PART - II

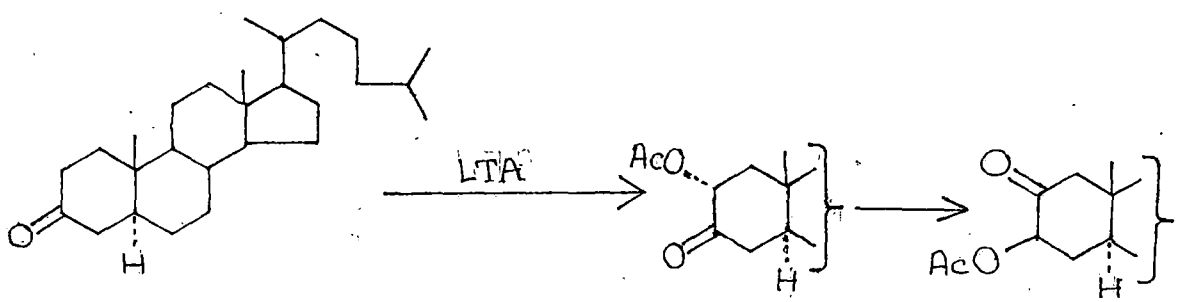
ACETOXYLATION OF FRIEDELIN BY LEAD (IV) ACETATE AND ANTIOCTANT BEHAVIOUR OF 2-ACETOXY KETONES

CHAPTER - I

A Short Review on "α" -acetoxylation of Steroid and Triterpene Ketones with Pb(IV) Acetate and The Mechanism of the Reaction:

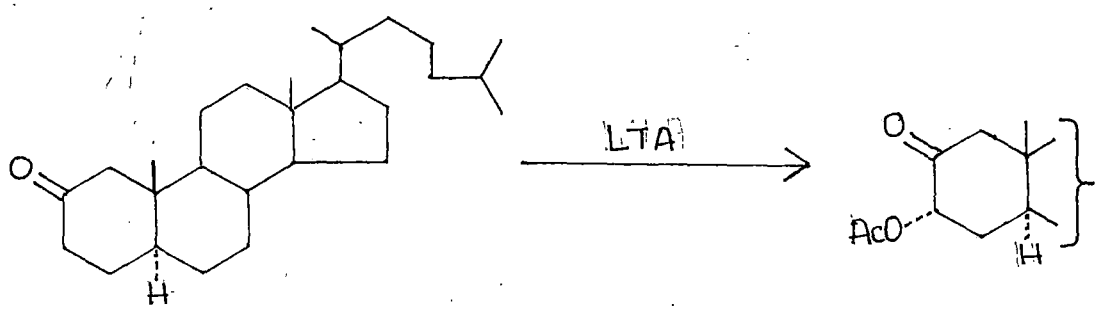
(A) Lead tetraacetate acetoxylation of 2-Keto and 3-Keto Steroids

(1) Henbest and co-workers[1] carried out Pb(IV) acetate (LTA) acetoxylation of cholestan-3-one 1 at room temperature in the presence of BF_3 as catalyst. 2α -acetoxy cholestan-3-one 2 was obtained as the only isolable ketone. The best yield (50%) was obtained by using benzene or benzene-isopropanol as reaction solvent. Reaction in ether or acetic acid gave the same acetoxy ketone with some α,β -unsaturated ketone. Structure 2 for the acetoxylation product was established by reduction with LAH to afford 2α, 3β-diol as the main product. Absorption on active alumina converted the acetoxy ketone 2 into isomer 3 , the isomerisation proceeds by enolisation and acyl group migration via a cyclic intermediate.



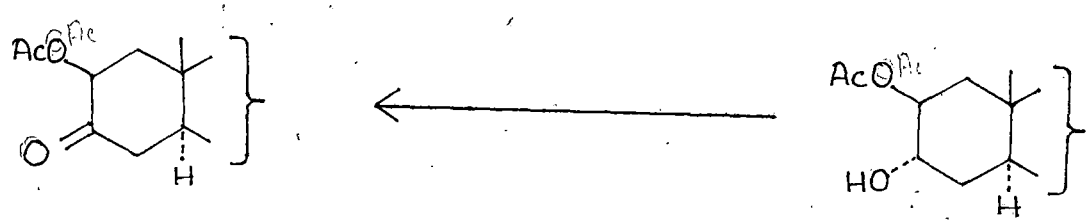
1 2 3

BF_3-catalysed reaction of cholestan-2-one 4 with Pb (IV) acetate in acetic acid gave an acetoxy ketone different from compound 3 and therefore considered to be 3α-acetoxy cholestan-2-one 5.



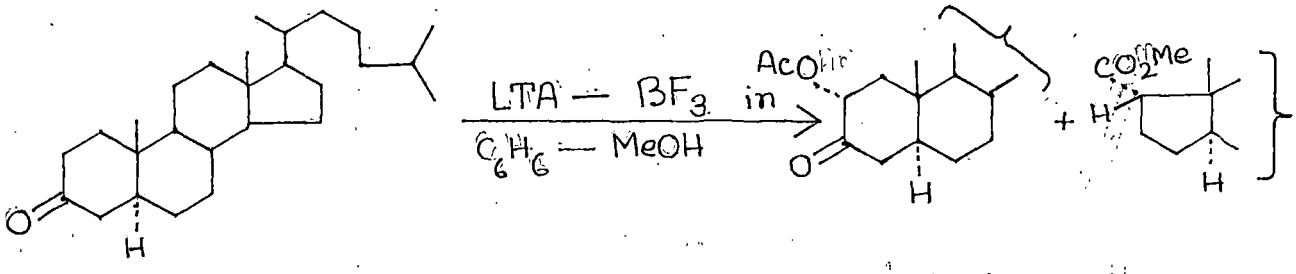
4 5

The rotatory dispersion of these three acetoxy ketones 2, 3, 5 and the remaining isomer 6 obtained by oxidation of the acetoxy alcohol 7 were discussed, the most striking feature being the reduced amplitude caused by introduction of an axial acetate group.



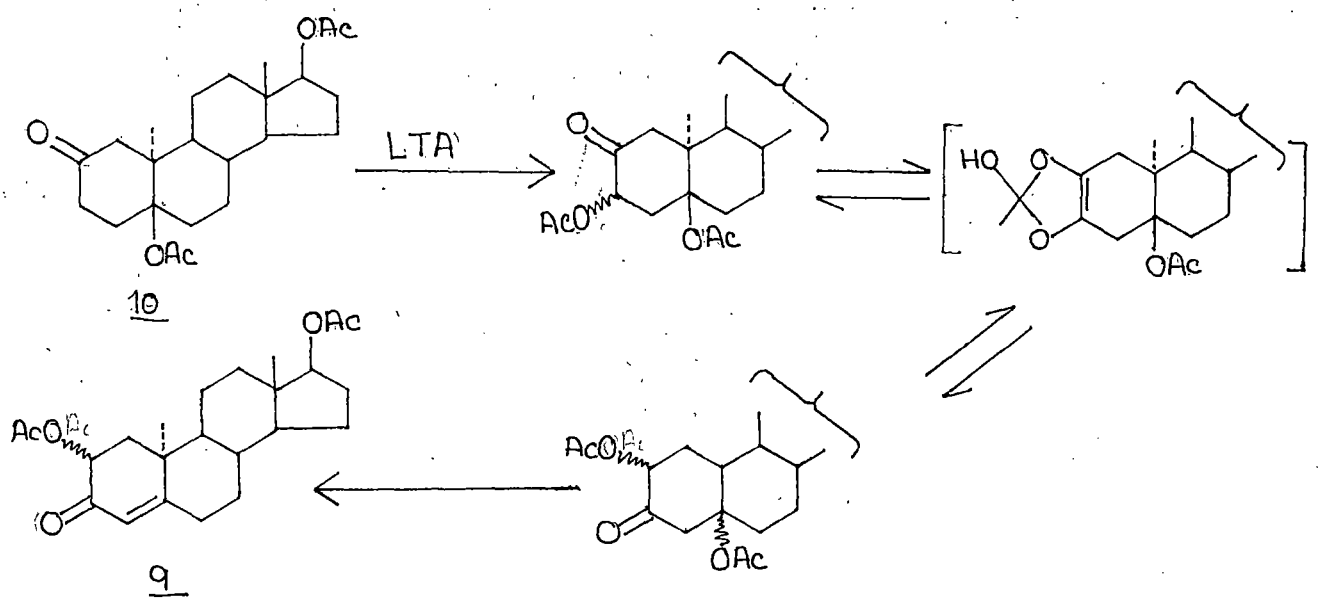
6 7

Henbest and co-workers[2] also noticed that when acetoxylation of 5α-cholestan-3-one 1 was carried out with Pb(IV) acetate - BF_3 in benzene-methanol, in addition to the normal product 2α-acetoxy cholestanone 2 (47%), a ring contracted product methyl A-nor cholestan-2α-carboxylate (7%) 8 was also formed. The ester was also obtained (11%) when 3,3-dimethyloxy cholestane was used as a substrate. When methanol was replaced by ethanol or propan-2-ol the product 2 was only isolated and the ring contracted product 8 could not be detected. The compound 8 is one of the main products of the Favorski reaction of 2α-bromo-5α-cholestan-3-one[3].



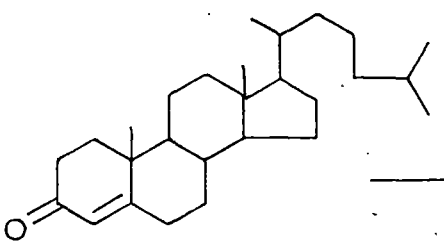
1 2 8

An interesting rearranged product 9 was obtained by Jeger and his co-workers[4] from 2-oxo-5, 17β-dihydroxy-10α-androstane diacetate 10. The pathway suggested for its formation has been presented below.



(ii) Lead tetra acetate reaction of cholest-5-en-3-one and 4-en-3-one :

Fieser and Stevenson[5] reported the oxidation of Δ^5-cholestene-3-one 11 with lead tetraacetate at 15-25° and isolated Δ^5-cholestene-4α acetoxy-3-one 12 as the major crystalline product. Structure and configuration has been deduced by extensive degradative studies. 4α-substituent is equatorial and should have greater stability than an epimeric β-group. Steric repulsion between the 1,3 related C_{10} methyl group and C_4 β-substituent should further impede introduction of a 4 β-substituent.



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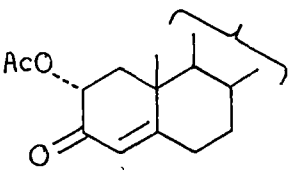
LTA



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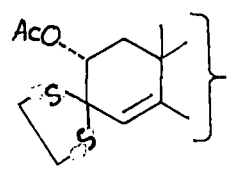
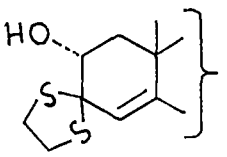
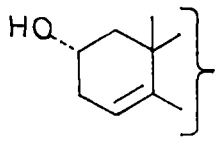
AcOH - Ethane dithiol in BF_3



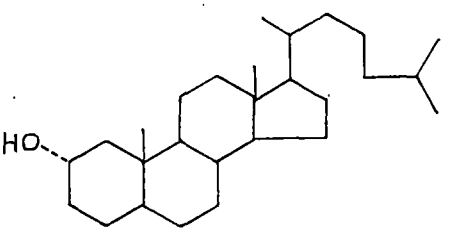
KOH



Raney - Ni in acetone



Pt - Catalyst in AcOH



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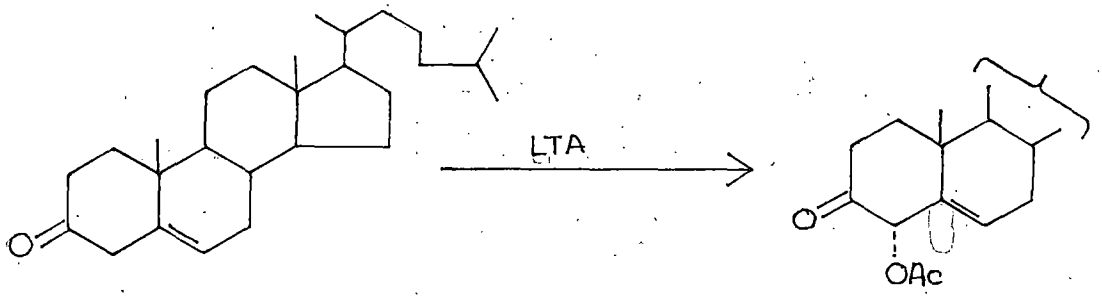


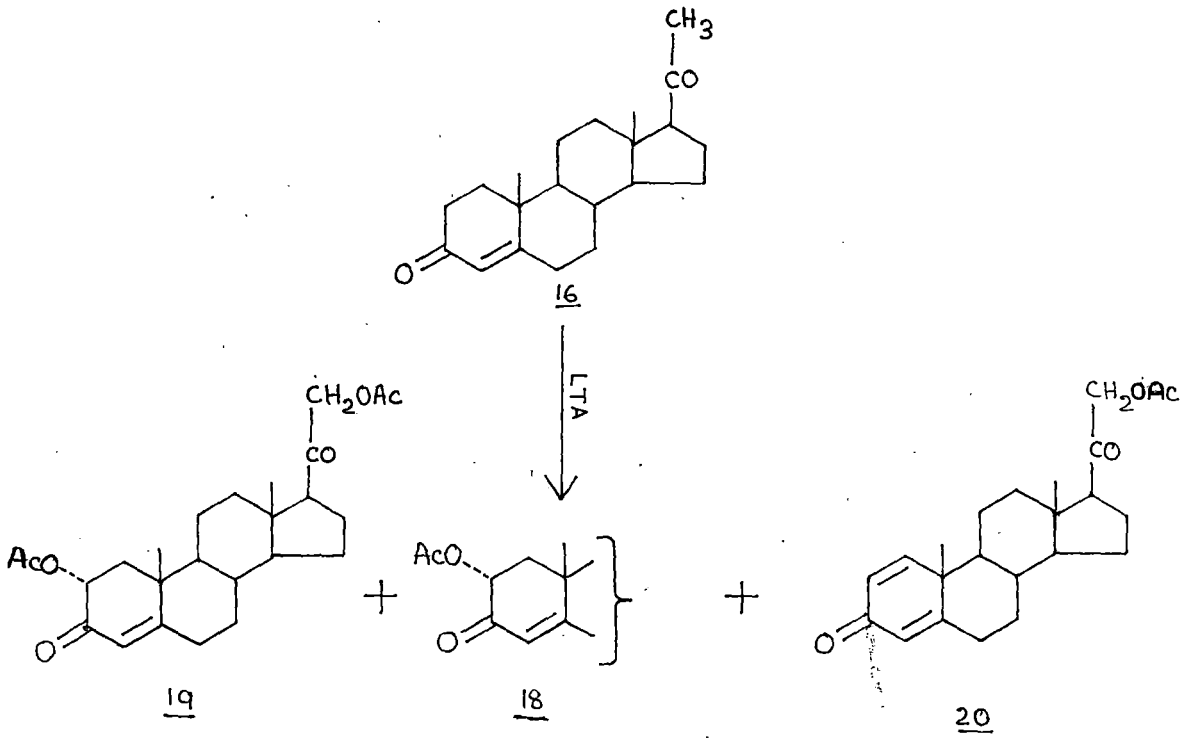
11 12

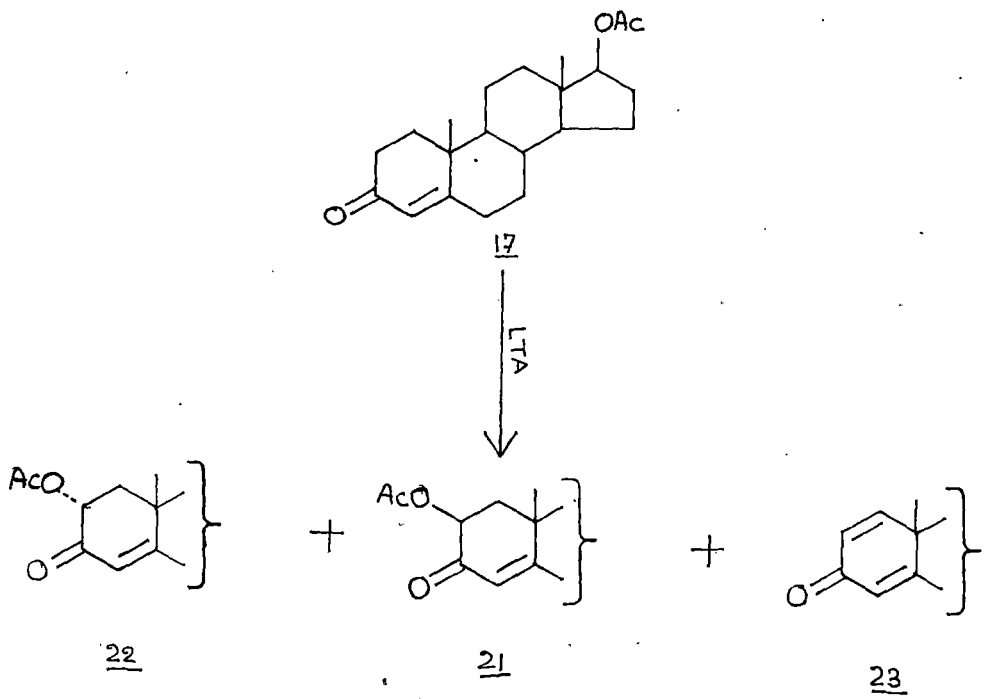
In contrast, the conjugated ketone cholest-4-en-3-one 13 proved less reactive but also gave acetoxylation, in this case at the 2-positionto afford 14[6] with lead tetra acetate in 95% acetic acid. Seebeck and Reichstein[7] also obtained the same product with acetic acid - acetic anhydride. The 2-acetoxy group was shown to be α-oriented by degradation[6] to the known cholestane-2α-ol 15.

(iii) Reaction of lead tetraacetate with progesterone 16 and textosterone 17 :

Clarke and co-workers[8] conducted lead tetraacetate oxydation on progesterone 16 in acetic acid at 85-90° for 6 hr. Three reaction products were obtained by chromatography on Silica gel : 2α-hydroxy progesterone acetate 18 (8%), 2α, 21-dihydroxy progesterone diacetate 19 (16%) and 1,4-pregnadien -21 ol-3, 20 dione acetate 20 (5.1%).

Under almost same condition of acetoxylation, testosterone acetate 17 afforded same mixture of 2β-(unstable configuration) and 2α-(stable configuration) hydroxy testosterone diacetates 21 and 22 as reported by Sondheimer et al[9] and in addition a


CH3
CO
O
16
LTA
CH2OAc
CO
AcO
O
19
+
AcO
O
18
+
CH2OAc
CO
O
20

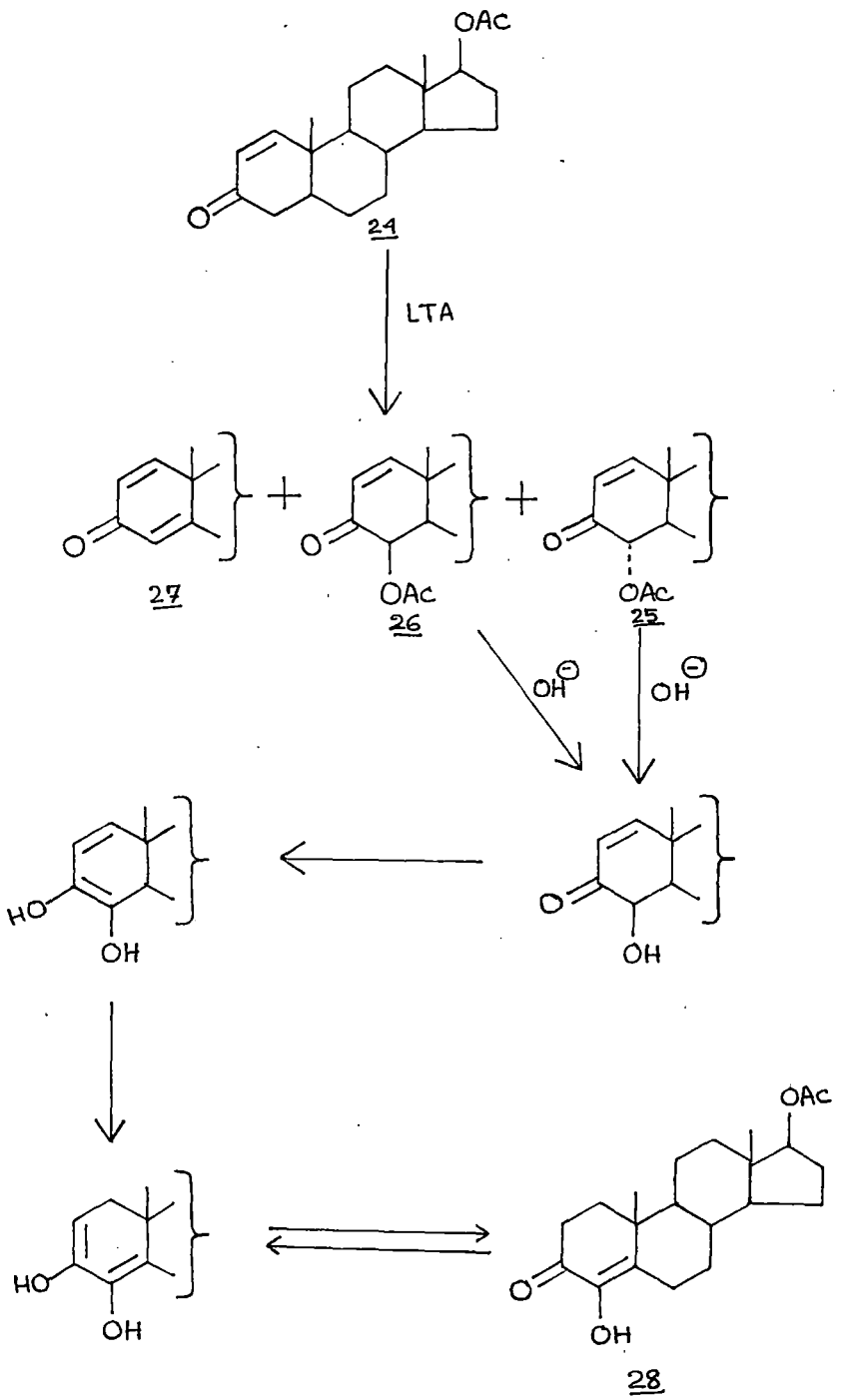

OAc
O
17
LTA
AcO
O
22
+
AcO
O
21
+
O
23

1.5% yield of 1,4-androstedien-17β-ol-3-one acetate 23. 2β-isomer 21 can be easily epimerized to 2α-isomer 22.

(iv) Lead tetraacetate oxidation of 17β-hydroxy 5α-androst-1-en-3-one acetate 24 :

Kaufmann[10] observed that 17β-hydroxy 5α-androst-1-en-3-one acetate 24 on treatment with lead tetraacetate in acetic acid heated on steam bath for 5 hrs furnished 4α, 17β-dihydroxy-5α-androst-1-en-3-one diacetate 26, its 4β-epimer 25 together with the $\Delta^{1,4}$-3-ketone 27. The less soluble β-isomer was separated by direct crystallisation and the α-isomer and the doubly unsaturated ketone by chromatography. The structures of 25 and 26 have been established through alkaline hydrolysis whereby both compounds are converted to the known 4-hydroxy testosterone 28.

Under these conditions, the Δ^1-double bond shifts through different enol intermediates as shown above. The configuration of the 4-acetoxy group has been determined in 25 as α and in 26 as β on the basis of molecular rotation changes relative to the parent compound 24. The UV absorption of 26 shows a λ_{max} at 235 nm, whereas the α-isomer 25 has the same λ_{max} at 230 nm as the parent compound 24. The bathochromic shift caused by the β-substitution confirms the fact that the latter is accompanied by strain in ring A.

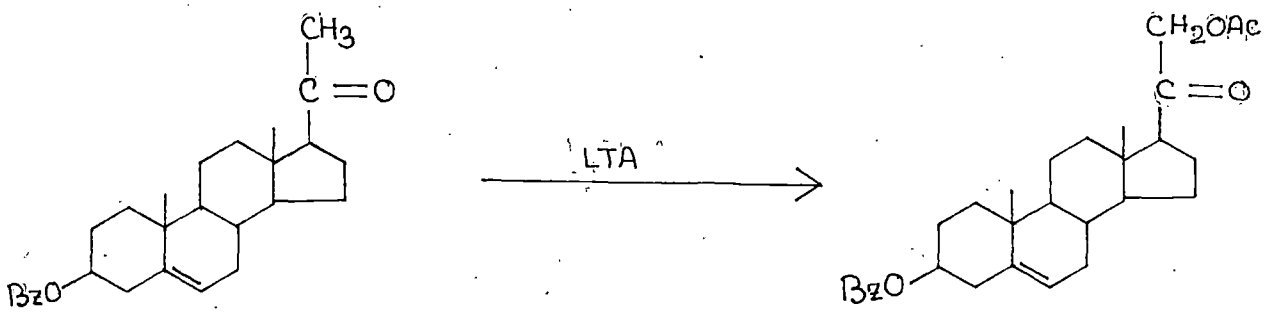

OAc
O
21
LTA
O
27
OAc
26
OAc
25
OH⊖
OH⊖
HO
OH
O
OH
HO
OH
OAc
O
OH
28

(v) Reaction of 3-oxo-4, 5-oxido steroids with lead tetraacetate:

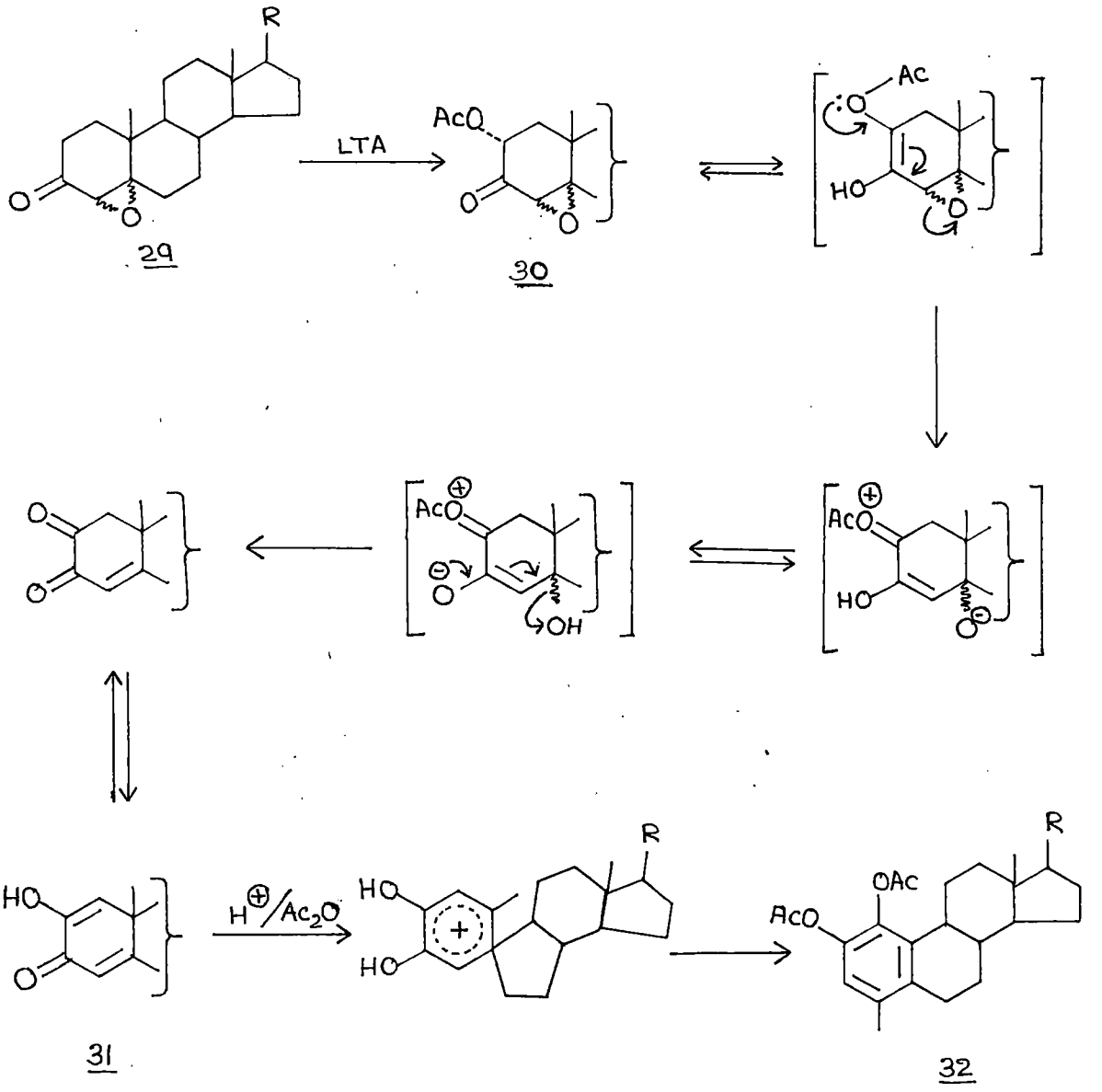
Mihailovic and co-workers[11] observed that treatment of 3-oxo-4,5-oxido steroids 29 with lead tetraacetate in benzene in the presence of $CaCO_3$ resulted in acetoxylation in the 2α-position 30 which was proven by independent synthesis of acetoxylated compounds. The products of this reaction rearrange even under very mild condition e.g. chromatography on Silica or or alumina, to the corresponding 2,3-dioxo Δ^4-compounds 31 which readily undergo dienone phenol rearrangement to afford A-ring aromatic steroids 32. NMR spectra have been extensively applied to elucidate the structure and conformation of the various intermediates. A mechanism of this new transformation has been presented (Scheme - I).

(B) Reaction of lead tetraacetate with 20-keto and 11-keto steroids :

(i) In course of his work on the synthesis of dosoxy corticosterone from pregnenolone Girl[12] carried out reaction of pregnenolone benzoate 33 with lead tetraacetate in acetic acid-acetic anhydride on water bath for 2 hrs and obtained 21-acetoxy derivative 34 (yield ~ 25%).

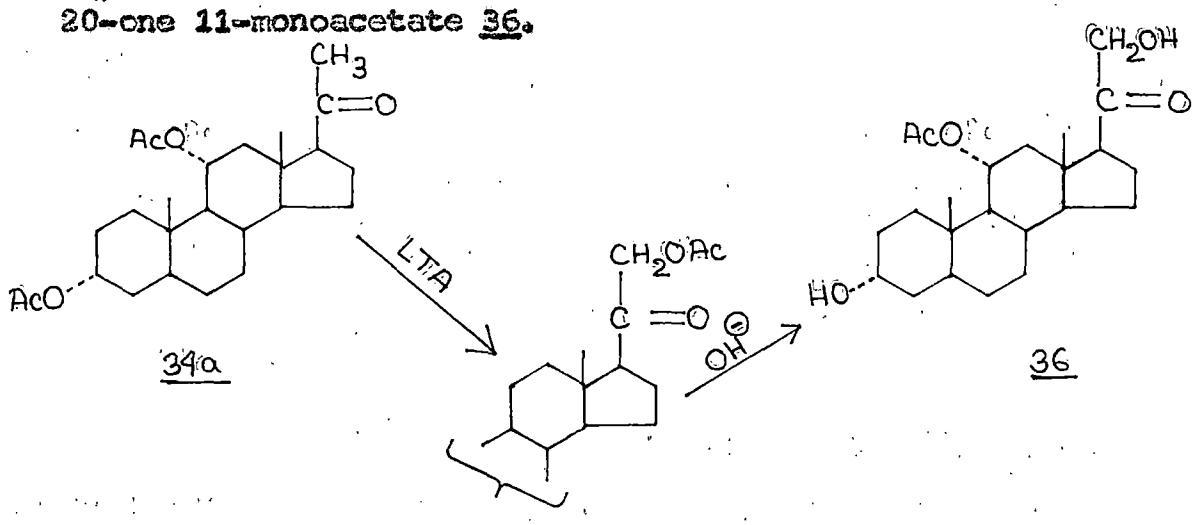


33 34



Scheme - I

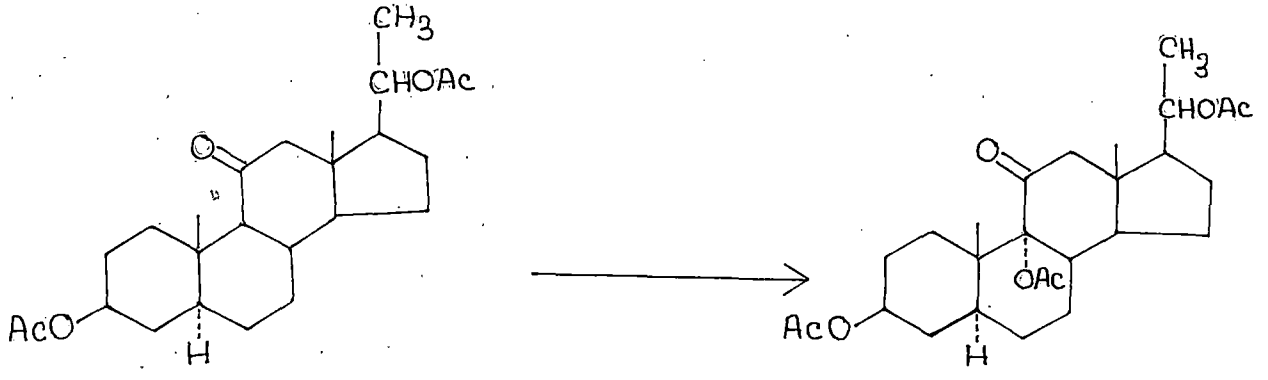
(ii) During the synthesis of Δ^4-pregnene-11, 21-diol, 3,20 -dione diacetate, Djerassi and co-workers[13] performed acetoxylation of pregnan 3α, 11α-diol 20-one diacetate 34a with lead tetraacetate in glacial acetic acid and acetic anhydride at 75° for 16 hrs to afford pregnane-3α, 11α, 21-triol-20-one triacetate 35 (yield 42.5%) which was hydrolysed to pregnane-3α, 21-diol 20-one 11-monoacetate 36.



(iii) Henbest and co-workers[14] carried out detailed studies on acetoxylation of 11-and 20-oxo steroids with lead tetraacetate in the presence of boron trifluoride. Attemptsto use other Lewis acid were unsuccessful in benzene or benzene-methanol. With acetic acid as solvent proton acids did not catalyze the acetoxylation efficiently. Pregnan-20-ones and pregnane 11,20 -dienes react with lead tetraacetate at 25° in the presence of borontrifluoride to give the corresponding 21-acetoxy compounds. The best yield (86%) of 21-acetoxy compounds was obtained, when 5% methanol in C_6H_6 was used as a solvent in the presence of borontrifluoride catalyst at room temperature. Earlier the 21-acetoxylation of 20-oxo steroids with lead tetraacetate in

acetic acid-acetic anhydride has been reported to give yields ranging from 3% from progesterone to 62% from 3α, 11α-diacetoxy 5α-pregnan-20-one. It has been suggested that under the condition stated above borontrifluoride is converted into the protonic acid $H^{+}MeOBF_3^{-}$. Benzene-acetic acid gave 23% yield and no acetoxy-compound when benzene alone was used.

The steroids containing 11-oxo group are relatively unreative e.g. 3β, 20β-diacetoxy 5α-pregnan 11-one 37 gave only 3% monoacetoxylated product in benzene methanol containing BF_3. The same compound was obtained in 15% yield from reaction at 50° in acetic acid. It was formulated[14] as the 9α-acetoxy compound 38 which furnished a triol on alkaline hydrolysis. Acetic anhydride pyridine afforded diacetate and vigorous treatment only afforded the triacetate. The difficulty of esterification of the third hydroxy group is consistent with it being tertiary (9α). When ^1H NMR of the triacetate was compared with the diacetate a new peak corresponding to acetoxy group was shown.

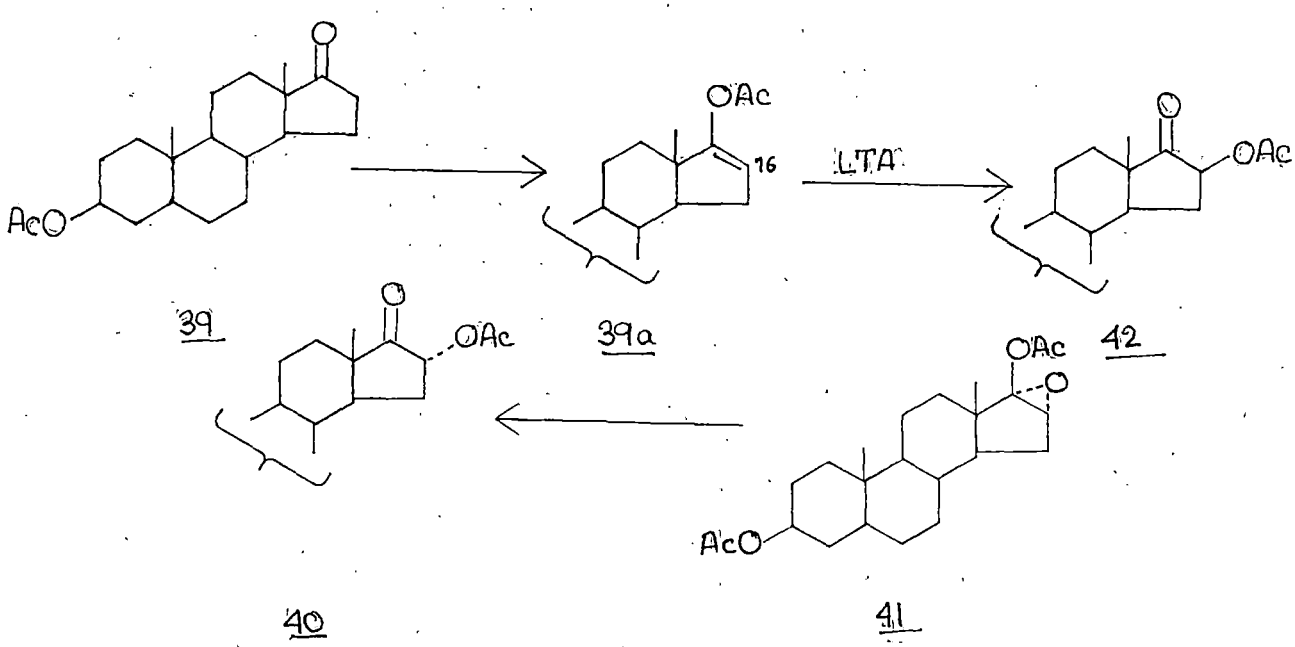


37 38

Both showed a sharp peak at τ 7.6 ascribed to the two protons at the C_{12}-position and no peak corresponding to the >CHOAC of the newly introduced acetoxy group. These observation confirmed the tertiary nature of the introduced acetoxy group and excluded the position of the substituent at C_{12} position. Molecular rotation differences measurements[14] of this and other model compounds substantiated this assignment.

(C) Reaction of 17-keto steroid with lead tetraacetate:

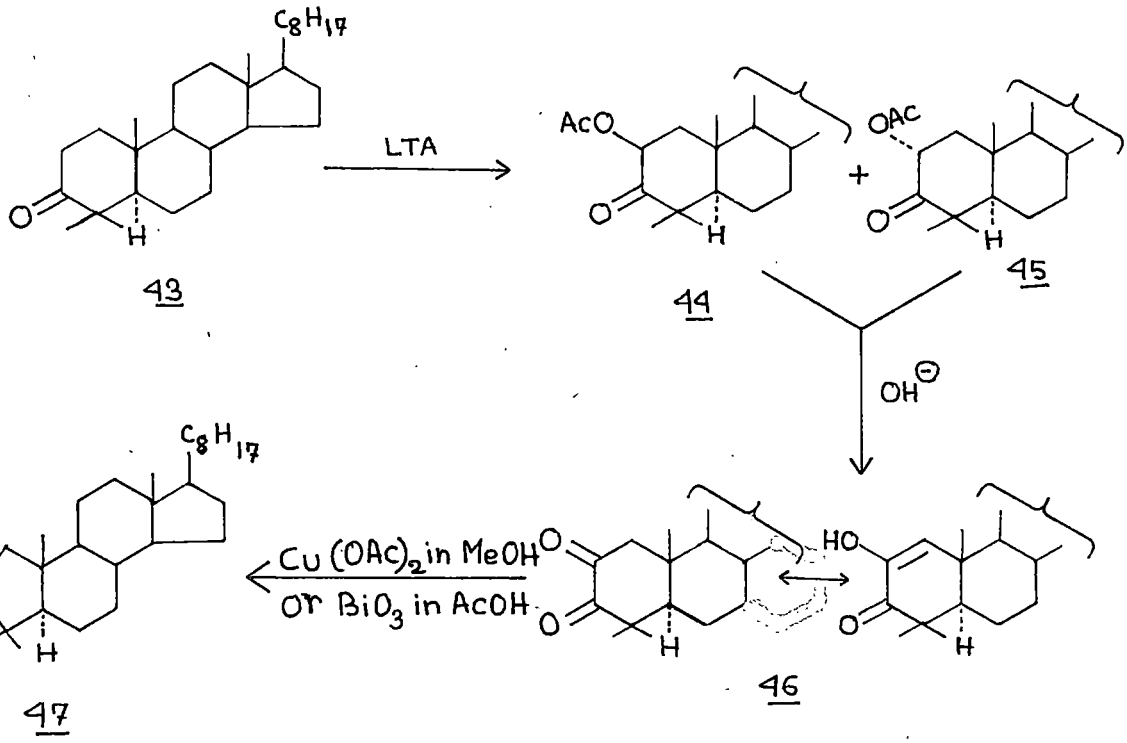
Johnson et al[15] observed that the enol acetate 39a of 3β-acetoxy androstance-17-one 39 with lead tetraacetate at room temperature furnished 57% yield of an α-acetoxy ketone characterized as 3β, 16-diacetoxy androstane-17-one42.They proposed its formation by attack of acetoxy free radical or cation at the nucleophilic 16-position of the enol acetate 39a. It was distinctly different from previously known 16α-acetoxy ketone 40 of known configuration, obtained by the rearrangement[16] of epoxy acetate 41. This lead to the inference that this isomer was the 16β-epimer 42.



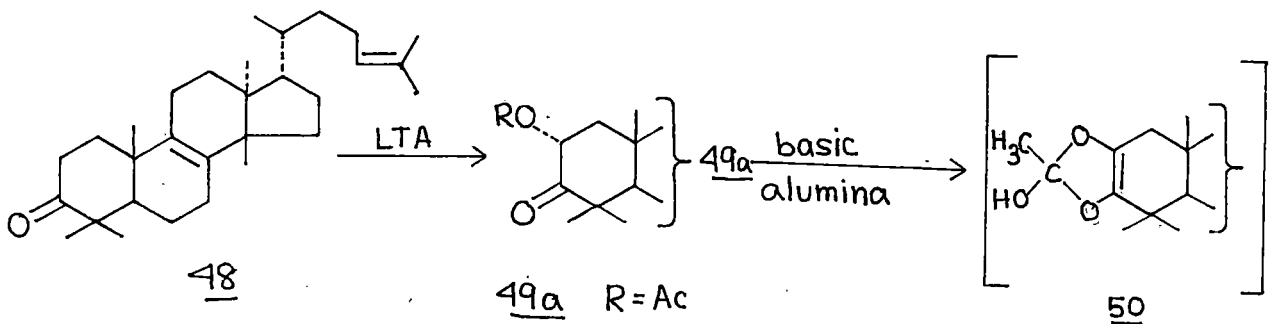
(D) Reaction of 4,4-dimethyl 3-keto steroids with lead tetraacetate :

Jones and co-workers[17] prepared several 2-substituted derivatives of 4,4-dimethyl cholestan-3-one with a view to comparing with certain bitter principles which have been assigned comparable structures for ring A.

Acetoxylation of 4,4-dimethyl cholestan-3-one 43 with lead tetraacetate in AcOH gave a mixture from which the two epimeric 2-acetates m.p. 115° and 147° were isolated. Both were also obtained by acetolysis of 2β-bromo-4,4-dimethyl cholestan-3-one. The $\Delta\lambda_{max}$ and $\Delta\nu_{max}$ (C = O) for both compounds compared with the parent ketone were ± 0 Å and + 24 cm^{-1}, again indicative of the equatorial conformation of the acetoxy group in both cases. The correlation between wave length shifts and the conformation of the acetoxy group is however, they commented, not always valid. The acetate m.p. 147° shows the greater positive amplitude in its Cotton effect. A 2β-bromo and 2β-methoxy 4,4-dimethyl cholestan-3-one shows bigger positive amplitude than the corresponding 2α-derivatives, the acetate of m.p. 147° must be 2β-acetoxy cholestan-3-one 44 with ring A in a flexible conformation and the acetate m.p. 115° is the corresponding 2α-acetate 45. The diosphenol 46 obtained by hydrolysis of the acetates 44 and 45 underwent benzilic acid rearrangement to give the hydroxy acid 47. Consideration of the stereochemistry of the rearrangement indicates that attack of OH^- at either position 2 or 3 of the diketo form of 46 will lead to a β-orientation for the hydroxyl group of the hydroxy acid.



43 44 45 46 47



48 49a 49a R=Ac 49b R=H 50 51

(E) Acetoxylation of the tetracyclic 3-keto triterpene, euphene-3-one with lead tetracetate :

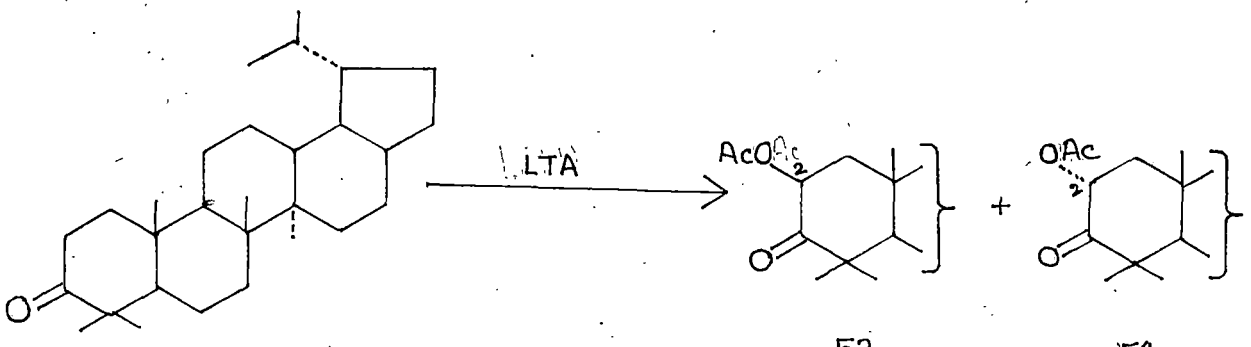
During their work on the introduction of certain groups in ring A of euphol for biological testing to evaluate anti-tumor activity, Lavie and co-workers[18] conducted acetoxylation of euphene-3-one 48 using lead tetraacetate in acetic acid in the presence of BF_3. They isolated the acetoxy ketone which was assigned 2α-equatorial acetoxy configuration 49a . This was due to the approach of the reagent from the less hindered rear face of the molecule. Evidence from PMR has been obtained. The proton at C-2 displayed a quartet of lines centered at τ 4.30 (J_{ae} = 6.5 eps and J_{aa} = 13.0 eps). Upon acid hydrolysis it afforded 2α-hydroxy-3-keto derivative 49b, ν_{max} 1718 cm^{-1}. On passing through a column packed with basic alumina 49a underwent isomerisation to 51. The isomerisation proceeds by enolisation and acyl group migration probably through the cyclic intermediate 50. The rearranged acetoxy ketone 51 which was obtained by various methods described by the authors[18] is, therefore, thermodynamically the most stable derivative in this series.

(F) Lead tetraacetate acetoxylation of pentacyclic 3-keto triterpenes :

i) Reaction of lupanone 52 with lead (IV) acetate :

In connection with the preparations of lupane-1,2-and 2,3-diols McGinnis and co-workers[19] treated lupanone 52 with

lead tetraacetate in acetic acid at 100° for 4 hr and obtained 2β-isomer 53 as the major product and 2α-acetoxy ketone 54 in small amount. The IR and UV spectra of the acetoxy ketones 53 and 54 resemble each other very closely. This is to be expected since the 2α-compound 54 existing in a chair-like conformation and the 2β-isomer 53 in a flexible (boat-like) form will both have equatorial acetoxy groups[17]. However, clear configurational evidence follows from the comparison of the ORD dispersion data for these compounds with those of similar products of established structure, the characteristic differences between the epimers arising from differences in conformation of the rings (Chart I).



52 53 54

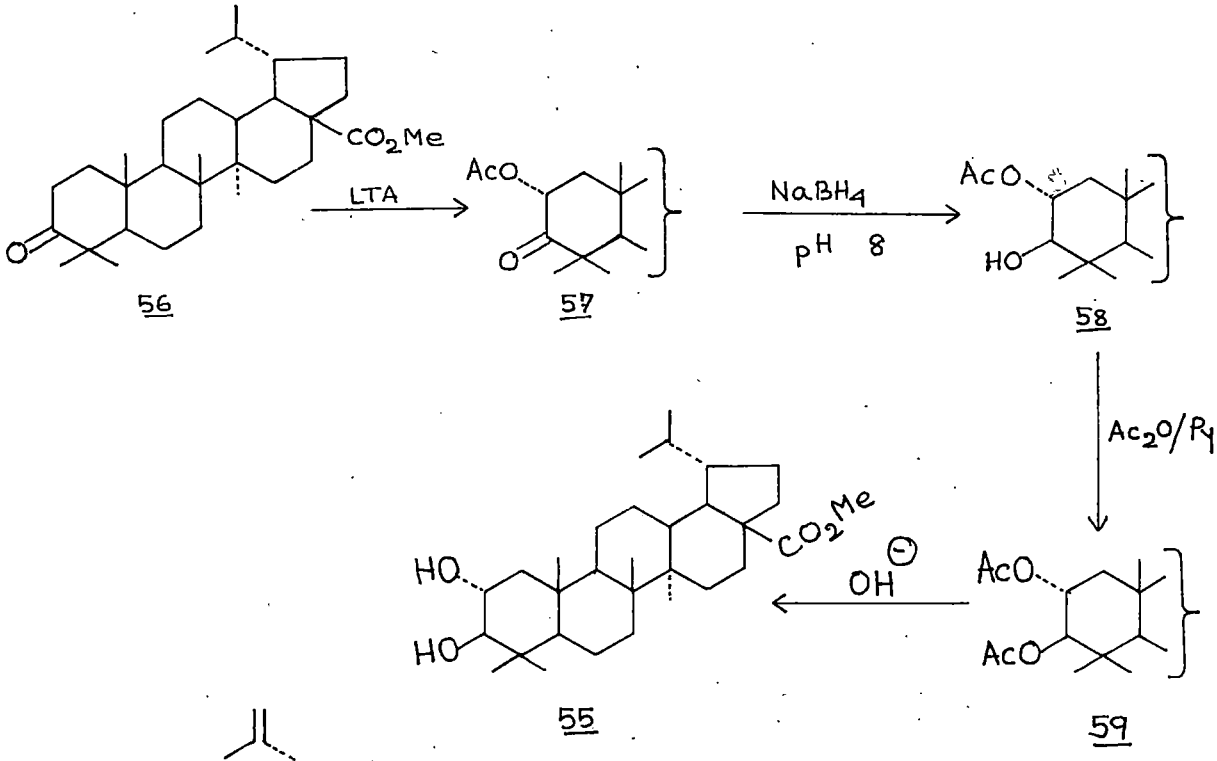
Chart I

	Amplitude* 4,4-dimethyl 5α-cholestan-3-one[17]	Lupan-3-one
2H	- 11°	- 10°
2α-OAc	+ 38°	+ 61°
2β-OAc	+124°	+123°
Δ(2α-OAc)	+ 49°	+ 71°
Δ(2β - OAc)	+135°	+133°

* The difference between the molecular rotation x 10^{-2} at the peak and trough of the Cotton effect.

ii) Lead (IV) acetoxylation of methyl 3-oxo-lupan-28-oate 56:

In achieving partial synthesis of methyl dihydroalphitolate 55 Cheung and Feng[20] carried out acetoxylation α to the 3-oxo group of methyl 3-oxo lupan-28-oate 56 using lead tetraacetate as the key step. This reaction thought to proceed via the enol[21] is expected to yield a product resulting from attack from the less hindred α-side. Even under the mild conditions in which BF_3 catalyst was used[1], an acetoxy ketone $C_{33}H_{52}O_5$ was obtained. The NMR spectrum of the product shows, besides methyl signals due to CH_3CO_2- (τ 7.9) and $-CO_2CH_3$ (τ 6.3) groups, a one-proton quartet centered at τ 4.4. This low-field signal forming the X-part of an ABX system, may be assigned to a methine hydrogen α both to an acetoxy and a carbonyl group. The wide separation (18 Hz) between the outer signals of the quarter



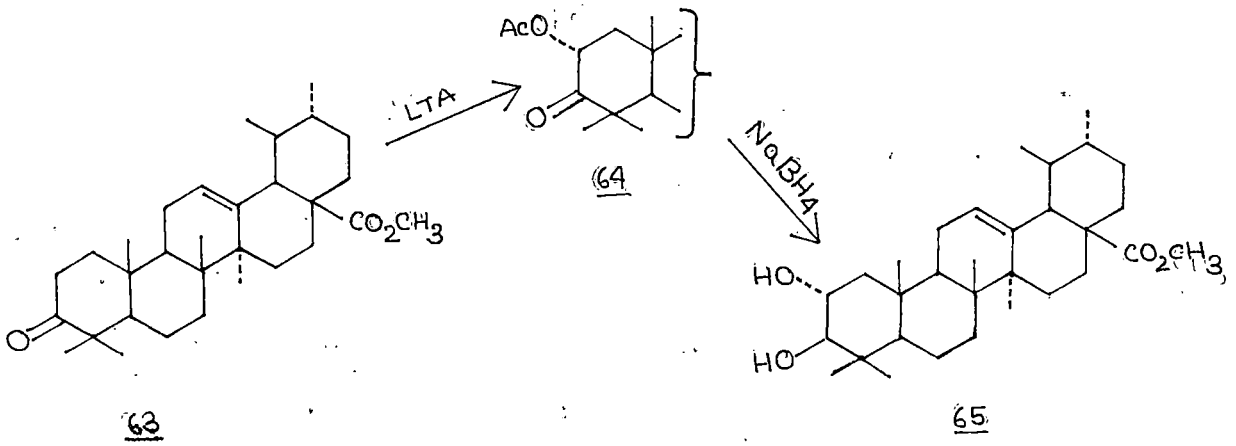
56 57 58 59 55 61 62 60

(J_{AX} + J_{BX}) suggestsan axial configuration for this hydrogen. NMR data are thus in accord with formulation of this product as the 2α-acetoxy-3-ketone 57, borohydride reduction of which at pH 8 to reduce isomerisation gave the crystalline 2α-acetoxy, 3β-alcohol 58 as the major product. The NMR spectrum supported the assigned diequatorial configuration at position 2 and 3. On acetylation it afforded 2α, 3β diacetate 59 which on hydrolysis furnished the targetted compound methyl dihydro alphitolate 55.

(iii) Reaction of methyl betulonate 61 and methyl ursolate 63 with lead tetraacetate :

Kulshreshtha and Rastogi[22] accomplished the partial synthesis of methyl alphitolate 60 starting from methyl betulonate 61. 61 was treated with lead tetraacetate in dry benzene-acetic acid containing acetic anhydride, refluxed for 5.5 hr to afford 2α-acetoxy-3-keto derivative 62. NMR showed a signal for acetoxy group at 2.12 ppm and that for axial methine proton on C-2 bearing the acetoxy group as a quartet at 5.6 ppm (J ≅ 13 and 6 Hz). This confirmed that the introduced acetoxy group on C-2 had an equatorial configuration. This acetoxy ketone on $NaBH_4$ reduction gave methyl alphitolate 60. The stereochemistry of the hydroxy groups was established by NMR spectrum which showed a 1H-doublet at 2.93 ppm (J = 9 Hz) and a 1H multiplet at 3.66 ppm (about 26 Hz wide) due to the methine protons on carbons bearing the hydroxyl groups. The position and splitting pattern of these protons was in agreement with 2α, 3β-configuration of the hydroxyls in the molecule.

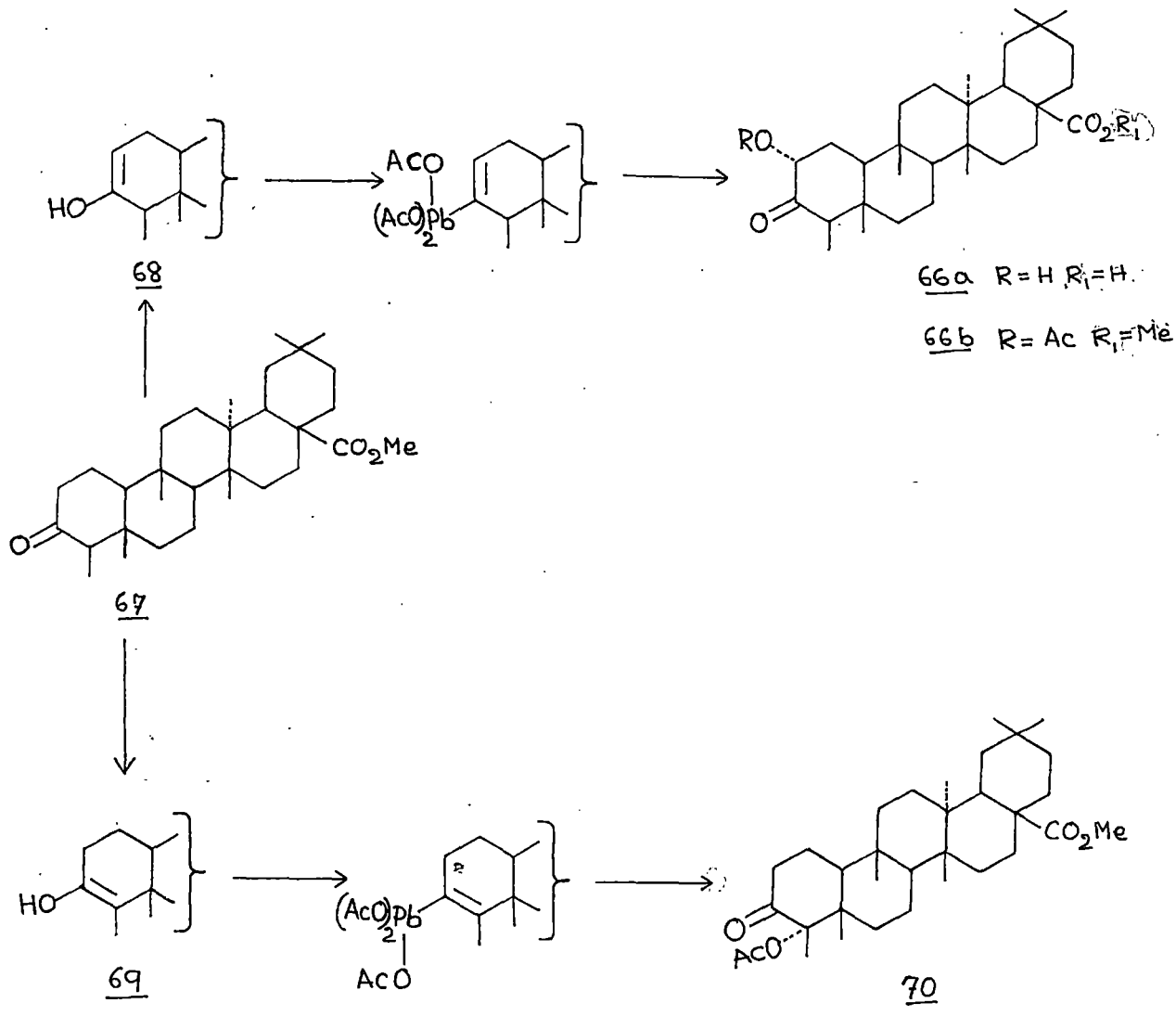
Methyl ursolate 63 on lead tetraacetate reaction[22] under the same condition described above gave 2α-acetoxy 3-keto derivative 64 as an amorphous powder which was characterised by its NMR spectrum. This on $NaBH_4$ reduction gave methyl 2α-hydroxy ursolate 65 m.p. 205°, yield 26.7%, which was characterised by IR and NMR.



63 65

(iv) Lead (IV) acetate oxidation of methyl 3-oxo-canophylate 67

During their work on the structure elucidation of 2α-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid 66a obtained from the plant Euonymus revolutus (celastraceae), Kumar and co-workers[23] carried out a partial synthesis of its acetoxy methyl ester derivative 66b. Methyl-3-oxo-canophyllate 67 was treated with lead tetraacetate in glacial AcOH and BF_3-ether at 27°C for 2 hr in the dark. Since this reaction is believed to go via enolisation, the formation of two enols has been envisaged 68 and 69 (Scheme - II). Acetoxylation would then occur to the less hindered α-face, thus giving rise to two


HO
ACO
(AcO)2Pb
RO
O
CO2R1
68
66a R=H R1=H
66b R=Ac R1=Me
CO2Me
O
67
HO
69
(AcO)2Pb
AcO
O
AcO
CO2Me
70

Scheme-II

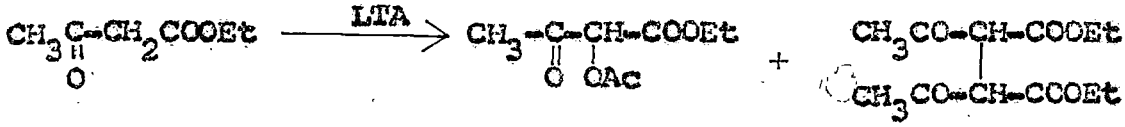
monoacetates 66b (30%) and 70 (60%)[24]. The less polar compound 66b showed IR bands at 1745, 1720 and 1235 cm^{-1} and ^1H NMR resonances at δ 4.95 (1H, m $W_{\frac{1}{2}}$= 7 Hz, 2β-H), 3.66 (3H, S, CH_3O), 2.12 (3H, S, CH_3CO) and 1.03-0.69 (7 x CH_3). The more polar compound 70 exhibited IR bands at 1755, 2725 and 1235 cm^{-1} and ^1H NMR peaks at δ 3.66 (3H, S, CH_3O), 2.06 (3H, S, CH_3CO), 1.83 (3H, S, 23-CH_3) and 1.06-0.72 (6 x CH_3).

Mechanism of "α"-acetoxylation of ketones with lead tetraacetate

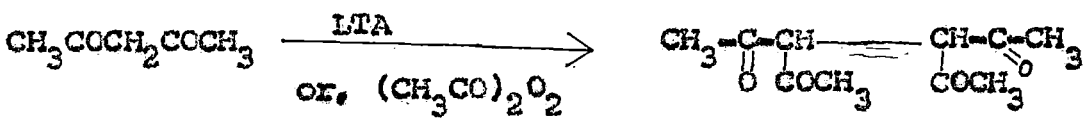
Because of its potential synthetic applications, quite a good amount of work on the mechanistic aspects of the lead tetraacetate reaction of ketone has been carried out.

From the studies of the kinetics of the reactions between lead tetraacetate and acetone, acetophenone and its p-chloro and p-bromo derivatives in acetic acid Ichikawa and Yamagudhi[25] noted that the process is of first order with respect to the ketone and independent of the lead tetraacetate concentration and similar to the rates of halogenation of ketones. These observations indicate that the enolization of the ketone is the rate determining step. The case of oxidation of β-diketones and β-oxo-esters, studies conducted by Cavill and Solomon[26], support the above hypothesis. In addition, the dimeric products 73 and 75 isolated from the oxidations indicate a free-radical mechanism e.g. ethyl acetoacetate 71 in benzene at 10° readily afforded ethyl α-acetoacetate 72 and ethyl α,α-diacetyl succinate 73 and acetyl acetone 74 gave 3,4-diacetyl hexane-2,5 dione 75 which was also obtained from the reaction of acetyl acetone with

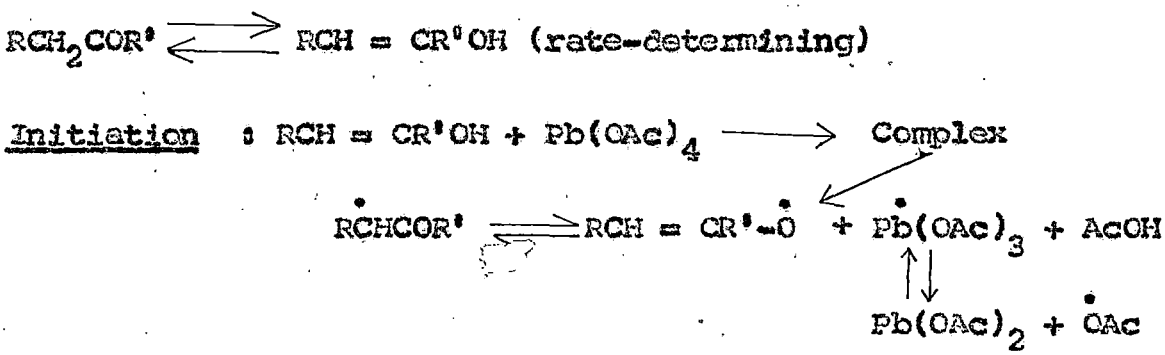
acetyl peroxide at 80°.



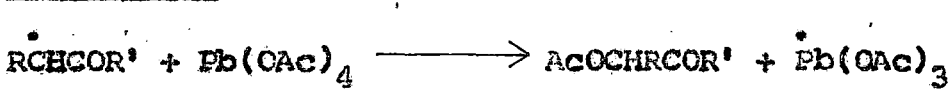
71 72 73



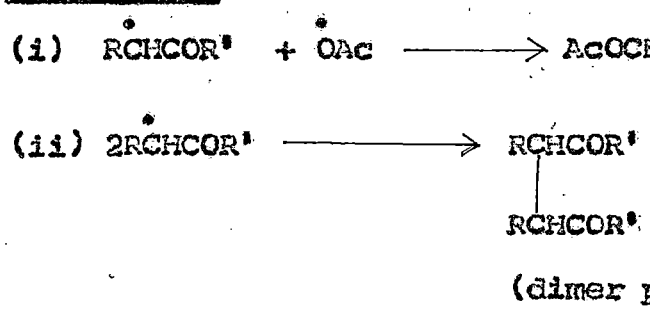
74 75



Propagation:



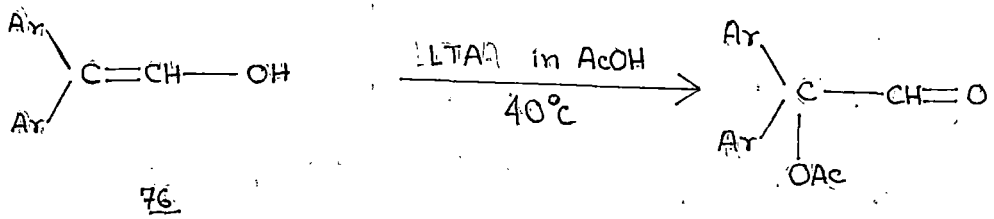
Termination:



(dimer product)

Fuson and co-workers[27] conducted studies on the reaction of vinyl alcohols with lead tetraacetate. Five 2,2 diaryl vinyl

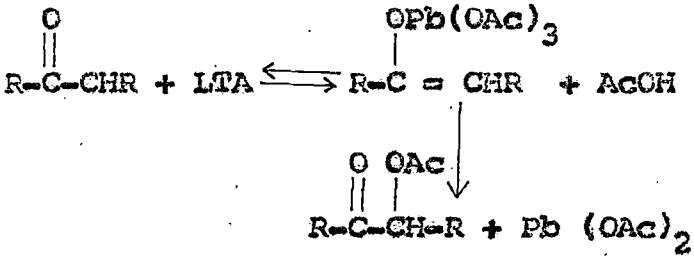
alcohols of the type 76 - 2,2-dimesityl vinyl alcohol, 1-mesityl-2-phenyl, 2-(3-bromomesityl)-2-phenyl, 2-isodiaryl-2-phenyl and 2-mesityl-2-(p-tolyl) vinyl alcohols were treated with lead tetraacetate in acetic acid at 40° to afford corresponding acetoxylated products 77 in high yield (~85%). This observation that the carbonyl compounds which exist primarily in their enol form react with lead tetraacetate with unusual ease would seem to lend further support to the proposal, put forward by Cavill and Solomon[26], that enolisation is the rate-determining step in acetoxylation by lead tetraacetate.



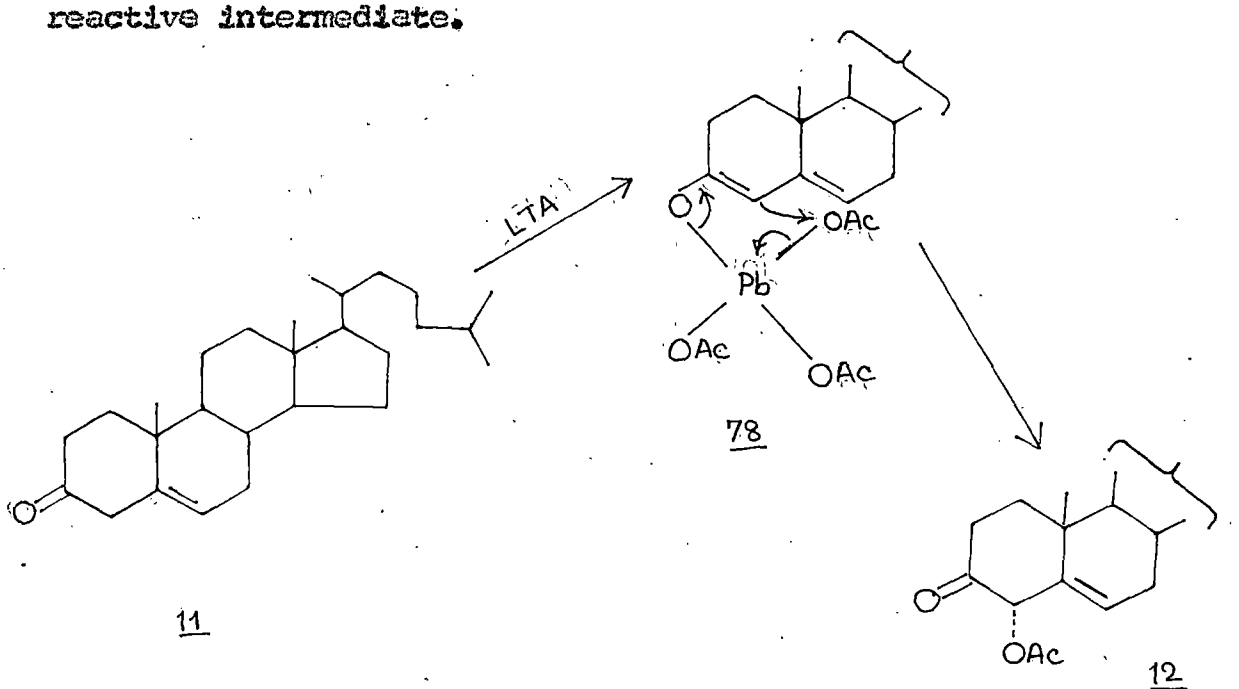
76 77

During their study on the mechanism of oxidation of ketones by selenium dioxide Corey and Schaefer[28] proposed that the rate determining step in the oxidation of desoxy benzoin is the formation of an enol selenite ester directly from the ketone by a process mechanistically related to enolisation in which the electrophilic-nucleophilic pairs are $H_3SeO_3^+$ and H_2O (acid catalysed process) and H_2SeO_3 and OAc^- (base-catalysed process). This type of mechanism perhaps is operative in case of α-acetoxylation of ketones by lead tetraacetate. The formation of enol-lead triacetate derivative may be involved directly from

the ketone followed by subsequent internal rearrangement-elimination.



The formation of 4α-acetoxy-cholest-5-en-3-one 12 from cholest-5-en-3-one 11 studied earlier by Fieser and Stevenson[5] can now be interpreted as a preferential α-face attack upon the enolic-3, 5-diene. The stereochemistry of acetoxylation has a resemblance with the sterically-controlled 4α-deprotonation of the Δ^5-3-ketone[29] but electrophilic attack at C-4 rather than at C-6 in the neutral enol is abnormal and probably suggests that acetoxy transfer occurs via a cyclic transition state 78 with the reagent bonded to the C_3-oxygen substituent. This enol triacetoxy plumbate has also been advocated by Corey[28] as a reactive intermediate.

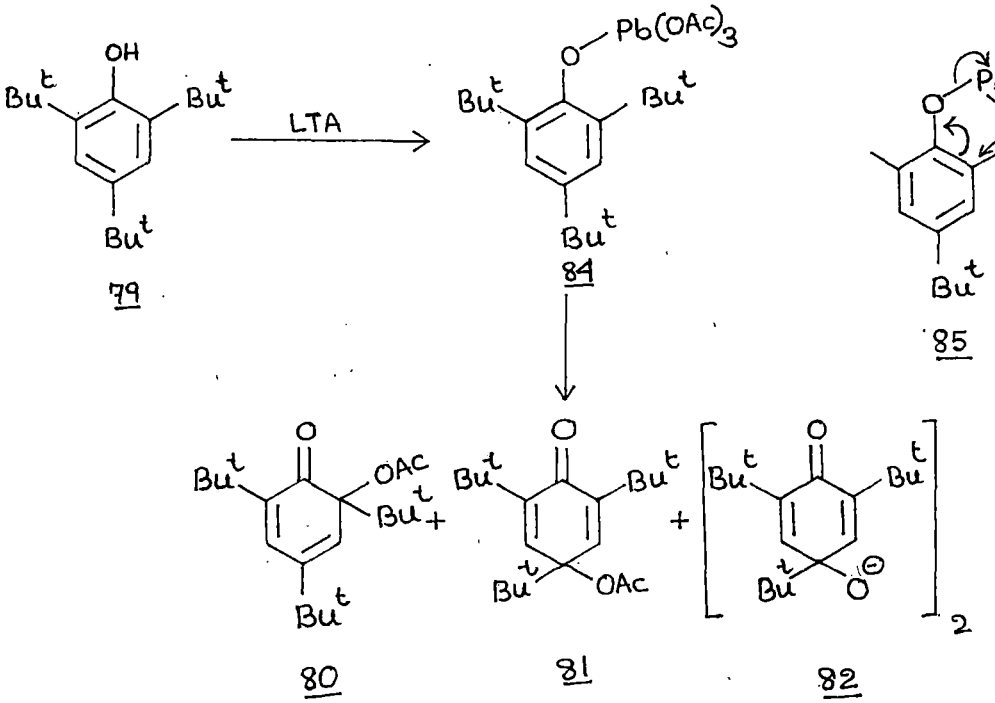


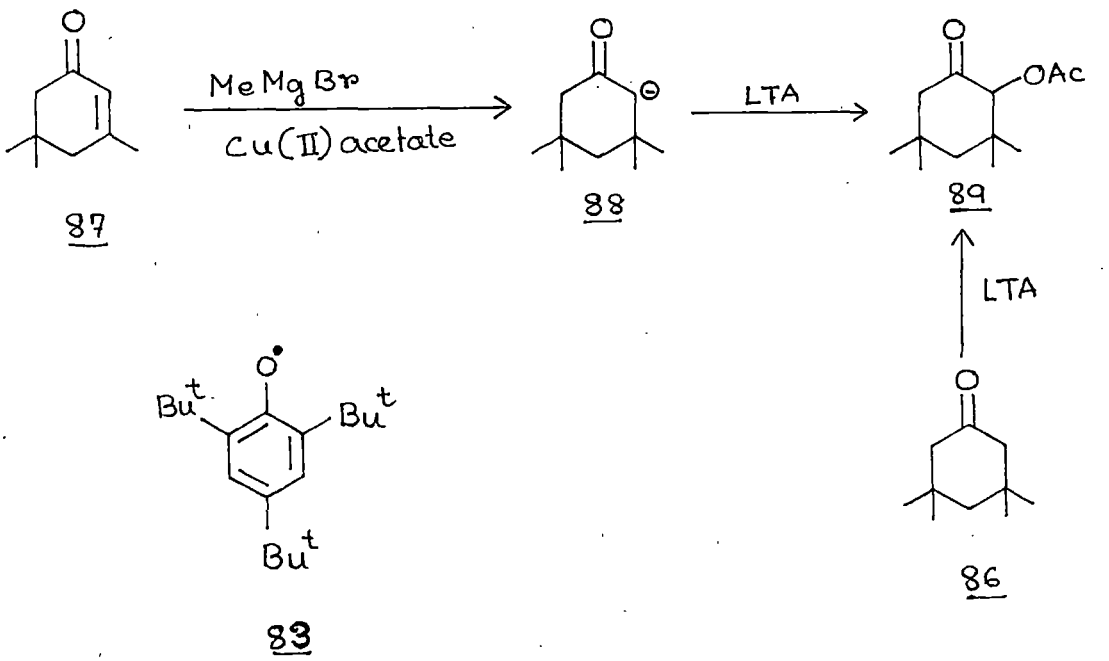
11 78 12

The rapid reaction of enols seems to suggest a mechanism similar to that suggested for the oxydation of monohydric phenols where the reaction is believed to proceed through an intermediate organolead ester[28,30,31].

Harrison and Norman[31] carried out lead tetraacetate oxidation of 2,4,6-tri-t-butyl phenol 79 in acetic acid, benzene and dichloromethane and obtained 2-acetoxy derivative 80, 4-acetoxy derivative 81 (2:4:1) and a peroxy derivative 82. In the presence of methanol, the methoxy analogues of the acetoxy derivatives along with the acetoxy derivatives are also formed. This together with the finding that the 2,4,6-tri-t-butyl phenoxyl radical 83 is relatively inert towards lead tetraacetate, provided evidence that the products are derived from two-electron oxidations. They invoked the formation of aryloxy lead derivative 84 which suffers heterolysis either before or synchronously with reaction of methanol or acetic acid as a nucleophile. The much higher 2:4-ratio for acetoxylation than for methoxylation suggested that acetoxylation at the 2-position, at least in part, occurs intramolecularly by the electron redistribution as shown in 85.

Hanbest and co-workers[1,14] added boron tri-fluoride etherate to mixture of ketones with lead tetraacetate in benzene containing 5% methanol and obtained excellent yields of 'α'-acetoxy ketones from C_2-, C_3- and C_{20}-ketones[14]. The exact mechanism is uncertain, but boron tri-fluoride may function in this solvent mixture as the proton acid, $H^+MeOBF_3^-$ which promotes enolisation[14]. This interesting finding that ketones are more


OH
Bu^t
LTA
Pb(OAc)3
Pb(OAc)2
OAc
79
84
85
80
81
82
2


MeMgBr
Cu(II) acetate
LTA
OAc
87
88
89
86
83

reactive under condition favourable for enolisation, strongly supports the proposition that the enol form is to be regarded as the reactive species.

Ellis[32] observed that the formation of acetoxy derivative takes place at a position "α" to a carbonyl group even when other positions are available. Ellis[33] also presented convincing evidence in support of the enolate anion as an intermediate for the acetoxy ketone. He conducted reaction of lead tetraacetate with enolates. Since the enol acts as a nucleophile the corresponding enolate ion should react more rapidly. He reasoned that the enolate would not only be more nucleophilic than the enol but could be obtained in a much higher concentration. Isophorone 87 was treated with Grignard reagent to generate enolate ion 88 which was trapped with lead tetraacetate at room temperature for 18 hrs to give the known acetoxy ketone 89 in high yield (60%). Thus, the enolate reacted much faster than the ketone 86 to produce the α-acetoxy ketone in much better yield.

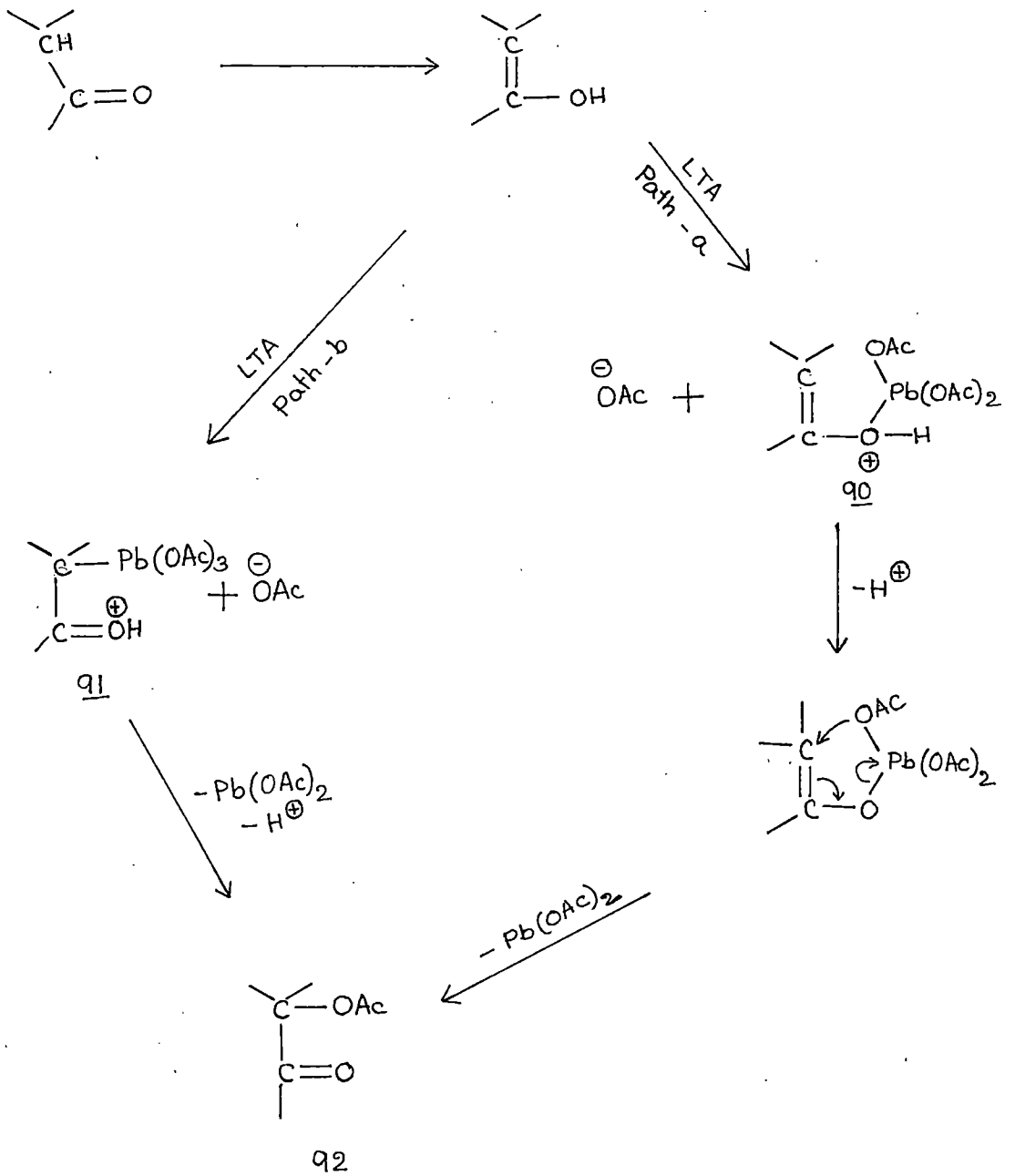
2-Adamantanone which can not enolize, was recovered unchanged on treatment with lead tetraacetate suggesting that an enol is a required intermediate in the formation of acetoxy ketones.

All of the previous results point to the involvement of the enol form of the carbonyl group. However, Moon and Bohm[34] carried out lead tetraacetate reaction with unsymmetrical ketones, 2-butanone, 2-octanone, 3-methyl-2-butanone and phenylacetone.

They argued that if enolization is indeed the rate-controlling factor this should be reflected in deuterium exchange studies. They used NMR spectroscopy for studying the rates of enolisation at the two positions of these ketones. Their deuterium exchange study indicated that 2-butanone had a faster rate of enolisation for the methylene position than for the methyl position. For 2-octanone and 3-methyl-2-butanone, the rate of enolisation for both positions was nearly equal. While for phenyl acetone the rate of enolisation for the methylene group was greater than for the methyl group. The detailed study carried out by them[34] indicates that the products ratio of acetylation and enolisation rates do not correspond well. These workers, therefore, suggested that although enols were clearly involved in the reaction, enolisation may not always be the rate determining step.

The initial site of attack of lead tetraacetate on the enol form has not been determined although attack at the oxygen atom[35] seems to be inferred by most workers by analogy with the reactions of alcohols.

In conclusion, normal pathway for lead tetraacetate acetoxylation of ketones may be represented schematically as illustrated below[35]. The reaction may involve an initial (Scheme III) electrophilic attack on the lone pair of the -OH group, generated by enolisation of α-methine ketones, to produce organo lead intermediate 90 (via pathway a) followed by intramolecular donation of an acetoxy group to the adjacent carbon to give the acetoxy ketone 92. Alternatively, initial attack may occur at the methine carbon (via pathway b) to produce the ester 91


CH
C=O
C
C—OH
LTA
Path - a
LTA
Path - b
⊖
OAc +
OAc
Pb(OAc)2
C
C—O—H
⊕
90
-H⊕
Pb(OAc)3 ⊖
+ OAc
C
⊕
C=OH
91
OAc
Pb(OAc)2
C
C—O
-Pb(OAc)2
-H⊕
-Pb(OAc)2
C—OAc
C=O
92

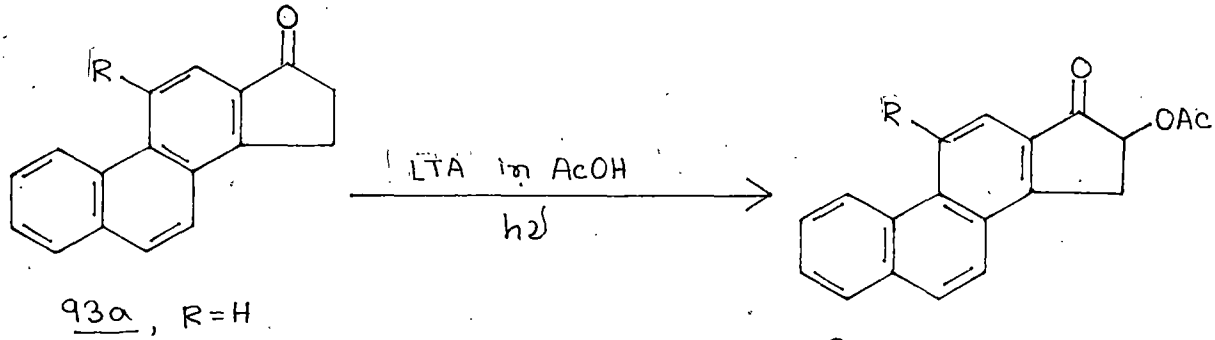
Scheme - III

which subsequently by an internal 1,2-acetoxyl migration or an external attack by acetate ion[35] yields the acetoxy ketone 92 (Scheme - III).

Hanbest et al[1,14] concede that by-products arising from dehydrogenative coupling at high temperature are indicative of a competing radical reaction. Isolation of the dimeric products 73 and 75 from the lead tetraacetate reaction of ethyl aceto-acetate and acetyl acetone, respectively by Cavill and Solomon[26] lends support to the high temperature radical reaction pathway.

Cavill and Solomon[26] further noticed that the dehydro-dimer 75 can be obtained under radical generating condition using acetyl peroxide. Coombs[36] carried out lead tetraacetate acetoxy-lation of 15,16-dihydro cyclopenta (a) phenanthrene-17-one 93a and its 11-methyl hologue 93b under photolytic condition and obtained the corresponding acetoxy-ketone 94a and 94b in moderate yields.

Thus, the foregoing observations lead to the proposition that lead tetraacetate acetoxylation of ketones under certain conditions can be operated through radical mechanism.



93a, R = H

93b, R = Me

94a, R = H

94b, R = Me