PART - I

PHOTOCHEMICAL SYNTHESIS OF THE NATURALLY OCCURRING TRITERPENE LACTONE, 3β-HYDROXY LUPAN - 28, 13β - OLIDE AND CHIROPTICAL (CD) MEASUREMENT OF THIS AND RELATED LACTONES

CHAPTER - I

A Short Review on the Mechanism of Intramolecular Cyclization of Alcohols by Oxidation with Pb(IV) Acetate or by Hypohalite Reaction.

Because of its potential synthetic applications intramolecular cyclization of alcohols to tetra hydro furans and at lesser extent tetrahydro pyrans by oxidation with Pb(IV) acetate (LTA) or by hypoiodite reactions, has been widely studied. A good amount of the mechanistic study has also been carried out[1,2]. Here a brief report is presented on the mechanistic aspects of this synthetically useful reaction.

The successful methods developed so far for the functionalization of angular methyl groups or substitution of methylene and methine hydrogens proceed through high energy intermediates which can attack unactivated C-H bonds. For achieving desired selectivity, the attacking species is generated at a centre which is sterically fixed in close proximity to the carbon being substituted. On close inspection of Dreiding models it is apparent that the rate of hydrogen abstraction reaches a maximum at the inter nuclear distances between oxygen and the substituted carbon of 2.5-2.7A^{o}[1]. The rate rapidly falls off with increasing distance and becomes very slow at a distance above 3A^{o}. The yields are still fairly high if the stable conformer of the substrate maintains the optimal C-C distance, even though the oxygen and the substituted carbon is not rigidly fixed.

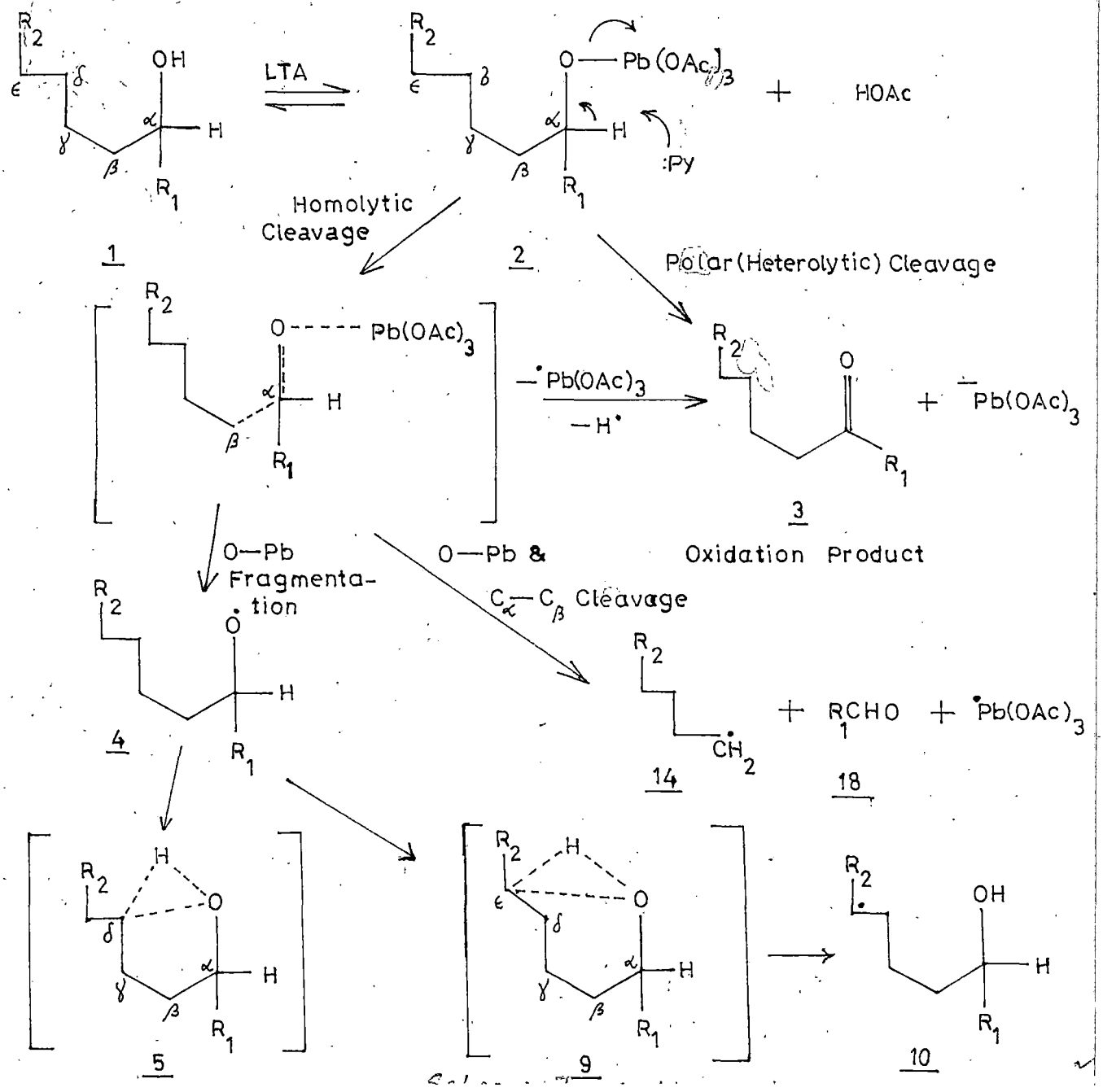
(A) Oxidation with Lead tetraacetate:

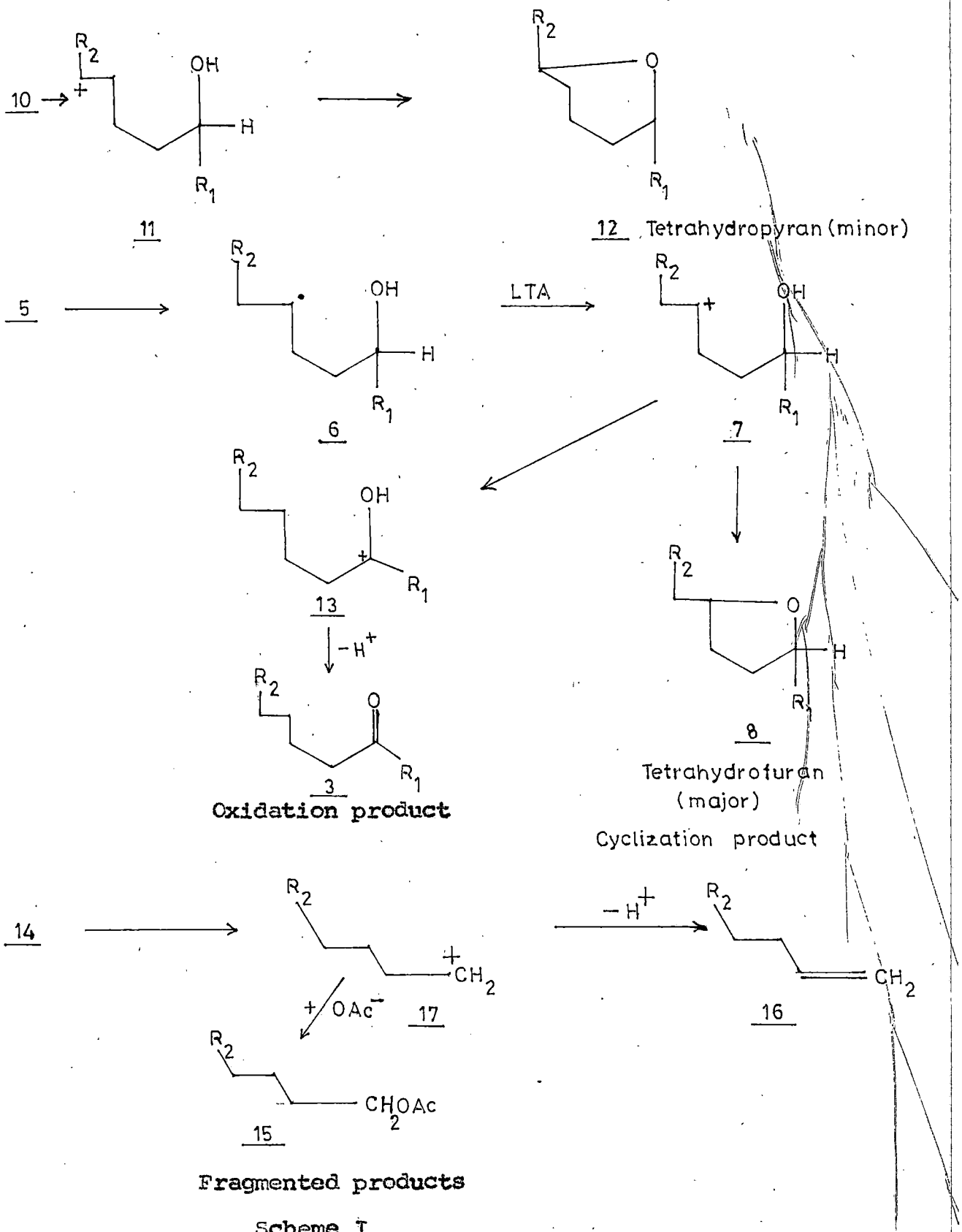
The initial intermediate resulting from the interaction of lead tetraacetate with an alcohol is thought to be an alkoxy lead acetate species which can decompose either thermally or photolytically. The overall cyclization[3,4] is considered to proceed via the mechanism depicted in Scheme I. This organo lead intermediate 2 which is formed reversibly from alcohol 1, has never been isolated but is generated in situ and hence intermolecular hydrogen abstraction e.g. from the solvent does not reduce the yield of product, provided that an excess of oxidant is present.

From the model experiments with different aliphatic alcohols it has been shown that apart from synthetically most important cyclic ethers other two i.e. oxidation and fragmentation products are also formed in comparable yields. In addition, acetylation product of the starting alcohol is also formed occasionally. The orientation of these three different types of products in the lead tetra acetate reaction depends on the substrate and the conditions[5,6]. Almost the same results were obtained by Mihailovic[5] and co-workers using aliphatic primary and secondary alcohols in the range C_5 - C_8 and by Kalvoda[6,3] employing 4β , 6β and 11β hydroxy steriods as substrates.

The cyclic ethers are obtained in 40-50% yield using a non polar solvent e.g. benzene and the yield of oxidation product, the ketone 3, is low. Increasing the amount of pyridine,

a polar solvent, in benzene or in pyridine alone with alcohol having potential cyclization site the orientation is effectively reversed and yield of carbonyl compounds considerably increase and lesser yields of cyclic ethers are obtained. In pyridine alone yield of carbonyl compounds may be so increased (~80%) that it becomes synthetically useful technique to afford ketone from alcohol under very mild condition[7].




10
11
12 Tetrahydropyran (minor)
5
6
LTA
7
13
-H+
3
Oxidation product
8
Tetrahydrofuran
(major)
Cyclization product
14
17
+OAc⁻
15
Fragmented products
-H+
16

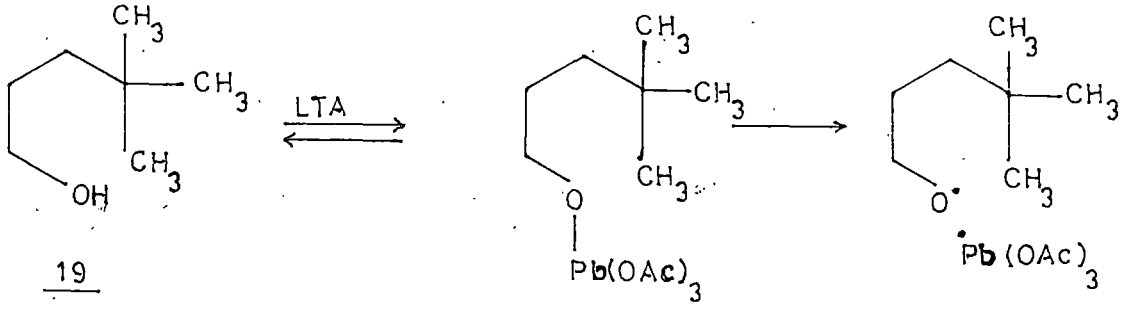
Scheme I

In general, the presence of pyridine strongly favours the dehydrogenation of the alcohols to corresponding aldehyde or ketone and the cyclization and fragmentation are suppressed. Detailed studies concerning the effect of polar and non polar solvents and other evidence led to the supposition that alkoxy lead triacetate intermediate 2 may suffer a rapid polar elimination of an α-proton (H^+) and $Pb(OAc)_3^-$ by the action of a base to give a ketone 3 heterolytically or a slower homolysis of the O-Pb bond to furnish the alkoxy radical 4. The formation of which can be induced thermally[3,5] or photolytically by U.V. radiation at room temperature[11,12]. With a view to gaining an insight concerning the relative importance of these two routes triaryl methanols were subjected to oxidative reaction with lead tetraacetate in acetic acid, acetonitrile and benzene by Norman and Watson[9]. Based on analysis of rearrangement products they presented evidence to demonstrate that in the first two solvents the reaction predominantly follows ionic path while that reaction in benzene predominately goes through free radical chain mechanism occurring respectively through the heterolysis and homolysis of the O-Pb bond of the alkoxy lead derivative. The radical rearrangement was initiated by perkadox (di - isopropyl peroxy dicarbonate) and in benzene it was inhibited by p-benzoquinone, a radical inhibitor. Mention may be made in this context that the e.s.r spectra of alkoxy radicals are difficult to observe in solution because the P_x and P_y orbitals are degenerate allowing the unpaired electron

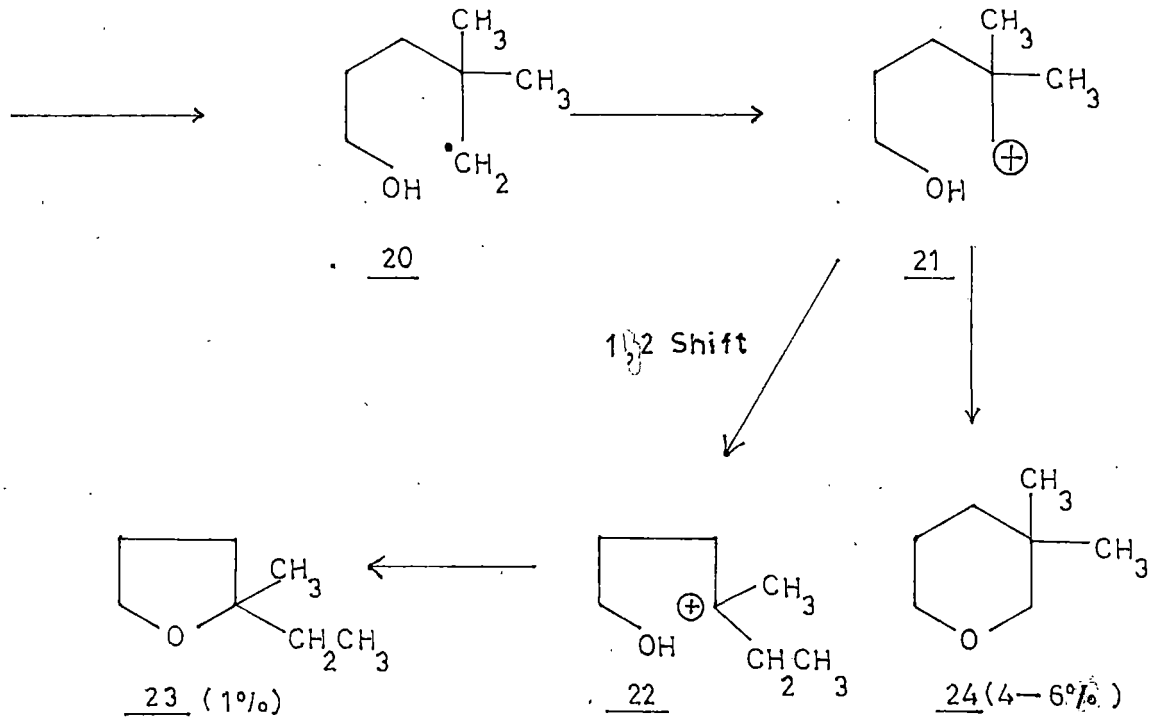
to have orbital angular momentation about the Z-axis with consequent broadening of the spectrum[10].

The most important step in the entire lead tetraacetate reaction sequence is the cyclization which is actually responsible for functionalization at "unactivated" carbon atom. The ability of alkoxy radical 4 to effect cyclization by abstracting a H atom intramolecularly by attacking a suitably placed C-H bond on the δ-carbon atom giving ultimately an ether 8, tetrahydrofuran, preferentially and at lesser extent gives rise to tetrahydropyran 12 by extraction of H from ϵ carbon atom. The predominant formation of five membered cyclic product 8 rather than six-membered tetrahydropyran 12 which are formed in low yield even with substrates for which five-membered cyclization can not occur, is explained in terms of the relative stability of the transition state 5 as against the cyclic seven-membered analogue 9 which would be necessary for cyclization at the ϵ-C atom to a tetrahydropyran product. Based on the studies of lead tetraacetate cyclization of steriod alcohols[8] it appears that a linear conformation of C, H and O in the transition state 5 or 9 is not indispensable for hydrogen transfer. However, for aliphatic alcohols[13,14] if the linearity factor is of importance, both the ring transition states 5 and 9 should be of similar energy, but tetrahydrofuran formation would again be preferred to tetrahydropyran formation, since

the probability of attaining an approximate linear conformation of C, H and O in the transition state is higher in a quasi-six-membered ring corresponding to 5 than in a quasi-seven-membered ring corresponding to 9. It has been postulated that ethers are formed via the hydroxy alkyl carbonium ion 7 or 11 generated from the hydroxy alkyl radical 6 or 10 by one electron oxidation with lead tetraacetate or lead triacetate radical $[\cdot Pb(OAc)_3]$. The formation of a small amount of the rearranged ether, 2-ethyl-2-methyl tetrahydrofuran 23 from 4,4-dimethyl-1-pentanol 19 indicates that cyclization reaction possesses a carbonium ion character[15b]. Since the available evidence indicates that alkyl radicals usually do not undergo 1,2-hydrogen or 1,2 alkyl shift[16], it is necessary to assume that the hydroxy alkyl radical 20 is transformed to a primary carbonium ion 21 by a one-electron oxidation process. This primary neopentyl type carbonium ion 21 can either undergo cyclization to afford the normal reaction product i.e. tetrahydropyran 24 or else it can rearrange by a 1,2 methyl shift to the more stable carbonium ion 22 which will then yield the five-membered cyclic ether 23.

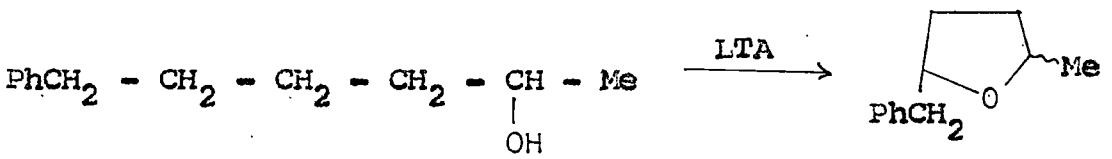


19

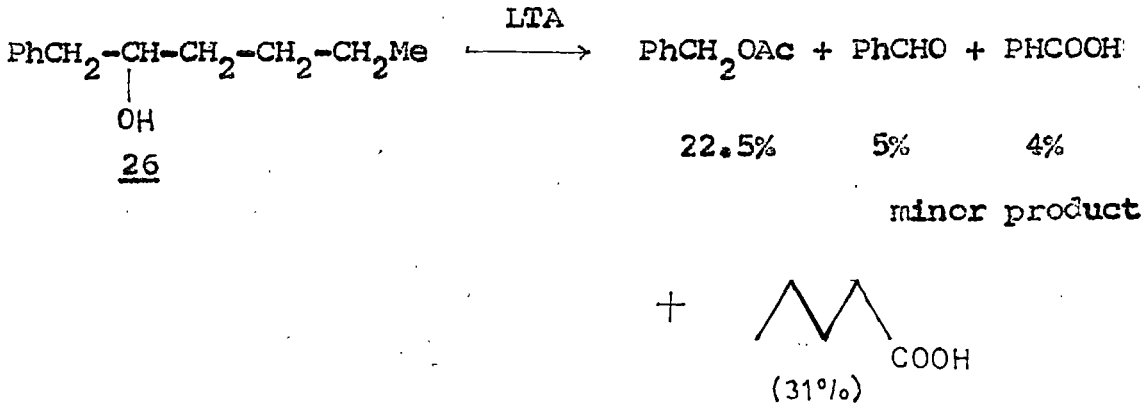


Though the ethers 2,5 dialkyl tetrahydrofurans[15c] obtained from lead tetraacetate cyclization of unbranched 2-hexanol, 2-, 3- and 4- octanols or 3-, 4- and 5 nonanols etc. in benzene are non-stereoselective[15d,26] under either thermal[15d,15c,26] or UV - photolytic conditions[12,15d] the cis : trans ratio of the diastereoisomeric ethers is in the range 40-45 : 60-55. A similar cis : trans ratio (46:54) was also observed for the diastereometric mixture of 2,5-dimethyl tetrahydrofuran obtained by heating 5- hexen- 2 ol with 20% sulphuric acid. It is an acid catalyzed intramolecular cycloaddition reaction for δ, ϵ -unsaturated alcohols and is believed to proceed via a carbocation[15f]. These results, once again, strongly support the intermediacy of δ or ϵ hydroxy carbonium ion 7 or 11, at least in case of conformationally flexible alcohols.

The alternative to and competing with cyclization under homolytic conditions is fragmentation of the alkoxy radical into a carbonyl compound 18 and an alkyl radical 14 which affords a mixture of stable products by further transformation. The fragmentation of the $C_\alpha - C_\beta$ bond in the intermediate may become a serious competitor with cyclization when the substituents on C_α carbon are such that the carbonyl fragment 18 is stabilized due to a decrease in strain[15,16] relative to the substrate and when the substituents on C_β have a stabilizing effect[15a,16a,17-19] on the radical fragment 14. For example, when the radical 14 is benzyl, fragmentation dominates and cyclization is effectively inhibited. An interesting illustrative example of this can be seen with the alcohols 25 and 26 both of which on cyclization should afford tetrahydrofuran 27. While 25 yields the ether 27, the compound 26 for which homolysis of the $C_\alpha - C_\beta$ bond would give a benzyl radical, fragmentation only and no cyclization was encountered.



25 27 (39%)

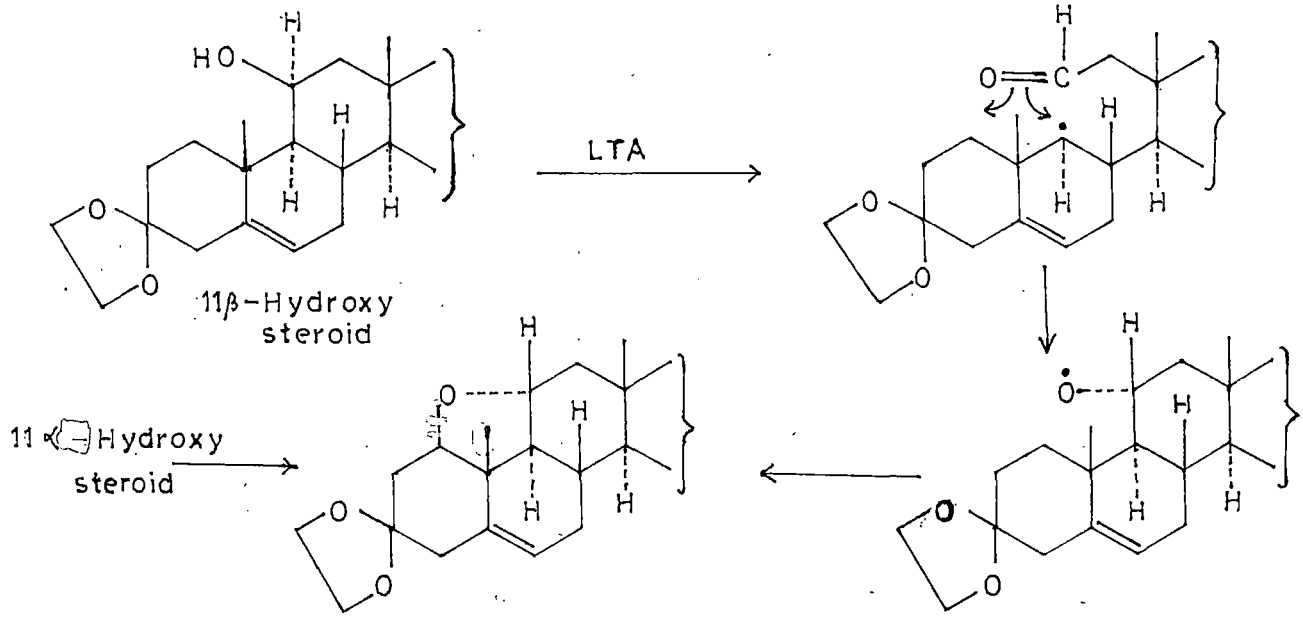


It has been observed that increasing the dilution of alcohols in benzene the yields of corresponding ketones decrease while the yields of cyclic ethers increase suggesting that a decrease in polarity of the reaction medium displaces the ratio of competing mechanisms in favour of the homolytic process. Addition of glacial acetic acid to benzene increases the reaction time of the lead tetraacetate oxidation, reduces the yield of the corresponding carbonyl compounds and enhances the yield of cyclic ethers. This happens because acetic acid lowers the concentration of the alkoxy lead triacetate 2 by displacing the equilibrium in the direction of starting alcohol. Furthermore, it being an acid, does not assist heterolytic cleavage of the alkoxide by eliminating α-proton. On the other hand, it should not markedly prevent homolytic decomposition of the same alkoxide 2 and the subsequent cyclization and fragmentation. Under the conditions of thermal decomposition of the lead alkoxide in acidic medium (addition of acetic acid) a

saturated 6β -hydroxy steroid is converted into the 6β , 19 ether in yield as high as 90% with only 6.5% of ketone being formed[6].

The importance of the carbonyl forming fragmentation varies according to the method of oxy radical generation and is most pronounced in the lead tetraacetate reaction, less in nitrite photolysis and even less in hypohalite reactions. In general, the structure of the alkoxy radical determines the degree of fragmentation i.e. if a gain in energy accompanies the fragmentation its rate is enhanced.

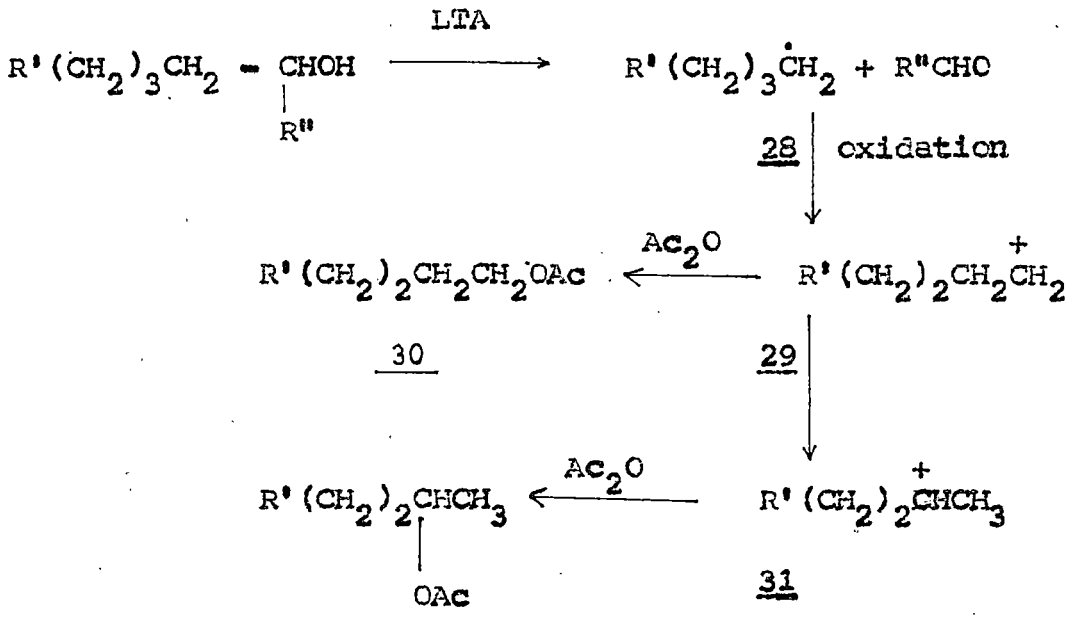
Tertiary, secondary and primary alcohols undergo fragmentation and suggestion has been made that the complexing of the oxidant with the carbonyl or incipent carbonyl group facilitates this reaction[3]. This would also explain the recombination process of the carbon radical with the carbonyl fragment, as depicted below, which occasionally results in epimerization at one or two asymmetric centres[6,23].



Since the lead tetraacetate fragmentation of alcohols is similar to the fragmentation process of alkoxy radical[13,20], but may also show specific feature[8], it is suggested[8] that the lead tetraacetate fragmentation which involves the scission of the bond between the carbinol carbon atom and the β-carbon atom in the alkoxy lead triacetate 2, it is a homolytic process proceeding through a transition state with alkoxy radical character[21], but somewhat differs in the geometry of its basic skeleton from "free" alkoxy radicals generated from other sources[20]. It has been demonstrated in case of hydroxy steroids[6] that the ratio of cyclic ether formation to fragmentation is practically independent on reaction conditions. It may, therefore, be considered that the transition state of type 2 is the common precursor to both processes.

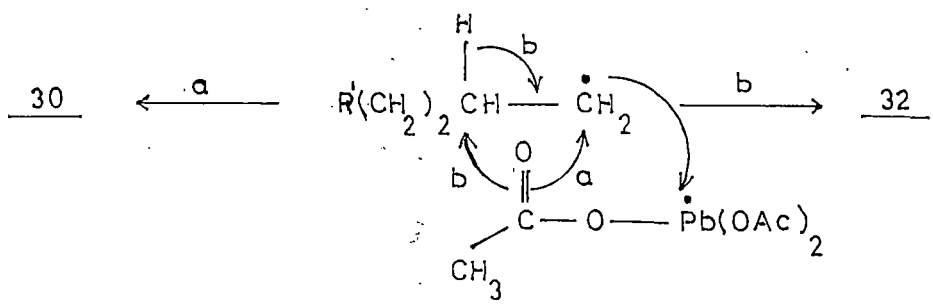
Evidence has been presented[8,21-23] that in addition to the carbonyl fragmentation product 18, the primary decomposition product of the alkoxide 2 is an alkyl radical 14 and not a carbonium ion which would be formed by a heterolytic process[24]. However, the distribution of olefinic fragmentation products in the lead tetraacetate oxidation of a 19-hydroxy-5β-steroid[21] suggests that the alkyl radical 14 may be subsequently oxidized (by lead containing species) to the corresponding carbonium ion 17[25].

Convincing evidence that such an oxidation of alkyl radical to the corresponding carbonium ion occurs in the fragmentation process has been advanced by Mihailovic and his co-workers[26]. They have been able to isolated both the unrearranged[30] and rearranged acetates[32] as indicated below:



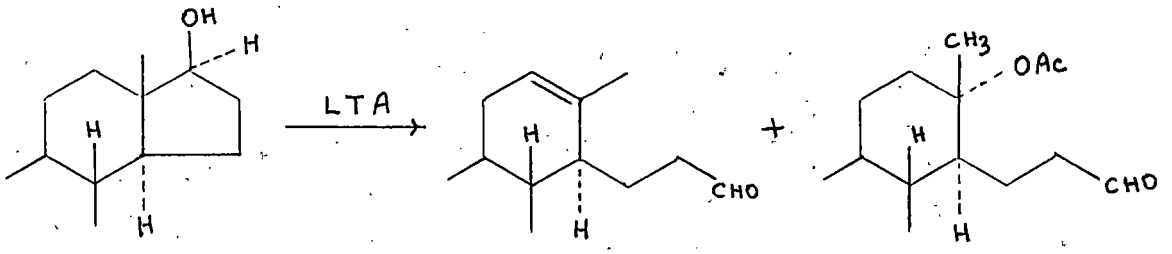
Since it appears that radicals do not rearrange via 1,2 shifts of hydrogen or alkyl groups[16], the formation of 2-alkyl acetate 32 must have occurred by oxidation of the 1-alkyl radical 28 to the corresponding primary carbonium ion 29, followed by rearrangement involving 1,2 hydride shift

to the more stable secondary carbonium ion 31 which collapses to 32 on addition with acetate ion. They also have suggested a possibility that in fact "free" carbonium ions are not generated and the oxidation of the 1-alkyl radical 28 and acetoxylation with or without rearrangement, take place in a simultaneous, multicentre reaction step:



Mention may be made in this context that when no suitable C-H bond is accessible to the alkoxy radical, generated by lead (IV) acetate reaction under non-polar condition for cyclization, fragmentation of alcohols occurs[30,48]. Secondary alkoxy radicals derived from alcohols adjacent to quarternary centres e.g. 1α or 1β -OH[49], 3β -OH 4,4-dimethyl[22], 17β -OH[22] and 21-OH 20 cyclic ketal[22] of steroids gave fragmentation products which were unsaturated carbonyl compounds and/or

acetoxy derivatives resulting from combination of alkyl and acetoxy radicals e.g.



Levi and co-workers[50] utilized this reaction for the synthesis of naturally occurring A-ring seco acids of triterpene α and β amyrine series.

Thermal vs. Photolytic Reactions

Many disadvantages of the thermal lead tetraacetate oxidation can easily be overcome in photo decomposition of lead alkoxide[27]. A very clean one electron transfer from oxygen to lead can be induced on irradiation of the lead alkoxide with light[6] of wave length above 300 nm. Since the photolysis can be effected at ambient temperature where the rate of base-catalysed two electron transfer which is responsible for the oxidation of secondary alcohols to ketones, is very low and hence a base such as pyridine can be safely used to increase the rate of lead alkoxide formation. Reaction time is also considerably reduced (30-150 min as compared with 10-15 hours

in the thermolysis). Because of specific excitation of the radical process on irradiation, selectivity of the reaction increases too. Therefore, ketals, ketones, double bonds etc. which are susceptible to attack by lead tetraacetate at higher temperatures, remains unaffected. It appears to be an extremely efficient, mild and simple procedure for intramolecular functionalization. Furthermore, yields are consistently higher in the photolytic than in the thermal reaction.

Finally, worth mentioning is a good example of the unexpected intricacies which may often arise in reactions involving lead tetracetate. It has been observed that the ketone 3 may also arise from the route (2 → 4 → 5 → 6 → 7 → 13), which prior to final proton loss involves a 1,4 hydrogen shift (7 → 13), detected by deuterium labelling[28,29].

Hypohalite Reactions:

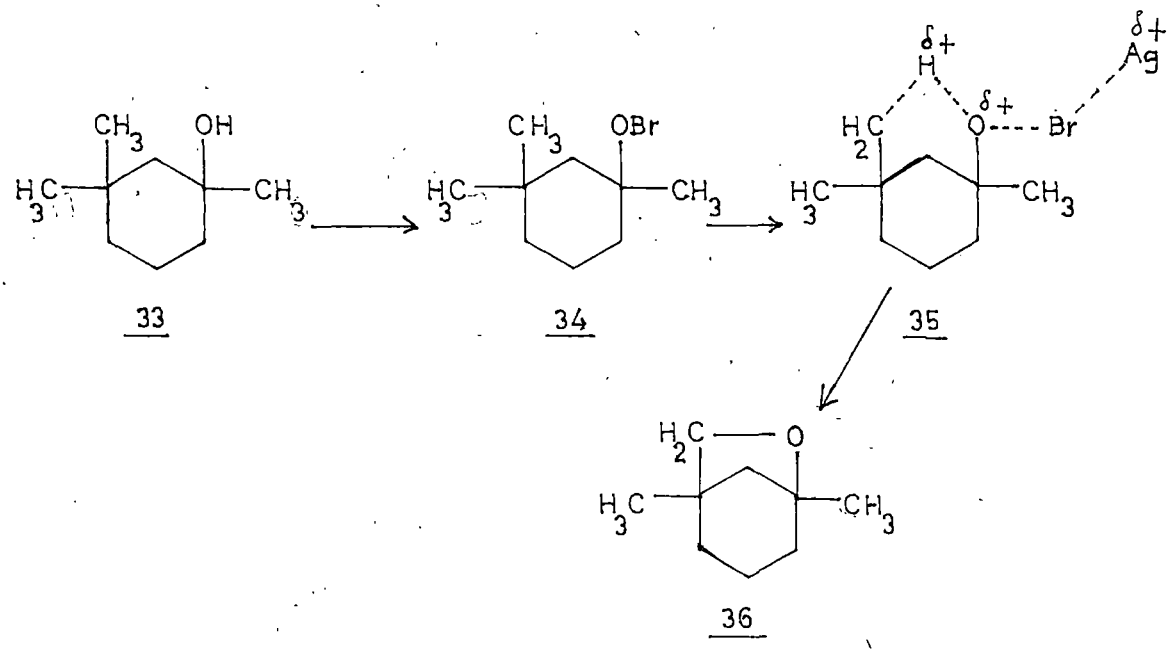
Hypohalites on homolysis furnish alkoxy radicals which can give rise to ethers by attacking unactivated carbon-hydrogen bonds[1,3a]. The primary product generated from photolysis is a 1,5-halohydrin, the stability of which increases in the order on passing from iodo to bromo to chlorohydrins. In many cases halohydrins are converted to tetrahydrofurans spontaneously by elimination of hydrogen halide while in some cases by base treatment. Isolation of halohydrins have been achieved in some instances[31]. As the base catalysed heterolytic

decomposition of hypoiodite is most efficient and as it (or iodine) does not react with carbon-carbon double bonds or carbonyl groups[30] under neutral condition, functionalisation via hypoiodite has been studied most and lesser extent via hypobromite. Hypohalites are more conveniently prepared from alcohols with Hg(II) oxide and halogen[32], with tertiary butyl hypohalite and halogen[32] and with acetyl hypohalites[33] which are conveniently obtained from heavy metal acetates such as silver acetate, mercuric acetate with bromine or iodine and very efficiently from lead (IV) acetate and iodine.

For the generation of hypohalites, solvents saturated hydrocarbons e.g. cyclohexane and halogenated hydrocarbons e.g. dichloromethane and carbon tetrachloride are preferable to aromatic solvents such as benzene in which the yield is considerably low as evidenced from the observation that oxidation of 20- hydroxy steroids to 18, 20- hemiacetals gave 50-75% yields in cyclohexane whereas in benze afforded only 20-30% yields[1].

For tetrahydrofurans generated from reactions of alcohols with silver oxide, acetate (or other silver salts) - bromine in the dark, the mechanistic propositions advanced are controversial[34,38]. Sneen and co-workers[34] observed that in the reaction with tertiary alcohols 1,3,3-trimethyl cyclohexanol 33 corresponding bromo hydrin could not be detected and proposed that silver ion acts as electrophilic catalyst to promote ~~direct~~

direct conversion of the hypobromite 34 to the ether 36 via a transition state 35 having oxygen with cationic character[35].



33 34 35

36

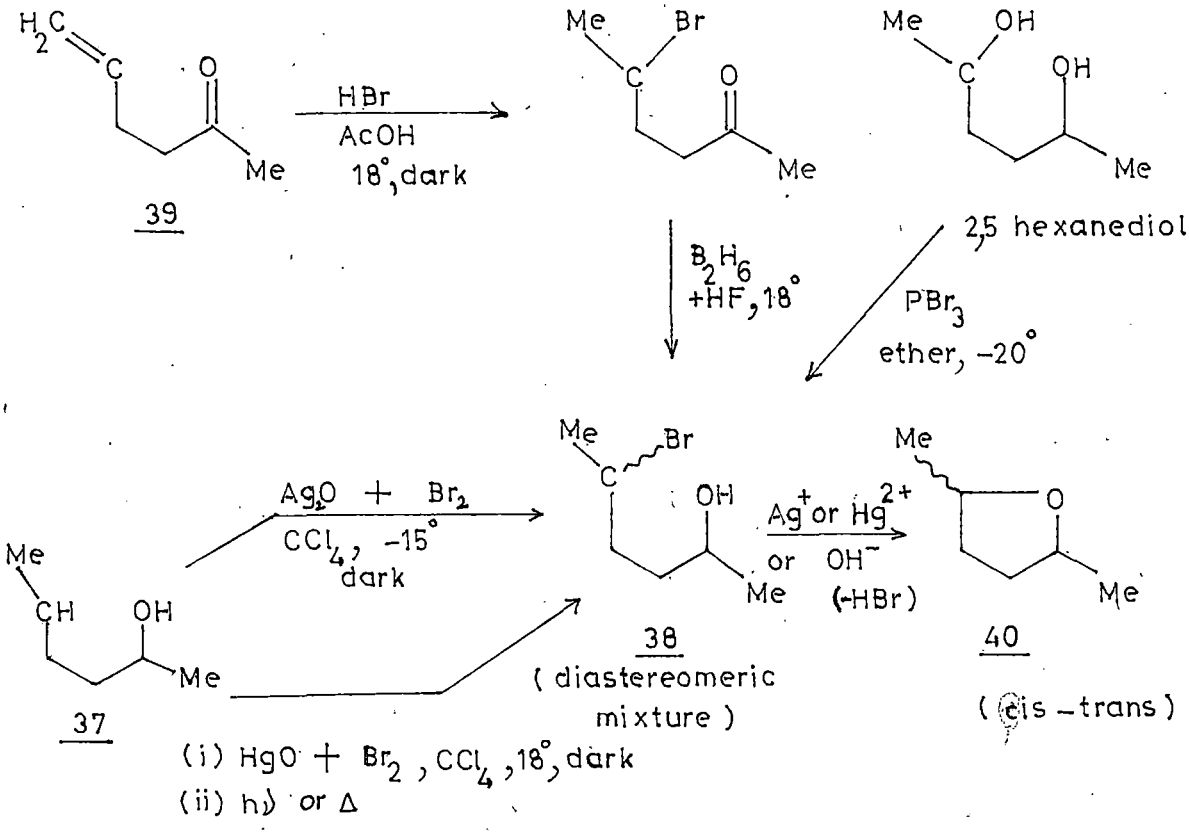
The heterolytic nature of the reaction is supported by the observations that it takes place readily in the absence of light and is unaffected by free-radical inhibitors[34]. Supporting evidence which is not inconsistent with this view was also sought from solvent[36] and anion effects[37]. It has been noted that the reactions of secondary alcohols with silver oxide-bromine[36] is auto catalysed and yield is considerably improved by adding tetrahydrofuran to the reaction mixture. This result strongly support a mechanism with an ion pair transition state containing some positive charge on oxygen which is probably solvated by tetrahydrofuran, making ketone formation electronically and/or sterically unfavourable[36]. Roscher[37] studied the

reaction of various alcohols including cholestan 6β-ol with different silver salts and bromine. The formation of ether and ketone depends on silver salt used-silver carbonate and silver acetate favour ether formation while silver oxide mainly ketone. This result is also consistent with ion pair transition state in which anion plays an important role.

In contrast, based on the following findings, suggestion has been made that silver salt-bromine induced cyclization of alcohols also proceeds by homolytic process : (I) comparable product distribution in the processes which are known to involve alkoxy-radicals as intermediates and in the silver acetate - bromine reaction of alcohols in the dark[38], (II) loss of optical activity on the asymmetric δ-carbon atom in the dark silver oxide-bromine cyclization of (+)-(s)-2,5-dimethyl-2-heptanol[39], (III) measurements of deuterium isotopic effect using δ-deuterio alcohols as substrates have revealed that the relative rates of, and activation free energy differences for, intramolecular 1, 5-abstraction of the diastereotopic hydrogens from the δ-carbon atom are comparable in both the dark silver oxide-bromine reaction and the lead tetraacetate oxydation of alcohols[40] which is believed to proceed homolytically (vide supra), (IV) the detected intermediacy of the tertiary δ-bromo hydrin in the reaction of 2-methyl-2-pentanol with mercuric oxide-bromine in the dark and in the presence of some silver oxide[41].

Definitive evidence in support of free-radical mechanism for silver salt-bromine reaction has been presented by

Mihailovic and his co-workers[15c]. When 2-hexanol 37 was treated with silver oxide-bromine in carbon tetrachloride solution in the dark at -15° the resulting filtered solution exhibited the presence of 5-bromo 2-hexanol 38 by spectroscopic measurements (IR and NMR), which increase only slightly upon irradiation with tungsten lamp (500 W) or heating at 45°-60° in the dark. Amount of formation of 38 by similar reaction from 37 with mercuric oxide-bromine was small, but it increased considerably upon irradiation or heating at 60° in the dark. The δ -bromo hydrin 38 from both reactions was compared and found to be identical with a synthetic product obtained via 5-hexen-2-one 39 according to the scheme II. These results in conjunction with the findings (i) that 38 in carbon tetrachloride is not converted to ether 40 when heated at 35°-40° for 24 hrs (in the dark or day light) or upon irradiation with visible or UV light at room temperature for 8 and 4 hr, respectively and (ii) that it cyclises quantitatively to 2,5-dimethyl tetrahydrofuran 40 when treated in carbon tetrachloride or pentane solution at room temperature in the dark or in daylight with silver oxide, silver acetate, silver carbonate or mercuric oxide, indicate that in the silver salt-bromine reaction of aliphatic alcohols, silver catalyses in the dark homolysis of the hypobromite to the alkoxy radical.



Scheme II

As electrophilic catalyst, this silver cation is very effective to bring about ring closure of the intermediate δ-bromo hydrin 38 to the tetrahydrofuran product 40, whereas the catalytic effect of mercury cation in the dark in the mercury salt-bromine reaction on the hypobromite decomposition is much weaker and mercury ions are also slower in effecting eliminative cyclisation of the δ-bromo alcohol (38 ⟶ 40, scheme II)[15c].

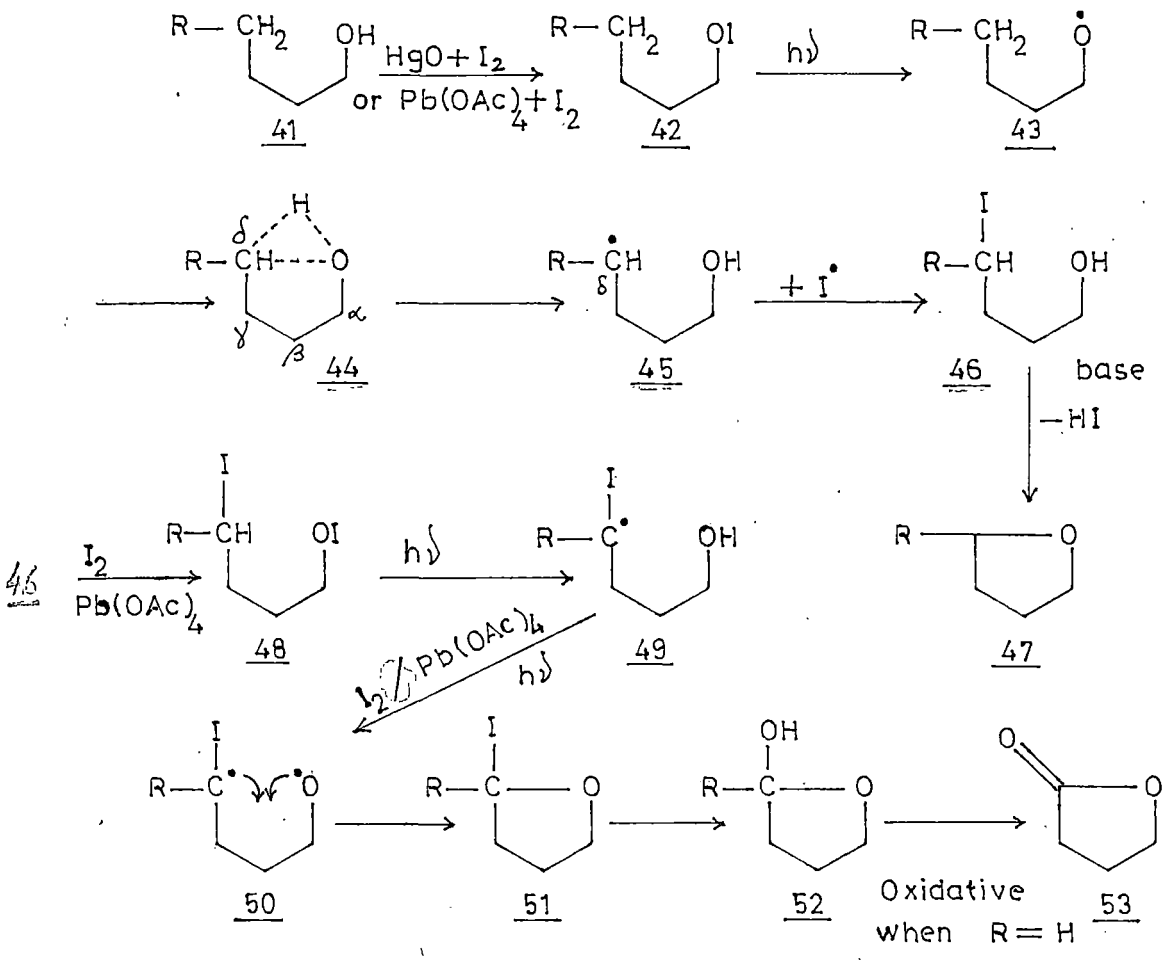
From the discussion presented above, it seems that the controversy concerning the duality of mechanism of the cyclisation of hypobromite reaction of alcohols-heterolysis[34,35] vs

homolysis[38,15c] has not been completely resolved, but a possible solution lies in the free-radical pathway not being of the propagated chain type i.e. not long chain radical process but rather an intramolecular process involving either a four-centre exchange or a radical transfer reaction[30] within a "solvent cage" i.e. may be of radical pair (cage) type[1,34b,41]. This has also been supported from the steric course (stereochemistry) consideration of the heavy metal salt-halogen reactions[15c].

For synthesis purpose,photolytic decomposition of hypoiodites generated from alcohols in situ by means of mercuric oxide-iodine or lead tetraacetate-iodine has been extensively utilized for the preparation of quite a large number of cyclic ethers[3,8,30]. From a practical view point the mercuric oxide-iodine procedure appears to be the simplest[32] and only gives rise to ether. Reaction with lead tetraacetate-iodine are frequently complicated by bifunctional attack resulting in the generation of intermediate iodo-ethers which after hydrolysis afford lactols. The hydroxy and iodo compounds are readily oxidised to the corresponding lactones with chromium trioxide.

The hypoiodites are formed through the esterifying action of hypoiodus acid generated in situ from the mercuric oxide and iodine[32].

In general, the hypoiodite reaction sequences appear to be of the type depicted in scheme III[42].



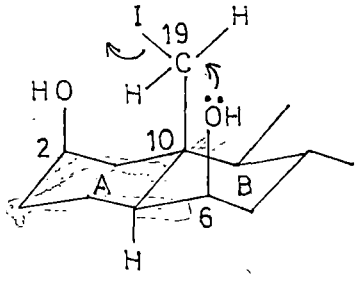
Scheme III

The alkyl hypoiodites 42 generated from alcohols 41 in situ either by esterifying action of hypoiodus acid obtained from mercuric oxide-iodine or by exchange reaction with acetyl hypoiodite obtained very efficiently from lead tetraacetate-iodine, are highly unstable species and baffled all attempts

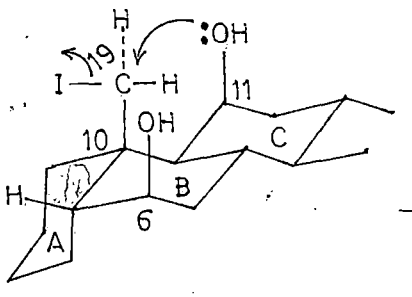
for isolation. Homolysis of 42 gives rise to highly reactive alkoxy radical 43. The thermal hypoiodite decomposition can be induced by excited iodine molecule and it has been demonstrated that in cyclohexane, light with a wavelength of 500-550 nm is very effective[1]. An ordinary 500 W tungsten lamp has been found to be preferable as an irradiation source to a high-pressure mercury UV Lamp[43]. The alkoxy radical 43 is capable of intramolecular hydrogen abstraction which preferably takes place from δ-C through more stable six membered transition state 44 to afford hydroxy alkyl radical 45 (discussed at length is case of lead tetraacetate oxidation, vide supra). The radical 45 is converted to ~~1,5~~-iodohydrin intermediate 46 by capturing an iodine atom. The iodohydrin 46 is capable of undergoing two different courses of reaction. It can give rise to the ether 47 directly by a base-catalysed elimination of hydrogen iodide. In non polar solvents e.g. cyclohexane ionic hydrogen iodide elimination from the iodohydrin 46 is slow, thereby allowing 46 to be converted into an iodohypoiodite 48 which through a postulated sequence (48 → 49 → 50 → 51) is transformed to iodo ether 51.

The formation of cyclic ethers 47 arising from mono functionalization or of the iodo ethers 51 derived from difunctionalization is considerably dependent on the particular steroid sites concerned and has been elegantly interpreted in terms of steric and conformational effects of 42. The formation

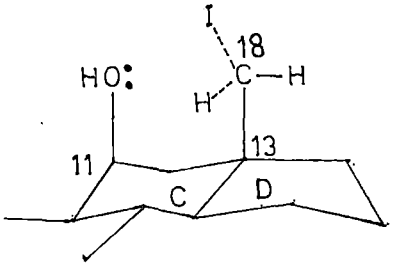
of cyclic ether 47 closely competes with the introduction of a second substituent leading to iodo ether 51 and greatly influenced by the readiness of the - CH_2I group to assume the required conformation. The rotation of an axial - CH_2I group (46, R = H) in a polycyclic saturated system is severely hindered by axial substituents on the same face; therefore, preferred orientations for both ~~an~~ 18-CH_2I 54 and 19-CH_2I 55 in steroid can be represented:



55



56



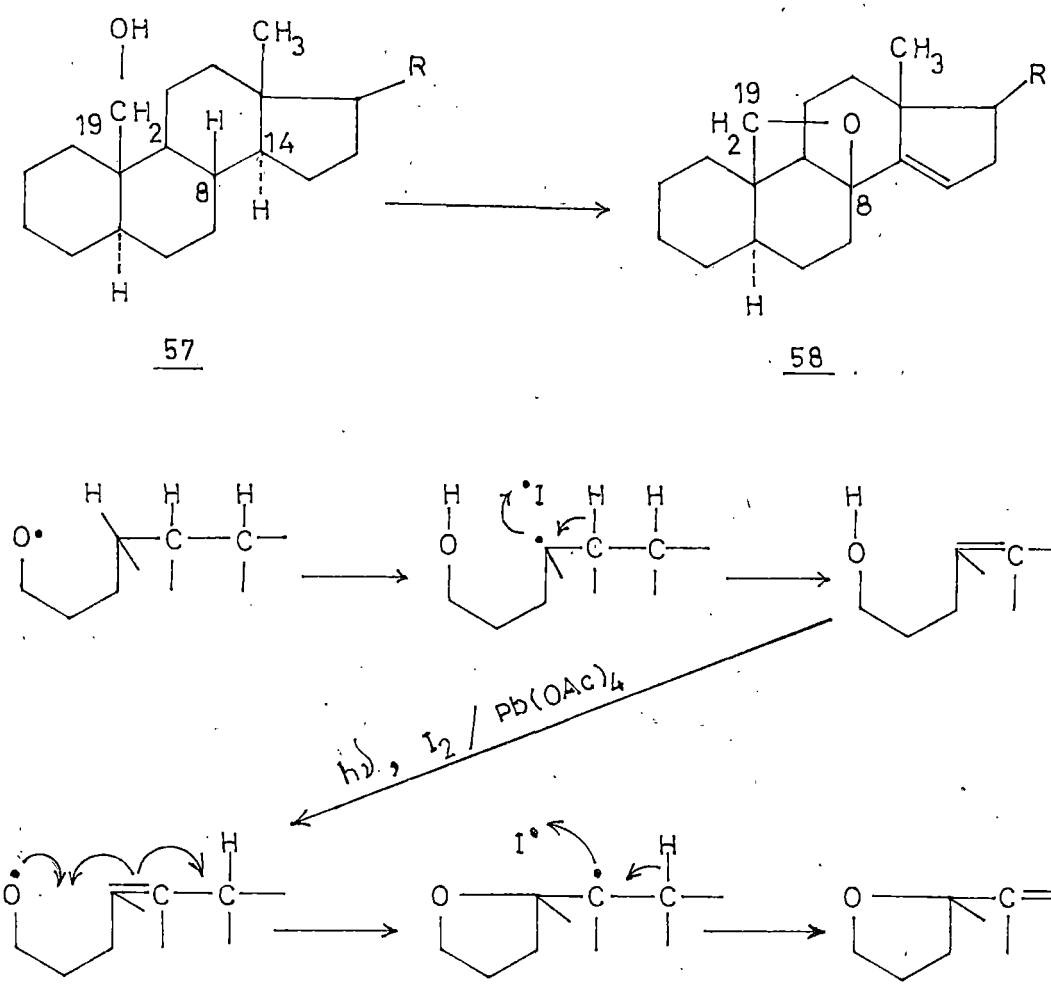
54

In 6β-hydroxy-19-iodo steroid (55) the orientation of the reactive centres O ----- CH_2 -----I closely resembles the arrangement of the transition state of an SN_2 displacement reaction and hence lowers the activation energy for the transition 46 ⟶ 47. Suggestion has been made that the conformation indicated in 55 also facilitates an analogous radical displacement reaction [SH_2 , 48 ⟶ 47] of the iodine atom at C-19 by a 6β-oxy radical resulting from the homolytic decomposition of the O-I

bond in 48. In such cases only ethers 47 can be expected[1]. If the oxygen atom in 55 is placed at position 2β, 4β, or 11β the linear relationship of C-CH_2-I cannot be attained[46] and hence the reaction should proceed with a second hydrogen abstraction from 46 to 51. The same arguments apply to 11β oxy derivatives with respect to an 18 -CH_2I group in 54. Here also products of type 51 are expected.

In steroids of the 5β-H series, however, the situation with respect to C-19 substitution changes as depicted in 56. Displacement is now favoured from 11β and abstraction from 6β leading to 11β, 19 ethers and 6β, 19 lactol are the principal products[45,46,47].

Abstraction of hydrogen is most facile from a tertiary centre ($-\overset{|}{C}-H$) requiring less energy than from a secondary carbon ($>C<^{H}_{H}$), which in turn is more reactive than a methyl group ($-C<^{H}_{H}$). The calculated increments in activation energy each 4 K Cal/mole favouring tertiary hydrogen abstraction. This property has been exploited in the selective attack of 19-alkoxy radicals on the 8β-hydrogen (57 ⟶ 58)[21]. However, the process has been complicated by the occurrence of elimination - addition - elimination sequences[30] which yields the unsaturated cyclic ether 58. The general mechanism portrayed in Scheme IV has been proposed[30] for its formation.



Scheme IV

An alternative mechanism[42] has been proposed for the second stage i.e. the formation of bifunctional product iodo ether 51 (Scheme III) through the intermediacy of a cyclic iodo-radical 60 arising from iodo alkoxy radical 59 by homolysis of iodo hypoiodite 48. This could then donate an electron to an iodine atom to form the iodonium oxide 61. Final loss of

a proton with rearrangement would afford the iodo ether 51.