Reaction of 4β-Acetoxy-5β-cholestan-3-one 60 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 29)

4β-Acetoxy-5β-cholestan-3-one 60 (120 mg., m.p. 104-107°) and 0.86 g. of potassium acetate in 4.8 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 19 hr. Work up gave 114 mg. of slightly brown oil. Based on t.l.c. (solvent B) and n.m.r. data, it was estimated that the crude product was composed of Δ^5-cholesten-4-one 7 (15%, Rf 0.35), 3β-acetoxycholestan-4-one 57 (70%, Rf 0.26), 4β-acetoxy-5β-cholestan-3-one 60 (10%, Rf 0.26) and 5α-acetoxycholestan-4-one 58 (trace, Rf 0.21). Separation on a thick layer (solvent B) gave rise to two bands. Band 1 (Rf 0.35) on extraction yielded 19 mg. of Δ^5-cholesten-4-one 7, which after two recrystallizations from acetone afforded 5 mg. of colorless plates, m.p. 106-111°. Band 2 (Rf 0.26) on work up gave 80 mg. of crude 3β-acetoxycholestan-4-one 57, which after three recrystallizations from 95% ethanol afforded 47 mg. of colorless plates, m.p. 108-118°.

Reaction of 2β-Acetoxy-5β-cholestan-3-one 59 with Potassium Acetate in Acetic Acid at 133-135° (Reaction 30)

2β-Acetoxy-5β-cholestan-3-one 59 (90 mg., m.p. 146-150°) and 0.6 g. of dried potassium acetate in 3.5 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 48 hr. Work up gave 90 mg. (100%) of crude oil. T.l.c. (solvent B) showed two spots, Rf 0.26, 0.21, in almost equal amounts. The n.m.r. spectrum indicated that one of the components was starting material. No unsaturated ketone was detected on the t.l.c. plate. Separation on a thick layer (solvent B) gave two bands. Band 1 (Rf 0.26) on extraction afforded 36 mg. of solid, whose n.m.r. spectrum was identical with that of starting material. Band 2 (Rf 0.21) on extraction gave 30 mg. of 3α-acetoxy-5β-cholestan-2-one 97, which after two recrystallizations from 95% ethanol gave 17 mg. of colorless flakes, m.p. 158-170° (lit.[94] m.p. 168-169°).

3α-Acetoxy-5β-cholestan-2-one 97 was also independently prepared by the basic hydrolysis and reacetylation of 2β-acetoxy-5β-cholestan-3-one 59. The two samples had identical n.m.r. spectra.

I.r. spectrum: νmax 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 0.65 (3H, s., C-18 methyl), 1.09 (3H, s., C-19 methyl), 2.15 (3H, s., CH_3COO-), 5.25 ppm (1H, m., C-3 H)*

O.R.D.: $[\alpha]_{308}$-690 (trough), $[\alpha]_{270}$+684 (peak) (c, 0.438)

Reaction of 2β-Acetoxy-5β-cholestan-3-one 59 with Potassium Acetate in Acetic Acid at 220-230° (Reaction 31)

2β-Acetoxy-5β-cholestan-3-one 59 (91 mg., m.p. 129-140°, once recrystallized crude product of the acetolysis of 4β-bromo-5β-cholestan-3-one 3 in acetic acid) and 0.63 g. of dried potassium acetate in 3.0 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220-230° (furnace temperature reading) for 4 hr. Work up gave 82 mg. (95%) of brown oil. The t.l.c. (solvent A) and n.m.r. data revealed that the crude product was Δ^5-cholesten-4-one 7 (80%, Rf 0.44) and Δ^4-cholesten-3-one 5 (10%, Rf 0.30). Purification on a thick layer (solvent B) gave 30 mg. of Δ^5-cholesten-4-one 7, which after three recrystallizations from acetone gave 10 mg. of colorless plates, m.p. 110-112°.

*The low field proton (δ 5.25) was resolved into broad quartet (J=7,11 Hz.) at 100 MHz.

Reaction of 2α-Acetoxycholestan-3-one 18 with Tetramethylammonium Acetate in Acetone at Reflux (Reactions 32 and 33)

2α-Acetoxycholestan-3-one 18 (500 mg., m.p. 122-124°) and 570 mg. of tetramethylammonium acetate in 35 ml. of dried acetone was refluxed on a steam bath for one day. The t.l.c. (solvent B) of the reaction mixture showed two spots in a ratio of ca. 3:7, corresponding in Rf values to 3β-acetoxycholestan-2-one 39 (Rf 0.48) and 2α-acetoxycholestan-3-one 18 (Rf 0.40). The reaction mixture was refluxed for another three days. Work up gave 456 mg. (91%) of amorphous solid. T.l.c. and n.m.r. data showed that the crude product was composed of 3β-acetoxycholestan-2-one 39 (60%, Rf 0.48) and 2α-acetoxycholestan-3-one 18 (40%, Rf 0.40). No trace of unsaturated ketone was detectable on the t.l.c. plate. One recrystallization from 95% ethanol gave 204 mg. (40%) of 3β-acetoxycholestan-2-one 39, m.p. 141-144.5°. One more recrystallization raised the m.p. to 144-145° (lit.[22] m.p. 145.5-146.1°). The n.m.r. spectrum showed that the mother liquor was mainly 2α-acetoxycholestan-3-one 18, no trace of 4α-acetoxycholestan-3-one 19 was detectable.

Reaction of 4α-Acetoxycholestan-3-one 19 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 34)

4α-Acetoxycholestan-3-one 19 (198 mg., m.p. 136-138.5°) and 242 mg. of tetramethylammonium acetate in 16 ml. of dried acetone were refluxed on a steam bath for 12 hr. Work up gave 197 mg. (99%) of solid which was shown by t.l.c. (solvent A) and n.m.r. to be mainly the starting material. No trace of 3β-acetoxycholestan-4-one 57 or any unsaturated ketone was detectable on the t.l.c. plate.

Reaction of 4β-Acetoxy-5β-cholestan-3-one 60 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 35)

4β-Acetoxy-5β-cholestan-3-one 60 (49 mg., m.p. 103.5-108.5°) and 50 mg. of tetramethylammonium acetate in 4.0 ml. of dried acetone were refluxed on a steam bath for 2 days. Work up gave 48 mg. (97%) of brown oil. N.m.r. and t.l.c. (solvent A) showed that it was mainly the starting material. No trace of 3β-acetoxycholestan-4-one 57 and any unsaturated ketone was detectable on the t.l.c. plate.

Reaction of 2β-Acetoxy-5β-cholestan-3-one 59 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 36)

2β-Acetoxy-5β-cholestan-3-one 59 (90 mg., m.p. 146-150.5°) and 120 mg. of tetramethylammonium acetate in

8 ml. of dried acetone were refluxed on a steam bath for 4 hr. Work up gave 90 mg. (100%) of crystalline solid. Both n.m.r. and t.l.c. (solvent B) data indicated that the crude product was mainly the starting material. T.l.c. data revealed ca. 5% conversion into a spot corresponding in Rf value (0.21) to 2α-acetoxy-5β-cholestan-3-one 91 or 3α-acetoxy-5β-cholestan-3-one 97. No trace of unsaturated ketone was detected on the t.l.c. plate.

Reaction of 2α-Acetoxy-5β-cholestan-3-one 91 with Tetramethylammonium Acetate in Acetone at Reflux (Reaction 37)

2α-Acetoxy-5β-cholestan-3-one 91 (3 mg., m.p. 135.5-137.5°) was treated with 0.15 ml. of a solution of tetramethylammonium acetate in acetone* at reflux. The course of the reaction was followed by t.l.c. (solvent B), at five-minute intervals. After 0.5 hr., the conversion of 2α-acetoxy-5β-cholestan-3-one 91 (Rf 0.21) into 2β-acetoxy-5β-cholestan-3-one 59 (Rf 0.26) was ca. 30%. No trace of unsaturated ketone was detected on the t.l.c. plate.

Reaction of 2α-Acetoxycholestan-3-one 18 with γ-Collidine

2α-Acetoxycholestan-3-one 18 (95 mg., m.p. 122-124°)

*Prepared from 0.60 g. of tetramethylammonium acetate in 40 ml. of acetone and 1 ml. of methanol.

and 3.0 ml. of γ-collidine were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 210-220°C in an oil bath for 12 hr. After being cooled to room temperature, the tube was opened and the reaction mixture was concentrated at room temperature under reduced pressure to remove most of the γ-collidine. The residue was acidified with 10% hydrochloric acid to Congo Red, and then extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water and then dried. Removal of ether left 85 mg. (90%) of brown oil. T.l.c. (solvent A) and n.m.r. data indicated that the crude product was a mixture of 3β-acetoxycholestan-2-one 39 (50%, Rf 0.48) and 2α-acetoxycholestan-3-one 18 (50%, Rf 0.40). No unsaturated ketone was detected by t.l.c. Separation of the crude product on a thick layer plate (solvent A) gave two bands. Band 1 (Rf 0.48) on extraction gave 39 mg. of 3β-acetoxycholestan-2-one 39, which after two recrystallizations from 95% ethanol gave 19 mg. of colorless plates, m.p. and m.m.p. 143-145°. Band 2 (Rf 0.40) on extraction gave 13 mg. of 2α-acetoxycholestan-3-one 18, which after two recrystallizations from 95% ethanol gave 11 mg. of colorless plates, m.p. and m.m.p. 121-123°.

Reaction of 4α-Acetoxycholestan-3-one 19 with γ-Collidine

4α-Acetoxycholestan-3-one 19 (89 mg., m.p. 135.5-142.5°) and 3.0 ml. of γ-collidine were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 215° in an oil bath for 21 hr. After being cooled at room temperature, the reaction mixture was concentrated at room temperature under reduced pressure to remove most of the γ-collidine. The residue was acidified with 10% hydrochloric acid and extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water and then dried. Removal of ether left 90 mg. of semicrystalline solid, which was shown to be mainly the starting material by the n.m.r. spectrum. The crude reaction product was retreated with 3.0 ml. of γ-collidine at 250° for 20 hr. Work up as described above gave 50 mg. (58%) of brown oil. Analysis by a combination of t.l.c. (solvent A) and n.m.r. data indicate that it was a mixture of Δ^5-cholesten-4-one 7 (80%, Rf 0.44) and Δ^4-cholesten-3-one 5 (20%, Rf 0.30).

Reaction of 5α-Acetoxycholestan-4-one 58 with γ-Collidine

5α-Acetoxycholestan-4-one 58 (90 mg., m.p. 147-148.5°) in 3.0 ml. of γ-collidine was sealed under a nitrogen atmosphere in a Pyrex thick-walled tube and heated at 215° in an oil bath for 18 hr. After being cooled to room

temperature, the reaction mixture was concentrated at room temperature under reduced pressure to remove most of the γ-collidine. The residue was acidified with 10% hydrochloric acid and then extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water, and then dried. Removal of ether gave 85 mg. of brown oil, λmax 241 nm (ε 1,160, based on the estimated molecular weight of 412). A combination of t.l.c. (solvent A), n.m.r., and u.v. data indicated that the crude product was a mixture of Δ^5-cholesten-4-one 7 (18%, Rf 0.44), an acetoxyketone (10%, Rf 0.48), and starting material (70%, Rf 0.40). Separation of the crude product on a thick layer (solvent A) gave 30 mg. of an oil, λmax 241 nm (ε 3,020). Based on n.m.r. and u.v. data, it was estimated to be a mixture of 46% of Δ^5-cholesten-4-one 7 and 54% of what was probably 3β-acetoxycholestan-4-one 57. Band 2 (Rf 0.40) on extraction yielded 30 mg. of an oil, which was shown by n.m.r. to be essentially pure 5α-acetoxycholestan-4-one 58. Two recrystallizations from 95% ethanol gave 22 mg. of colorless plates, m.p. and m.m.p. 146.5-148°.

Dehydrobromination of 3α-Bromocholestan-4-one 88 with γ-Collidine

3α-Bromocholestan-4-one 88 (47 mg., m.p. 125.5-127.5°) and 0.8 ml. of γ-collidine were heated at 155° in an oil bath for 3.5 hr. After being cooled to room temperature, the reaction mixture was concentrated at room temperature under reduced pressure to remove most of the γ-collidine. The residue was acidified with 10% hydrochloric acid and then extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water and then dried. Evaporation of ether left 45 mg. of crude oil. N.m.r. and t.l.c. data showed that it was mainly starting material. The crude oil was retreated with 0.8 ml. of γ-collidine at 175° (oil bath temperature) for 18 hr. Work up as described above gave 22 mg. (66%)* of brown oil, λ max 225 nm (ϵ 5,600). T.l.c. (solvent A) and n.m.r. data showed it was a mixture of 3α-bromocholestan-4-one 88 (30%, Rf 0.66) and Δ^2-cholesten-4-one 11 (70%, Rf 0.46). The n.m.r. spectra revealed no trace of the olefinic proton or the C-19 methyl group of Δ^5-cholesten-4-one 7. Purification of the crude product on a thick layer (solvent A) followed by two recrystallizations from acetone yielded 2 mg. of

*The low yield was due partly to loss in manipulation.

Δ^2-cholesten-4-one 11, m.p. 89-91° (lit.[86] m.p. 73-93°).

U.v. spectrum: λmax 226 nm (ϵ 7,830) [lit.[86] 239 nm (ϵ 10,400)]

N.m.r. spectrum: δ 0.67 (3H, s., C-18 methyl), 0.88 (3H, s., C-19 methyl), 6.00 (1H, d., J=10 Hz., C-3 H), 6.75 ppm (1H, m., C-2 H)

2-Acetoxycyclopentanone 104(5)

Cavill's procedure[95] for acetoxylation of ketones was followed.

Cyclopentanone 115(5) (84 g., 1 mol.) and 443 g. (0.8 mol.) of 80% lead tetra-acetate in 600 ml. of benzene (distilled from sodium) were heated at 80° until negative starch-iodide test was obtained (overnight). The reaction mixture was a dark brown solution at the end of the reaction. Work up by washing the reaction mixture with water and removal of benzene at room temperature under reduced pressure gave 42 g. of dark brown oil. Distillation through the 8" spinning band column at 15 Torr yielded 18.8 g. of cyclopentanone 115(5), b.p. 37-38°/15 Torr, and 6.3 g. (6%) of 2-acetoxycyclopentanone 104(5), b.p. 115-117°/15 Torr, (lit. b.p. 85°/0.07 Torr[96], 104°/10 Torr[97]).

I.r. spectrum: ν max 1760 (ester C=O) and 1745 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 2.12 (3H, s., CH_3COO-), 5.10 ppm (1H, triplets of multiplets, C-2 H)

Mass spectrum: m/e 142 (weak, M^+), 99 ($M-CH_3CO^+$)

2-Acetoxycyclohexanone 104(6)

(a) By acetylation of 2-hydroxycyclohexanone. 2-Hydroxycyclohexanone (Aldrich) was acetylated with acetic anhydride according to the procedure of Szmuszkovicz and Born.[98] 2-Acetoxycyclohexanone 104(6), m.p. 33-37°, was obtained in 78% yield (lit.[98] m.p. 35-36°).

I.r. spectrum: νmax 1750 (ester C=O) and 1730 cm^{-1} (ester C=O)

N.m.r. spectrum: δ 2.13 (3H, s., CH_3COO-), 5.17 ppm (1H, b.q., J=7,11 Hz., C-2 H)

Mass spectrum: m/e 156 (M^+), 113 ($M-CH_3CO^+$)

(b) By acetoxylation of cyclohexanone 115(6) with lead tetra-acetate.[95] Cyclohexanone (5 g., 0.051 mol.) was acetoxylated with 22.6 g. (0.042 mol.) of 80% lead tetra-acetate in 40 ml. of benzene according to the procedure of Cavill and coworkers.[95] The crude product was fractionally distilled through the 8" spinning band column under reduced pressure. 2-Acetoxycyclohexanone 104(6), b.p. 48-50°/0.2 Torr, was obtained in 26% yield. One recrystallization from petroleum ether (b.p. 30-60°) gave

colorless prisms, m.p. 33-37° in 22% overall yield.

(c) By epoxidation of cyclohexanone enol acetate. The procedure of Rogic[99] was followed with slight modifications. Cyclohexanone 115(6) (11.0 g., 0.11 mol.), 32.0 g. of freshly distilled isopropenyl acetate,* and 100 mg. of p-toluenesulfonic acid was refluxed at 130° (oil bath temperature) for 5.5 hr. G.l.p.c. of the reaction mixture showed the complete absence of starting material. Excess isopropenyl acetate was distilled through the 18" spinning band column under ca. 30 Torr. The residue was further fractionally distilled under 7 Torr to give 14.0 g. (90%) of cyclohexanone enol acetate, b.p. 56-57°/7 Torr, single peak on g.l.p.c. analysis (lit. b.p. 180-181°,[100] 74-76°/16 Torr[39]).

N.m.r. spectrum: δ 2.05 (3H, s., CH_3COO-), 5.32 ppm (1H, m., C-2 H)

Cyclohexanone enol acetate (7.0 g., 0.05 mol.) was epoxidized with 0.055 mol. of m-chloroperbenzoic acid in 40 ml. of chloroform at -10° according to the procedure of Williamson and coworkers.[39] Crude 1-acetoxy-1,2-oxidocyclohexane, obtained in 80% yield, was heated on the steam bath

*It was found that the rate and the yield of enol acetate formation depended on the purity of isopropenyl acetate used. In other runs where isopropenyl acetate directly from bottle (Eastman) was used, it took one to two days for the reaction to go to completion at 150°, and cyclohexanone enol acetate was isolated in only 50-60% yield.

for 1 hr. to rearrange it into acetoxyketone. Distillation of the crude product through the 18" spinning band column yielded 5.4 g. of 2-acetoxycyclohexanone 104(6), b.p. 102-104°/7 Torr, which after one recrystallization from petroleum ether (b.p. 30-60°) gave a first crop of 3.2 g. of colorless prisms, m.p. 34-36°, and a second crop of 0.9 g., m.p. 32-34°. The total overall yield from cyclohexanone enol acetate was 61%.

2-Acetoxycycloheptanone 104(7)

(a) By acetoxylation of cycloheptanone 115(7). Cavill's procedure for acetoxylation of ketones was followed.[95] Cycloheptanone 115(7) (11.2 g., 0.1 mol.) and 443 g. (0.085 mol.) of 85% lead tetra-acetate in 30 ml. of benzene (distilled from sodium) were heated at 80°C on steam bath until negative starch-iodide test was obtained (overnight). The mixture was washed with water, and then dried. Removal of benzene at room temperature under vacuum gave 13.4 g. of oil. Distillation through the 8" spinning band column gave 2.8 g. of cycloheptanone, b.p. 36-38°/2 Torr, and 5.4 g. (32%) of 2-acetoxycycloheptanone 104(7), b.p. 78-80°/0.9 Torr (lit.[103] b.p. 120-122°/10 Torr).
I.r. spectrum: ν max 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: 2.02 (3H, s., CH_3COO-), 5.40 ppm (1H, unresolved quartet due to further coupling, C-2 H)

Mass spectrum: m/e 170 (weak, M^+), 127 ($M-CH_3CO^+$)

(b) By epoxidation of cycloheptanone enol acetate. Cycloheptanone enol acetate was prepared in a manner similar to that of cyclohexanone enol acetate. Cycloheptanone 115(7) (33.6 g., 0.3 mol.), 90 ml. of isopropenyl acetate and 50 mg. of p-toluenesulfonic acid was refluxed at 180° (oil bath temperature) for one day. Excess isopropenyl acetate was distilled through the 18" spinning band column under ca. 30 Torr. The residue was further distilled through spinning band column under 15 Torr to give 39.1 g. (84.7%) of cycloheptanone enol acetate, b.p. 65-67°/15 Torr, single peak on g.l.p.c. analysis.

I.r. spectrum: max 1750 (ester C=O) and 1675 cm^{-1} (C=C)

Cycloheptanone enol acetate (39.0 g., 0.25 mol.) was epoxidized with 0.27 mol. of m-chloroperbenzoic acid in 15.0 ml. of chloroform at -10° as in the case of cyclohexanone enol acetate. The crude 1-acetoxy-1,2-oxido-cycloheptane was warmed on steam bath for one hour to rearrange it into acetoxyketone. Distillation through the 18" spinning band column under reduced pressure afforded 30.0 g. (71%) of 2-acetoxycycloheptanone 104(7), b.p. 84-85°/1.5 Torr, single peak on g.l.p.c. analysis.

2-Acetoxycyclooctanone 104(8)

Cavill's procedure[95] for acetoxylation of ketones was followed.

Cyclooctanone 115(8) (6.1 g., 0.05 mol.) and 25.9 g. (0.04 mol.) of 80% lead tetra-acetate in 40 ml. of benzene (distilled from sodium) were heated at 80° until negative starch-iodide test was obtained (4 hr.). The mixture was washed with water, and then dried. Removal of benzene gave 7.7 g. of oil. Distillation through the 8" spinning band column under reduced pressure gave three fractions: b.p. 30-40°/0.6 Torr, 1.3 g., mainly starting material; b.p. 80-90°/0.6 Torr, 4.3 g. (48%), mainly 2-acetoxycyclooctanone 104(8), containing ca. 10% of starting material; b.p. 100-105°/0.018 Torr, 0.52 g., mainly 2,8-diacetoxycyclooctanone. The 2-acetoxycyclooctanone fraction was further fractionally distilled to give 1.8 g. (20%) of material, containing less than 3% of cyclooctanone, b.p. 79-80°/0.6 Torr (lit.[104] b.p. 86-87.5°/1.1 Torr).

I.r. spectrum: νmax 1745 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 2.12 (3H, s., CH_3COO-), 5.23 ppm (1H, b.q., J=4,7.5 Hz., C-2 H)

Mass spectrum: m/e 184 (weak, M^+), 141 ($M-CH_3CO^+$)

2-Acetoxycyclononanone 104(9)

2-Hydroxycyclononanone was synthesized from dimethyl azeleate by acyloin condensation following the procedure of Organic Syntheses.[105] Material of b.p. 89°/1.5 Torr was obtained in 20% yield.* No attempt was made to crystallize the compound (lit.[106] m.p. 43°).

I.r. spectrum: νmax 3450 (O-H) and 1715 cm^{-1} (C=O)

N.m.r. spectrum: δ 3.84 (1H, b.s., O-H), 4.26 ppm (1H, q., J=4.5,5 Hz., C-2 H)

2-Hydroxycyclononanone (1.7 g.) was refluxed with 12 ml. of acetic anhydride under a nitrogen atmosphere for 1 hr. Excess acetic anhydride was removed by evaporating on rotary evaporator. The residue was distilled at 0.6 Torr to give 1.10 g. of 2-acetoxycyclononanone 104(3), b.p. 93-95°/0.6 Torr, single peak on g.l.p.c. analysis.

I.r. spectrum: νmax 1750 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 2.12 (3H, s., CH_3COO-), 5.11 ppm (1H, q., J=4,7 Hz., C-2 H)

Analysis: Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15

Found : C, 66.03; H, 9.20

Mass spectrum: m/e 155 ($M-CH_3CO^+$)

*The poor yield was due partly to loss in manipulation.

2-Acetoxycyclododecanone 104(12)

Cavill's procedure for acetoxylation of ketones was followed.[95]

Cyclododecanone 115(12) (5.0 g., 0.028 mol.) and 14.2 g. (0.025 mol.) of 80% lead tetra-acetate in 30 ml. of benzene (distilled from sodium) were heated at 80° until negative starch-iodide test was obtained (overnight). The mixture was washed with water, and then dried. Removal of benzene gave 6.1 g. of partially crystalline material. The crude product was distilled at 0.3 Torr to remove cyclododecanone. The residue was recrystallized from petroleum ether to give 1.60 (26%) of 2-acetoxycyclododecanone 104(12) as colorless prism, m.p. 81-82°. A small amount of sample was recrystallized once more from petroleum ether and sublimed at 15 Torr to give material for analysis, m.p. 82.3-83.0°.

I.r. spectrum: ν max 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 2.13 (3H, s., CH_3COO-), 5.17 ppm (1H, q., J=4,5.5 Hz., C-2 H)

Analysis: Calcd. for $C_{14}H_{26}O_3$: C, 69.96; H, 10.07

Found : C, 70.42; H, 10.21

Mass spectrum: m/e 240 (weak, M^+), 197 ($M-CH_3CO^+$)

2-Benzoyloxycyclohexanone 125

2-Hydroxycyclohexanone (3.8 g.) was treated with 10 ml. of benzoyl chloride and 10 ml. of pyridine at room temperature for 2 hr., then at 80° for 10 min. The reaction mixture was diluted with water and extracted with ether. The combined ether layers were washed with 10% hydrochloric acid, water, 5% aqueous sodium bicarbonate solution and dried. Removal of ether and one recrystallization from ether gave 3.2 g. (44%) of 2-benzoyloxycyclohexanone 125 as colorless prisms, m.p. 84-84.5° (lit.[101] m.p. 85-86°).

I.r. spectrum: νmax 1735 (ester C=O) and 1725 cm^{-1} (ketone C=O)

N.m.r. spectrum: δ 5.40 (1H, b.q., J=11.7 Hz., C-2 H), 7.43 (3H, m., aromatic protons), 8.10 ppm (2H, m., aromatic protons)

Mass spectrum: m/e 218 (M^+)

cis-2-Acetoxy-6-methylcyclohexanone 105

2-Chloro-2-methylcyclohexanone was synthesized from 2-methyl-cyclohexanone and sulfuryl chloride according to the procedure of Organic Syntheses[102] in 68% yield, b.p. 40-42°/2.5 Torr.

I.r. spectrum: ν max 1720 cm^{-1} (C=O)

N.m.r. spectrum: δ 1.62 (3H, s., CH_3-) 2.96 ppm (2H, m., C-6 H)

2-Chloro-2-methylcyclohexanone (6.3 g.) and 8.4 g. of potassium acetate in 50 ml. of acetic acid were refluxed under nitrogen for 4 hr. The reaction mixture was diluted with water and extracted with ether. The ether extracts were combined, washed with 5% aqueous sodium bicarbonate solution and dried. Removal of ether by simple distillation gave 6.0 g. of slightly brown oil. Distillation through the 8" spinning band yielded 4.3 g. of colorless oil. N.m.r. and g.l.p.c. showed it was a mixture of cis-2-acetoxy-6-methylcyclohexanone 105 and 2-acetoxy-2-methylcyclohexanone 106* in a ratio of ca. 4:1. Two recrystallizations from petroleum ether (b.p. 30-60°) gave 1.5 g. of cis-2-acetoxy-6-methylcyclohexanone 105 as colorless plates, m.p. 54-55° (lit.[96] m.p. 50-52°).

N.m.r. spectrum: δ 1.05 (3H, d., J=6.5 Hz., CH_3-), 2.14 (3H, s., CH_3COO-), 5.18 ppm (1H, b.q., J=6,12 Hz., C-2 H)

Cyclohexanone-1-^{13}C 115(6)-1-^{13}C

(a) Preparation of lithium sand. Lithium metal ribbon (1.78 g., 0.15 g. atom, Foote Mineral Company) and

*Tentative assignment based on the peaks at δ 1.44, s., for CH_3-; 2.11, s., for CH_3COO-.

50 mg. of sodium metal* were put in a one-necked 250-ml. round bottom flask** containing 120 ml. of mineral oil. The flask was swept with argon (Union Carbide) for several minutes, then a high speed stainless-steel stirrer was attached to the flask. The flask was heated in an oil bath at 220-230° and the stirrer was started to whip the molten metal into very fine particles. When the desired fineness, as judged by visual estimation, was obtained, the flask was allowed to cool gradually*** and the speed of the motor was reduced. After the oil had cooled below 100°, the stirrer was stopped and disconnected from the flask. The flask was again swept with argon and the sand was ready for use. The sand prepared in this way retained its activity for several days if the flask was properly stoppered.

(b) 1,5-Dilithiopentane 129[68,69] The reaction vessel was a three-necked 250-ml. round bottom flask. One side arm was fitted with a gas inlet tube and the other side arm was fitted with a low temperature thermometer. After the lithium sand in mineral oil, as prepared in (a) above, was poured into the flask, the center neck of the flask was fitted

*The presence of catalytic amount of sodium was essential to give a satisfactory yield of alkyllithium, see (b).
**Molten lithium seemed to corrode the glass slightly. When a Quick-Fit flask was used, it usually broke during the cooling period. It was necessary to use Lab-Glass flask or Pyrex flask.
***Slow cooling seemed to give more reactive lithium sand.

with a sintered glass filter stick which reached to the bottom of the flask. The top of the filter stick had been bent into an inverted U-shape and was connected to a disposal flask. As the content in the flask was stirred by a magnetic bar, the argon pressure was applied to force the mineral oil through the filter stick, leaving lithium sand in the flask. In the same manner, the lithium sand was washed with two 50-ml. portions of anhydrous ether (dried over sodium). After 100 ml. of anhydrous ether was added to the flask, the filter stick was replaced by a 50-ml. pressure-equalized dropping funnel which now also served as a gas outlet. The argon flow was reduced to a slow rate and 11.5 g. (0.05 mol.) of 1,5-dibriomopentane 126 (AR grade, redistilled) in 50 ml. of anhydrous ether was put into the dropping funnel. About 3 ml. of the dibromide solution was added into the flask, and the reaction was initiated at room temperature by vigorous stirring. The reaction flask was then cooled to -20° in a Dry Ice-acetone bath, and the remaining dibromide solution was added dropwise during 1.5 hr. with continuous stirring. After the addition was completed, the reaction mixture was stirred for 0.5 hr. at 10°. Another 50 ml. of ether was added to make the total volume up to 200 ml. An aliquot (4 ml.) of the solution was taken out by a hypodermic syringe and

titrated with standard sec-butyl alcohol solution for the yield of organometallic compound. o-Phenanthroline was used as an indicator for the titration.[71] Yields varies from 74% to 84% with the usual yield being around 80% when the lithium sand, prepared as in (a) above, was used. If the lithium sand was prepared without the added sodium, the yield of organolithium compound varied erratically from 0% to 20%.

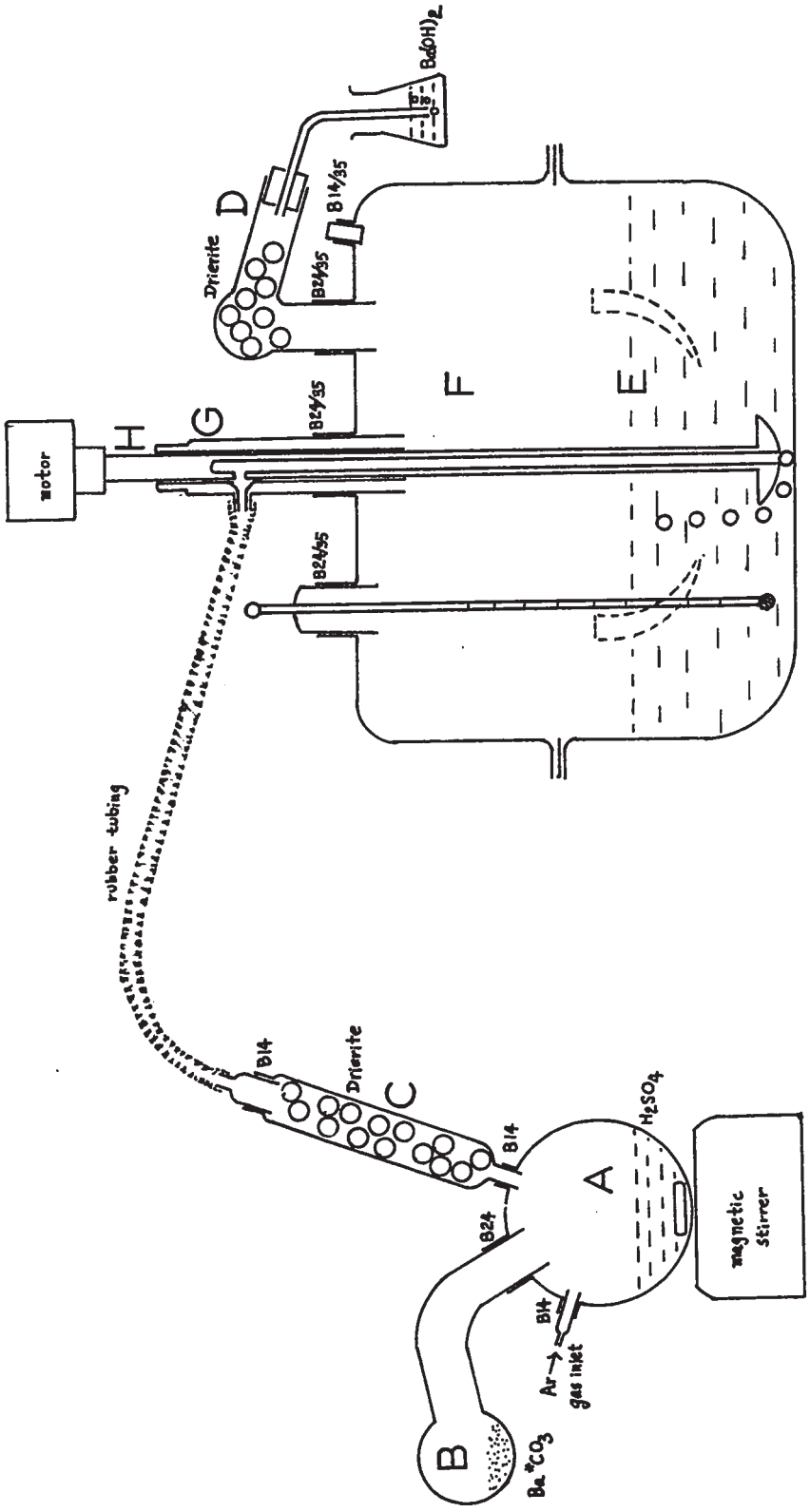
(c) Carbonation of 1,5-dilithiopentane 129. The apparatus employed is illustrated in Fig. 9. It was composed of a carbon dioxide generator and a raction vessel. The carbon dioxide generator consisted of a 100-ml. three-necked round bottom flask A for sulfuric acid, a 25-ml. glass bulb B with a bent neck for addition of barium carbonate, and a drying tube C containing Drierite which served also as a gas outlet. The third neck of flask A is used as a gas inlet.

While 1,5-dilithiopentane 129 was being prepared, concentrated sulfuric acid (50 ml.) and a magnetic bar were put in the flask A, and barium carbonate-^{13}C (6.6 g., 0.033 mol., 61% enriched) was placed in tube B. The whole system was swept by argon for several minutes and was ready for use.

The reaction vessel was a 1-l. reaction flask E with

side indentations (ACE Glass 6477) and a flask head F with three B24/35 necks in line plus a B14/35 neck (ACE Glass 6488). The center neck was fitted with a Trubore bearing G with a side opening for gas inlet (ACE Glass 9368) and a hollow glass stirring rod H with vanes attached to a solid disc (ACE Glass 9380). The side opening in the bearing G corresponded to the hole drilled in the stirring rod H, so that the gas could travel down the rod through the hollow disc. One side neck of the flask head F was fitted with a thermometer, and the other side neck was left open. The B14/35 neck was closed with a stopcock.

The carbon dioxide generator was connected by a piece of rubber tubing to the side opening of G. The reaction vessel was swept with a slow stream of argon when the dilithiopentane 129 solution, prepared as described in (b) above, was filtered through a filter stick into the reaction vessel. After the filtration was completed, another 100 ml. of anhydrous ether was added and a drying tube D containing Drierite was connected to the side neck formerly left open. The outlet of the drying tube I was led by a piece of rubber tubing to a flask containing saturated barium hydroxide solution which served both as a trap for carbon dioxide and as a gas bubbler to estimate the flow rate of argon.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$BaCO_3$
Ar → gas inlet
H_2SO_4
magnetic stirrer

Fig. 9

The reaction flask E was cooled in an ice bath to 10°, the dilithiopentane solution in it was stirred vigorously,* and the argon flow was adjusted to a very slow rate. With the concentrated sulfuric acid in the flask A stirred smoothly by the magnetic bar, barium carbonate-^{13}C was added slowly from the bulb B. Usually 10-15 min. were required to complete the addition. The argon flow was then increased to drive all of the carbon dioxide into the dilithiopentane solution. On the addition of 1 ml. of 1% o-phenanthroline etheral solution through the B14/35 neck, the solution in the flask E turned immediately to reddish brown. Methyl iodide (4 ml.) was added and the reddish-brown color gradually faded (5 min.). After 200 ml. of ice-water was added to hydrolyze the reaction mixture, the argon flow and the stirring were stopped. During the entire carbonation and hydrolysis process, the temperature of the reaction flask E was maintained at 10-20° by the ice-water bath.

The ether layer was separated from the aqueous layer, washed with 5% aqueous sodium bisulfite solution, water, and then dried. Removal of ether by simple distillation left 5.5 g. of slightly brown oil. Bulb-to-bulb

*Vigorous stirring was essential to minimize the formation of polymeric material.

distillation (15 Torr, oven temperature 60-160°) gave 1.81 g. (55% based on barium carbonate-^{13}C) of cyclohexanone-1-^{13}C 115(6)-1-^{13}C, single spot on t.l.c. The purity was verified by g.l.p.c. analysis to be higher than 95%.

I.r. spectrum: νmax 1720 (^{12}C=O) and 1680 cm^{-1} (^{13}C=O) in a ratio of ca. 1:2

Mass spectrum: m/e 99 and 98 (M^+)

Calculation based on M^+ peaks showed that the ^{13}C-enrichment was 59%.

2-Acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C

Cyclohexanone-1-^{13}C 115(6)-1-^{13}C (4.05 g.) was converted into its enol acetate by heating at 130° for 5.5 hr. with 11.2 ml. of freshly distilled isopropenyl acetate in the presence of 37 mg. of p-toluenesulfonic acid as a catalyst. Excess isopropenyl acetate was distilled at 30 Torr through the 8" spinning band column, and the residue was purified by bulb-to-bulb distillation (15 Torr, oven temperature 80-110°) to give 5.62 g. (91%) of cyclohexanone-1-^{13}C enol acetate. The purity was verified by g.l.p.c. analysis to be higher than 90%.

The crude cyclohexanone-1-^{13}C enol acetate (5.62 g., 37.4 mmol.) in 14 ml. of chloroform was epoxidized with

43.9 mmol. of m-chloroperbenzoic acid at -10°. Crude epoxy acetate, obtained in 80% yield, was thermally rearranged (100°) to the acetoxyketone. Purification by bulb-to-bulb distillation (4 Torr, oven temperature 100-110°) gave 4.57 g. (73% from enol acetate) of 2-acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C. One recrystallization from petroleum ether (b.p. 30-60°) yielded 3.58 g. (59% from enol acetate) of colorless prisms, m.p. 32-37°.

I.r. spectrum: νmax 1750 (ester C=O), 1730 (ketone ^{12}C=O), and 1690 cm^{-1} (ketone ^{13}C=O), the latter two in a ratio of ca. 1:2

Mass spectrum: m/e 156, 157 (M^+), 113, 114 ($M-CH_3CO^+$)

Calculations based on M^+ peaks showed that the ^{13}C-enrichment was 61%.

^{13}C-n.m.r. spectrum: δ_c 20.4 (s., CH_3-), 23.9 (s., C-4), 27.3 (s., C-5), 33.3 (s., C-3), 40.7 (overlapping s. and d., J=40 Hz., C-6), 76.7 (overlapping s. and d., J=40 Hz., C-2), 169.1 (s., $CH_3\underline{C}OO$-), 203.1 ppm (s., enhanced, C-1)

Reaction of 2-Acetoxycyclopentanone 104(5) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 133-135° (Reaction 38)

2-Acetoxycyclopentanone 104(5) (400 mg., b.p.

115-117°/ 15 Torr) and 0.62 g. of dried potassium acetic-d_3* in acetic acid-d_4 were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 6 hr. Work up gave 50 mg. (12%) of brown oil. Purification by bulb-to-bulb distillation yielded 15 mg. (4%) of 2-acetoxycyclopentanone 104(5) as a colorless oil. The purity was shown by g.l.p.c. analysis to be higher than 96%.

I.r. spectrum: νmax 2930,2860 (strong, C-H), 2210,2110 (weak, C-D), 1760 (ester C=O) and 1745 cm^{-1} (ketone C=O)

Mass spectrum: m/e 143-147 (weak, M^+), 99-105 ($M-CH_3CO^+$)

Calculations based on $M-CH_3CO^+$ peaks revealed the extent of deuteration of ring protons to be d_0 2.6%, d_1 6.8%, d_2 29.3%, d_3 52.7%, d_4 2.9%, d_5 4.1%, d_6 0.7%.

Reaction of 2-Acetoxycyclopentanone 104(5) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 220° (Reaction 39)

2-Acetoxycyclopentanone 104(5) (315 mg., b.p. 115-117°/15 Torr) and 0.52 g. of dried potassium acetate-d_3 in 3.0 ml. of acetic acid-d_4 were sealed under a nitrogen

*Potassium acetate-d_3 was prepared by neutralizing acetic acid-d_4 with 1N aqueous potassium hydroxide solution to a phenolphthalein end point and then evaporating to dryness at 0.6 Torr at 100°. The dry, flaky foam was used without further purification.

atmosphere in a thick-walled Pyrex tube and heated at 220° in an oil bath for 15 hr. Work up gave only 26 mg. of brown residue. No 2-acetoxycyclopentanone 104(5) was detectable from g.l.p.c. analysis of the crude product.

Reaction of 2-Acetoxycyclohexanone 104(6) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 140° (Reaction 40)

2-Acetoxycyclohexanone 104(6) (200 mg., m.p. 33-37°) and 0.40 g. of dried potassium acetate-d_3 in 2.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 140° in an oil bath for 12 hr. Work up gave 115 mg. (57%)* of oil. Purification on thick layer (solvent A) gave 68 mg. (34%) of oil, which after one recrystallization from petroleum ether (b.p. 30-60°) yielded 43 mg. (22%)* of colorless prisms, m.p. 34-38°.

I.r. spectrum: νmax 2930, 2860 (strong, C-H), 2210, 2110 (medium, C-D), 1750 (ester C=O) and 1730 cm^{-1} (ketone C=O)

Mass spectrum: m/e 158-165 (M^+), 114-120 ($M-CH_3CO^+$)

*Reaction with potassium acetate in acetic acid under the same condition gave a 92% yield of crude product, and a 77% yield of pure crystalline product.

Calculations based on M-CH_3CO^+ peaks showed the extent of deuteration of ring protons to be d_2 12.8%, d_3 44.5%, d_4 12.0%, d_5 29.7%.

Reaction of 2-Acetoxycyclohexanone 104(6) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 220° (Reaction 41)

2-Acetoxycyclohexanone 104(6) (300 mg., m.p. 33-37°) and 0.51 g. of dried potassium acetate-d_3 in 3.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220° (furnace temperature reading) for 14 hr. Work up gave 120 mg. (40%)* of brown oil, which was purified on a thick layer (solvent A) to give 49 mg. (17%)* of slightly brown oil, single t.l.c. spot and single peak on g.l.p.c. analysis. Bulb-to-bulb distillation (0.2 Torr, oven temperature 45-50°) gave 40 mg. (13%)* of colorless oil, which crystallized on standing at room temperature for several days.

I.r. spectrum: νmax 2930, 2860 (medium, C-H), 2210, 2110 (strong, C-D), 1750 (ester C=O) and 1730 cm^{-1} (ketone C=O)

Mass spectrum: m/e 162-170 (M^+), 118-124 (M-CH_3CO^+)

Calculations based on M^+ peaks showed that the extent of deuteration of the molecule was d_6 0.17%, d_7 0.4%,

*Reaction with potassium acetate in acetic acid under the same condition gave 70% yield of the crude product, and 40% yield of pure crystalline product.

d_8 1.6%, d_9 6.1%, d_{10} 21.9%, d_{11} 37.8%, d_{12} 32.1%.

Calculation based on M-CH_3CO^+ peaks showed that the extent of deuteration of ring protons was d_5 1.2%, d_6 6.3%, d_7 17.8%, d_8 37.5%, d_9 35.5%, d_{10} 1.6%.

Reaction of 2-Acetoxycyclohexanone 104(6) with Acetic Acid-d_4 at 215° (Reaction 42)

2-Acetoxycyclohexanone 104(6) (300 mg., m.p. 33-37°) in 3.0 ml. of acetic acid-d_4 was sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 215° in an oil bath for 48 hr. Work up gave 60 mg. (20%) of brown oil. Purification on a thick layer (solvent A) yielded 25 mg. (8%) of a slightly brown oil, which after bulb-to-bulb distillation (0.6 Torr, oven temperature 50°) afforded 20 mg. (7%) of 2-acetoxycyclohexanone 104(6) as a colorless oil.

I.r. spectrum: νmax 2930, 2860 (medium, C-H), 2210, 2110 (medium, C-D), 1750 (ester C=O) and 1735 cm^{-1} (ketone C=O)

Mass spectrum: m/e 162-168 (M^+), 115-124 (M-CH_3CO^+)

Calculation based on M-CH_3CO^+ peak showed that the extent of deuteration of ring protons was d_3 2.4%, d_4 9.1%, d_5 16.8%, d_6 22.1%, d_7 26.3%, d_8 10.2%, d_9 13.1%.

Reaction of 2-Acetoxycyclohexanone 104(6) with Potassium Acetate in Propionic Acid at 133-135°

2-Acetoxycyclohexanone 104(6) (300 mg., m.p. 33-37°) and 0.50 g. of dried potassium acetate in 3.0 ml. of propionic acid was heated under a nitrogen atmosphere at 133-135° (solution temperature) for 24 hr. Work up gave 100 mg. (33%) of brown oil. The n.m.r. spectrum of the crude product revealed the complete absence of propionoxyl group.

Reaction of 2-Acetoxycyclohexanone 104(6) with Potassium Acetate in Propionic Acid at 220°

2-Acetoxycyclohexanone 104(6) (400 mg., m.p. 33-37°) and 0.60 g. of dried potassium acetate in 4.0 ml. of propionic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220° in an oil bath for 42 hr. Work up gave 240 mg. (60%) of brown oil. The n.m.r. spectrum showed the complete exchange of acetoxyl group for the propionoxyl group (δ 1.20, t., J=7 Hz., and 2.42, q., J=7 Hz., for CH_3CH_2COO-).

Reaction of 2-Acetoxycycloheptanone 104(7) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 240° (Reaction 43)

2-Acetoxycycloheptanone 104(7) (300 mg., b.p.

78-80°/0.9 Torr) and 0.50 g. of dried potassium acetate-d_3 in 3.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 240° in an oil bath for 20 hr. Work up and bulb-to-bulb distillation of the crude product yielded 30 mg. (10%) of a colorless oil, which showed three peaks on g.l.p.c. analysis. Purification by preparative g.l.p.c. (column temperature 140°) yielded ca. 15 mg. (5%) of partially deuterated 2-acetoxycycloheptanone 104(7), single peak on g.l.p.c. analysis.

I.r. spectrum: νmax 2930, 2860 (strong, C-H), 2210, 2110 (medium, C-D), 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

Mass spectrum: m/e 175-184 (weak, M^+), 128-140 ($M-CH_3CO^+$)

Calculation based on $M-CH_3CO^+$ peaks showed that the extent of ring deuteration was d_1 0.3%, d_2 0.7%, d_3 4.7%, d_4 18.2%, d_5 31.3%, d_6 13.1%, d_7 16.3%, d_8 6.5%, d_9 4.9%, d_{10} 2.6%, d_{11} 1.4%.

Reaction of 2-Acetoxycycloheptanone 104(7) with Potassium Acetate in Acetic Acid at 250°

2-Acetoxycycloheptanone 104(7) (20.0 g., b.p. 78-80°/0.9 Torr) and 25.0 g. of dried potassium acetate in 150 ml. of acetic acid were sealed under a nitrogen atmosphere in five thick-walled Pyrex tubes and heated at

250° (furnace temperature reading) for 2 days. Work up yielded 4.50 g. (22.5%) of a dark-colored oil. Bulb-to bulb distillation (2 Torr, oven temperature 150°) gave 2.52 g. of pale green oil, λmax 272 nm (shoulder) (ϵ 850). The n.m.r. spectrum revealed the complete absence of starting material. The g.l.p.c. show two main peaks A and B accounting for ca. 60% of the total material. Fractional distillation through the 8" spinning band column at 4 Torr gave the following fractions:

Fraction	Temp.	Weight (g.)	Main component
1	89-97°	0.32	A
2	97-102°	0.32	A
3	105-106°	0.15	A
4	106-113°	0.32	A + B
5	113-120°	0.58	B
6	120°	0.53	B

Chromatography of Fractions 2 and 3 (0.47 g.) on 15 g. of silica gel and elution with 1:1 petroleum ether-benzene gave 265 mg. of colorless oil, which was shown by g.l.p.c. to contain ca. 95% of compound A, for which all physical data are consistent with the unsaturated γ-lactone structure 121.

U.v. spectrum: λmax 215 nm (ϵ 10,700)

I.r. spectrum: νmax 1760 cm^{-1} (C=O)

N.m.r. spectrum: δ 5.99 (1H, d., J=6 Hz., vinylic proton at α-position), 7.45 ppm (1H, d., J=6 Hz., vinylic proton at β-position)

Mass spectrum: m/e 152 (M^+)

Fractions 5 and 6 (1.11 g.) were chromatographed on 60 g. of silica gel packed in petroleum ether. Elution with the same solvent gave 280 mg. of semicrystalline material, which after two recrystallizations from acetone gave 107 mg. of compound B, m.p. 60-62.2°, as colorless crystals. The crystals slowly turned brown on exposure to air and light. All the physical data of compound B are consistent with the tetrasubstituted furan structure 124.

U.v. spectrum: λmax 227 nm (ϵ 7,700)

I.r. spectrum: νmax 1445 cm^{-1}

N.m.r. spectrum: δ 1.71 (b.), 2.31 (b.), and 2.68 ppm (b.) in a ratio of 3:1:1, no low field absorption

Analysis: Calcd. for $C_{14}H_2O$: C, 82.30; H, 9.87; O, 7.83

Found : C, 81.02; H, 9.64; O, 8.95*

Reaction of 2-Acetoxycyclooctanone 104(8) with Potassium Acetate-d_3 in Acetic Acid-d_4 (Reaction 44)

2-Acetoxycyclooctanone 104(8) (465 mg., b.p. 79-80°/0.6 Torr) and 1.0 g. of dried potassium acetate-d_3

*The high oxygen analysis value might be due to the ready air oxidation of furan.

in 6.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 220° in an oil bath for 24 hr. and then at 240° for 40 hr. Work up gave 230 mg. (50%) of a brown oil. Purification by bulb-to-bulb distillation (0.3 Torr, oven temperature 90-110°) yielded 60 mg. (14%) of partially deuterated 2-acetoxycyclooctanone 104(8) as colorless oil, single peak on g.l.p.c. analysis.

I.r. spectrum: νmax 2930, 2860 (strong, C-H), 2210, 2110 (medium, C-D), 1745 (ester C=O) and 1725 cm^{-1} (ketone C=O)

Mass spectrum: m/e 141-149 ($M-CH_3CO^+$)

Calculation based on $M-CH_3CO^+$ peaks showed that the extent of ring deuteration was d_0 2%, d_1 2%, d_2 2%, d_3 7%, d_4 27%, d_5 50%, d_6 3%, d_7 5%.

Reaction of 2-Acetoxycyclononanone 104(9) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 240° (Reaction 45)

2-Acetoxycyclononanone 104(9) (340 mg., b.p. 93-95°/0.6 Torr) and 0.55 g. of dried potassium acetate in 3.4 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 240° in an oil bath for 40 hr. Work up gave 267 mg. (81%) of brown oil. Purification by bulb-to-bulb distillation (0.4 Torr) gave 75 mg. (22%) of partially deuterated

2-acetoxycyclononanone 104(9) as a colorless oil, single peak on g.l.p.c. analysis.

I.r. spectrum: νmax 2930, 2860 (strong, C-H), 2210, 2110 (medium, C-D), 1750 (ester C=O) and 1730 cm^{-1} (ketone C=O)

Mass spectrum: m/e 155-170 ($M-CH_3CO^+$)

Calculation based on $M-CH_3CO^+$ peaks showed that the extent of deuteration of ring protons was d_0 3.3%, d_1 1.6%, d_2 1.6%, d_3 2.7%, d_4 5.3%, d_5 12.5%, d_6 14.2%, d_7 25.7%, d_8 9.8%, d_9 13.5%, d_{10} 3.4%, d_{11} 3.8%, d_{12} 1.1%, d_{13} 1.0%, d_{14} 0.5%.

Reaction of 2-Acetoxycyclododecanone 104(12) with Potassium Acetate-d_3 in Acetic Acid-d_4 at 240° (Reaction 46)

2-Acetoxycyclododecanone 104(12) (200 mg., m.p. 81-82.5°) and 1.0 g. of dried potassium acetate-d_3 in 6.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 240° * in an oil bath for 57 hr. Work up gave 120 mg. (60%) of a brown oil, whose main component was 2-acetoxycyclododecanone 104(12) as shown by t.l.c. and i.r. data. Sublimation at 15 Torr gave 58 mg. (29%) of solid, which after two recrystallizations from 95% ethanol gave 15 mg. of partially

*Rearrangement at 220° for 40 hr. introduced an average of less than five deuterium atoms into the molecule as shown by n.m.r. integration of the crude reaction solution.

deuterated 2-acetoxycyclododecanone 104(12), m.p. 79-80.5°, single spot on t.l.c.

I.r. spectrum: νmax 2930, 2860 (medium, C-H), 2210, 2110 (strong, C-D), 1745 (ester C=O) and 1730 cm^{-1} (ketone C=O)

Mass spectrum: m/e 254-264 (very weak, M^+), 205-220 ($M-CH_3CO^+$)

Calculations based on $M-CH_3CO^+$ peaks showed that the extent of ring deuteration was d_8 0.4%, d_9 0.6%, d_{10} 1.4%, d_{11} 2.4%, d_{12} 3.7%, d_{13} 5.7%, d_{14} 6.7%, d_{15} 8.3%, d_{16} 7.9%, d_{17} 10.8%, d_{18} 10.8%, d_{19} 15.4%, d_{20} 15.7%, d_{21} 10.4%.

Reaction of 2-Benzoyloxycyclohexanone 125 with Potassium Acetate-d_3 in Acetic Acid-d_4 at 133-135° (Reaction 47)

2-Benzoyloxycyclohexanone 125 (200 mg., m.p. 84-84.5°) and 0.40 g. of dried potassium acetate-d_3 in 2.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 150° in an oil bath for 40 hr. Work up gave 150 mg. (75%) of crude oil. Recrystallization from ether gave 130 mg. (65%) of partially deuterated 2-benzoyloxycyclohexanone 125 as colorless prisms, m.p. 85-85.5°.

I.r. spectrum: νmax 3030, 2930, 2860 (strong, C-H), 2210, 2110 (weak, C-D), 1735 (ester C=O) and 1725 cm^{-1} (ketone C=O)

Mass spectrum: m/e 220-224 (M^+)

Calculation based on M^+ peak showed that the extent of deuteration was d_2 3.8%, d_3 24.2%, d_4 14.0%, d_5 58.0%.

Reaction of 2-Benzoyloxycyclohexanone 125 with Potassium Acetate-d_3 in Acetic Acid-d_4 at 170° (Reaction 48)

2-Benzoyloxycyclohexanone 125 (210 mg., m.p. 84-84.5°) and 0.40 g. of dried potassium acetate-d_3 in 2.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 170° in an oil bath for 43 hr. Work up gave 95 mg. (45%) of brown oil. Recrystallization from ether gave 55 mg. (26%) of partially deuterated 2-benzoyloxycyclohexanone 125 as colorless prisms, m.p. 84-85.5°.

I.r. spectrum: νmax 3030, 2930, 2860 (strong, C-H), 2210, 2110 (weak, C-D), 1735 (ester C=O) and 1725 cm^{-1} (ketone C=O)

Mass spectrum: m/e 221-225 (M^+)

Calculation based on M^+ peaks showed that the extent of deuteration was d_3 2.1%, d_4 19.2%, d_5 78.7%.

Reaction of 2-Benzoyloxycyclohexanone 125 with Potassium Acetate-d_3 in Acetic Acid-d_4 at 180-185° (Reaction 49)

2-Benzoyloxycyclohexanone 125 (200 mg., m.p. 84-85°) and 0.40 g. of dried potassium acetate-d_3 in 2.0 ml. of acetic acid-d_4 were sealed under a nitrogen atmosphere in

a thick-walled Pyrex tube and heated at 180-185° in an oil bath for 43 hr. Work up gave 90 mg. (45%) of brown oil. Two recrystallizations from ether gave 3 mg. (1.5%) of partially deuterated 2-benzoyloxycyclohexanone 125, m.p. 84-85.5°. Mass spectrum showed it was mainly pentadeuterated with no d_6-component.

Reaction of 2-Benzoyloxycyclohexanone 125 with Potassium Acetate in Acetic Acid at 195°

2-Benzoyloxycyclohexanone 125 (200 mg., m.p. 84-85.5°) and 0.40 g. of dried potassium acetate in 2.0 ml. of acetic acid were sealed under a nitorgen atmosphere in a thick-walled Pyrex tube and heated at 195° in an oil bath for 6 hr. Work up gave 100 mg. (5%) of brown oil. The n.m.r. spectrum of the crude product showed the presence of a substantial amount of acetoxyl group (δ 2.13, s.). Recrystallization from ether gave 43 mg. (21%) of 2-benzoyloxycyclohexanone 125 as colorless prisms, m.p. 84-85°.

Reaction of cis-2-Acetoxy-6-methylcyclohexanone 105 with Potassium Acetate in Acetic Acid at 133-135°

cis-2-Acetoxy-6-methylcyclohexanone 105 (183 mg., m.p. 54-55°) and 0.30 g. of dried potassium acetate in

2.0 ml. of acetic acid were refluxed (solution temperature 133-135°) under a nitrogen atmosphere for 17 hr. Work up and purification by bulb-to-bulb distillation yielded 130 mg. (71%) of colorless oil. N.m.r. and g.l.p.c. analyses revealed it was a mixture of cis-2-acetoxy-6-methylcyclohexanone 105 (δ 1.05, d., J=6.5 Hz., for CH_3-; 2.14, s., for CH_3COO-; 5.18, m., for C-2 H) and 2-acetoxy-2-methylcyclohexanone 106 (δ 1.44, s., for CH_3-; 2.11, s., for CH_3COO-) in a ratio of ca. 4:1.

Reaction of cis-2-Acetoxy-6-methylcyclohexanone 105 with Potassium Acetate in Propionic Acid at 133-135°

cis-2-Acetoxy-6-methylcyclohexanone 105 (300 mg., m.p. 54-55°) and 0.50 g. of dried potassium acetate in 3.0 ml. of propionic acid were heated under a nitrogen atmosphere at 133-135° (solution temperature) for 6 hr. Work up gave 280 mg. (93%) of a brown oil. The n.m.r. spectrum showed the complete exchange of the acetoxyl group for the propionoxyl group. G.l.p.c. analysis showed the crude product was a mixture of at least three compounds. The major compound, accounting for ca. 60% of the crude product, was probably cis-2-propionoxy-6-methylcyclohexanone (δ 1.05, d., J=6.5 Hz., for CH_3-; 1.20, t., J=7 Hz., for CH_3CH_2COO-; 5.18, m., for C-2 H).

Reaction of 2-Acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C with Potassium Acetate in Acetic Acid at 142-144°

2-Acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C (400 mg., m.p. 32-37°) and 0.80 g. of dried potassium acetate in 40 ml. of acetic acid were sealed under a nitrogen atmosphere in a thick-walled Pyrex tube and heated at 142-144° for 12 hr. The reaction mixture was diluted with 160 ml. of water, neutralized with 18 g. of sodium bicarbonate, and then extracted with ether. The combined ether extracts (40 ml.) were washed with 5% aqueous sodium bicarbonate solution, and then dried. Removal of ether by simple distillation gave 370 mg. (92%) of slightly brown oil, which after one recrystallization from petroleum ether (b.p. 30-60°) yielded 307 mg. (77%) of 2-acetoxycyclohexanone-1-^{13}C as colorless prisms, m.p. 33-38°, single spot on t.l.c. (solvent A).

I.r. spectrum: νmax 1750 (ester C=O), 1730 (ketone ^{12}C=O) and 1690 cm^{-1} (ketone ^{13}C=O), the latter two in a ratio of ca. 2:1

^{13}C-n.m.r. spectrum: δ_c 20.4 (s., CH_3-), 23.9 (s., C-4), 27.3 (s., C-5), 33.3 (m., C-3), 40.7 (m., C-6), 76.7 (s., enhanced, C-2), 169.1 (s., $CH_3\underline{C}OO$-), 203.1 ppm (s., enhanced, C-1)

Reaction of 2-Acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C with Potassium Acetate in Acetic Acid at 216-218°

2-Acetoxycyclohexanone-1-^{13}C 104(6)-1-^{13}C (1.40 g., m.p. 32-37°) and 2.80 g. of dried potassium acetate in 14 ml. of acetic acid were sealed under a nitrogen atmosphere in seven thick-walled Pyrex tubes and heated at 216-218° in an oil bath for 22 hr. The combined reaction mixture was diluted with 300 ml. of water, neutralized with 57 g. of sodium bicarbonate and then extracted with ether. The combined ether extracts (300 ml.) were washed with 5% aqueous sodium bicarbonate solution and water, and then dried. Removal of ether by simple distillation left 1.05 g. (75%) of brown oil. Purification on eight 20 x 20 cm. thick layers (solvent A) yielded 611 mg. (44%) of slightly brown oil. One recrystallization from petroleum ether gave 304 mg. (22%) of 2-acetoxycyclohexanone-^{13}C as colorless prisms, m.p. 33-35°, single spot on t.l.c.

I.r. spectrum: ν_{max} 1750 (ester C=O), 1730 (ketone ^{12}C=O), and 1690 cm^{-1} (ketone ^{13}C=O, very weak)

^{13}C-n.m.r. spectrum: δ_C 20.4 (s., weak, CH_3-), 23.9 (s., C-4), 27.3 (s., C-5), 33.3 (s., C-3), 40.7 (s., C-6), 76.7 (s., C-2), 169.1 (s., weak, $CH_3\underline{C}OO$-), 203.1 ppm (s., C-1)

APPENDIX

DEHYDROBROMINATION OF 3α-BROMOCHOLESTAN-4-ONE

In the course of their work on the bromination of ketosteroids, Shoppee and coworkers[86] treated 3α-bromocholestan-4-one 88 with boiling γ-collidine and assigned the structure of Δ^2-cholesten-4-one 11 to the crystalline product isolated in 90% yield. However, the u.v. data, λ_{max}^{EtoH} 239 nm (ε 10,000), reported for the compound was not consistent with the structure. The extinction coefficient was in the usual range for transoid enones, but the absorption maximum was too far from the predicted value (227 nm). Since collidine-dehydrobromination was well-known[43] to give both normal and rearranged elimination products, the sample obtained by Shoppee and coworkers might be a mixture of Δ^2-cholesten-4-one 11 and Δ^5-cholesten-4-one 7, thus explaining the abnormal u.v. data. In view of our finding that formation of Δ^5-cholesten-4-one 7 is preferred to that of Δ^2-cholesten-4-one 11 in acetic acid, it seemed worthwhile to reinvestigate Shoppee and coworkers' reaction. To our surprise, the crude product only contained

Δ^2-cholesten-4-one 11, no trace of Δ^5-cholesten-4-one 7 was detectable in the n.m.r. spectrum. Physical constants of the crystallized material agreed with those reported by Shoppee, except u.v. data, λ_{max}^{EtoH} 226 nm (ϵ 7,800).

REFERENCES

1. A. Butenandt and A. Wolff, Ber., 68 2091 (1935).
2. (a) E. J. Corey, J. Am. Chem. Soc., 75 4832 (1953).
   (b) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, J. Am. Chem. Soc., 74 2828 (1952).
3. A. Butenandt and L. Mamoli, Ber., 68 1854 (1935).
4. A. Butenandt and J. Schmidt, Ber., 67 1901 (1934).
5. A. Butenandt and L. Mamoli, Ber., 68 1850 (1935).
6. A. Butenandt and H. Dannenberg, Ber., 69 1158 (1936).
7. A. Butenandt and H. Dannenberg, Ber., 71 1681 (1938).
8. L. Ruzicka, Pl. A. Plattner and R. Aeschbacher, Helv. Chim. Acta, 21 866 (1938).
9. A. Butenandt, L. Mamoli, H. Dannenberg, L.-W. Masch and J. Paland, Ber., 72 1617 (1939).
10. H. Dannenberg, Abhandl. Preuss. Akad. Wiss., 21 3 (1939).
11. R. B. Woodward, J. Am. Chem. Soc., 63 1123 (1941), 64 76 (1942).
12. A. Butenandt and G. Ruhenstroth-Bauer, Ber., 77 397 (1944).
13. A. Windaus, Ber., 3 488 (1920).
14. G. Richard, Compt. rend., 200 1944 (1935).

15. O. Wallach, Ann., 414 296 (1918).

16. E. S. Wallis, E. Fernholz and F. T. Gephart, J. Am. Chem. Soc., 59 137 (1937).

17. L. F. Fieser and M. Romero, J. Am. Chem. Soc., 75 4716 (1953).

18. L. F. Fieser and R. Stevenson, J. Am. Chem. Soc., 76 1728 (1954).

19. N. J. Turro and W. B. Hammond, Tet., 24 6029 (1968).

20. E. L. Eliel in M. S. Newman's "Steric Effects in Organic Chemistry" John Wiley, New York, N.Y., 1959, page 97.

21. C. Djerassi and D. Marshall, J. Am. Chem. Soc., 80 3986 (1958).

22. K. L. Williamson and W. S. Johnson, J. Org. Chem., 26 4563 (1961).

23. J. C. Sheehan and W. F. Erman, J. Am. Chem. Soc., 79 6050 (1957).

24. L. Ruzicka, Pl. A. Plattner and M. Furrer, Helv. Chim. Acta, 27 727 (1944).

25. K. L. Williamson, private communication.

26. W. S. Johnson, J. Dolf Bass and K. L. Williamson, Tet., 19 861 (1963).

27. F. G. Bordwell and K. M. Wellman, J. Org. Chem., 28 1347 (1963).

28. F. G. Bordwell and K. M. Wellman, J. Org. Chem., 31 351 (1966).

29. P. L. Julian, L. Bauer, C. L. Bell and R. E. Hewitson, J. Am. Chem. Soc., 91 1690 (1969).

30. K. L. Williamson and W. S. Johnson, J. Am. Chem. Soc., 83 4623 (1961).

31. A. E. Bradfield, A. R. Penfold and J. L. Simonsen, J. Chem. Soc., 2744 (1932).

32. (a) Y. Satoh, M. Mukoh, Y. Ogaki, T. Takahashi, T. Kimura, H. Aoki and A. Hogitani, Bull. Chem. Soc. Japan, 39 855 (1966).

(b) T. Takahashi, Y. Satoh and A. Hgitani, Nippon Kagaku Zasshi, 89 974 (1968).

(c) J. Y. Satoh and T. T. Takahashi, Chem. Comm. 1714 (1970).

33. W. B. Smith and C. Gonsalez, Tet. Let., 5751 (1966).

34. R. H. DeWolfe and W. G. Young, Chem. Rev., 56 753 (1956).

35. V. Rosnati, G. Pagani and F. Sannicolo, Tet. Let. 1241 (1967).

36. F. G. Bordwell and M. W. Carlson, J. Am. Chem. Soc., 92 3370 (1970), 92 3377 (1970).

37. R. C. Cookson and S. H. Dandegaonker, J. Chem. Soc., 352 (1955).

38. G. Stork and W. N. White, J. Am. Chem. Soc., 78 4609 (1956).

39. K. L. Williamson, J. I. Coburn and M. F. Herr, J. Org. Chem., 32 3934 (1967).

40. (a) D. A. H. Taylor, Chem. and Ind. London, 250 (1954).
(b) E. J. Corey and R. A. Sneen, J. Am. Chem. Soc., 77 2505 (1955).

41. H. P. Sigg and Ch. Tamm, Helv. Chim. Acta, 43 1402 (1960).

42. (a) E. Grunwald and S. Winstein, J. Am. Chem. Soc., 70 846 (1948).
(b) A. H. Fainberg and S. Winstein, J. Am. Chem. Soc., 78 2770 (1956).

43. E. W. Warnhoff, J. Org. Chem., 27 4587 (1962).

44. D. R. Marshall, Ph.D. Thesis, Univ. of Weatern Ontario, 1968.

45. G. Bellucci, F. Macchia and V. Malaguzzi, Tet. Let. 4973 (1966).

46. L. Mamlok, Bull Soc. Chim. France, 3466 (1965).

47. (a) E. S. Lewis, J. T. Hill and E. R. Newman, J. Am. Chem. Soc., 90 662 (1968).
(b) H. L. Goering, Record Chem. Progr., 21 109 (1960).

48. D. H. R. Barton, P. D. Magnus and M. J. Pearson, Chem. Comm., 550 (1969).

49. C. W. Shoppee, M. E. H. Howden, R. W. Killick and G. H. R. Summers, J. Chem. Soc., 630 (1959).

50. J. C. Sheehan and R. M. Wilson, J. Am. Chem. Soc., 89 3457 (1967).

51. K. L. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz and W. S. Johnson, J. Org. Chem. 27 1612 (1962).

52. A. Nickon and J. L. Lambert, J. Am. Chem. Soc., 88 1905 (1966).

53. R. B. Loftfield, J. Am. Chem. Soc., 73 4707 (1951).

54. J. B. Stothers, Quart. Rev., 19 144 (1965).

55. F. A. L. Anet and P. M. Henrichs, Tet. Let., 829 (1970).

56. N. Heap and G. H. Witham, J. Chem. Soc. (B), 164 (1966).

57. B. W. Roberts, S. C. Welch and D. A. Steed, Chem. Comm. 535 (1969).

58. H. O. House "Modern Synthetic Reactions", Benjamin, New York, N. Y., 1965, p. 21.

59. S. Nishimura, M. Shimahara and M. Shiota, Chem. and Ind. London, 1796 (1966).

60. G. F. H. Green and A. G. Long, J. Chem. Soc., 2532 (1961).

61. T. Nakano, M. Hasegawa and C. Djerassi, Chem. Pharm. Bull. Japan, 11 465 (1963).

62. P. Striebel and Ch. Tamm, Helv. Chim. Acta, 37 1094 (1954).

63. L. Caglioti, G. Cainelli, G. Maina and A. Selva, Gazz. Chim. Ital. 92 309 (1962).

64. J. McKenna, J. K. Norymberski and R. D. Stubbs, J. Chem. Soc., 2502 (1959).

65. L. F. Fieser and M. Fieser "Steroids", Reinhold, New York, N. Y., 1959, p. 271.

66. I. M. Heilbron, W. Shaw and F. S. Spring, Rec. Trav. Chim., 57 529 (1938).

67. L. F. Fieser and X. A. Dominiguez, J. Am. Chem. Soc., 75 1704 (1953).

68. (a) R. West and E. G. Rochow, J. Org. Chem., 18 1739 (1953).

(b) Private communication with R. West.

69. (a) M. Ryang, Y. Sawa, T. Hasimoto and S. Tsutsumi, Bull. Chem. Soc. Japan, 37 1704 (1964).

(b) C. Tamborski and H. Rosenberg, J. Org. Chem., 25 246 (1960).

(c) P. G. Beinert and J. Parrod, Makromol. Chem., 70 61 (1964).

(d) Private communication with C. W. Kamienski.

70. (a) J. A. Beel, W. G. Koch, G. E. Tomasi, D. E. Hermansen and P. Fleetwood, J. Org. Chem., 24 2036 (1959).

(b) C. W. Kamienski and P. L. Esmay, J. Org. Chem., 25 1807 (1960).

71. S. C. Watson and J. F. Eastham, J. Organometal. Chem., 9 165 (1967).

72. G. E. Coates, "Organo-Metallic Compounds", John Wiley, New York, N. Y., 1956. p. 20.

73. M. Jorgenson, Org. Reactions, Vol. 18 p.1

74. Organic Syntheses, 35 39

75. E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, J. Am. Chem. Soc., 73 1144 (1951).

76. G. H. Douglas, P. S. Ellington, G. D. Meakins and R. Swindlles, J. Chem. Soc., 1720 (1959).

77. D. H. R. Barton and W. J. Rosenfelder, J. Chem. Soc., 1048 (1951).

78. H. Hauptmann, J. Am. Chem. Soc., 69 562 (1947).

79. A. Fürst and Pl. A. Plattner, Helv. Chim. Acta, 32 275 (1949).

80. A. Fürst and R. Scotoni jr., Helv. Chim. Acta, 36 1332 (1953).

81. I. Malunowicz, J. Fajkos and F. Sorm, Coll. Czech. Chem. Comm., 25 1359 (1960).

82. A. W. Langer, Jr., Trans. N Y Academy Science 27 741 (1965).

83. W. G. Dauben, R. A. Micheli and J. F. Eastham, J. Am. Chem. Soc., 74 3852 (1952).

84. Organic Syntheses, Coll. Vol. II, p. 139.

85. G. H. Alt and D. H. R. Barton, J. Chem. Soc., 4284 (1954).

86. C. W. Shoppee and R. E. Lack, J. Chem. Soc., 3271 (1961).

87. H. H. Inhoffen, G. Koch, I. Nebel and G. Kolling, Chem. Ztg., 74 309 (1950).

88. D. J. Collins, J. Chem. Soc., 3919 (1959).

89. D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, J. Chem. Soc., 2876 (1955).

90. J. F. Eastham, G. B. Miles and C. A. Krauth, J. Am. Chem. Soc., 81 3114 (1959).

91. V. A. Petrow, O. Rosenheim and W. W. Starling, J. Chem. Soc., 135 (1943).

92. S. Lieberman and D. K. Fukushima, J. Am. Chem. Soc., 72 5211 (1950).

93. H. H. Inhoffen, G. Kolling, G. Koch and I. Nebel, Chem. Ber., 84 361 (1951).

94. Y. Satoh, T. Kimura, T. Takahashi, Y. Tajima and A. Hagitani, Nippon Kagaku Zasshi, 90 500 (1969).

95. G. W. K. Cavill and D. H. Solomon, J. Chem. Soc., 4426 (1955).

96. M. E. Kuehne and T. J. Giacobbe, J. Org. Chem., 33 3359 (1968).

97. H. W. Wanzlick, G. Gollmer and H. Milz, Chem. Ber., 88 69 (1955).

98. J. Szmuskovicz and H. Born, J. Am. Chem. Soc., 75 3350 (1953).

99. M. M. Rogic, Tet., 21 2823 (1965).

100. I. V. Machinskaya, J. Gen. Chem. USSR, 22 1159 (1952).

101. C. L. Stevens and T. Tazuma, J. Am. Chem. Soc., 76 715 (1954).

102. Organic Syntheses, Coll. Vol. IV, p. 840.

103. W. Treibs and P. Grossmann, Chem. Ber., 90 103 (1957).

104. A. C. Cope and P. E. Burton, J. Am. Chem. Soc., 82 5439 (1960).

105. Organic Syntheses, 37 8

106. V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, Helv. Chim. Acta, 30 1741 (1947).