PART — I

STUDIES ON THE REDUCTION WITH LITHIUM-ETHYLENEDIAMINE ON TRITERPENOIDS

CHAPTER—I

A SHORT REVIEW ON THE METAL DISSOLVING REACTIONS IN PRESENCE OF BASES:

Metals in presence of bases are known as a reducing agent for the organic compounds since early years. While considering this type of reagents, the first example which should be taken under consideration is the well known Birch reduction. Birch reduction[1—5] is the name given to the reaction of unsaturated organic compounds with alkali metals and alcohols in liquid ammonia. This method was first used for aromatic compounds in 1937 by Wooster[6], who showed that benzene and its derivatives were reduced by sodium in liquid ammonia in the presence of an alcohol, while this reaction did not take place in absence of alcohol. However, the general recognition and broard application of this reaction was achieved only after a series of investigations by Birch[7] published from 1944 onwards. In the performance of the Birch reduction, a number of experimental variants have been proposed which differ from one another by the ratio and order of addition of the reagents — the alkali metal, the ammonia, and the alcohol — and also by the presence or absence of supplementary solvents. Since the reaction was carried out in

liquid ammonia, its temperature range was determined by the boiling and solidification points of ammonia (from -34°C to -80°C). According to Birch method[8], the alkali metal — sodium or potassium was added to a well stirred mixture of an alcohol (taken in stoichio-metric amount with respect to the metal), liquid ammonia, and the substance to be reduced. The method was applicable predominantly to simple aromatic compounds; for more complex compounds (methyl ester of hexestrol and estradiol) the yield fell sharply[9] mainly because of the low solubility of the compounds to be reduced. The modification has been found applicable mainly for the reduction of polycyclic derivatives of anisole, primary steroid estrogens.

Regel and coworkers[10] observed that aromatic systems could be reduced by lithium in presence of ethylene-diamine. This was the first method where alkali metal was used in presence of base without taking alcohol as solvent. The authors observed that in this reducing system aromatic rings were reduced to mono olefins and to cyclo paraffin. It reduced phenols, cleaved ethers, reduced ketones to alcohols, acetylenes, terminal and internal olefin to alkanes. The reaction was studied in different condition changing the amount of lithium or ethylene-diamine. It was observed that the extent of reduction increased with an increase in the

amount of lithium used and again addition of the lithium in portions increased the amount of reduction but in a very slow rate caused a decrease in the yield of reduced material. The authors applied the reaction on a number of compounds as shown in the following (table—1):

Table—1

Starting material	Comp. Moles	M per mole comp. moles	Ethylene diamine (ml.)	Products	Yields%
$\Delta^{9,10}$-Octalin	0.20	4.0	375	trans decalin	36.9
Phenanthrene	0.05	14.4	200	decahydro and dodecahydro phenanthrene	90
Anthracene	0.05	28.0	300	dodecahydro and tetradecahydro-anthracene	95
Benzene	0.30	4.8	375	cyclohexene cyclohexane	51.0 1.4
Benzyl alcohol	0.20	16.0	400	hexahydro benzyl alcohol	38.5
Phenol	0.40	4.4	375	phenol Δ^{2}-cyclohexenone cyclohexanone cyclohexanol cyclohexene cyclohexane	53.9 6.5 1.6 1.1 1.5 1.6
Heptanone-3	0.30	4.0	375	heptanol-3	29.6
Di-n-hexyl ether	0.20	8.0	400	hexene-2	30.5

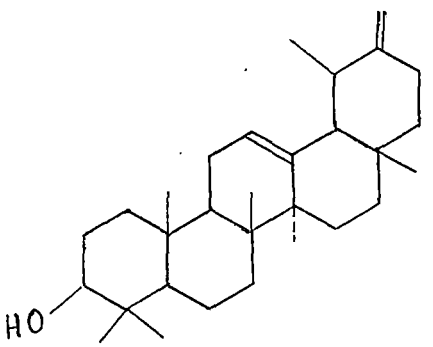
Table—1(Contd.)

Starting material	Comp. Moles	Li per mole comp. moles	Ethylene diamine (ml.)	Products	Yields %
Heptene-1	0.32	1.0	300	heptane heptene-2	41 13
Decene-1	0.30	2.4	150	decane decenes with internal double bond	47.2 13.8
Heptene-2	0.40	4.0	375	heptane heptene-1 heptenes with internal double bond	81.8 absent 2.6
Heptyne-1	0.20	10.0	300	heptane heptenes heptyne	50.9 absent absent
Octene-1	0.40	3.0	375	octane octenes with internal double bond	84.8 3.4
Octene-1	0.40	3.0	375	octane octenes with internal double bond	76.5 12.5

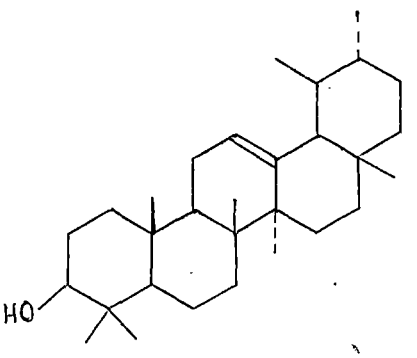
From table-1 it was found that terminal acetylenes and both terminal and internal olefins were reduced to alkanes by lithium and ethylene diamine. In contrast to sodium in liquid ammonia, it reduced acetylenes to olefins but not non conjugated internal olefins at all and reduced terminal olefins only in the presence of a proton donar. Under conditions, lithium in ethylene diamine where terminal olefin was

not completely reduced but entirely isomerised to internal olefins. It was also shown that the isomerisation was catalysed by the amide $H_2N—CH_2—CH_2—\overset{-}{N}H\overset{+}{L}i$.

Corey and coworkers[11] applied the reaction on triterpenoid observed that selective reduction of olefinic double bond occurred by the use of lithium in presence of ethylene diamine. They obtained compound 2 from compound 1.



1



2

Regel and coworkers[12] studied a number of reactions using lithium in presence of ethylene diamine on different organic compounds containing double bonds. The authors observed isomerisation of olefinic double bond as well as dehydrogenation occurred during reaction condition.

Isomerisation of terminal olefins to internal olefins[12]:

When metallic sodium was added to ethylene-diamines at a temperature of 80°—115°, there was a rapid reaction with evolution of hydrogen gas. A dark blue material formed at the surface of the metal; when the solution was stirred the colour quickly spreaded throughout the liquid. On continued heating the blue colour gradually faded and disappeared leaving a colourless or pale yellow solution. They thought that lithium in presence of ethylene diamine formed first N-lithiodiamine 3.

$$Li + H_2N\,CH_2CH_2NH_2 \longrightarrow \tfrac{1}{2}H_2 + H_2NCH_2CH_2NH\,Li$$

3

The N-lithio-ethylene diamine 3 thus formed was responsible for isomerisation as catalyst. When 1-octene was heated with a solution of 3 in ethylene diamine, the material which was recovered (90% yield) consisted entirely of internal olefins. Neither 1-octene nor octane was detected. In the same manner 4-methyl-cyclohexene was isomerised to 1-methyl cyclohexene.

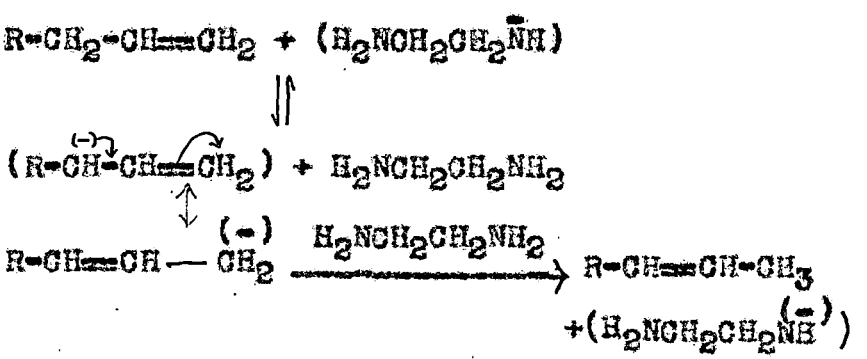
• dienes

Dehydrogenation of cyclic dienes[12]:

Regel and coworkers[12] observed that when 4-vinyl cyclohexene 4 was added to a solution of N-lithioethylene diamine 3, there was a rapid evolution of hydrogen gas. The product obtained in 67% yield, consisted entirely of ethyl benzene 7. The dehydrogenation reaction was apparently general; d-limonene (1-methyl-4 isopropyl pentyl cyclohexene) and α -phellandrene (2-methyl-5-isopropyl-1,3-cyclohexadiene) both yielded p-cymene. The dehydrogenation reaction with 3 was essentially quantitative in a few minutes at 100°C. The reaction was done with sodium in ethylene-diamine also but the rate was found to be slower. There the compound $H_2NCH_2CH_2NHNa$ 6 was formed as an intermediate.

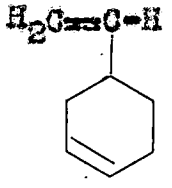
Mechanism suggested for two reactions:

The authors suggested the following mechanisms for the isomerisation as well as dehydrogenations:

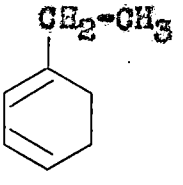


They were unable to describe the mechanism in view point for the role of metal ion. It did not seem likely that the structure of lithium and sodium compounds were different or that the high viscosity of the solution of 6 would be so great for an effect upon the rate of isomerisation. The reaction was discussed in an incomplete view point which considered only anion part.

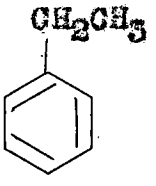
The mechanism for dehydrogenation of diene, the first step for 4-vinylcyclohexene 4 was considered to be the isomerisation to a conjugated diene 5



4



5

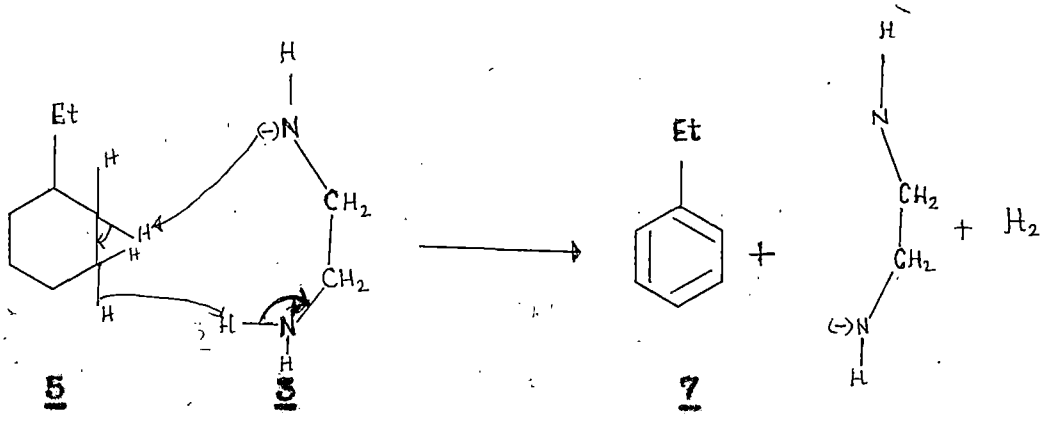


7

This was suggested by the fact that 6 would not dehydrogenate d-limonene (where the bonds must first isomerise to a conjugated system), but would dehydrogenate ∝-phallendene (where the double bonds were already conjugated). Both 3 and 6 readily removed protons from cyclic conjugated diene where by 6 must be a slow process.

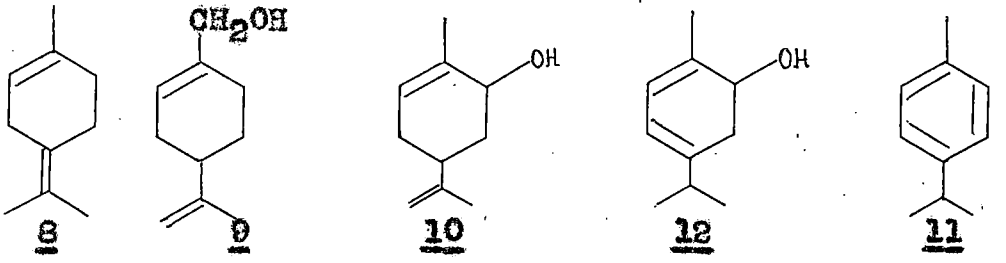
The path from 5 to ethyl benzene 7 was explained by the bidentate character of ethylenediamine made it

possible to visualize a concerted reaction in which 5 and 3 formed a cyclic intermediate.



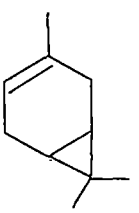
5 3 7

Tyagi, Ghatge and Bhattacharyya[13] applied the reaction of lithium in ethylenediamine on different terpenes. They found terpinolone 8, perillyl alcohol 9, and carveol 10 when treated with the reagent gave p-cymene 11 in good yield. Formation of p-cymene 11 from carveol 10 presumably proceeded through the conjugated alcohol 12 followed by dehydration. In case of perillyl alcohol 9 because of the absence of an ∝-hydrogen, the allylic double bonds must have isomerised followed by dehydration and rearrangement to form 11.

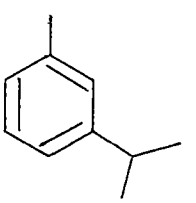


8 9 10 12 11

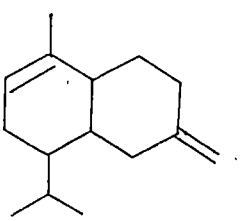
The authors[13] also examined the behaviour of the reagent on many terpenoids containing cyclo-propane and cyclobutane rings. Δ^3 Carene 13 gave in quantitative yields of cymenes which from comparative IR, analysis was found to be a mixture of p-cymene 11 and m-cymene 14 i.e. the cyclo-propane ring having been opened in two ways in conformity with the reactivity of Δ^3-carene.



13

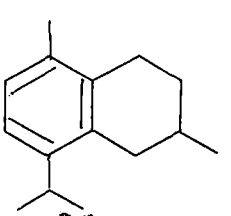


14



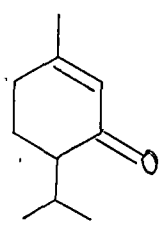
15

The sesquiterpenes like γ_1-cadinene 15 when treated with the same reagent converted to calaminine 16, presumably with migration of the methylenic double bond across a ring followed by aromatization of one of the rings. Aromatization of the other ring could not be effected by repeating the treatment or using excess of the reagent.

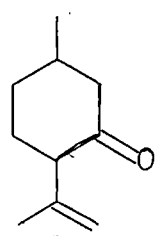


16

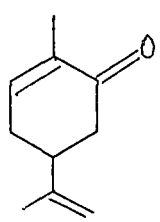
The reaction of lithium in ethylenediamine was extended to terpene ketonic systems. The possibility of using a monoethenoid ketone through its potential enolic form to give a phenol on dehydrogenation was examined. The conjugated ketone dl-piperitone 17 on treatment with this reagent remained unaltered and did not form any thymol as might have been anticipated. The unconjugated ketone isopulegone 18 partly isomerized to the conjugated ketone 19. Carvone 20 containing two double bonds, however, gave a quantitative yield of carvacrol 21. From that it was clear that aromatization of a ketonic system of the p-menthone series, the presence of two double bonds was essential. It was also noted that though isopulegone 18 partially isomerised to the conjugated ketone the double bond in the corresponding alcohol, isopulegol 22 did not migrate; the migration appeared to have prevented by the hydroxyl group.



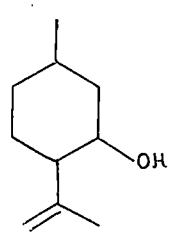
17



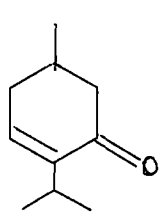
18



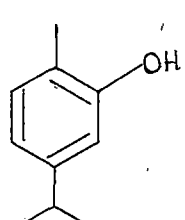
20



22

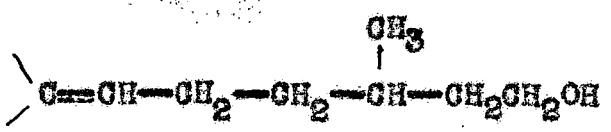


19

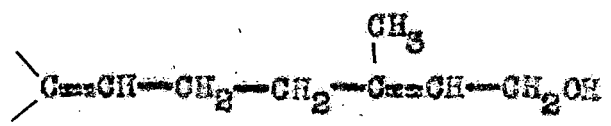


21

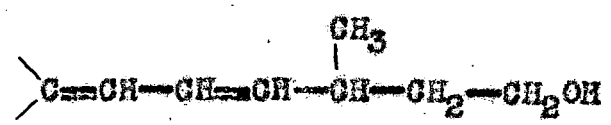
The reaction of lithium in ethylenediamine was also examined by the same authors[13] on the acyclic systems. The monoethenoid alcohol citronellol 23 remained unaltered. No migration of double bond to give rise to an allylic alcohol was noticed. In the case of geraniol 24 the allylic double bond actually migrated away from the alcoholic group to furnish the conjugated diene alcohol 25.



23



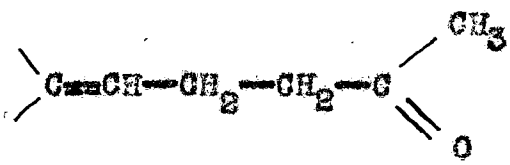
24



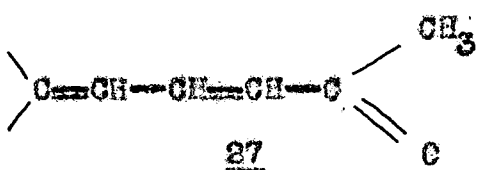
25

Lithium in ethylenediamine reaction was applied on one acyclic ketone 26, which gave the fully conjugated dienone 27 evidently formed through dehydrogenation, but

because of its unstable nature, it could not be isolated in pure form. The impure specimen gave characteristic colour reaction, showed expected U.V. absorption — λ_{max} 223 nm (ϵ 4385) and 266 nm (ϵ 557).



26



27

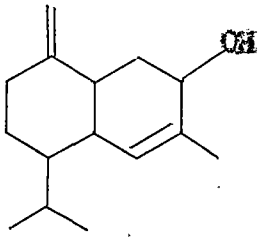
Smith and coworkers[14] observed the dehydrogenation of aliphatic and aromatic alcohols to carbonyl compounds in the presence of lithium metal in ethylenediamine. The result of different reactions are summerized in table-2.

Table—2

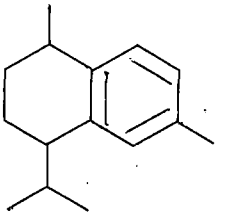
Alcohol	Carbonyl product	% yield
Cyclohexanol	Cyclohexanone	54
2-methyl cyclo-hexanol	2-methyl cyclohexanone	38
n-pentyl alcohol	n-valeraldehyde	66
2-hexanol	n-butyl methyl ketone	45
2-phenyl alcohol	Phenyl acetaldehyde	25
1-phenyl ethanol	Acetophenone	24
Benzyl alcohol	Benzaldehyde	80

Tyagi, Ghatge and Bhattacharyya[15] observed that lithioethylenediamine was an excellent reagent for the partial aromatization of cadinenic terpenens. The crystalline alcohol khusinol 28 on treatment with this reagent yielded the hydrocarbon 29; the purity of which was evidenced by a single peak on the VPC column. As the formation of the hydrocarbon 29 involved the ellimination of the hydroxyl group of khusinol, it must be represented by the structure 29 and not by 16, a product

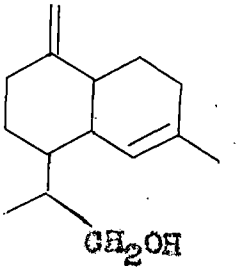
which was previously obtained by the dehydrogenation of γ_1-cadinene 15 by this reagent. Similarly on treatment with the reagent the crystalline alcohol khusol 30 afforded the partially aromatized alcohol 31. Formation of such a product retaining the hydroxyl group intact was not normally possible during dehydrogenation using conventional reagents.



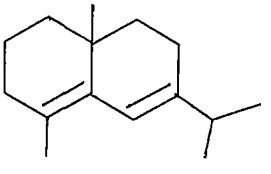
28



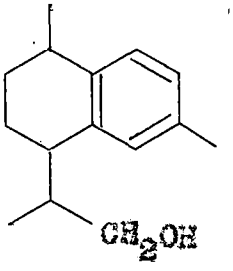
29



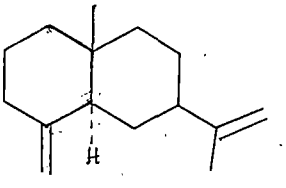
30



33



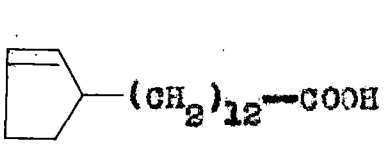
31



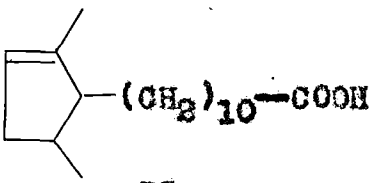
32

β-selinene 32 under the same condition showed facile transformation to the heteroannuler diene (+) δ -selinene 33. This diene contained only one assymetric centre with a

β-oriented methyl group at C-10. Chaulmoogric acid 34 having disubstituted double bond was completely converted



34



35

to isochaulmoogric acid 35 having trisubstituted double bond, when reacted with lithioethylenediamine.

Baumel and Harris[16] observed that lithiated derivatives of diamines could be used to metalate a variety of weekly acidic compounds. N-lithioethylenediamine reacted smoothly with a variety of amines like aniline, diphenylamine and hydrocarbons like florene, indene, phenyl acetylene etc. at room temperature. In general the product isolated was a 1:1 crystalline solid complex of lithiated derivative with ethylenediamine. Exceptions were observed in the case of acetylenes. When acetylene was introduced into a slurry

$$RH + H_2NCH_2CH_2NHLi \rightleftharpoons RLiNH_2CH_2CH_2NH_2$$

of N-lithioethylenediamine above the decomposition temperature of lithium acetylide — ethylenediamine a solid product obtained which contained 87% dilithium acetylide and 13% ethylenediamine.

The basis for the reaction between hydrocarbon and amine with N-lithioethylenediamine depends on their relative acidities. In the absence of other effects, the most acidic hydrogen atom of the hydrocarbon or amine must be acidic than the most acidic hydrogen on ethylenediamine.

$$RH + H_2NCH_2CH_2NHLi \rightleftharpoons RLi + H_2NCH_2CH_2NH_2$$

Complex formation was also considered to be an important factor in the overall reaction:

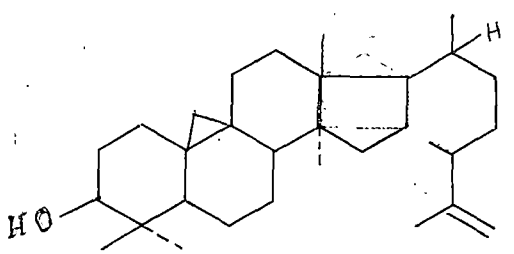
$$RLi + H_2NCH_2CH_2NH_2 \longrightarrow RLiNCH_2CH_2NH_2$$

The complex might be prepared in an one step process from lithium metal in hydrocarbon solvents, since the N-lithioethylenediamine could be prepared in situ. While using one step process reduction of the hydrocarbons could complete with metalation because of the potentially reductive nature of Li-diamine system. But indene and fluorene could be reduced by lithium in dimethoxyethane. If indene was present initially in the preparation of indenyllithumdiamine complexes varying amounts of reduction to indene

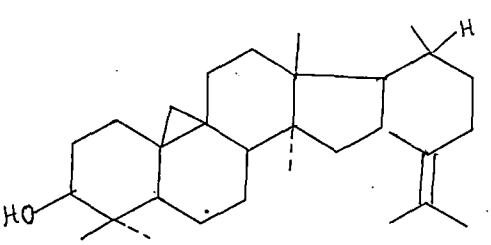
could occur depending on the diamine employed. Indene reduction could be avoided by preparing lithiated diamine before introducing indene to the system.

Sodium powder instead of lithium powder was also used for metallation in presence of ethylenediamine. Apparently N-sodioethylenediamine formed at the metal surface making it resistant for further attack by ethylenediamine. If however an appropriate RH compound was present to react with the formed N-sodioethylenediamine, fresh metal surface was exposed and overall reaction proceeded to completion. Acetylene hydrocarbons reacted with sodium and ethylenediamine in toluene at 35°C to form the corresponding sodium acetylide. Amines would not react with sodium and ethylenediamine under any condition tested.

Narula and Sukh Dev[17] applied the reaction of Li in presence of ethylenediamine for the isomerisation of cycloaudenol 36 on exposure to N-lithioethylene diamine at 120°-125° gave the isopropyledene isomer 37 in 92% yield



36



37

Barton and coworkers[18] reported that sterically hindered alcohols were conveniently and efficiently converted into the corresponding alkanes by metal amine reduction of the derived esters with carboxyllic acid. The only side reaction was the regeneration of the starting alcohol. Different reaction which were done are summerized in table-3. The readily available acetate esters were admirable substrate. The authors used mainly lithium in ethylamine as the reducing system, but other metals (Na, K) and other amines were also effective.

Table-3

Starting Material	Product (% yield)
1. 3β, 6β-diacetoxy-5α-cholestane	5α-cholestane-3β-ol (46) 5α-cholestane-3β, 6β-diol(35)
2. 3β,6β-diacetoxy-5α-cholestane	5α-cholestane-3β-ol (60) 5α-cholestane-3β,6β-diol(25)
3. 3β,6β-dibenzoyloxy-5α-cholestane	5α-cholestane-3β,6β-diol(80)
4. 3β,6β-diformyloxy-5α-cholestane	5α-cholestane-3β,6β-diol(86)
5. 3β,6β-diisobutyryloxy-5α-cholestane	5α-cholestane-3β-ol(16) 5α-cholestane-3β,6β-diol (55)

Table—3(contd.)

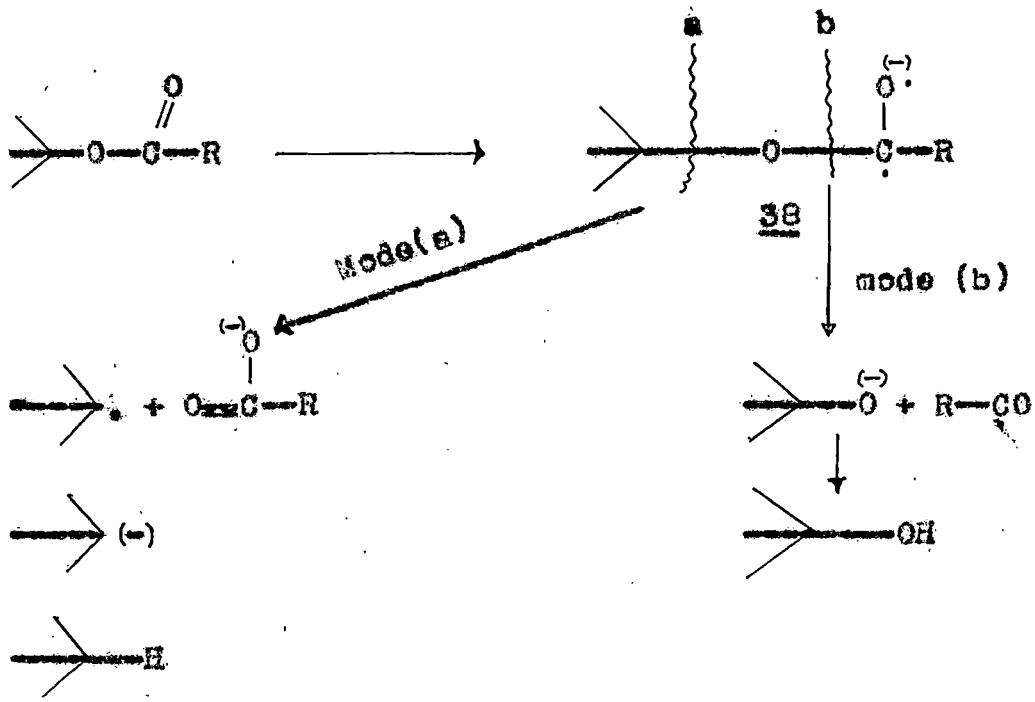
Starting Material	Product (% yield)
6. 3β,6β-diformyloxy-5α-cholestane	5α-cholestane-3β-ol (71) 5α-cholestane-3β,6β-diol(19)
7. 3β,6β-dipropanoyloxy-5α-cholestane	5α-cholestane-3β-ol (15) 5α-cholestane-3β,6β-diol (61)
8. 3β,6β-dipivaloyloxy-5α-cholestane	5α-cholestane-3β-ol (73) 5α-cholestane-3β,6β-diol(16)
9. 3β,5α-diacetoxycholestane	5α-cholestane-3β-ol (66) cholestane-3β,5α-diol (8)
10. 3β-5α-6β-triacetoxy cholestanol	Cholesterol (81) Cholestane-3β,5α,6β-triol
11. 3β,12-α-diacetoxy-13α-oleanane	13α-oleanane-3β-ol (85)
12. 3β,25-diacetoxy-5α-lanost-8ene	5α-lanost-8-en-3β-ol (75) 5α-lanost-8-en-3β-25-diol (10)
13. Caryolan-1-ol-acetate	Caryolane (80)

Except for entries 2,4,6 and 8 (K-Bu^t NH_2-18-crown-6), Li-EtNH_2 was used.

From the above table-3, it was clear that acetates of sterically hindered secondary alcohols and of tertiary alcohols were reduced by lithium in ethyl amine to afford predominantly the corresponding alkanes rather than the parent alcohols.

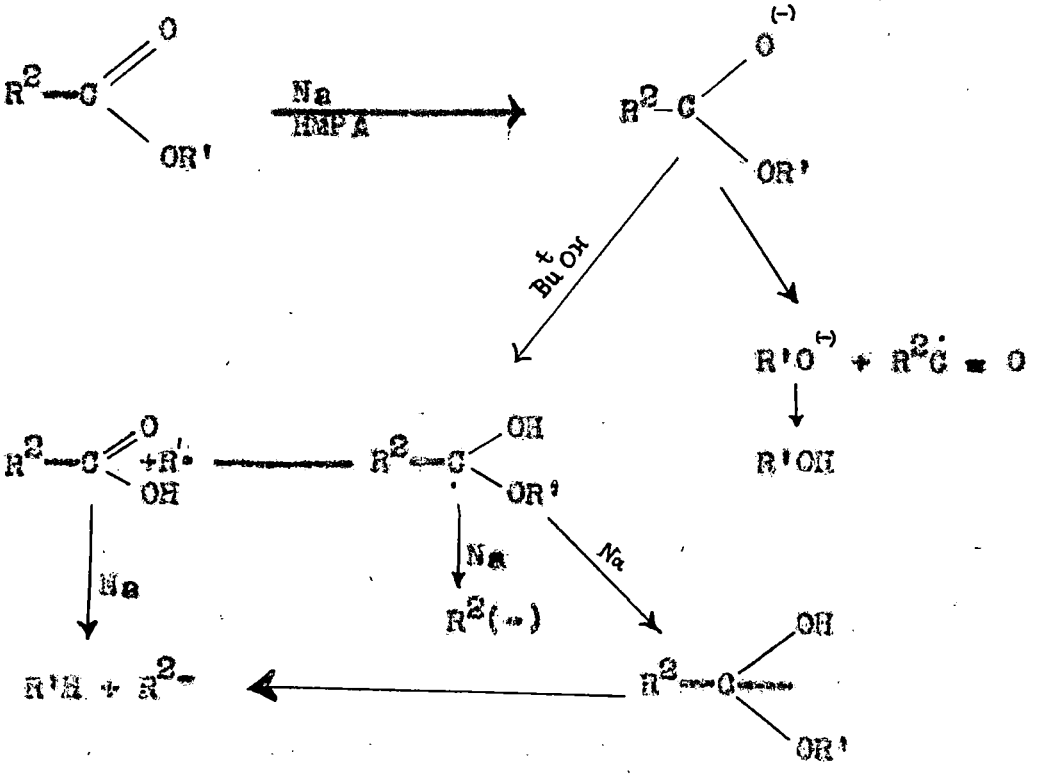
Reduction of esters of tertiary alcohols by the metals in presence of bases suggested the authors to assume in favour of a mechanism of the reactions involving radical fragmentation of the initially formed radical ion 38 in Scheme 1. Mode (a) and thence deoxygenation, evidently became the favoured process when cleavage of the C—O bond is attended by a sufficient release of unfavourable steric interactions. Otherwise mode (b) was preferred and the alcohol is regenerated. Under the reaction condition, reduction of radicals to the corresponding carbanions must be rapid. Thus the formation of cholesterol by the reduction of 3β,5α,6β-triacetoxy-cholestane was probably the result of displacement of the acetate group from C—6 by a carbanion at C—5. The fact that reduction only occurred with esters of sterically hindered alcohols confirms upon this method of selectivity for deoxygenation process.

Scheme—1



Deshyayes and Pete[19] reported a number of reduction examples of alkyl esters to alkanes by using sodium metal in presence of hexamethyl phosporic acid. The allyl esters of nonyl, heptyl, cyclohexyl, bornyl was examined by the workers. The mechanism which they proposed similar to the previous workers are shown in Scheme—2.

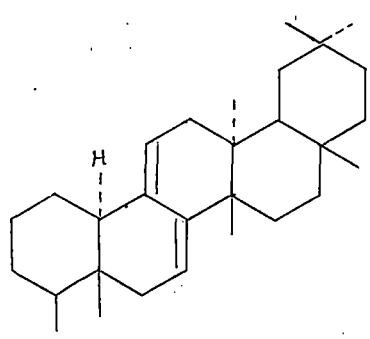
Scheme—2



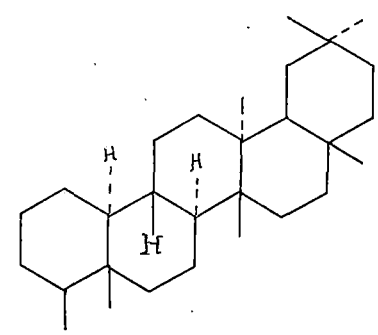
Tertiary butyl alcohol was added in the reaction mixture as a proton source. Reduction of tertiary esters gave the corresponding alkane quantitatively whereas primary and secondary esters lead to mixture of the corresponding alkane and alcohols in good yield.

Sengupta and coworkers[20] investigated the reaction of lithium in ethylendiamine on triterpenoids hetero-annuler 1,3 diene. Reduction of 25-norfriedolean-7,9(11),

diene 39 (0.15 g) was done in a solution of ethylenediamine (20 ml) with lithium (0.2 g) added in small pieces with stirring under nitrogen atmosphere and the mixture was refluxed for three hours. Solid ammonium chloride was added and the mixture was acidified with cold 6N HCl. After work up they isolated 25-nor-fried-oleanane, 40. It showed negative TNM test showing the absence of any double bond which was supported by NMR and IR spectrum. So the diene system was completely reduced.

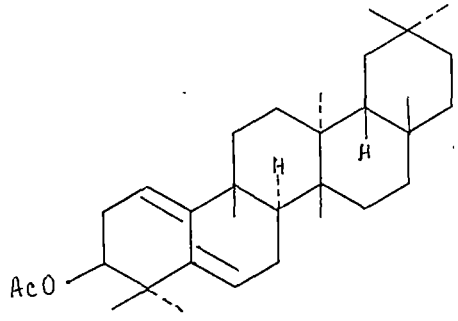


39

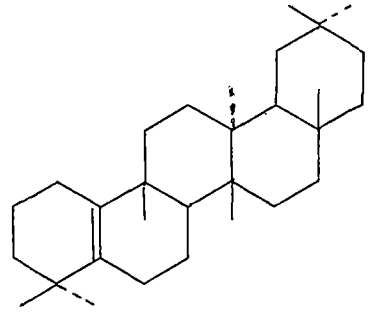


40

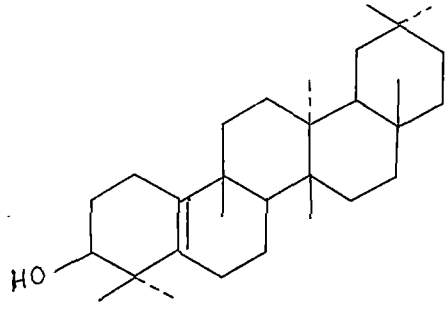
Reaction with lithium in ethylendiamine was reported by Sengupta et al on gluta-1(10), 5 dienyl-3β-acetate 41 and the products obtained were a mixture of deoxygenated and hydrolysed products. The products were respectively glut-5(10)-ene 42 and glut-5 (10) en—3β-ol 43. When multiflora-7,9(11)-dienyl-3β-acetate 44 were similarly reduced they isolated two compounds isomultiflorene 45 and iso— multiflorenol 46.



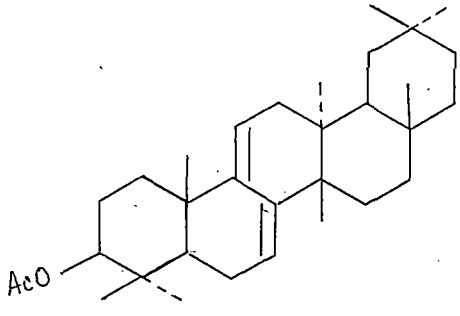
41



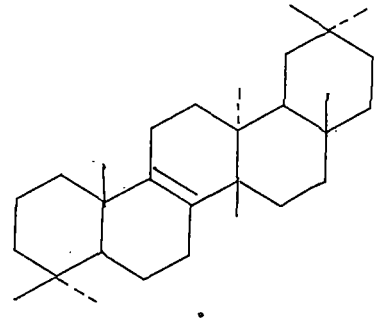
42



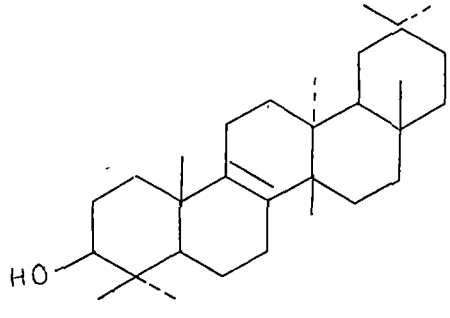
43



44

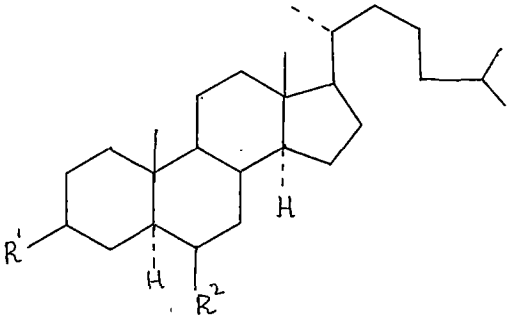


45



46

Barton and coworkers[21] studied the deoxygenation of carboxylic esters by alkali metals in organic bases. In the previous works by the workers[18] it was observed that typical diesters 47a and 47b gave 5∝-cholestan-3β-ol 47c (60 and 79% yield respectively) where the more hindered axial (6β) ester was selectively deoxygenated.



47a , $R^1 = R^2 =$ OAc

47b , $R^1 = R^2 = Bu^tCO_2$

47c , $R^1 =$ OH, $R^2 =$ H

47d , $R^1 = R^2 = R^3CO_2$

47e , $R^1 = R^2 =$ H

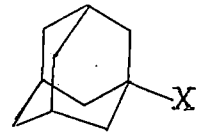
47f , $R^1 =$ H, $R^2 =$ OH

47g , $R^1 = R^2 =$ OH

47h , $R^1 = R^3CO_2$, $R^2 =$ H

The recent works by the authors[21] showed that the aliphatic or allycyclic esters normally react by mode (a)[18] provided that the medium is nucleophile-free.

Adamantane-1-carboxylic esters of sterols were taken for study. Adamentane carboxylate esters 48a and cyclic carbonates 48a and 49b were reduced by their addition in



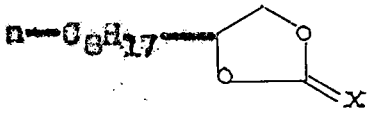
$\equiv R^S X$

48a, X = COCl	48e, X = CHO
48b, X = CO_2H	48f, X = $CH(-\bar{O})\bar{O}$ or $CH(-\bar{O})\bar{N}Et$
48c, X = CH_2OH	48g, X = CO_2Et
48d, X = CONHEt	48h, X = CO_2 $\lceil CH_2 \rceil_{17}$ Me

tetrahydrofuran to potassium and 18-crown -6 in t - butylamine. The products which were obtained in the reduction of esters are summerized in table—4. In table—4 reactions 1,2 and 4—7 were carried out using potassium and 18-crown-6 in t-butylamine at room temperature and reaction 3 with lithium and ethylamine at 17°C.

Table—4

Substrate	Products (% yield)
1. 47d	47a (45), 47c (27), 47g (8) 47f (6), 46b (92)
2. 48b	No reaction
3. 48b	48e (51), 48b (10), 48c (9)
4. 48g + 47e	47c (69), 47e (15), 48b (85)
5. 48h	$Me(CH_2)_{17}OH$ (53), $Me(CH_2)_{14}Me$ (41), 48b (90)
6. 49a	$n\text{-}C_8H_{17}CH(X)CH_2Y$, X=Y=OAC (67); X=H, Y=OAC + X=OAC, Y=H (5)
7. 49b	$n\text{-}C_8H_{17}CH(X)CH_2Y$, X=Y=OAC (35); X=H, Y=OAC (26); X=OAC, Y=H (8); $n\text{-}C_8H_{17}CH{=}CH_2$ (5)



49a, X = O
49b, X = S

In the reduction of the ester 47h the products which were obtained are summerized in table—5. In table—5,

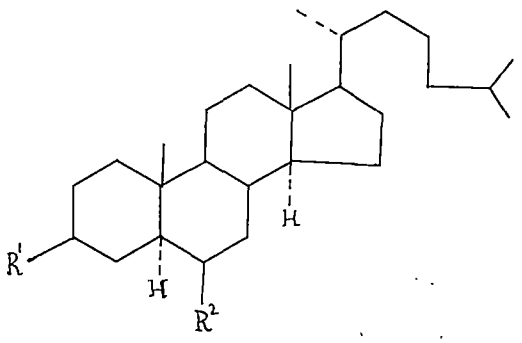
reactions were carried out at 46° (1,2), 20° (3—5), 17 (9—11) or -73°C (8) in t-butylamine and THF (1—3, 6,7), t-butylamine with potassium (4), 1,2-dimethoxyethane and iodomethane (5), THF and t-butylacetate (11).

Table—5

Amount/m. mol of Ester (47h), metal, 18 crown-6	% yield of products				
	47e	47c	48b	48c	48d
1. 1.04, 38, 11	43	57	96	2	-
2. 0.84, (34+18), (6+4)	32	68	81	0	-
3. 1.03, 13, 4	45	37	84	0	-
4. 1.03, 14, 4.5	45	44	93	7	-
5. 1.20, 28, 7	30	57	92	0	-
6. 1.09, 36, 6	27	66	77	5	-
7. 1.04, 36, 6	15	81	71	0	-
8. 1.17, 29, 0	1	93	0	69	0
9. 1.15, 22, 0	7	85	4	4	92
10. 1.17, 27.2, 0	4	84	4	65	0
11. 1.03, 65, 0	5	92	2	29	51
12. 0.45, 100, 0	0	58	0	66	0

In all cases reduction of ester 47b gave 5α-cholestane 47e and acid 48b with the latter substantially predominating. The possibility that this difference resulted from competative hydrolysis by adventitious water was unlikely since vigorous drying was used and in entry 5, (table—5) iodomethane was added before the ester to scavenge any water, the ratio of 47e : 48b was not increased. The yields of acid 48b and alkane 47e were decreased at lower temperature. Deoxygenation was a minor pathway on lithium-ethylamine reduction giving 47c and 48d. In the presence of excess electrons or at low temperature both transacylation (giving 48d) and radical anion fragmentation (giving 47e) were suppressed and the two electron Bouveault-Blanc products 47c and 48c formed. Entry 4 of table—4 showed that ester deacylation by an alkoxide competed with reduction. In entry 7 of table—4 predominance of primary acetate was consistant with deoxygenation via the radical anion, not the dianion.

Barton and coworkers[22] studied that primary and secondary alcohols could be easily deoxygenated by the reduction of their dialkylaminothiocarbonyl derivatives with potassium and 18-crown-6 to produce the corresponding alkanes.



47a, $R^1=R^2=OAc$,

47c, $R^1=OH$, $R^2=H$,

47e, $R^1=R^2=H$

47f, $R^1=H$, $R^2=OH$

47g, $R^1=R^2=OH$

50a, $R^1=R^2=MeS.CS.O$,

50b, $R^1=R^2=EtNH.CS.O$

50c, $R^1=R^2=CH_2-(CH_2)_3-N(CS.O)$

50d, $R^1=CH_2-(CH_2)_4-N-CS.O$, $R^2=H$

50e, $R^1=Et_2NCSO$, $R^2=H$

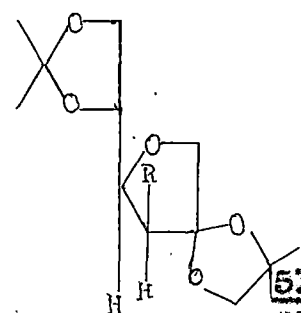
50f, $R^1=Me_2NCH_2CH_2N(Me)CS.O$, $R^2=H$

Reduction of dithiocarbonate 50a and thiocarbamates 50b, 50c, 50d, 50e, 50f and 51a were done with potassium in t-butylamine solubilised by 18-crown-6. The products which were obtained are shown in table—6.

Table—6

Entry	Starting material	Products (% yield)
1	50a	47e(38), 47c(19), 47g(8), 47f(2)
2	50b	47g(45), 47c(18)
3	50c	47c(62), 47f(15), 47c(12), 47g(5)
4	50d	47e(74), 47c(14)
5	50e	47e(86), 47c(6)
6	50e	47e(58), 47c(40)
7	50f	47e(83), 47c(12)
8	$Me(CH_2)_{17}O.CS.NEt$	$Me(CH_2)_{16}Me(87)$, $Me(CH_2)_{17}$-OH(12)
9	51a	51b(56), 51c(14)

All reductions were done at room temperature except entry-7 which was done at -30°C

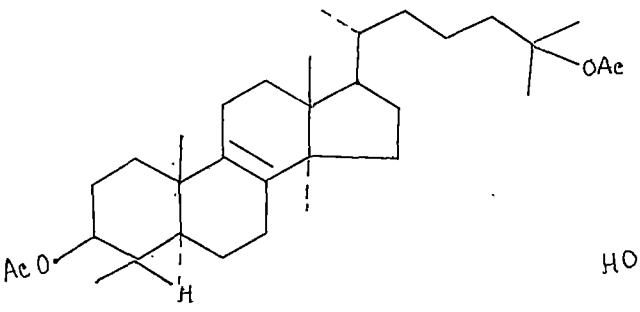


51a, $R=Et_2N.CS.O$
51b, R=OH
51c, R=H

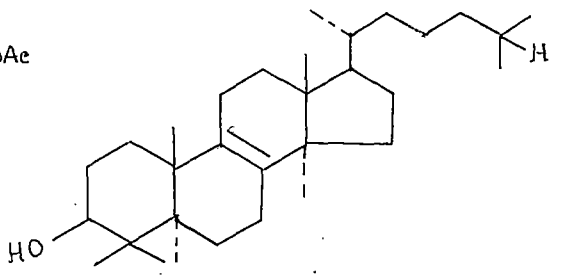
The primary and secondary alcohols were thus easily deoxygenated by this method of Barton and his co-workers[22] since the thiocarbamate derivatives were easily obtained from the corresponding alcohols.

Sengupta and coworkers[23] examined the reaction of Li in ethylenediamine on triterpene hindered esters. They observed methyl esters of oleanolic acid, crategolic acid, prodocarpic acid, ursolic acid were hydrolysed during the reaction condition and the corresponding acids were obtained.

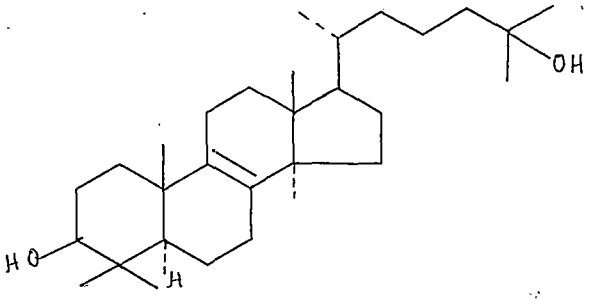
Barton and coworkers[24] observed from the previous works[21,22] and with some additional works[24] that sterically hindered esters were deoxygenated in presence of group IA metal in bases while the non hindered esters produced the corresponding alcohol. At ambient temperature the principal pathway on the dissolving metal reduction on alkyl carboxyllic esters was the formation of alkane and carboxyllic acid anion. They described the pathway as the alkyl-oxygen cleavage of the ester radical ion. They studied the reduction on sterol system where diesters were taken in sterically different environments. The compounds 52 and 53 when treated with lithium in ethylamine the products 54, 55 and 56 were obtained respectively. In compound 52 and 53 the acetoxy groups were in different sterical environments.



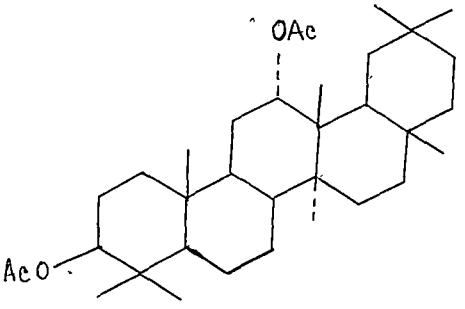
52



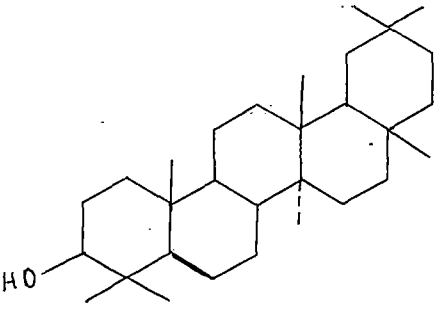
54 (75%)



55 (10%)



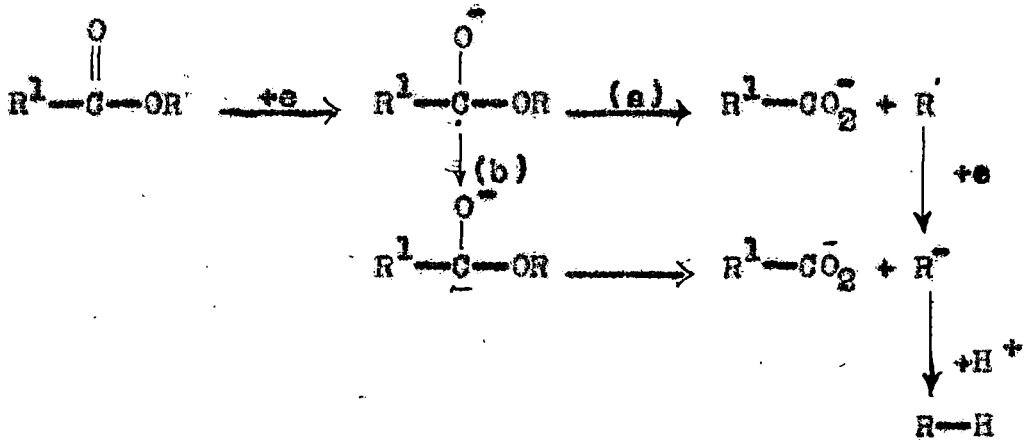
53



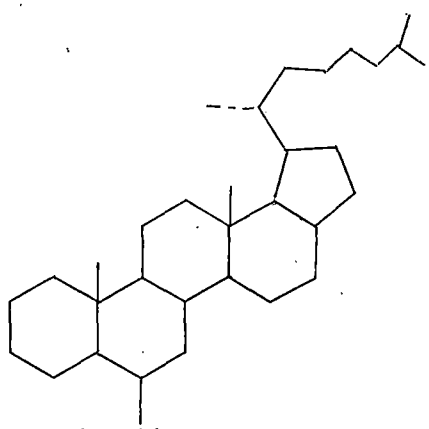
56

Possible mechanisms for the deoxygenation are shown in Scheme—3. In pathway (a) the initially formed radical anion fragments to give an alkyl radical and carboxylate anion. Alternatively, in pathway (b) the radical anion was further reduced to the dianion which then collapsed to yield a carbanion and carboxylate anion.

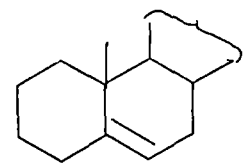
Scheme—3



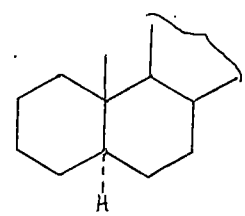
Reduction of 3β,5α-cyclocholesta-6β-yl acetate 57 gave cholest-5-ene 58 (85%) and 3β,5α-cyclocholestane 59 (15%). This result was consistant with the occurrence of pathway (a), since the rapid rearrangement of the 3β, 5α-cyclocholestan-6-yl radical would form stable cholest-5 en 3-yl, radical



57



58



59

The formation of cholest-5 ene 58 was presumably the result of displacement of the acetoxy group from C—6 by a carbanion at C—5.

These reductions supported the fact that the deoxygenation occurred predominatly, via the fragmentation of the radical anion (scheme—3).

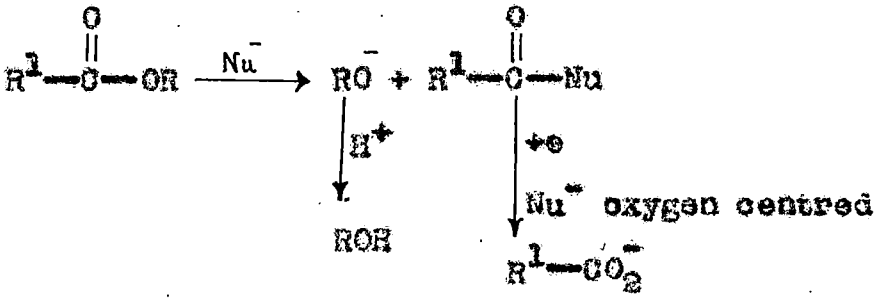
Both pathways in scheme—3 required that the acyl component of the ester was released at the carboxylate oxidation level. This point was established by the experiment viz. the reduction of adamantane-1-carboxyllic acid 48b

was studied. Controlled reduction of the compound was stable to treatment with potassium and 18-crown-6 in t-butylamine. Prolonged reduction of the compound 48b gave adamantane-1-carbaldehyde 48a and adamanten-1 yl methanol 48c, in addition to recovered acid 48b (10%).

The reduction of 5α-cholestane-3β,6β-diyl-bis (adamantane-1-carboxylate) 47d gave adamantane-1-carboxyllic acid 48b in 92% yield. The yield of the acid was higher than that of deoxygenation products. Competitive hydrolysis of the ester by adventitious water could have accounted for this fact, but seemed improbable in view of the precautions taken to ensure anhydrous conditions.

The process which competes with deoxygenation and in which the starting alcohol was regenerated assumed to be the deacetylation of the ester by some other neucleophile Nu^-. The process is shown in Scheme—4.

Scheme—4

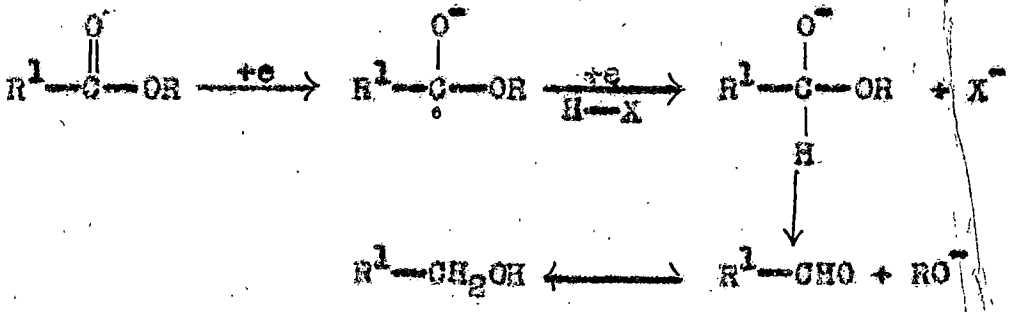


The newly formed ester where the nucleophile was oxygen centred, subsequent reduction of the ester, $R^1—\overset{O}{\overset{\|}{C}}—Nu$ took place and generation of carboxylate anion was observed. To prove the postulate the workers studied the reaction of a mixture of ethyl- adamantane-1-carboxylate 48g or ethyl acetate and 5α-cholestan-3β-ol 47c and isolated 5α-cholestane 47e. Reduction of 5α-cholestan-3β-yl adamantane-1-carboxylate 47h under various condition was studied. With lithium in ethylamine there was little deoxygenation or formation of adamantane-1-carboxyllic acid 48b. This was due to the occurrence of transacylation. This problem was overcome by the use of t-butylamine as solvent. At lower temperature transacylation was suppressed as was radical-anion fragmentation.

The source of nucleophile was established by the fact, tetrahydrofuran was fragmented by strong bases. 18-crown-6was broken down by treatment with potassium in t-butylamine. Deoxygenation by dissolving metal reduction of carboxylic esters was limited by competitive deacylation by solvent or crown ether derived nucleophiles. The selective deoxygenation of sterically hindered esters was a result of the suppression of this competitive deacylation.

The radical ion derived from the esters normally fragment to give the carboxylate anion and radical made the Bouveault-Blanc and acyloin reaction curiosities.[6] The Bouveault-Blanc reaction by protonation of ester radical anion concerted with the second electron transfer. This was shown in Scheme—5 which allowed the acyl-oxygen fission to take place with formation of the alkoxide and the aldehyde. Further reduction and protonation of the latter afforded the primary alcohol.

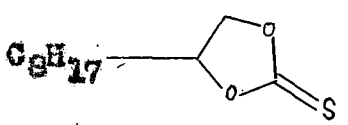
Scheme—5



The radical ion did not fragment immediately in ethanol solution was thought to result from solution of the anion by the solvent. Ester radical anions were sensitive to solvation and to temperature. At elevated temperatures in the presence of finely divided droplets of metal the reaction must be surface reaction in which

the ester radical anions remained bonded to the metal before coupling. While using liquid ammonia (-33°C) the radical ion which was formed could be trapped by alkylation as did not fragment quickly because of the low temperature.

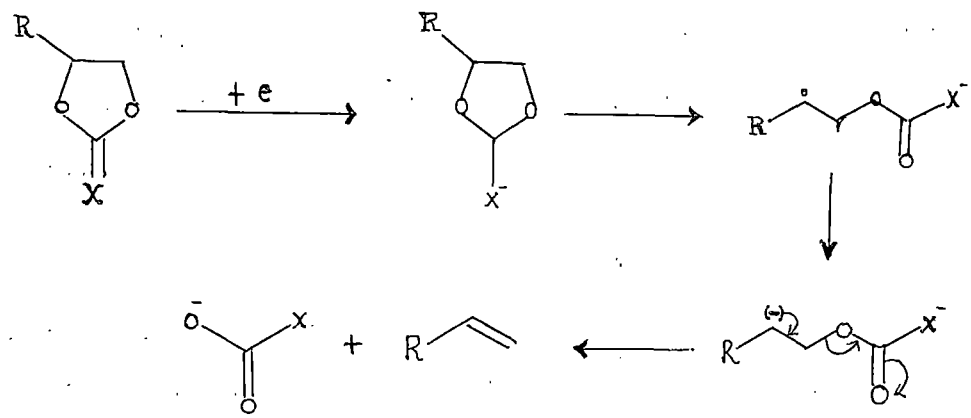
Barton and his coworkers[25] established a new method for deoxygenation of alcohols by reduction of the corresponding NN-dialkylamino thiocarbonyl oxyalkanes derivative with lithium in ethyl amine or potassium solubilised by 18-crown-6 in t-butylamine. Reduction of the 1,3-dioxolan-2-one or 2-thione derivatives were preparatively unsatisfactory. However formation of more decan-1-ol than decan-2-ol from the thions 60 was consistent with ring fragmentation at the radical- anion stage as shown in Scheme—6.



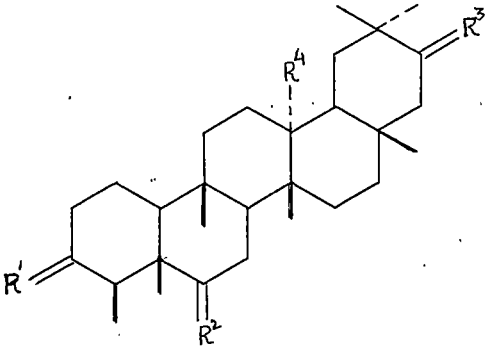
60

In general with the exception of xanthates and thiocarbamates all the alcohol derivatives were not efficiently deoxygenated.

Scheme—6



Gunatilak, Nanayakkara and Sultanbawa[26] used lithium-ethylenediamine reaction to establish the structure of kokzeylanol 61 and kokeyzeylmonol 62. Lithium-ethylene diamine reduction of kokzeylanol diacetate 63 followed by oxidation (CrO_3-pyridine) furnished friedelin 64 and similar treatment of kokzeylanol diacetate 65 gave friedelin-3,21-dione 66.



61, R^1=O; R^2= β-OH, α-H; R^3=H_2; R^4=CH_2OH

62, R^1=R^3=O; R^2= β-OH, α-H; R^4=CH_2OH

63, R^1=O; R^2= β-OAC, α-H; R^3=H_2; R^4=CH_2OAC

64, R^1=O; R^2=R^3=H_2; R^4=CH_3

65, R^1=R^3=O; R^2= β-OAC, α-H; R^4=CH_2OAC

66, R^1=R^3=O; R^2=H_2; R^4=CH_3.