P A R T - I

CHAPTER - I

The chemistry of terpenoids abounds in fascinating molecular rearrangements, which may be accomplished with relatively simple reagents. Besides demonstrating the combined role of steric and electronic factors in the study of reaction mechanism in general, the vast array of the rearrangement reaction has helped in ascertaining structures, stereochemistry and biogenetic pathway of formation of the terpenoids. The oxidative transformation, which are effected photochemically and by oxidants like mercuric acetate, lead tetra-acetate, chromic acid, N-bromosuccinimide, organic peracid, hydrogen peroxide etc. have been extensively studied[1-12]. Oxidation of triterpenoids by hydrogen peroxide with

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1. J.M.Allison, W.Lawrie, J. Mclean and G.R.Taylor, J.Chem.Soc. 3353 (1961); ibid J.Chem.Soc. 5224 (1961)
2. C.S.Chopra and (the late) D.E.White, Tetrahedron, 22, 897 (1966)
3. H.N.Khastgir and S.N.Bose, Tet.Lett. 1, 39 (1968)
4. S.N.Bose and H.N.Khastgir, J.Ind.Chem.Soc., 46, 860 (1969)
5. G.V.Baddeley, J.J.H.Simes and T.G.Watson, Tetrahedron, 26 (15), 3795 (1970)
6. S.P.Adhikary, W.Lawrie and J.Maclean, J.Chem.Soc(C), 1030(1970)
7. L.Ruzicka and E.Rey, Helv.Chim.Acta., 25, 171 (1942)
8. L.R.Row, C.S.Rao and T.S.Ramaiah, Ind.J.Chem., 6, 16 (1968)
9. I.Agata, E.J.Corey, A.G.Hortmann, J. Klein, S.Proskow and J.J.Ursprung, J.Org.Chem., 30, 1698 (1965)

selenium dioxide as catalyst are scanty. The reagents have, however, been used in the oxidation of acrolein[13], cyclo and bicyclo alkanones[14], and steroidal ketones[15,16]. In view of the fact that the succeeding chapter deals with oxidation of some triterpenoids by hydrogen peroxide in presence of selenium dioxide, it is pertinent to present in this chapter a brief account of different oxidative transformation reactions with selenium dioxide, hydrogen peroxide and a mixture of selenium dioxide and hydrogen peroxide.

Selective Oxidations with Selenium Dioxide

Selenium dioxide has been in use since Riley's pioneering work[17] in which he reported conversion of a monocarbonyl compound having an adjacent methylene unit to an α-dicarbonyl compound. The transformation of a ketone or an aldehyde to an α-dione, allylic oxidation and the conversion of a monoketone or a

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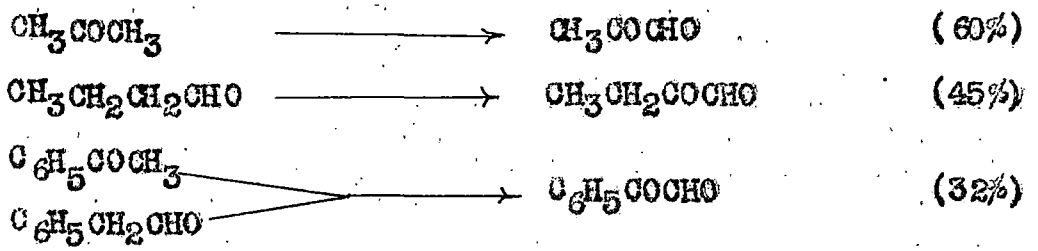
10. T. Mezzetti, G.Orzalesi and V.Bellavita, Plant Medica, 20(3), 244 (1971)
11. M. Fukuoka and S.Natori, Chem. Pharm. Bull., 20(5), 974(1972)
12. B.W.Finucane and J.B. Thomson, J.Chem.Soc. (Perkin I), 1856(1972)
13. W.S.Curtis and T.H.Roy, J.Org.Chem., 22, 746 (1957)
14. L.Stall and Jucker, Helv.Chim. Acta. 36, 268 (1953)
15. E. Caspi and S.N.Balasubrahmanyam, Tet. Lett. 745 (1963)
16. E. Caspi, Y. Shimizu and S.N.Balasubrahmanyam, Tetrahedron, 20, 1271 (1964)
17. H.L.Riley, J.F.Morley and N.A.C. Friend, J.Chem.Soc., 1932, 1875.

1,4, diketone to an α,β -unsaturated ketone or to an ene-dione are the major areas in which the reagent has found rather wide application.

Formation of α -dione

Both ketones and aldehydes would react with selenium dioxide to give reasonable yields of products as shown below.



Excellent yields can be obtained if the ketone being oxidised contains structural features which prevent side or competing reactions from occurring. Thus, A-nor allobetulone-3 and A-nor-4, 4-dimethyl cholest-5-ene-3-one both of which have the monoketone unit, partial structure 1, are oxidised to the diketone 2 in 87% and 92% yield[18].

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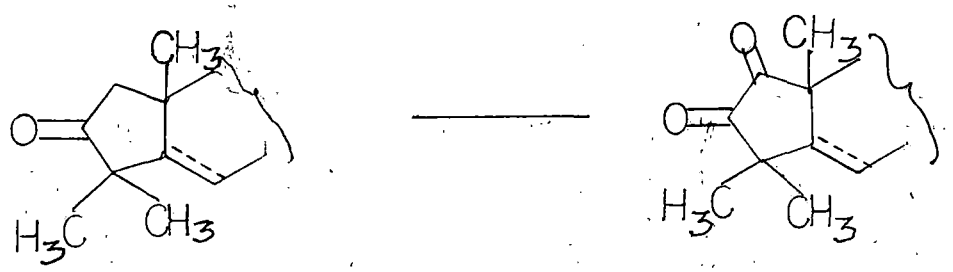
18. R. Hanna and G. Onrisson, Bull. Soc. Chim. Fr., 1945 (1961)



1 2

Mechanism:

The most critical study of the reaction was made by Corey and Schaefer[19], who studied the oxidation of desoxybenzoin in 70% acetic acid at 89.2°. They found the reaction to be second order; first order in ketone and first order in selenium (IV) reagent and to be catalyzed by added strong acid. Various p-substituted desoxybenzoins with substituents in the benzyl or benzoyl moiety were studied. Electron supplying substituents in the benzoyl increased the rate of reaction (ρ = -0.56) while the effects in benzyl group was to decrease the reaction rate (ρ = +0.25). This is what one would expect in acid catalyzed enolization process.

The reaction exhibited an isotope effect; kH/kD for dideutorio desoxybenzoin was 6.0 and for the oxalic acid catalyzed reaction it was 5.8. Fast reversible enolisation, followed by slow

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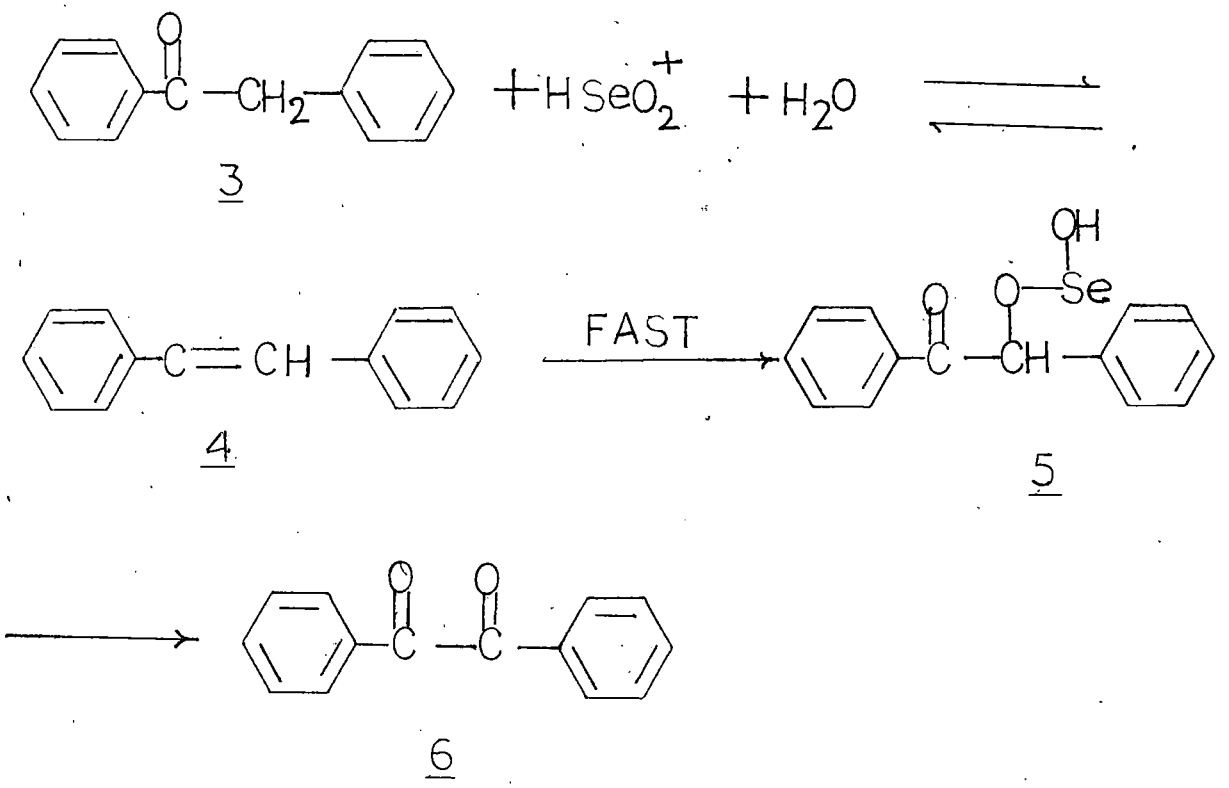
19. E.J. Corey and J.P. Schaefer, J.Am.Chem.Soc., 82, 918 (1960)

reaction of the enol with oxidant should have exchanged out the deuterium prior to reaction and kH/kD = 1.

The mechanism proposed by the authors involves attack of an electrophile, $HSeO_2^+$ or $H_3SeO_3^+$ and the nucleophile, H_2O, on desoxybenzoin, 3, in a slow step to give an end selenite ester, 4. The latter rearranges in a series of fast steps to an α - selenite (II) keto-ester 5 and finally to benzil 6 (Scheme-I).

Scheme - I



Allylic oxidation

After several publications on the oxidation of olefins[20-23], Guillemonat collected his observations in one report[24]. He found that the course of selenium dioxide oxidation of alkenes could be predicted from the following rules:

(i) The oxidations always occurred to alpha to the most substituted end of the double bond.

(ii) When the double bond was in a ring, whenever possible, oxidation occurred within the ring.

(iii) The order of preference for oxidation was $CH_2 > CH_3 > CH$.

(iv) When the double bond was terminated rather than the expected secondary alcohol or the derivative thereof, the primary alcohol was formed with the migration of the double bond.

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20. A. Guillemonat, Compt. Rend., 200, 1416 (1935)
21. A. Guillemonat, ibid 201, 904 (1935)
22. A. Guillemonat, ibid 205, 67 (1937)
23. A. Guillemonat, ibid 206, 1126 (1938)
24. A. Guillemonat, Ann. Chim. 11, 143 (1939)

Though the inadequacy of Guillemonat's proposal has been shown[25-27], the generalization is still valid with respect to site of attack in many cases.

Another early suggestion put forward by Waters without any experimental support was that the reaction involved neutral radical species[28]. Schaefer, Horvath and Klein[29] had shown that the reaction was unaffected by inhibitors and, therefore, could not be radical chain. That no free radical was generated in the system had been pointed out by Trachtenberg et al[30] as the system was incapable of initiating polymerisation of acrylonitrile under conditions of temperature and concentration, where acrylonitrile is rapidly polymerised if a source of free radical is present.

Wiberg[31] established that selenoxides, 7, rather than selenides as had earlier been proposed by Guillemonat was involved in the oxidation of cyclohexene in acetic acid - acetic anhydride

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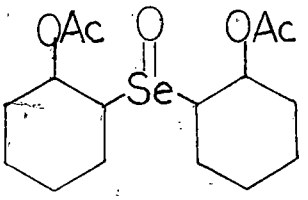
25. E.N.Trachtenberg in "Oxidation" Vol. 1 R.L.Augustine, Ed., Marcel Dekkar, New York, N.Y. 1969, pp 119-187.
26. R. Rabjon, Org. Reaction, 5, 331 (1949)
27. G.R.Watkins and G.W.Clark, Chem. Rev. 36, 235 (1945)
28. W.A.Waters, J.Chem.Soc., 1805 (1939)
29. J.P.Schaefer, B.Horvath and H.P.Klein, J. Org. Chem., 33, 2647 (1968)
30. E.T. Trachtenberg, C.H.Nelson and J.R.Carver, J.Org.Chem. 35, No. 5, 1653 (1970)
31. K.B.Wiberg and S.D.Nielsen, J.Org.Chem., 29, 3353 (1964)

reaction. Schaefer et al[29], however, showed that the analogus compound, 8, isolated from the oxidation of 1,3 diphenyl propene, 9, decomposes to 1,3 diphenyl-2-propene-1-ol acetate, 10, at too slow a rate to account for the main course of oxidation. The main pathway must involve solvolysis on an allylic selenite ester, although the structure of the latter has not been rigorously established.



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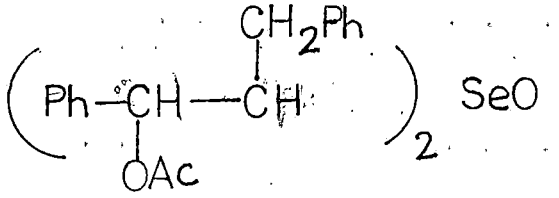

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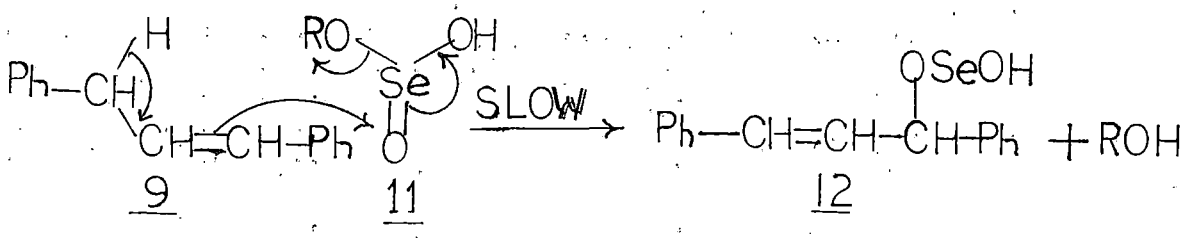
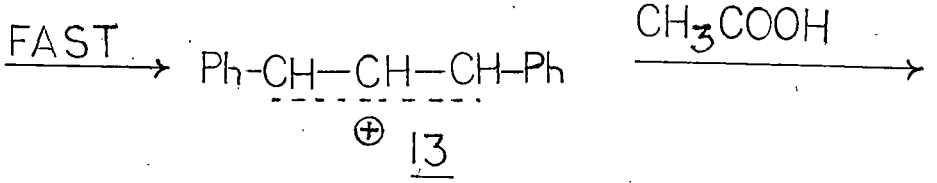
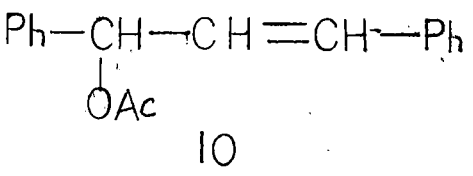
Scheme - II







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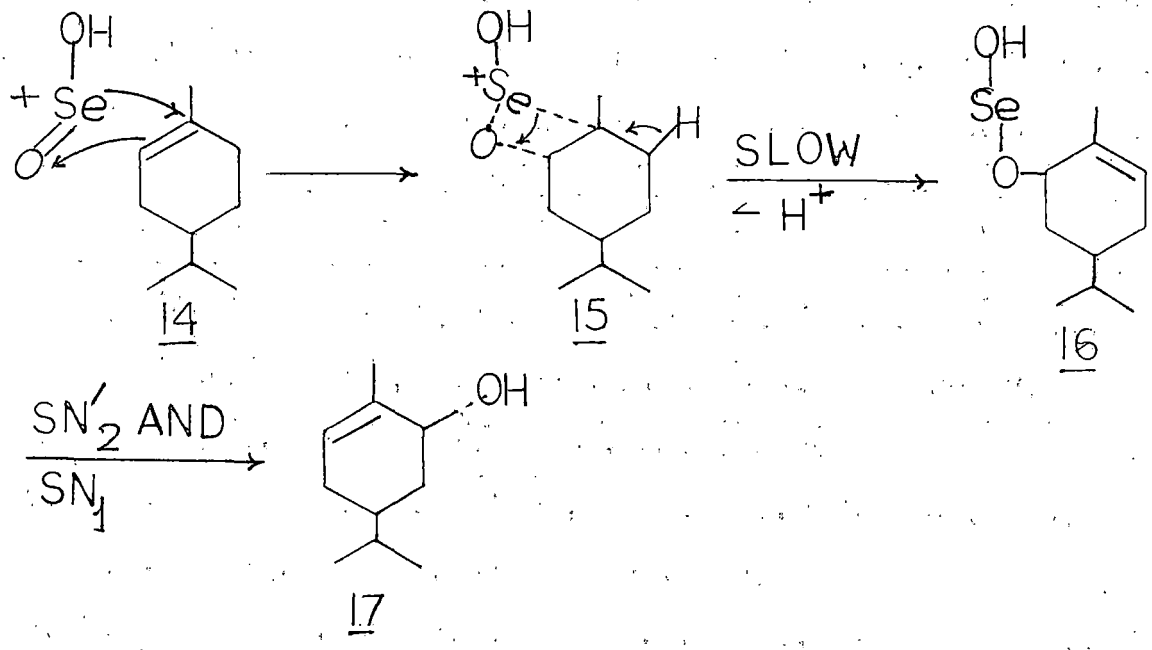
Since the selenium (II) ester formed, 12, was benzylic, the preference for ionisation (SN_1) rather than SN'_2 attack as found by Wiberg and Nielsen was possible[32]. Schaefer et al[33] pointed out that the intermediate which contains a C - Se bond is very likely a stable compound as are alkyl selenic acids. Thus, the intermediate as well as selenium (II) ester type intermediate, which contains on O-Se bond will not probably undergo solvolysis.

In order to explain the sterEochemical results obtained by oxidation of a number of cyclohexenyl system, Trachtenberg et al[34] proposed the following mechanism as shown in Scheme-III with D (+)-1-p-menthene as substrate.

Scheme - III



32. K.B. Wiberg and S.D. Nielsen, J. Org. Chem. 29, 3553 (1964)

33. Ref. 29 of this chapter.

34. E.N.Trachtenberg, C.H.Nelson and J.R. Carver, J. Org. Chem., 35, 1653 (1970)

The first step does not imply a concerted 2+2 cycloaddition but rather a typical Markovnikov type electrophilic addition with attack occurring through oxygen to generate positive character as the tertiary carbon, followed by cyclization. In agreement with electrophilic attack are the observations that dienes are more reactive than olefins — olefins reactivity increases with alkyl substitution and electron feeding groups slightly accelerate the rate of oxidation of 1,3 diphenyl propene[35].

Sharpless and Lauer[36] proposed different mechanism for allylic oxidation of olefins by selenium dioxide. As already discussed, Schaefer and Trachtenberg argue against involvement of allyl selenic acid, 19, because of the known inertness of benzyl selenic acid to solvolysis. However, a [2,3] sigmatropic rearrangement (path b, Scheme IV) of allyl selenic acid, 19, to a selenium (II) ester, 20, occurred to Sharpless et al as a likely alternative to the solvolysis pathway a. They suggested that the [2,3] sigmatropic shift indicated in the path b is a facile process (Scheme - IV).

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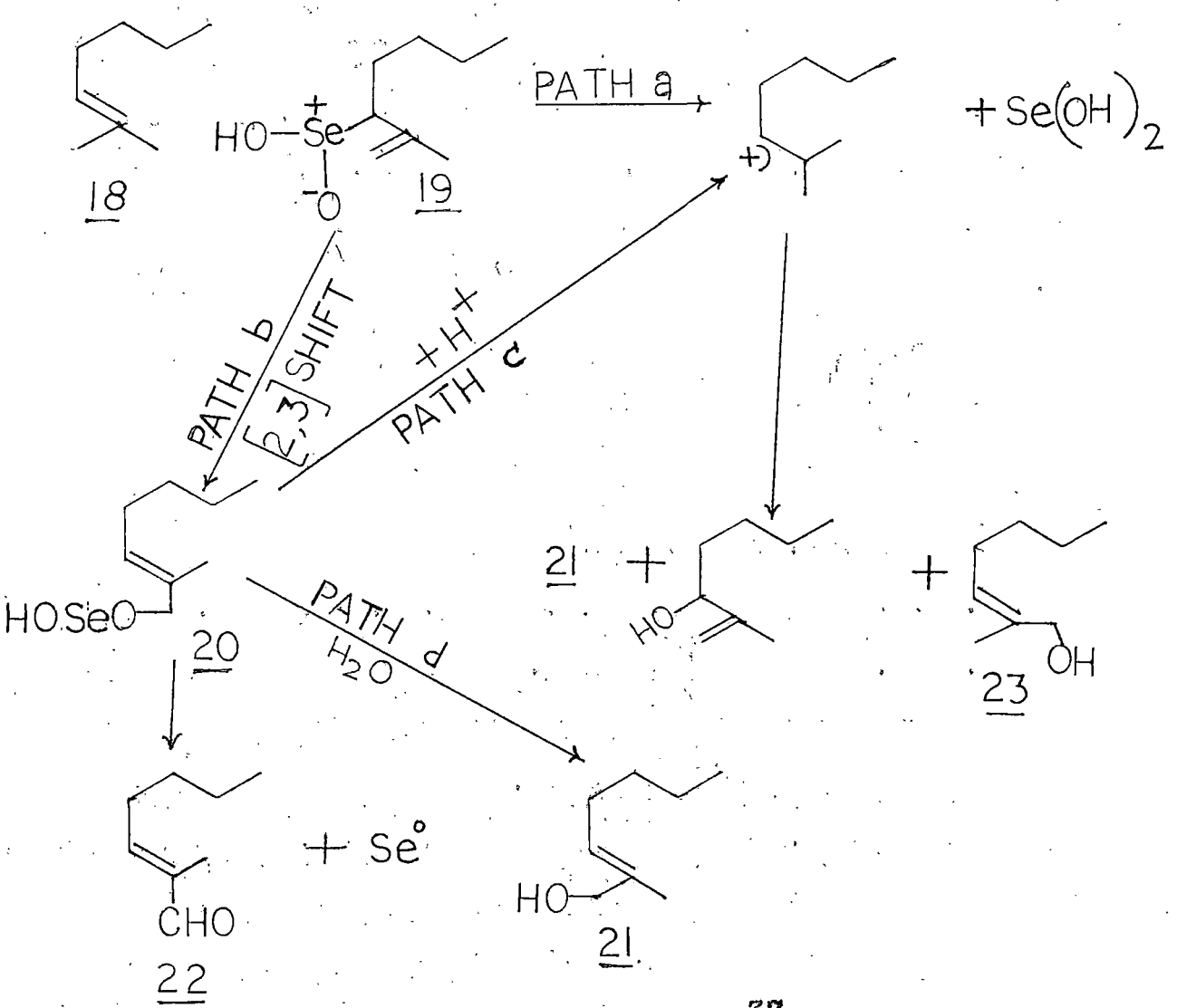
35. Ref. 29 of this chapter.

36. K.B. Sharpless and R.F. Lauer, J. Am. Chem. Soc., 94(2), 7154 (1972)

Scheme - IV



The authors had noted that Buchi and Wuest[37] had established that SeO_2 selectively attacks trisubstituted olefins such as, 18, to give only the (E) - alcohol, 21. The allyl selenic acid, 18, must

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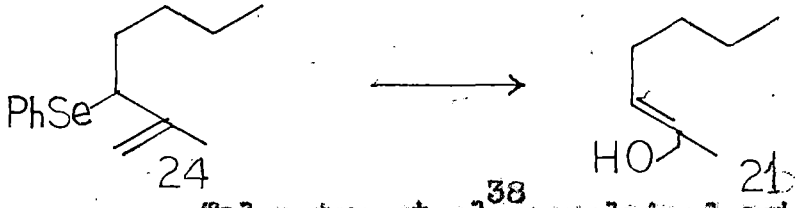
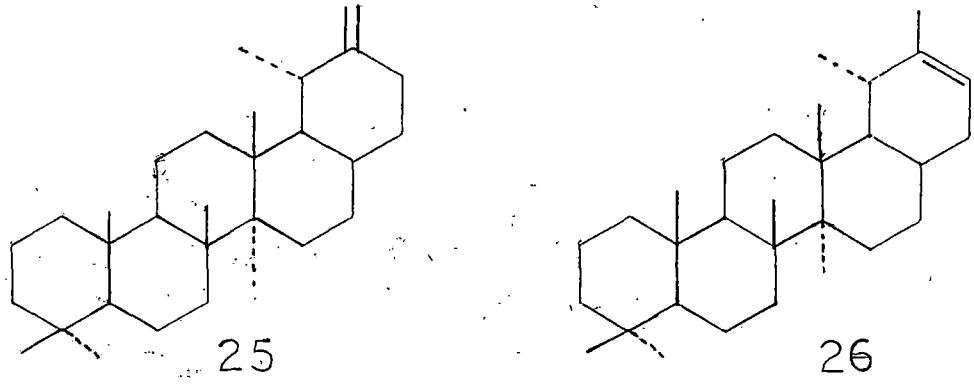
37. G. Buchi and H. Wuest, Helv. Chim. Acta., 50, 2440 (1967)

lead stereoselectively to the (E)-ester of 20 if the proposed rearrangement is correct. The mechanism was verified from the conversion of alkyl phenyl selenides 24 to 21.



24 21

Talapatra et al[38] explained oxidation of taraxastene, 25, and Ψ-taraxastene 26 to give the corresponding aldehyde[39]



25 26

on the basis of the mechanism shown in Scheme - V.

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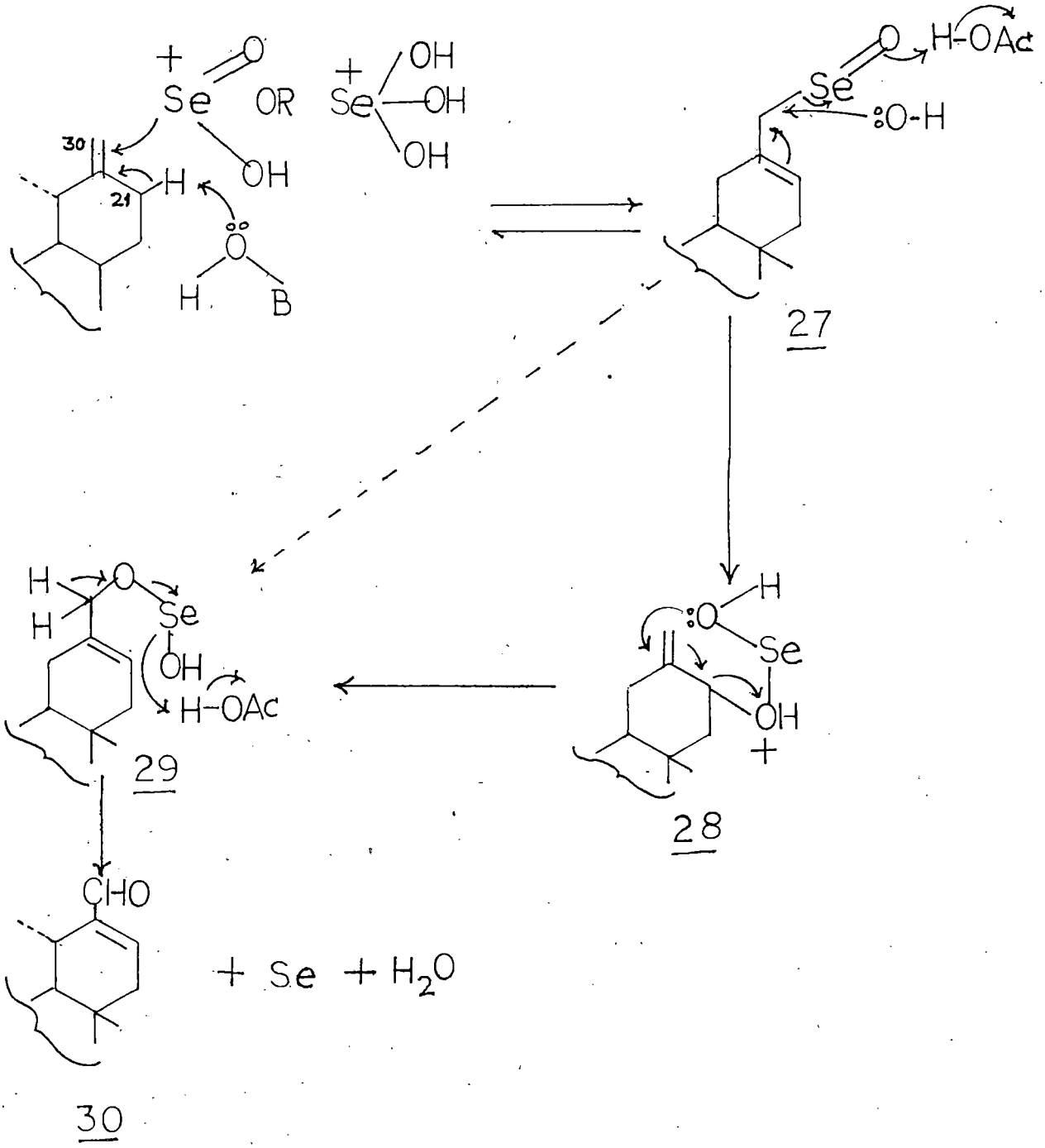
38. S.K. Talapatra, M. Bhattacharjee and B. Talapatra, Ind. J. Chem., 11, 977 (1973)

39. T.R. Ames, J.L. Beton, A.Bowers, T.G. Halsall and E.R.H. Jones, J. Chem. Soc., 1905 (1954)

Scheme - V


Se
OR
OH
30
21
H
O
H
B
OH
Se
OH
OH
O
H-OAc
Se
:O-H
27
H
H
O
Se
OH
H-OAc
29
H
:O
Se
OH
+
28
CHO
+ Se + H_2O
30

The electrophilic attack of $HSeO_2^+$ or $H_3SeO_3^+$ on the olefinic C-30 with simultaneous or subsequent nucleophilic attack on the allylic C_{21} -H leads to the formation of an unstable Se(IV) complex 27 possessing the more stable double bond parallel to the trans D/E ring juncture. The complex 27 undergoes successive rearrangements, as shown, to form the unstable Se(II) complex intermediate 28 and 29 involving 5 and 6 membered cyclic transition states respectively requiring low activation energies. The intermediate complex 29 could, alternatively, also arise directly from 27 involving a 3-membered transition state, as shown. Intermediate 29 then collapses to form the product 30 by loss of an allylic proton with concomitant deposition of selenium metal as depicted.

α,β dehydrogenation of Carbonyl Compounds

Riley reported[40] dehydrogenation of diethyl succinate to a mixture of the di and half ester of maleic acid. In 1947 Schwenk and Stahl[41] reported the discovery that selenium dioxide oxidation of a 12-keto steroid, 31, produced the $\Delta^{9,11}$-12 ketone of partial structure 32, and not the 11, 12 diketone.

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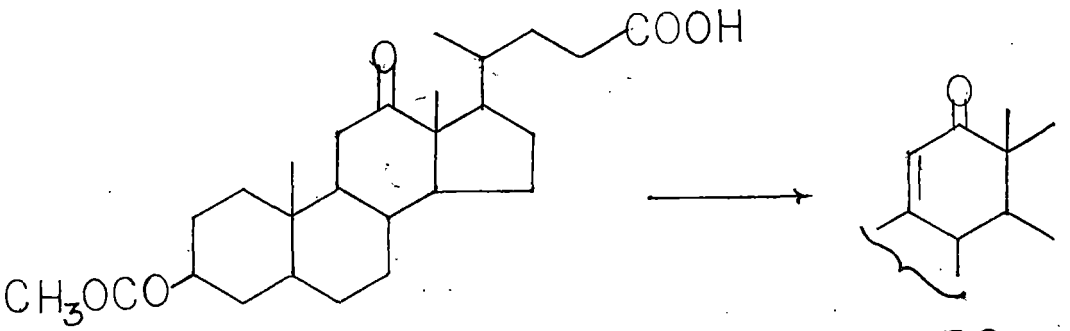
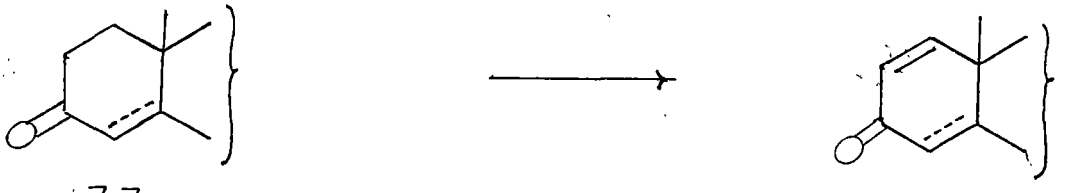
40. S. Astin, A.C.C. Newman and H.L. Riley, J. Chem. Soc. 391 (1933)

41. E. Schwenk and E. Stahl, Arch. Biochem., 14, 125 (1947)



31 32

Thus, dehydrogenation can occur without the presence of two straddling activating groups. Selenium dioxide introduces a double bond at the 1,2 position in either a 5α-3-keto steroid or Δ^4-3-keto steroid[42,43], partial structures being 33 and 34.



33 34

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42. C.Meystre, H.Frey, W.Voser and A.Wettstein, Helv.Chim.Acta. 39, 734 (1956)

43. S.A.Szpilfogel, T.A.P.Posthumus, M.S.deWinter and D.A.vanDrop, Rec.Trav.Chim., 75, 475 (1956).

Mechanism of α, β dehydrogenation:

1, 4 di-ketones:

The reaction exhibited a deuterium isotope effect of 6.5 (initial) when 1,1,2,2 tetradeuterio-1,2-dibenzoul ethane was at 90°. Schaefer[44] also showed that the biselenite ion, $HSeO_3^-$, was very likely not involved in the reaction since it did not oxidize acetone. 1,2 dibenzoyl ethylene, 38, is also oxidised but at an 1/30 th the rate of starting dione.

With these facts the following mechanism was proposed for acid catalysis: (1) production of the oxidant, $H_3SeO_3^+$, by protonation of selenious acid (Scheme VI); (2) attack of the oxidant on the substrate, 35, to give an enol selenite ester, 36, and (3) decomposition of 36 to the product via one of the two pathways. Path A involves rearrangement of 36 to the product α-selenium (II) keto ester, 37, and then to the product 38 by a 1,2 elimination. In path B 36 proceeds directly to the product 38 by 1,4 elimination. Path A is essentially the same mechanism and intermediates already proposed for α-dione formation (Scheme - I)[45].

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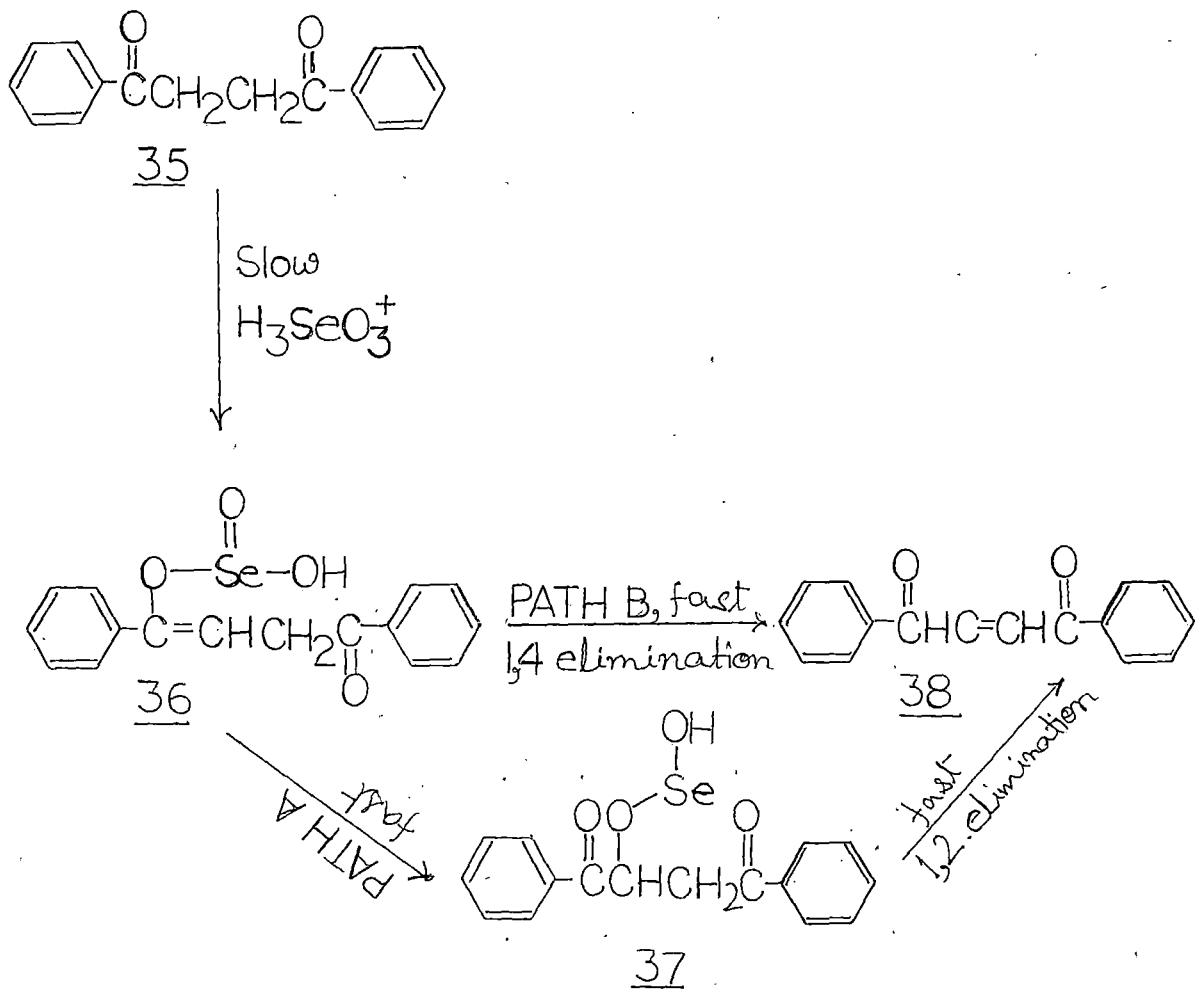
44. J.P.Schaefer, J.Am.Chem.Soc. 84, 713 (1962)

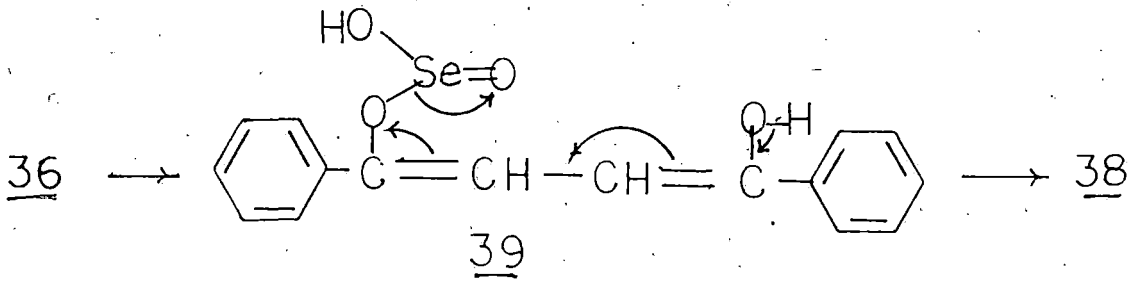
45. E.J. Corey and J.P.Schaefer, J.Am.Chem.Soc. 82, 918 (1960)

Scheme - VI



Of the two possibilities, the 1,4 elimination from the enol selenite ester, 36, is likely since this intermediate contains a doubly activated methylene unit. The latter simply requires an enolization to give the half ester of the dienol, 39, which can decompose to product 38 via bond migration, the driving force being the reduction of the selenium. The possibility of 1,2 elimination from the -selenium (II) keto ester, 37, appears

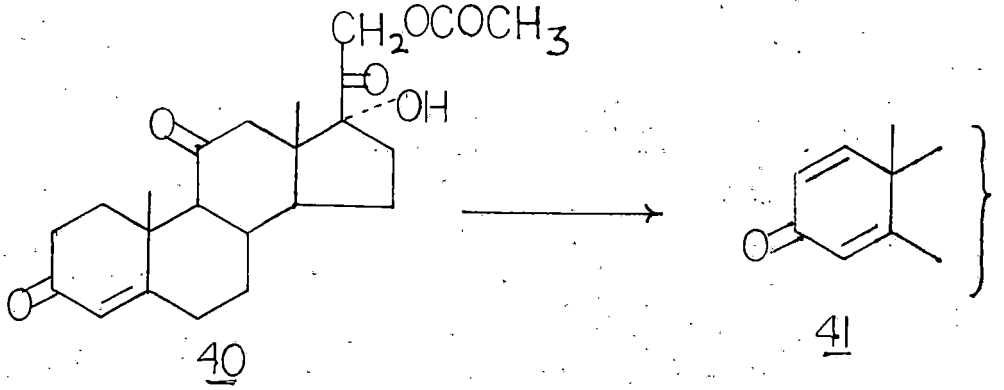
less likely in view of the fact that the alternative product of its decomposition, 1,4 diphenyl - 1,2,3 trioxobutane could not be detected[44].



36 → 39 → 38

Monoketones

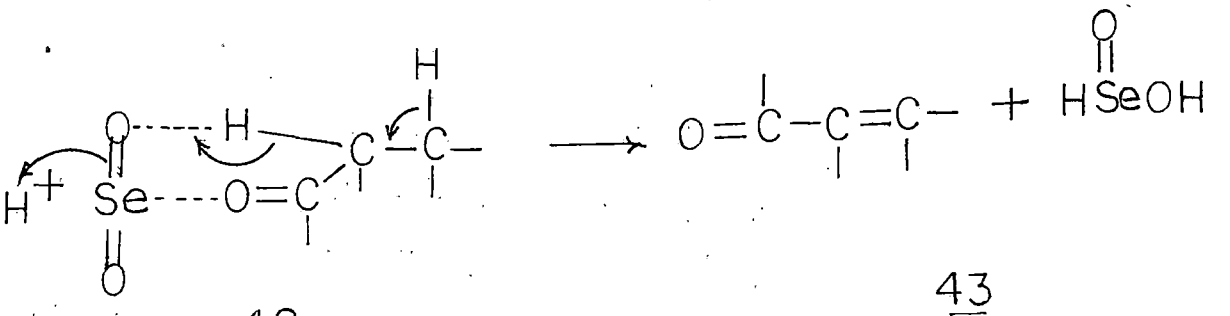
The kinetics of dehydrogenation of an α,β unsaturated ketone were studied by Langbein[46]. He obtained a second-order rate constant for the Δ^1 - dehydrogenation of cortisone acetate, 40, to 41, from a plot which contained the concentration of ketone and selenium dioxide. Langbein pictures a common intermediate, similar to 37, formed by direct attack of the oxidant



40 → 41

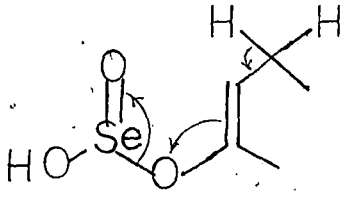
46. G. Langbein, J. Prakt. Chem. 18, 244 (1962)

on the ketone, which decomposes to form all the possible oxidation products. However, for α,β dehydrogenation, he considers the more plausible path as one that does not involve carbon-oxygen bond formation as 42.



42 43

A mechanism for the dehydrogenation of a monoketone may be proposed, which involves either 1,4 elimination from 44 or 1,2 elimination from 45 . These intermediates are similar to 36 and 37, but without a second carbonyl group to activate the beta position and, therefore, should be less prone to undergo elimination. In addition, 46 is an α-keto selenium (II) ester similar to 5, which has been proposed as an intermediate in α-dione formation.



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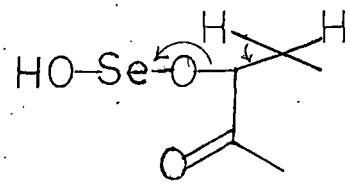

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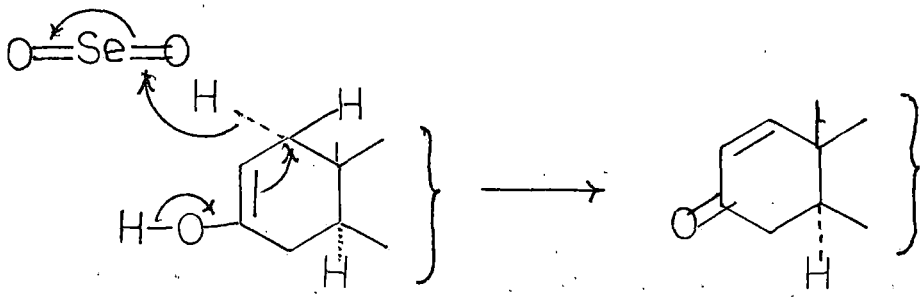

46

Another path, which circumvents the difficulty inherent in 44, would be direct attack on the allylic position in the enol, 46, by selenium dioxide to remove hydride ion. The preference is for the loss of C-1 hydrogen since C-1 hydrogen would require the oxidant to attack from the most hindered side due to the C-19 methyl group.

Why do some monoketones give α-diones and others α,β unsaturated ketones remain unanswered. This is assumed to be due partially to solvent effect. Tertiary alcohols are normally used to carry out the dehydrogenation reaction[42], but the reaction can be effected in acetic acid[47] or in aromatic solvents[48].

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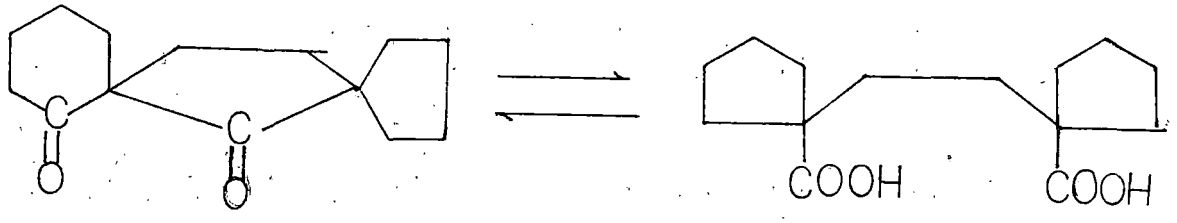
47. E.Schwenk and E.Stahd, Arch.Biochem. 14, 125 (1947)

48. H.J. Ringold, G.Rosenkranz and F.Sondheimer, J.Org.Chem., 21, 239 (1956)

α-Diones are generally produced using ethyl alcohol or dioxane[49]. The nature of the solvent effect, has, however, not been elucidated.

Selective Oxidations with Hydrogen Peroxide.

Manich[50] described the oxidation of a dispiro β-diketone, 47, with hydrogen peroxide in acetic acid solution to give α, α α′, α′, bis(tetramethylene) adipic acid, 48. It was not established whether the oxidising agent was hydrogen peroxide or peroxyacetic acid; the latter, of course, might be expected from reaction of the peroxide with acetic acid.

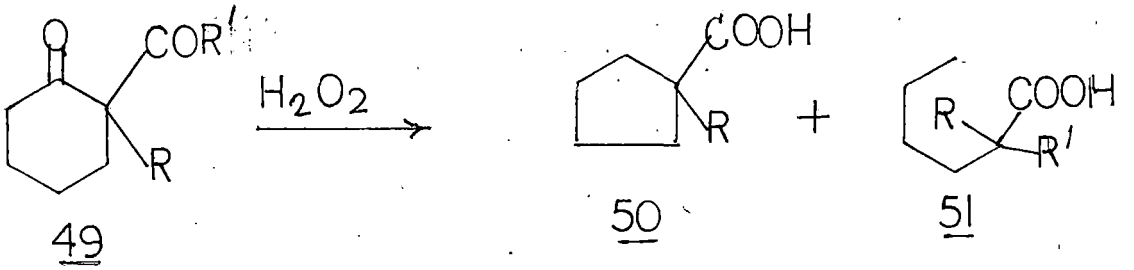


47 48

49. C.C.Hach, C.V.Banks and H.Diehl, Organic Syntheses, Coll. Volm 4, Wiley, p 229 (1963)

50. C. Mannich, Ber., 74, 1007 (1941)

Payne[51] studied oxidation of several 2-acylcyclo hexanones, 49, with hydrogen peroxide in tert-butyl alcohol solution at reflux. The reaction was found to proceed faster in presence of a trace of sulphuric acid.



49 50 51

Having achieved a rather facile oxidative ring contraction of a six membered ring to five, it was of interest to determine whether ring contraction of five membered ring to a four might be achieved. To this end, 2-acetyl cyclo pentanone 52, was oxidised in the usual way. An uncatalysed reaction was complete in sixteen hours at reflux to give α-methyl adipic acid, 53 in 93% yield. No evidence was obtained for the presence of even a trace of cyclobutane carboxylic acid.

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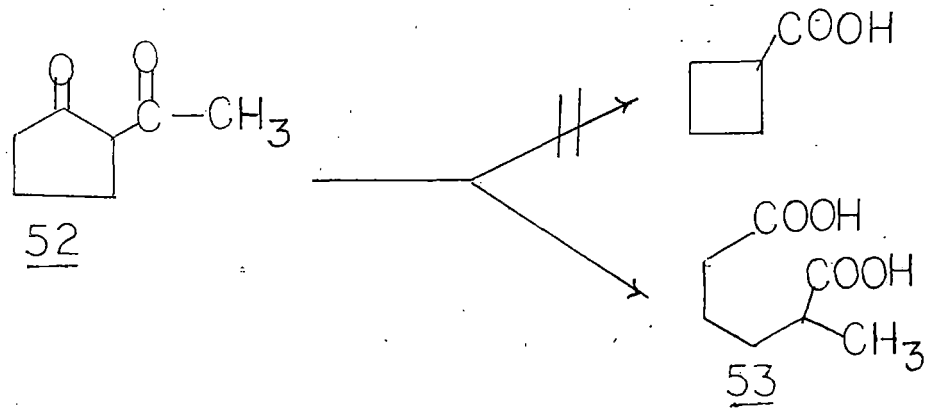
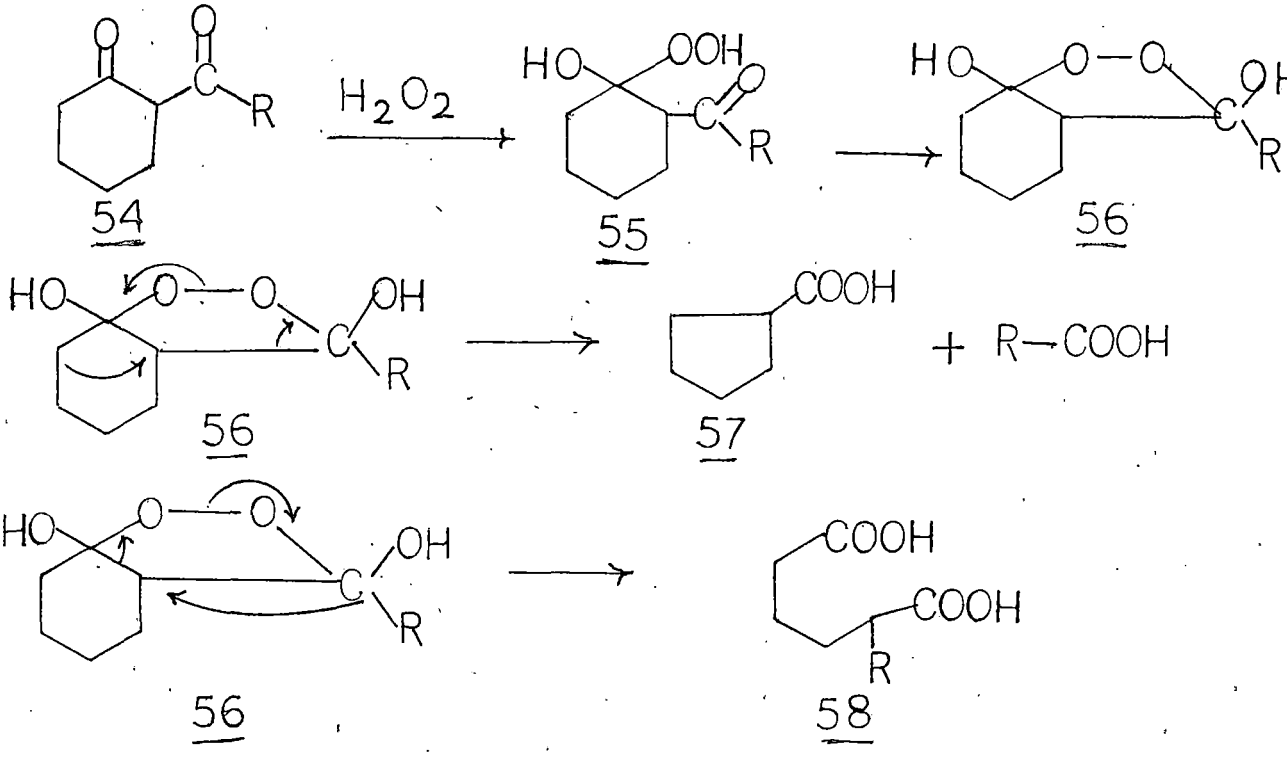
51. G.B. Payne, J. Org. Chem. 4793 (1961)



52 53

The reaction was proposed[50] to proceed by way of intermediates 55 and 56. In order to account for the two products, the breakdown of 56 was postulated by either of the following ways shown in Scheme - VII.

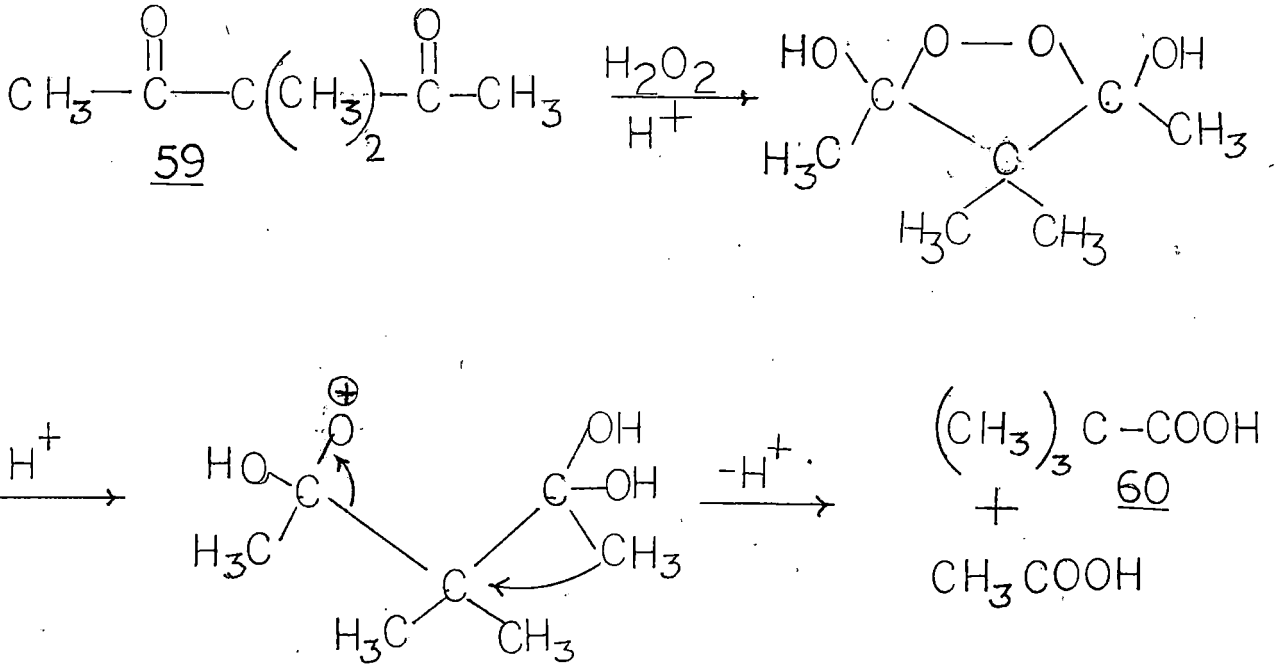
Scheme - VII



54 55 56 56 57 56 58

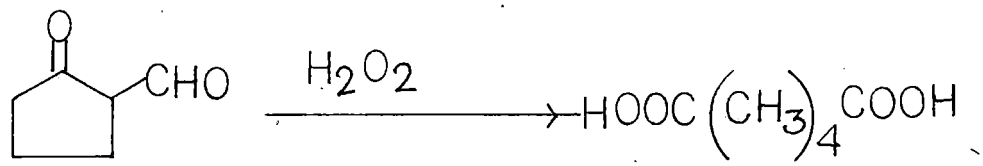
It was found that while 2,4 pentadione (acetyl acetone) did not undergo an oxidative rearrangement under similar conditions of reaction 3,3 dimethyl 2,4 pentadione, 59, behaved differently giving pivalic acid, 60, in 76% yield. The success achieved with 59 is believed to be a consequence of carbonium ion stabilization by the gem-dimethyl groups during breakdown of the cyclic peroxides (Scheme - VIII).

Scheme - VIII

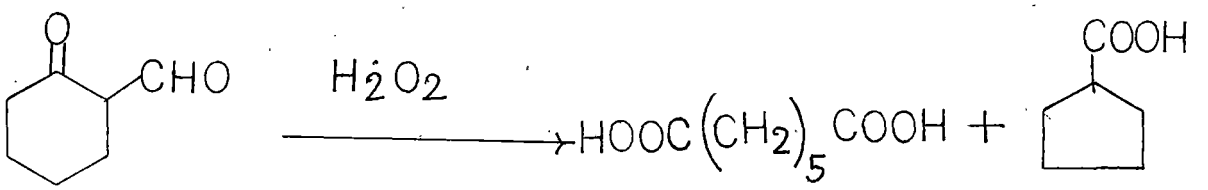


No isobutyric acid was identified as product from the oxidation of the monomethyl compound, 3-methyl 2,4 pentanedione. It was concluded, therefore, that one alkyl substituent does not provide sufficient carbonium ion stabilization to allow the rearrangement to proceed in the acyclic series.

Vinogradova et al[52,53] had shown that 2-formyl cyclopentanone 61, and 2-formyl cyclohexanone, 62, on treatment with aqueous hydrogen peroxide undergo unusual oxidation cleavage to produce dicarboxylic acid containing the same number of carbon atoms in the starting compound. It was also established that the cleavage of the six membered ketone completes with ring contraction to form cyclopentane carboxylic acid.



61



62

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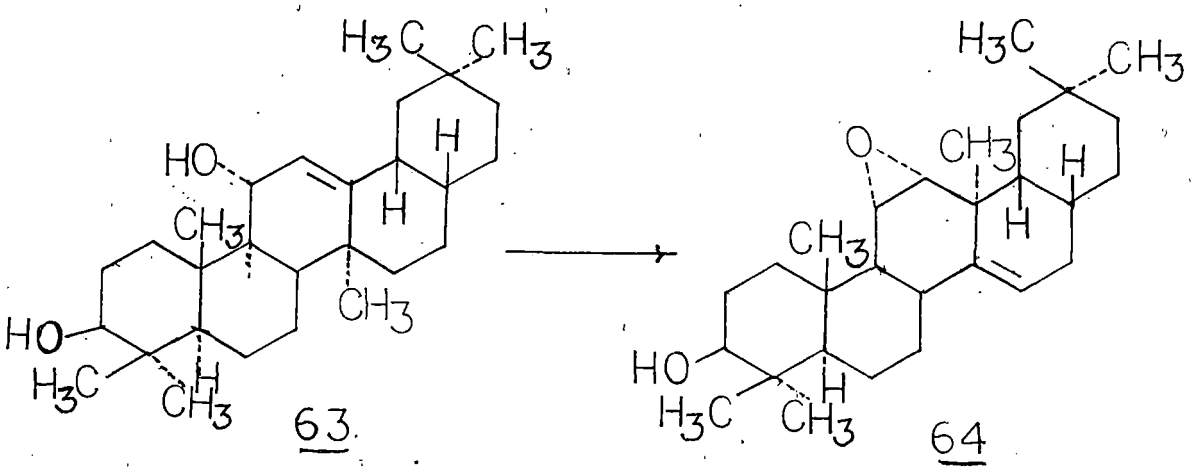
52. L.P. Vinogradova and S.I.Zavialov, Izv. Acad. Nauk SSR, Otd., Chim. Nauk 1717 (1960)

53. L.P.Vinogradova and S.I.Zavialov, Zh. Obsch. Khim., 30, 4110 (1960)

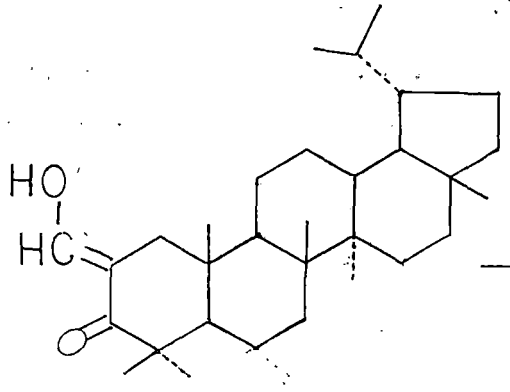
The mechanism of the reaction was considered to be the rearrangement of the corresponding peroxides in two possible directions as discussed under Scheme-VII.

Corey et al[54] made the surprising discovery that the 3β, 11α-dihydroxy- Δ^{12}-pentacyclic triterpenoids, 63, on treatment in methylene chloride with a solution of 30% hydrogen peroxide and p-toluene sulfonic acid in tert-butanol forms an epoxide, the 11α, 12α epoxide and undergoes a skeletal rearrangement by $C_{14} \longrightarrow C_{13}$ methyl migration and shift of the double bond, 64.

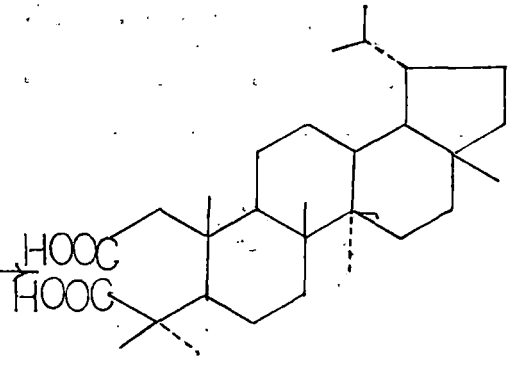


54. I. Agata, E.J. Corey, A.G. Hortnan, J. Khim, S. Proskow and J.J.Ursprung, J. Org. Chem. 30, 1698 (1965)

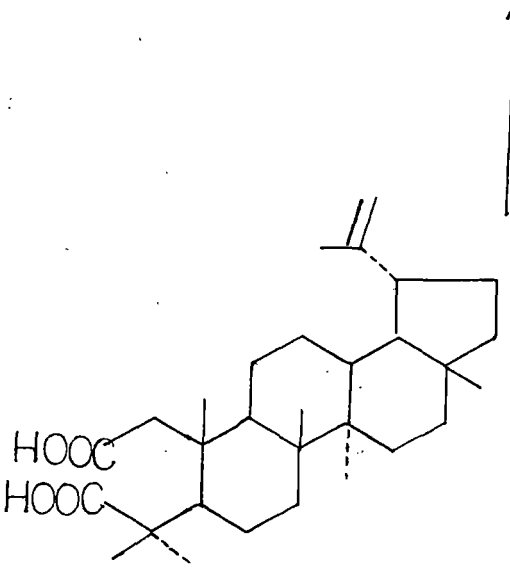
Another example of interest is the action of hydrogen peroxide on triterpenoids containing a hydroxymethylene ketone function. It has been observed that in absence of β,γ unsaturation and especially in alkaline media oxidative cleavage occurs producing 2,3 seco-acids. Thus, the ketone, 65, gave exclusively the diacid, 66, characterised as the ester, 67, which was also obtained from 68 by catalytic hydrogenation.



65

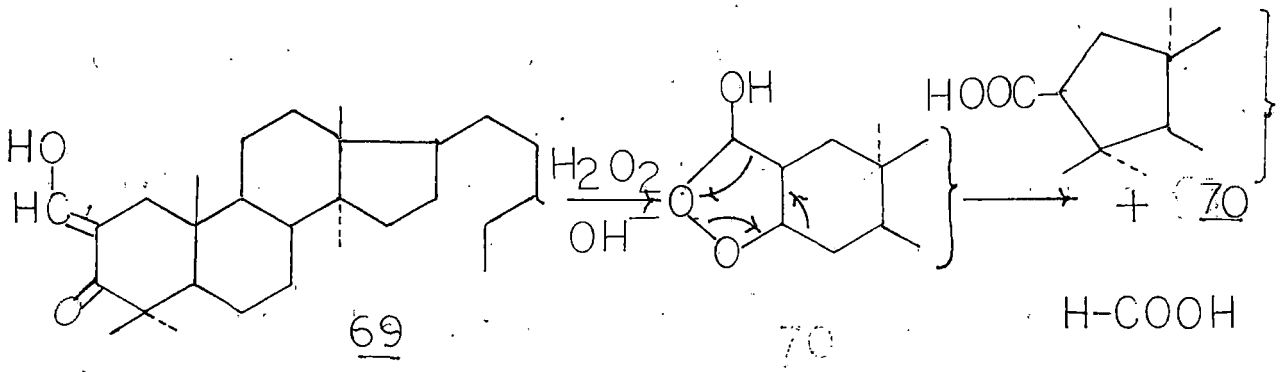


66 R=H
67 R=Me



68

It has been found that in the presence of β,γ unsaturation, ring contraction occurs. Thus, hydroxymethylene anhydrodihydro litsomentone, 69 undergoes a rearrangement[55] in presence of hydrogen peroxide in alkaline media producing 70.



Reactions involving Hydrogen peroxide and Selenium Dioxide.

It transpires from discussions in the preceeding sections that selenium dioxide and hydrogen peroxide have separately found wide application. Not too many reactions using hydrogen peroxide and selenium dioxide together are, however, known. The combination perhaps found application in the oxidation of acrolein to acrylic acid for the first time[56]. In another obviously different case[57],

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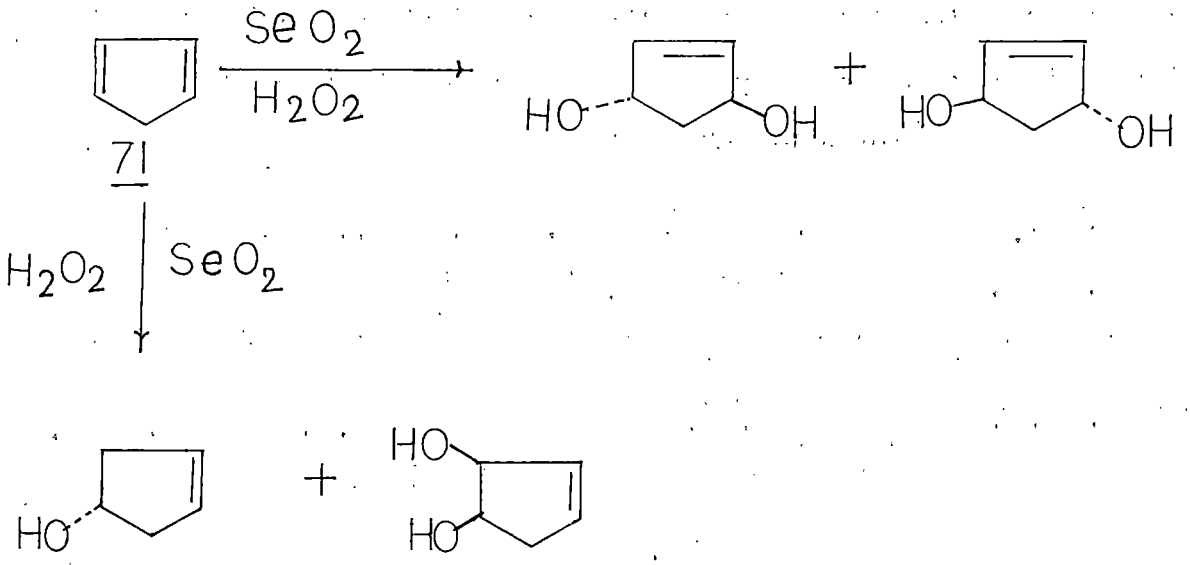
55. T.R.Govindachari, N.Viswanathan and A.R.Sidyaye, Ind. J. Chem., 10, 786 (1972)

56. Ref. 13 of this chapter.

57. L.Stall and H.Jucher, Helv.Chim.Acta., 36, 268 (1953)

the reagents have been used for hydroxylation of cyclopentane and cyclopentadiene, 71. The catalyst in this case is probably perselenic acid.



Oxidation of methylene groups adjacent to carbonyl groups with stoichiometric quantity of selenium dioxide to give α-diketones or keto aldehydes are well known. Payne et al[58] while studying the reactions of hydrogen peroxide in presence of selenium dioxide on cyclopentanone, cyclohexanone and cycloheptanone anticipated that the cyclic ketones might undergo the well known reaction with SeO_2 giving α-diketones, with H_2O_2 serving merely

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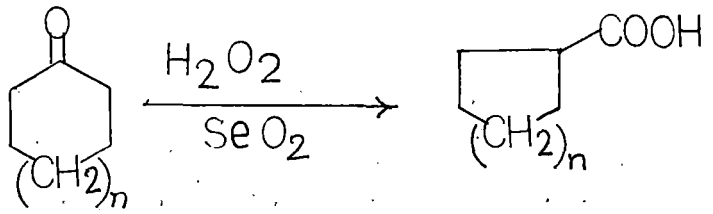
58. G.B.Payne and C.W.Smith, J. Org. Chem., 22, 1680 (1957)

to oxidise Se metal back to the dioxide. It was found, however, that along with other competing reactions all the three ketones underwent oxidative ring contraction to cyclohexane, cyclopentane and cyclobutane carboxylic acids in 34, 32 and 23% yields respectively.



72

n = 2 (34%)
n = 1 (32%)
n = 0 (23%)

Since the discovery that a mixture of SeO_2 and H_2O_2 transforms alicyclic ketones to ring contracted cycloalkane carboxylic acid, the rearrangement was extended to acyclic and alkylphenyl ketones by Sonoda et al[59]. In trying to hydroxylate olefins, 73, with hydrogen peroxide in the presence of selenium dioxide as catalyst and by using a mixed solvent of tert-butyl alcohol and a ketone, it was found by the workers that the oxidation of ketone, used as solvent, proceeded mainly to form carboxylic acid by the following equation;

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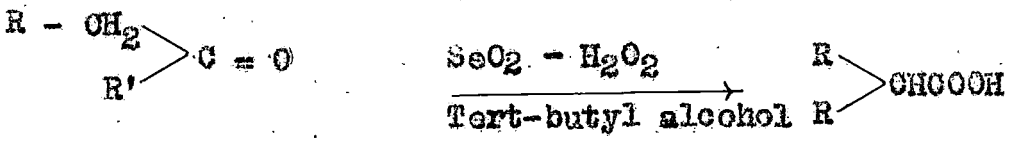
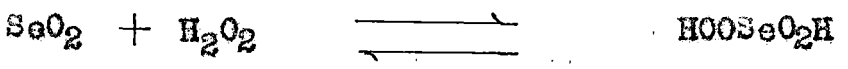
59. N. Sonoda and S. Tsutsumi, J. Org. Chem., 32(5), 505 (1969)



73

Acetone, methyl ethyl ketone, methyl n-propyl ketone and diethyl ketone were selected as starting materials. The main rearrangement observed is due to the migration of the alkyl group having a smaller number of carbon atoms to the α-carbon atom of the larger alkyl group and the migration of the alkyl group with a larger number of carbon atoms to the smaller one also occurs in some degree. The workers shared the view of Hughes and Martin[60] who proposed the formation of peroxyselenious acid, 74, in the course of the oxidation of selenium dioxide to selenic acid as shown below:



74

The following mechanism as shown in Scheme - IX was presumed by the workers.

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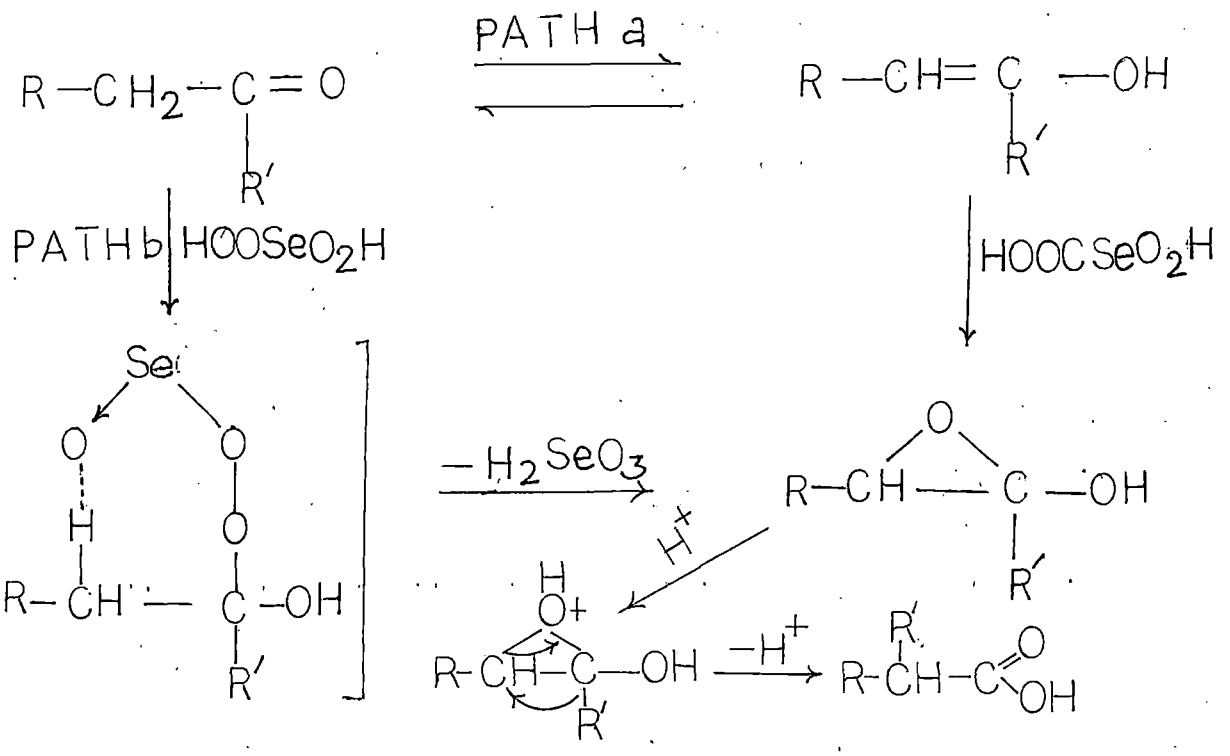
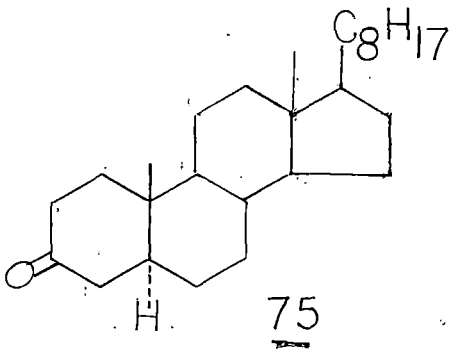
60. F.J. Hughes and D.S. Martin, Jr., J.Phys. Chem., 59 410 (1955)

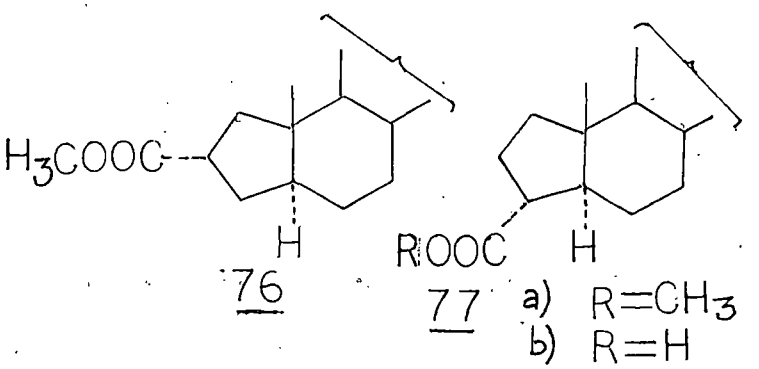
Scheme - IX



The reaction was also applied to several keto steroids. With 5α-cholestan-3-one, 75, a mixture of acid was obtained[61]. The acids after esterification were separated and characterised as 76 and 77 . The yields were 25% and 19.5% respectively.



75



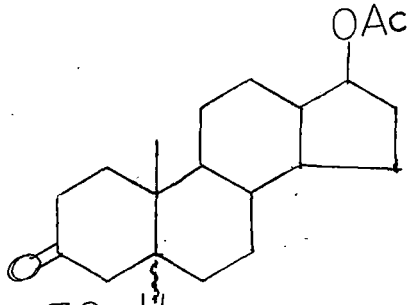
76 77 a) R=CH3 b) R=H

61. E. Caspi and S.N. Balasubramanyam, Tet. Lett., 745 (1963)

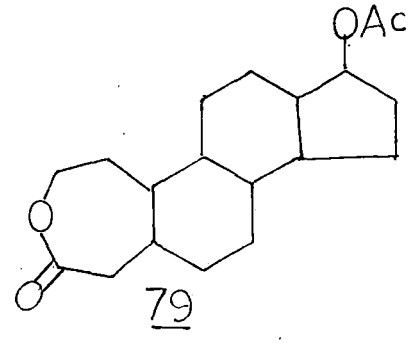
62. E. Caspi, Y. Shimizu and S.N. Balasubramanyam, Tetrahedron. 20, 1271 (1964).

Caspi et al[62] studied the reaction for steroidal 3-ketones of 5α and 5β series and found that the major reaction was not ring contraction but Baeyer-Villiger oxidation.

The compound with A/B trans junction, 17β-acetoxy-5 - α androstan-3-one, 78a, gave a lactone, 79 and two carboxylic acids, 80 and 81. The oxidation of 17β-acetoxy-5β-androstan-3-one, 78b, gave the lactone 82 as a single product.



78



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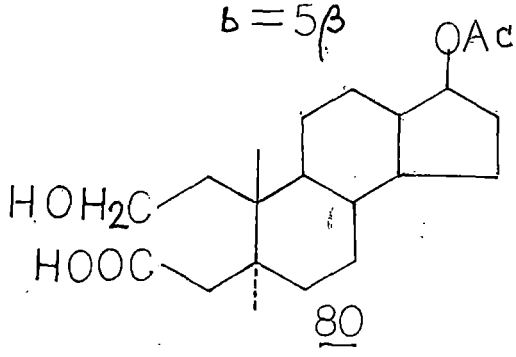

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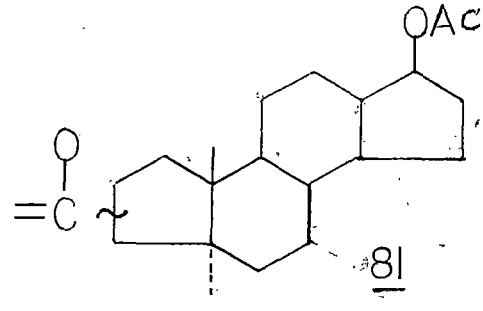

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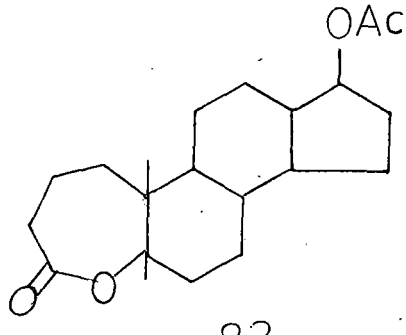

82

Hara et al[63], however, had shown that perbenzoic acid oxidation of 5α and 5β-3-ketones yielded mixture of lactones with an oxygen atom inserted in either side of the 3-oxo group. With the commonly used peracids it would seem that the reaction proceeds in a rather indiscriminate manner[64]. Caspi et al[62] employed nearly neutral condition and concluded that the direction of attack was more substrate dependent, and hence led to the formation mainly of single compound. For example, for A/B trans junction the 2,3 bond and for A/B cis junction the 3,4 bonds are cleaved. In their succeeding experiment Caspi et al[65] observed that no directional influence of ring A/B junction on the course of the reaction occurs.

Jerussi et al[66] studied the same reaction on 17β-acetoxy-5α-cholestan-3-one and reported formation of the products which were different from those previously published[67,68]. They carried out the reaction of 83, with selenic acid and 30% H_2O_2 in tert-butyl alcohol and the reaction yielded a complex mixture of acids. Esterification of the crude product with diazomethane followed by chromatography and several times crystallisation yielded 2α-

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63. S.Hara, N. Matsunoto and M. Tekenchi, Chem. and Ind., 2086(1962)

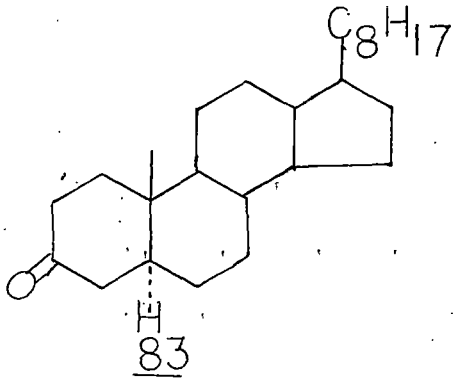
64. V.Prelog, L.Ruzicka, P.Meister and P.Wieland, Helv. Chim.Acta., 28, 618 (1945); 28, 1651 (1945)

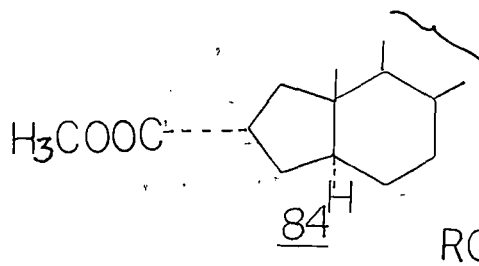
65. E. Caspi, Y.Shimizu and S.N.Balasubramanyam, Tetrahedron 20, 1271 (1964)

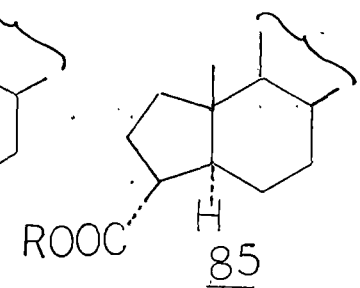
66. H.M.Hellman and R.A.Jerussi, Tetrahedron, 20, 741 (1964)

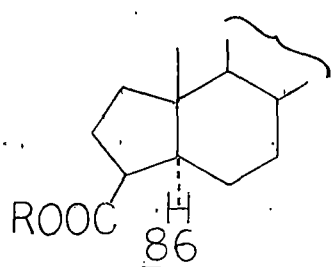
67. C. Biellmann and M.Rajic, Bull.Soc.Chim. Fr., 441 (1962)

carbomethoxy-A-nor-5α-cholestane, 84a, and 2,3-seco-5α-cholestane, 2,3 dioate, 87a and 86a; compound 85 was, however, not found.

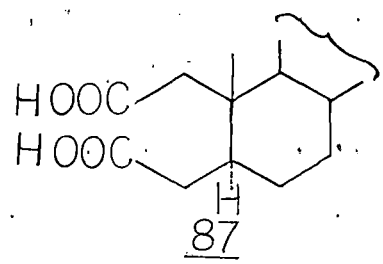








a $R=CH_3$
b $R=H$



a $R=CH_3$
b $R=H$

Hence isolation of 86a, the epimer of, 85, led Jerussi et al questioning the evidence as to the identity of the compound 85 given by the French workers[67]. However, for 85, the m.p. 51° and rotation $[\alpha]_D$ +11° were between those reported[69] for 85, m.p. 45-46°, $[\alpha]_D$ +1°, and for 87a, m.p. 60-63°, $[\alpha]_D$ +19°. Therefore, it was thought that the product assigned

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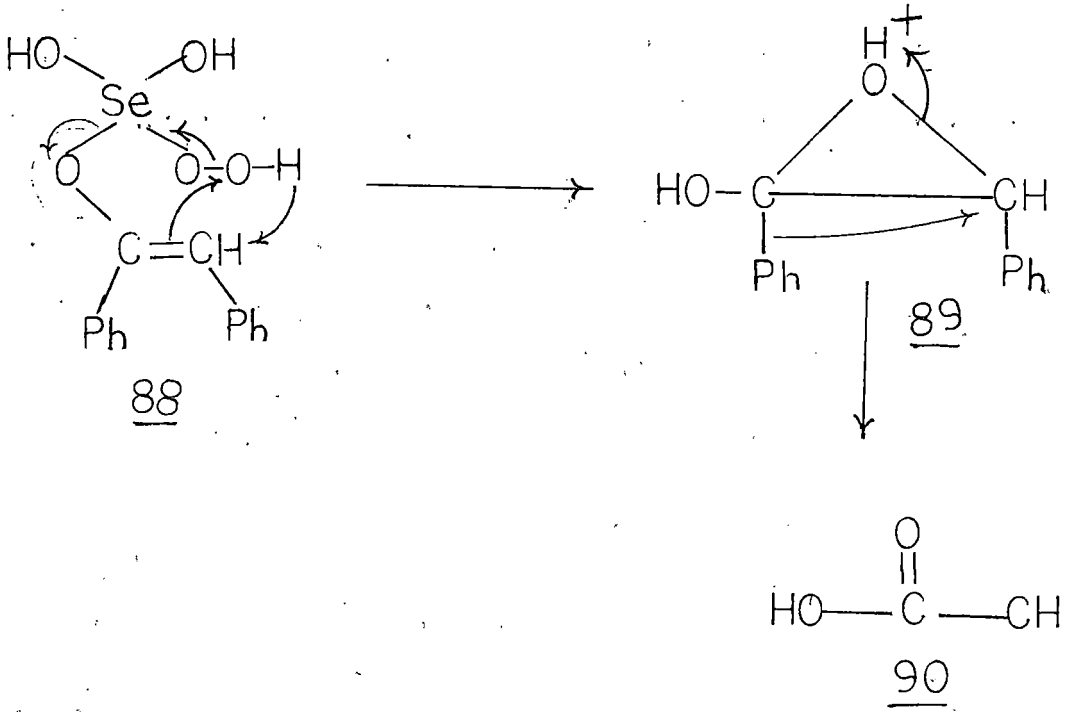
68. E. Caspi and S.N.Balasubramanyam, Tet. Lett., 12, 745 (1963)
69. D.E.Evans, A.C. De Paulet, C.W. Shoppee and F. Winterritz, J.Chem.Soc., 1451 (1957)

structure 85 by them[67] may actually be 87a reported by Jerussi[66].

A mechanism had been proposed by Sonoda and Tsutsumi for the rearrangement of deoxybenzoin[69] in which a peroxyselenious enol ester, 88, was postulated as an intermediate. This then undergoes intramolecular epoxidation to give the enol epoxide, 89, which rearranges as shown to give diphenyl acetic acid, 90. Opening of the epoxide, 89, in the manner proposed appears unlikely in view of the course of epoxide reactions in the acidic solution[71].

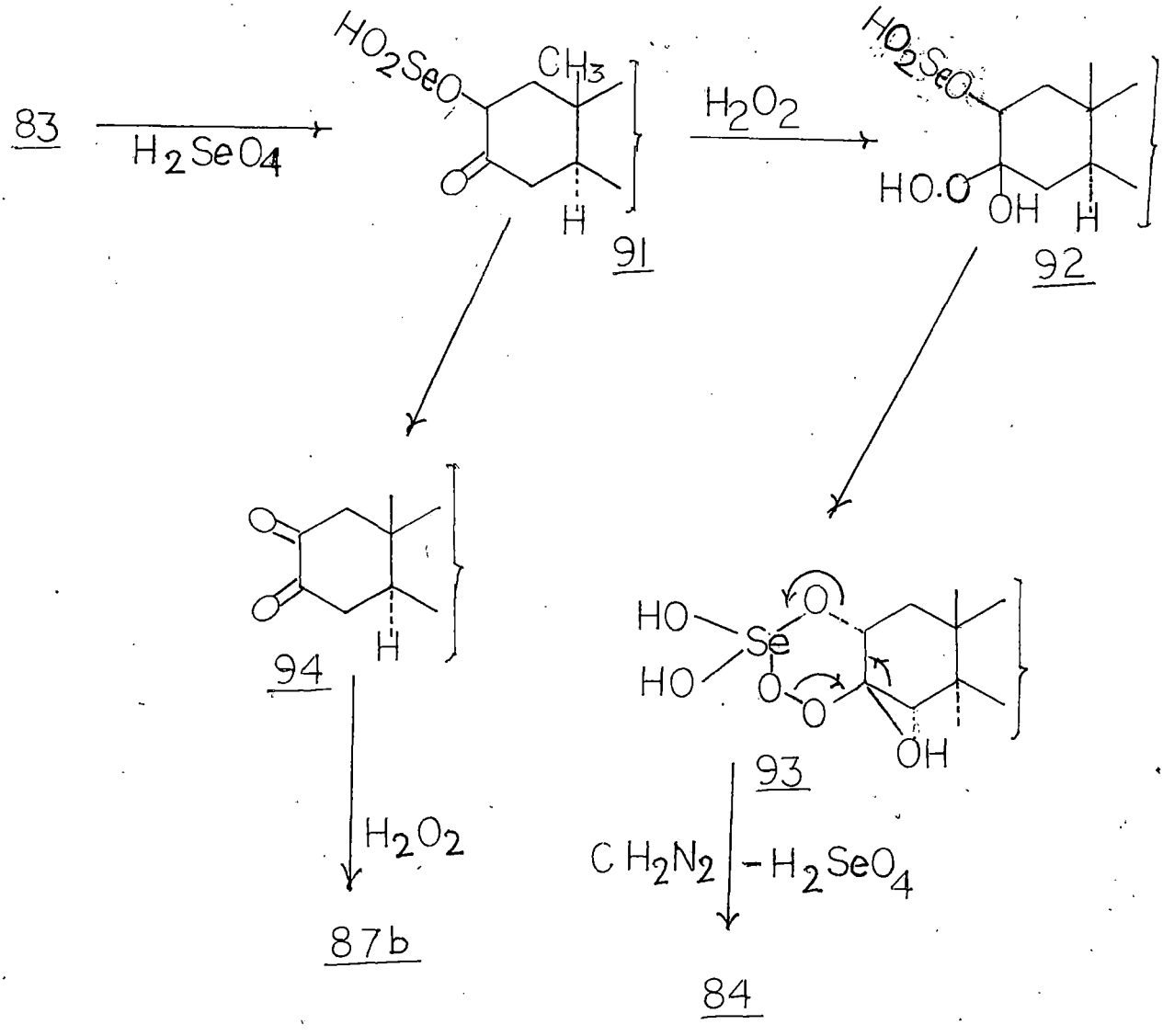


70. N.Sonoda and S.Tsutsumi, Bull. Chem.Soc.Japan, 34, 1006 (1961)

71. R.E.Parker and N.S.Isaacs, Chem.Revs., 59, 737 (1959)

Scheme - X summarizes the mechanism proposed by Jerussi et al[66]. All examples of oxidative rearrangement of ketones using H_2O_2 and selenic acid or SeO_2 have involved enolised ketone. Non-

Scheme - X



enolizable ketones, even those having α-hydrogen atoms fail to give the reaction[72]. Hence, it is plausible to assume that with steroid ketones also enolisation or enol ester formation is an essential step. An enol selenite ester, which rearranges to an α-keto selenium ester, has been proposed by Corey and Schaefer as an intermediate in the selenious acid oxidation of desoxybenzoin[73].

Hence, here the first step involves the interaction of ketone with selenic acid to give an α-keto selenite ester, 91. Attack by H_2O_2 on the carbonyl group of 91 gives 92. α-substituted hydroxy hydroperoxide such as 92 have been isolated by Kharasch and Sosnovsky[74] by treatment with α-bromo and α-chlorocyclohexane with H_2O_2. In the absence of a bulky α-group only dimer is isolated. Cyclisation of 92 gives the peroxide 93, which rearranges as indicated to give product 84. A cyclic peroxide has been proposed by Payne[75] to account for the formation of cyclopentane carboxylic acid from 2-acetylcyclohexanone and hydrogen peroxide. 91 can also go to the diketone, 94, which can be oxidised by H_2O_2 to 2,3 seco acid 87b.

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72. R.A.Jorussi, Ph.D. Diss., N.Y. Univ. (1961)

73. Ref. 43 of this chapter.

74. M.S.Kharasch and G.Sosnovsky, J.Org.Chem., 23, 1322 (1958)

75. G.B.Payne, J.Org.Chem., 26, 4793 (1961)