PART - I

STUDIES ON THE ACTION OF N-BROMO SUCCINIMIDE ON SOME TRITERPENOIDS IN DIMETHYL SULPHOXIDE

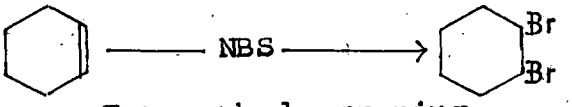
CHAPTER - I

A Short review on the action of N-Bromo succinimide on Triterpenoids and Steroids.

It has been found that triterpenoids undergo variety of rearrangements with simple reagents. These rearrangements also take place within the plant under different biogenetic conditions. Some important rearrangements take place under various oxidative conditions with reagents like mercuric acetate, lead tetraacetate, chromic acid, organic peracids, hydrogen peroxide, N-Bromosuccinimide. As we have carried out some reactions of NBS on triterpenoids it is felt necessary to give a brief account of the previous works on the oxidative transformation with the help of this reagent.

N-bromosuccinimide was first prepared by Seliwanow[1] in 1893. The use of N-bromoacetamide as an allylic brominating agent was prepared by Wohl and Jaschinowski[2] in 1919. Ziegler et al[3] also prepared eight other bromo imide but found them to be far less satisfactory than N-bromosuccinimide for allylic bromination. Many reviews have appeared on the action of N-bromosuccinimide; of them (a) Djerassi[4] and (b) Homer and Wenkelman[5] for allylic bromination and (c) Filler[6] on bromination and oxidation reactions are worthmentioning.

NBS also reacts with olefins to add bromine to the double bond or act as a source of hypohalous acid in aqueous solution. Braude et al (1952) have shown that the addition reaction is catalysed by tetra-alkyl ammonium salts, for e.g. cyclohexene in the presence of tetraethyl ammonium bromide form mainly 1:2 dibromocyclohexane.



Tetraethyl ammonium bromide

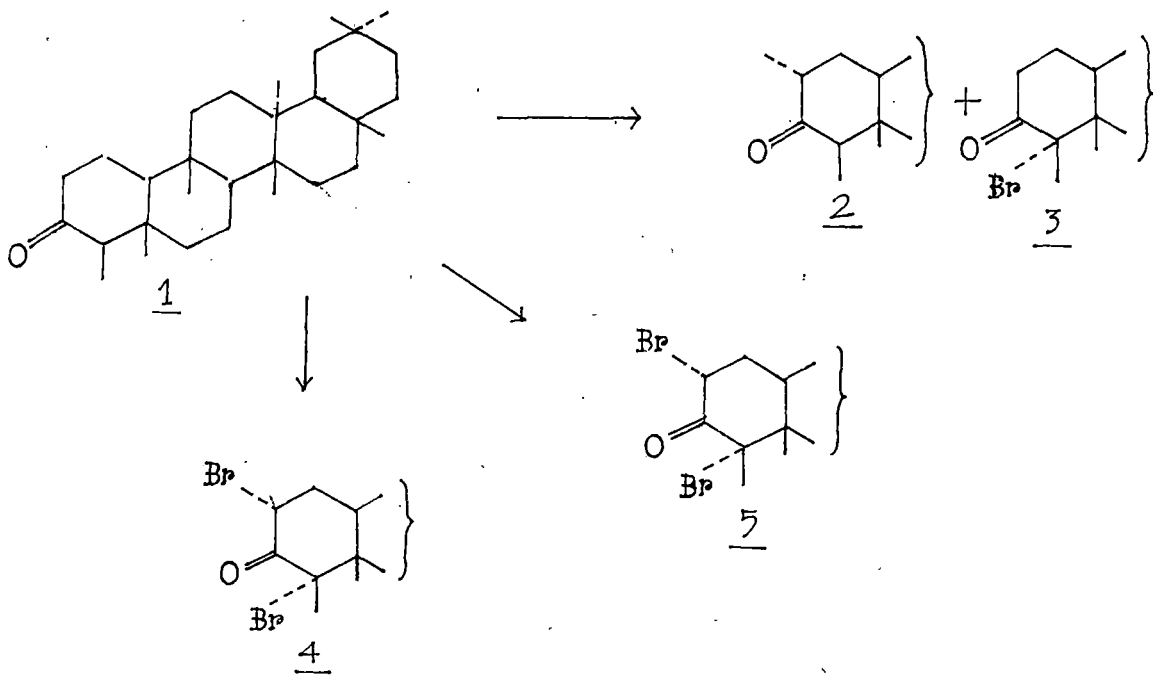
N-bromosuccinimide is also in extensive use since 1969 as an effective reagent for oxidation of allylic methylene to carbonyl function[7-9].

A brief review on the action of NBS on some triterpenoids and steroids is discussed below in order to explain the formation of the products of the reaction between lupenyl acetate and moretenyl acetate with NBS.

Action of NBS on Friedelin and its derivative[8-11]

Corey and Ursprung[10] have shown that friedelin 1 on direct bromination gave 2α-(axial)-bromofriedelin 2 and bromination of appropriate enol benzoate gave the isomeric 4α-(axial)-bromofriedelin 3. They have also prepared a dibromofriedelin 4 in presence of hydrobromic acid in chloroform. The dibromofriedelin 4 has been assigned as 2α-, 4α-dibromo-

friedelin from the uv absorption at 332 nm. Djerassi et al[12] have prepared another dibromofriedelin 5 by bromination of 2α-bromofriedelin 2 in acetic acid. They designated the compound as 2α-, 4β-dibromofriedelin 5 from the studies of uv (310.5 nm) and ORD.

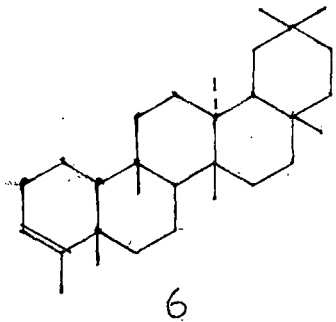


Takahasi and Currison[13] also prepared a dibromofriedelin by the action of bromine in chloroform and acetic acid on friedelin. But they could not assign the structure of this compound although the compound showed uv absorption at 320 nm.

Stevenson and co-workers[14,15] observed the reaction between friedelin and its derivatives with NBS. They found that friedelin 1 on treatment with molar equivalent of NBS in carbon

tetrachloride gave 4α-bromofriedelin 3 in satisfactory yield. They also isolated 2α-bromofriedelin 2 from 3 by further treatment of 3 with bromine in acetic acid. Hence, in this reaction isomerisation occurred rather than substitution. As was expected from this result, it was found that 4α-bromoketone 3, $[\alpha]_D$ + 92° was unstable in chloroform-hydrobromic acid, the presumed equilibrium mixture $[\alpha]_D$ -75°, being formed after 24 hours. 2α-bromofriedelin 2 also gave the same result on similar equilibriation.

For obtaining dibromofriedelin, since this route was unsuccessful, therefore an alternative method of treatment of 2α-bromofriedelin with NBS was attempted. Treatment of 2α-bromofriedelin with NBS gave an unsaturated monoketone $C_{30}H_{47}OBr$ which showed positive T.N.M test indicating thereby the presence of ethylenic linkage. UV, IR spectra of this ketone showed that the double bond was not conjugated to carbonyl group and the α-bromine atom retained an axial orientation. Since it was known that acid-isomerisation of Friedel-3-ene, 6 afforded a mixture of olean-13, 18-ene, 7 and 18α-olean-12-ene[14,15] 8, it was assumed this non-conjugated bromoketone had probably arisen by molecular rearrangement of 2α, 4α-dibromoketone intermediate (or derived radical or cation) with elimination of hydrobromic acid.



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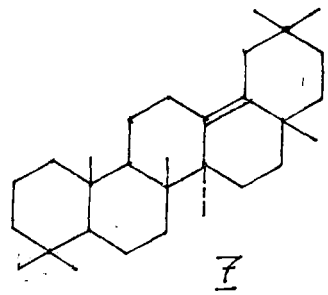

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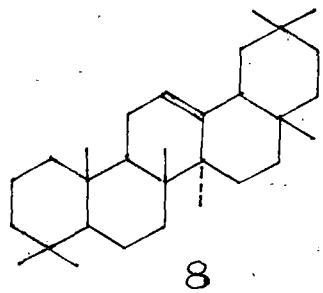

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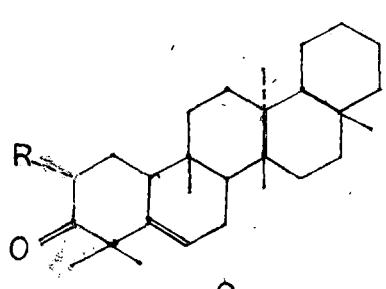
A precedent for such a rearrangement was provided by the action of silver acetate on 4α-bromofriedelin 3 to yield a product 7 which was shown to be a mixture[16] of alnus-5-ennone, 9 (R=H) and alnus-5(10)-enone, 10 (R=H). The probability that the unsaturated bromoketone derived from 2 could be represented as 2-bromo-alnus-enone 9 (R=Br) or 10 (R=Br) was excluded from the fact that the zinc debromination product in neutral solution was different from either alnus enone 9 or 10 (R = H).



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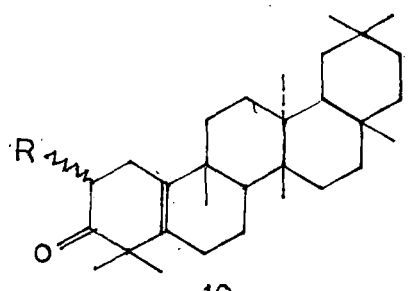

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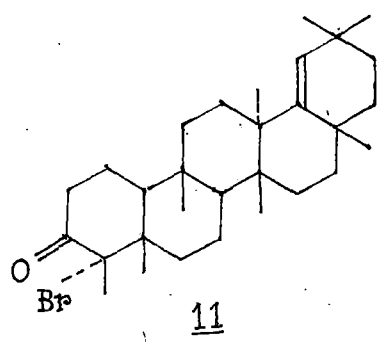
Treatments of 4∝-bromofriedelin 3 with NBS gave an isomeric non-conjugated axial bromo substituted ketone 11 $C_{30}H_{47}OBr$ which on dehydrobromination gave the identical ketone $C_{30}H_{48}O$, 12. Lithium aluminium hydride reduction of 12 gave an alcohol 16 and on Huang-Minlon reduction gave the hydrocarbon 15. From these observationsthe isomeric monobromoketones obtained from 2 and 3 were assigned structures 2-∝-bromofriedel-18-en-3-one 13 and 4∝-bromo-friedel-18-en-3-one 11 respectively. These assignments were also supported by specific rotation and ORD studies.



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Action of NBS on saturated hydrocarbon friedelane[11,17] 14 was also examined and they isolated an unsaturated hydrocarbon 15 identical in all respect with that obtained from Huang-Minlon reduction of 12. This fact suggested that the products obtained by the action of NBS on ketones 2 and 3 were ethylenic non-conjugated ketones and hence the attack has taken place at a site not activated by carbonyl group. The location of double

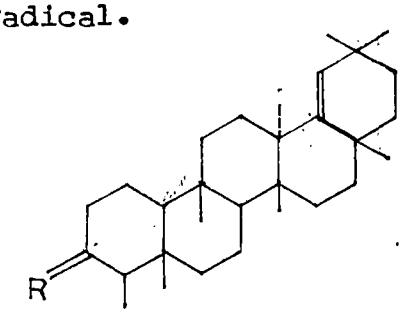
bond by NBS was established by the following way. The unsaturated hydrocarbon 15, resisted catalytic hydrogenation, yielded an oxide $C_{30}H_{50}O$ with perbenzoic acid showing thereby that the double bond has a degree of steric hindrance[18] comparable to the Δ^{12}-trisubstituted ethylenic linkage in β-amyrin series. The terminal uv absorption of 12, 15 and 16 indicated that the double bond was trisubstituted. The resistance of hydrogenation of 15 further suggested that the ethylenic system was not disubstituted and the friedelin skeleton does not permit the existence of a tetrasubstituted double bond.

^1H NMR spectrum of the ketone 12 showed a singlet which was attributed to an olefinic proton not conjugated with carbonyl group.

The location of double bond on bromo ketones 2, 3 and hydrocarbon 15 was thus restricted to position 1(10), 7 or 18. The position 1(10) and 7 were discarded by dehydrobromination of 11 with silver acetate. A dehydrobrominated product $C_{30}H_{46}O$ was isolated which gave uv absorption above 220 nm. Since there was no conjugation of carbonyl or ethylenic functions in this dienone, the original double bond could not be located in ring A and B. Although there had been much work on the synthetic application of allylic compounds[19].

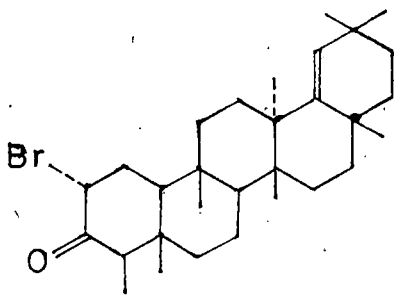
Comparatively little was known about the action of NBS on saturated systems. It has been proved that cyclohexane[20,21] and cycloheptane[21] yield cycloalkyl bromide with NBS under certain condition and decalin gave a tetrabromo octahydronaphthalene[22] which can also be obtained from probable intermediate 9, 10 octalin.

Cason et al[23] have also drawn attention to the fact that NBS is not a reagent of general applicability for the α-bromination of saturated esters due to selective attack on t-hydrogen at either sites of the molecule. In these experiments these workers established that in friedelin the tertiary α-hydrogen atom at position 4 was more reactive than secondary hydrogen atom at position 2 but the presence of a 2α-bromine atom effectively prevented the abstraction of a 4α-hydrogen atom by its 1,3 diaxial blocking effect to approaching succinimide radical.



R = O 12

R = OH, H 16



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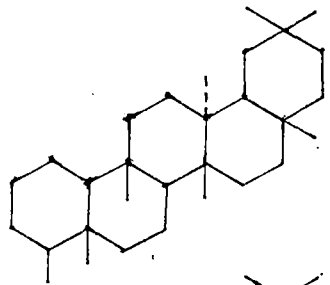

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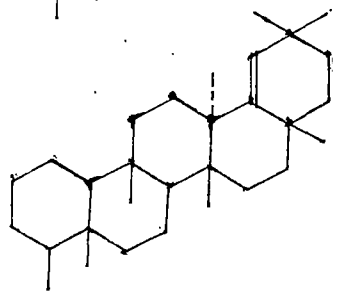

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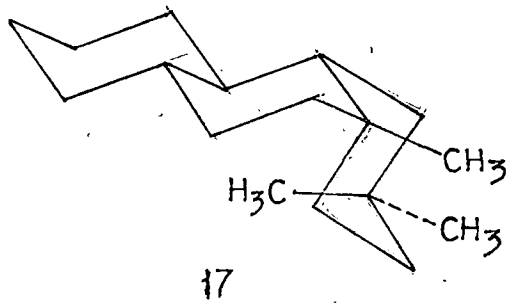
In absence of the activating C-3 carbonyl group or where there is a deactivation due to the steric influence of the neighbouring axial halogen, the most reactive hydrogen is the tertiary C-18. An examination of an all chair form 17 of friedelane showed that a severe steric interaction must exist between the 13α-and 20α-methyl groups due to its cis-junction at rings D and E. This interference is removed if the terminal E ring adopted a boat configuration 18 but as a consequence an unfavourable 1:4 diaxial boat prow and stern interaction results[24]. The steric strain inherent in both conformations with cis D/E system is relieved by dissociation of the 18β-hydrogen atom and formation of ethylenic trigonal system.



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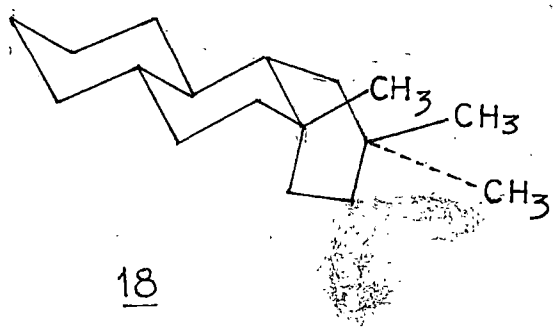

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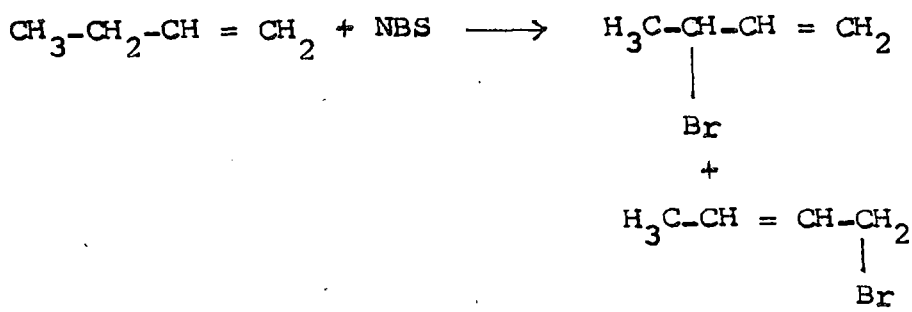
Bromine and NBS oxidation of saturated hydrocarbon, friedelane[17]

Olefins may be halogenated in the allylic position by a number of reagents. Nevertheless, NBS is by far the most common among them. An initiator usually a peroxide is needed with this reagent. The reaction is quite specific at allylic position and the yields are usually good. However, in the case of unsymmetrical allylic radical intermediate, allylic shifts can take place so as to give a mixture of both possible products.



When a double bond has two different α-positions (e.g. $CH_3-CH = CH-CH_2-CH_3$) then a secondary position is substituted more readily than the primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary position have been performed[19].

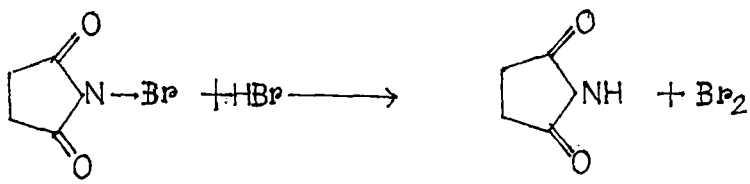
That the mechanism of allylic bromination is of the free radical type was demonstrated by Douben and McCoy[19]. They showed that the reaction was very sensitive to free radical initiators and inhibitors and indeed the reaction stopped unless at least

a trace of initiator was present. Subsequent work indicated that the species which actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amount of bromine, once it is formed, the main propagation steps are:

$$1.\ Br^{\circ} + RH \longrightarrow R^{\circ} + HBr$$

$$2.\ R^{\circ} + Br_2 \longrightarrow RBr + Br^{\circ}$$

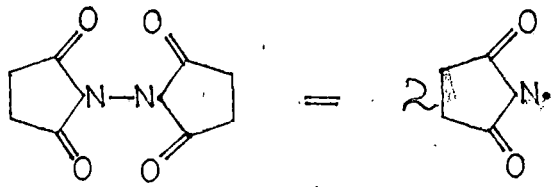
The source for bromine is a fast ionic reaction between NBS and the HBr liberated in step 1.



The formation of NBS is therefore to provide a source of Br_2 in a low steady state concentration and then use up the HBr liberated in step-1[25,26].

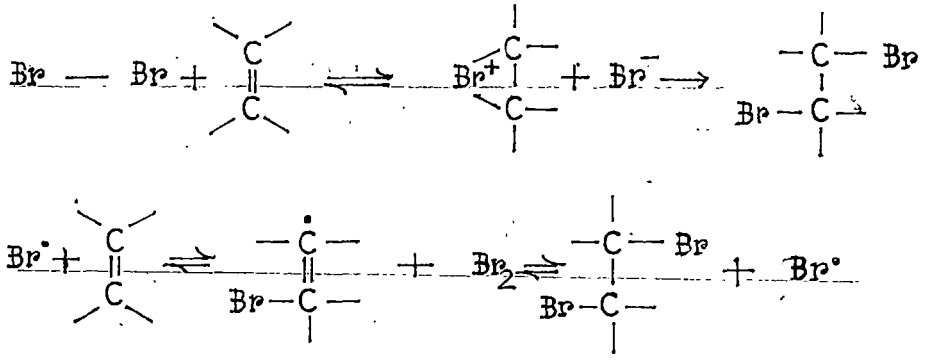
Previously it was supposed that the abstracting species was the succinimide radical **18a** but there is no much evidence that this species is involved in the reaction and is probably not even formed. The main evidence is that NBS and bromine show similar selectivity[27] that the various N-bromosuccinimide also show similar selectivity, which would not be the case if a

different species was abstracting in each case[28] and that 18a has proved itself to be a much less stable species that was originally thought, since its dimer show no tendency to dissociate[29].



18a.

That the reacting species Br_2 does not add to the double bond either by an ionic or free radical mechanism can be explained in the following way. The concentration of bromine is too low in the addition of double bond, only one attacking bromine atom of a bromine molecule is being attached to the substrate, whether the addition is electrophilic or free radical.



The other bromine comes from another bromine molecule. If the concentration of bromine is sufficiently low, there will not be a high probability that t he proper species will be in the vicinity once the intermediate forms and the equilibrium will lie to the left. That is why the rate of addition is slow so that the allylic substitution goes to completion successfully. If this is true then it should be possible to brominate an olefin in the allylic position without competition from addition, even in the case of NBS or similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed, so that it is not available to complete the addition step. This has been demonstrated by McGrath et al[30].

Stevenson et al[11,17] reported that when the saturated hydrocarbon friedelane 14 was oxidised by NBS, friedel-18-ene, 15 was obtained. In order to explain the function of NBS was to provide molecular bromine they compared the action of bromine in 14 in carbon tetrachloride solution.

A solution of bromine in carbon tetrachloride was added to friedelane, the colour of bromine being discharged and the reaction mixture was worked up in the usual way[11a]. Friedel-18-en 15 was obtained in comparative yield. This indicated that succinimide radical was not essential. By chromatographic examination no unchanged friedelane was recovered. However, they isolated an unstable bromofriedelane which readily transformed into friedel-18-ene. Consequently they considered the compound

to be an 18-bromofriedelane. The discrepancies and poor reproducibility reported[11a] in the bromination of 3-ketone friedelin by NBS, particularly in the formation of di and tribromo derivatives at C-2 and/or C-4 may be attributed to accompanying halogenation at C-18.

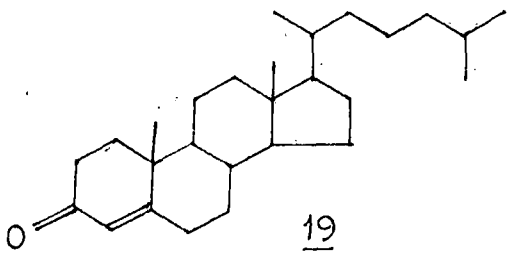
Bromination and Dehydrobromination

The ability of NBS to act as specific reagent for allylic brominations has been used to great advantage for the introduction of supplementary double bonds, particularly in cyclic systems. In this way, a variety of monosubstituted compounds have been converted to conjugated dienes and trienes, including the aromatization of substituted cyclohexenes and cyclohexadienes.

The method involves a two step bromination- dehydrobromination process. In many cases, the intermediate bromo compound is isolable and the second step proceeds after treatment of a base. There are numerous examples, in which the bromo intermediate is unstable under reaction conditions and spontaneously loses hydrogen bromide to form the final product. There is no definite structural guide which can be used to predict whether dehydrogenation will occur without the use of a base. A wide variety of substances have been used as base to effect the second step of the process namely tertiary amine, pyridine, quinoline, γ-collidine etc.

While a number of simple olefins have been converted to dienes in this manner, the method has found wide application in a wide range of natural products such as terpenes, steroids and alkaloids.

Δ^4 - cholesten-3-one, 19 on allylic bromination by NBS[31] gave 6-bromo compound 20, which on heating with collidine readily formed $\Delta^{4,5;6,7}$-cholestadien-3-one. In a similar manner $\Delta^{1,2;4,5}$-cholestadien-3-one was converted to $\Delta^{1,2;4,5;6,7}$ cholesta-trien-3-one.



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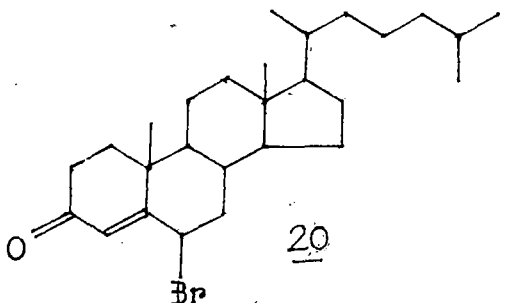

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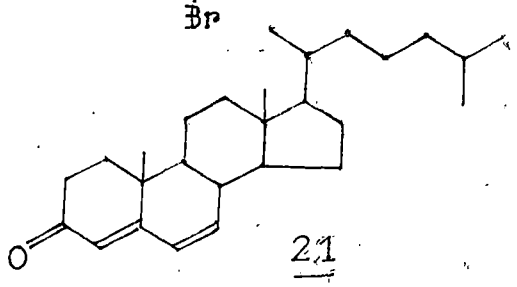

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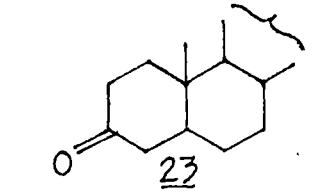
N. Rubin et al[32] provided an interesting example of allylic bromination with subsequent dehydrobromination. They treated Δ^2-3-acetoxy-cholestene 22 with NBS. The enol acetate of cholestanone 23 (ring A/B trans) reacted with NBS in CCl_4 to give a mixture of Δ^1 and Δ^4-cholesten-3-one 24 and 25 and 2-bromo cholestan-3-one 26, the amount of which increased with time at the expense of 24.



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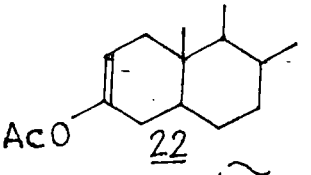

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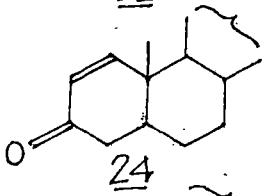

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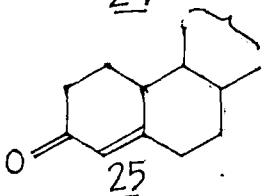

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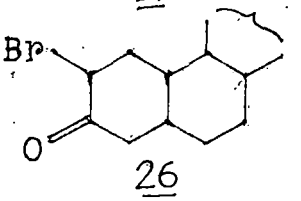

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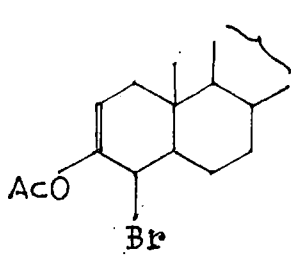
The origin of the reaction products has been attributed to the thermal and acid instability of the intermediate allylic bromination products, 27 and 28. The formation of the compound 25 has been explained on the basis of spontaneous loss of hydrogen bromide from 27 and then acid catalysed cleavage of the resulting enol acetate. Due to the absence of an available hydrogen for spontaneous dehydrogenation, 26 is more stable than 25. However, the rapid formation of 24 suggests the acid cleavage of 26 and the ketonisation of the resulting enol to produce β-bromo ketone, which possesses a hydrogen atom of an adjacent carbon atom.



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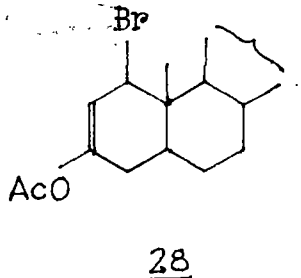

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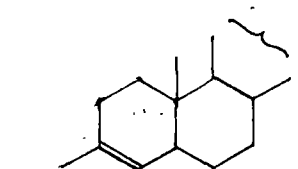
The reaction becomes more complex as the time increases because the formation of hydrogen bromide in the reaction mixture which catalyses the regeneration of 23 from 22 and results in the formation of free bromine by reaction with NBS. Bromine and 23 react to give a compound 26. Djerassi et al[33] obtained this compound from NBS and 22.

The reaction of NBS with Δ^3-acetoxy-coprostene 29 (ring A/B cis) indicated that in 27, the activation energy of both allylic position (C_2 and C_5) was of the same magnitude. The attack at the tertiary C_5 position was somewhat unexpected because it was thought that more vigorous activation would be required for this type of substitution by NBS.



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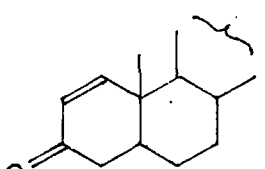

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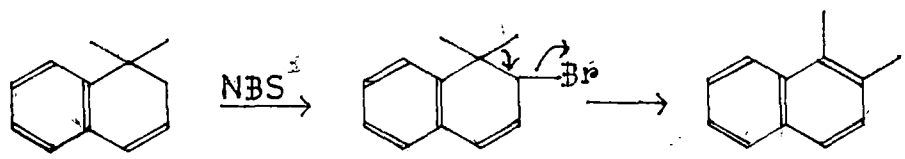
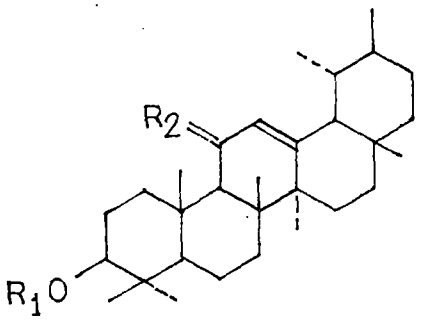
Steroid sapogenins containing Δ^5-3-OH group and a spiroketal side chain in the 16,17 position are selectively brominated in the 7-position with NBS under irradiation with artificial light. Dehydrobromination with collidine gives $\Delta^{5,7}$-sapogenins, useful as intermediates for synthetic hormones or after irradiation, as products with antirachritic activity[34]. The method has also been used in structural studies of the terpenoids[35]. Similar action of NBS on friedelin and bromofriedelin has also been reported[11b].

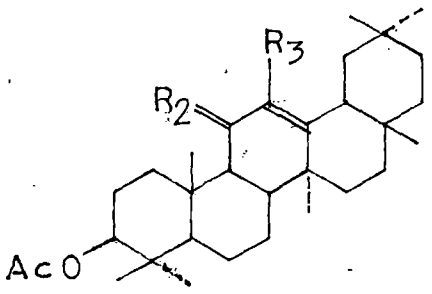
Barnes et al[36] showed that treatment of 1,1,6-trimethyl 1, 2 dihydronaphthalene with NBS gave an allylic bromide which aromatized to 1,2,6-trimethyl naphthalene by silver ion or heat (temperature of refluxing CCl_4).



Oxidation of allylic methylene to carbonyl group by NBS.

NBS is in wide use since 1969 as an effective reagent for oxidation of allylic methylenes to carbonyl function. Corsano et al[37] reported the formation of 3β-acetoxy-urs-12-ene-11-one 32 in 80% yield by direct oxidation of α-amyrin acetate 31 with NBS in aqueous dioxan solution.





31 R_1=Ac, R_2=H

32 R_1=Ac, R_2=O

33 R_1=Ac; R_2=H_2, R_3=H

34 R_1=Ac; R_2=O, R_3=H

35 R_1=Ac; R_2= α-OH, R_3=H

36 R_1=Ac; R_2=α-OMe, R_3=H

37 R_1=Ac; R_2= α-OAc, R_3=H

38 R_1=Ac; R_2= α-OH, R_3=Br

39 R_1=Ac; R_2=O, R_3=Br

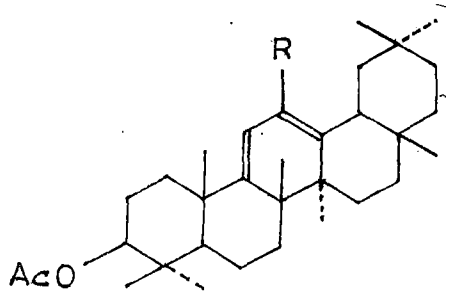
40 R_1=Ac; R_2=H_2, R_3=Br

Finucane and Thompson[38,39] reported an improved method for the direct oxidation of the allylic methylene to carbonyl by the action of NBS in the presence of visible light. They claimed that when trisubstituted olefins containing an allylic methylene group were treated with NBS in aqueous dioxane followed by irradiation with visible light, α,β-unsaturated ketones were obtained in near quantitative yield. Finucane et al[38] treated β-amyrin acetate 33 with NBS in aqueous dioxane in a typical

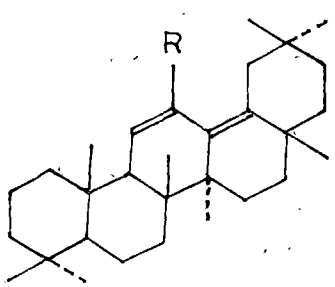
ambient light experiment as described by Corsano et al[37]. On chromatographic separation over silica gel they isolated starting material (Ca 40%), bromo compound (Ca 8%) and 3β-acetoxy olean-12-ene-11α-ol 35 (Ca 2%). Oxidation of 35 with CrO_3 in acetone afforded 3β-acetoxy-olean-12-en-11-one 34.

In another experiment the products were isolated by chromatography over alumina. The compounds isolated were β-amyrin acetate 33 (Ca 35%), 3β-acetoxy-olean-12-en-11-one 34 (Ca 40%), bromo compounds (Ca 10%) and polar materials (Ca 10%).

The polar fraction on elution with methanol was acetylated and rechromatographed. Products isolated were 11α-methoxy-olean-12-en-3β-yl acetate 36; 11α-hydroxy-olean-12-en-3β-yl acetate 35 and olean-9(11), 12-dien-3β-yl acetate 39 and a trace of 3β-, 11α-diacetate 37. The α-methoxy acetate 36 with paratoluene sulphonic acid in acetic anhydride yielded 3β-acetoxy-olean-11(12), 13(18)-diene 41 in quantitative yield.



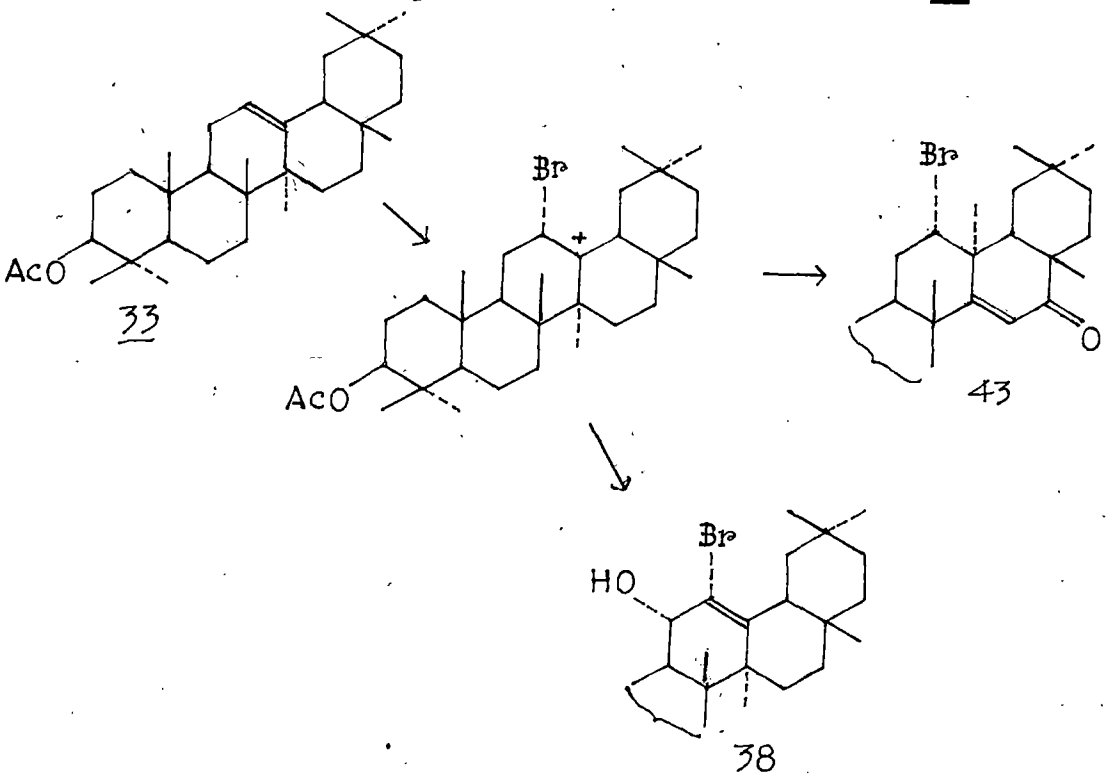
39 R = H
40 R = Br



41 R = H
42 R = Br

The bromo compounds were resolved by chromatography over alumina and fractionally crystallised into two components. The major product was a diol mono acetate ($C_{32}H_{51}O_3Br$) which was identified as 3β-acetoxy-12-bromo-olean-12-en-11-ol 38, from further acetylation, uv, NMR and TNM test. The minor component of the mixture of bromo compounds was identified as 12α-bromo-16-one 43 from the uv (λ_{max} 244 nm) and NMR spectra.

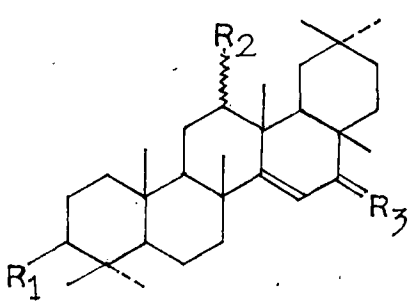
The mechanism proposed for the formation of 38 and 43 suggested that the initial α-face attack on β-amyrin acetate 33 at C-12 would lead to a carbonium ion. Elimination of a proton from C-12, followed by allylic hydroxylation would then lead to 38. Alternatively, migration of 14α-methyl group to C-13, elimination of a proton from C-15 and subsequent allylic oxidation would give the 12α-bromo-16-one 43.

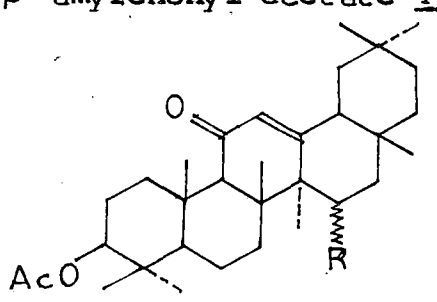


33 43 38

Thomson et al[39] carried out oxidation of taraxeryl acetate 44 by the method of Corsano et al[37] and obtained two major products to which they assigned the structure of 16-oxo-taraxeryl acetate 45 (Ca 30%) and 16 β-hydroxy-taraxeryl acetate 46 (Ca 30%). Treatment of 46 with chromic acid in acetone gave the unsaturated ketone 45. These authors also carried out the oxidation on 44 by the method described for β-amyrin acetate, which resulted in the formation of 12α-bromo-taraxer-12-en-16-one 47.

Oxidation of taraxeryl acetate in aqueous dioxane[38] for five and half hours in presence of $CaCo_3$ in visible light gave a compound 48, the structure of which was established as 11-keto-15-bromo-β-amyrin acetate, which in turn gave a halogen free compound 49 on treatment with zinc dust in acetic acid. Its structure was established as β-amyrenonyl acetate 49.





44 R_1=OAc, R_2=H, R_3=H$_2$

45 R_1=OAc, R_2=H, R_3=O

46 R_1=OAc, R_2=H, R_3= β-OH, α-H

47 R_1=OAc, R_2=Br, R_3=O

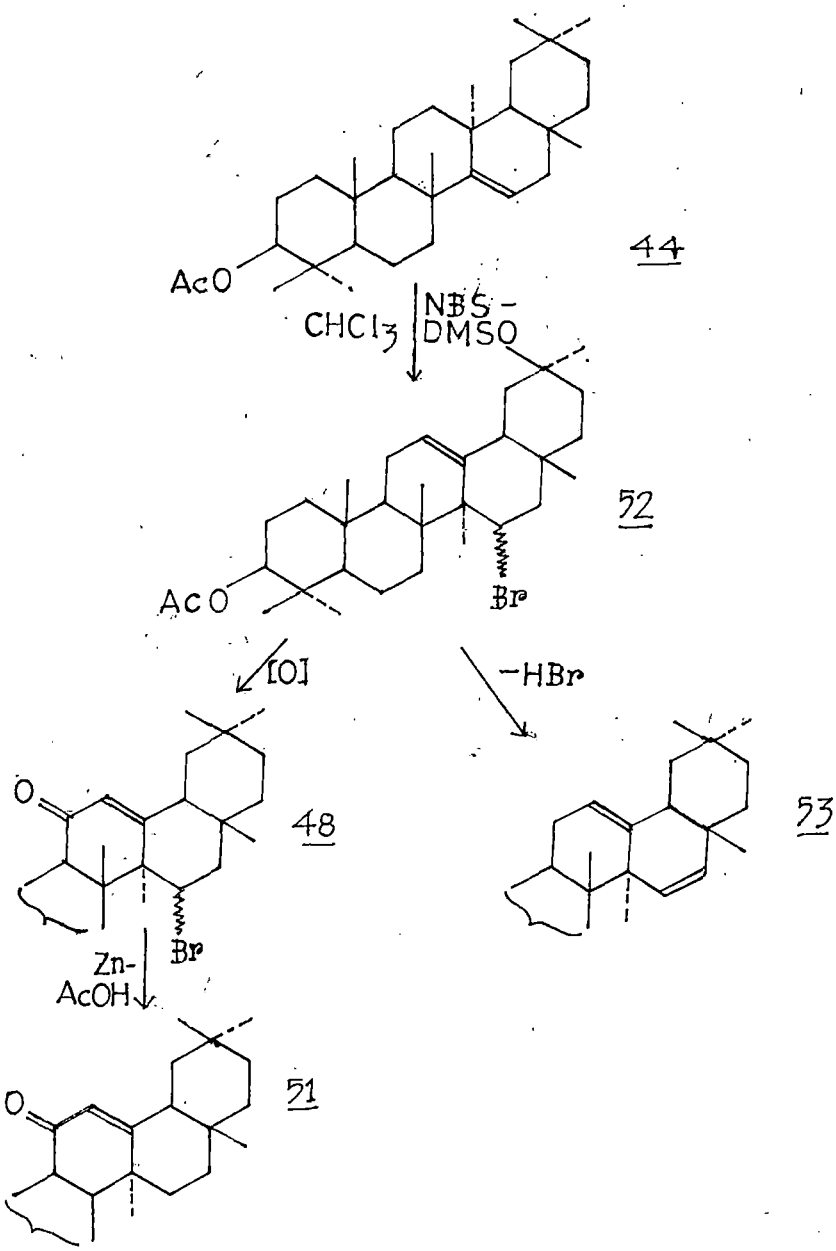
48 R=Br

49 R=H

Khastgir et al[40] repeated the oxidation study of taraxeryl acetate 44 with NBS in aqueous dioxan according to the method of Finucane and Thomson[39] but the products isolated were quite different from those reported by Finucane et al[39]. Khastgir et al observed that taraxeryl acetate 44 on oxidation with NBS in aqueous dioxan gave a mixture of two compounds which were separated by chromatography over alumina column followed by crystallisation.

The first solid $C_{32}H_{49}O_3Br$ m.p. 238-40° obtained on elution with petroleum ether in a column was characterised as 15-bromo- β-amyrenonyl acetate 50. Its structure was proved by the folowing reactions. On treatment with zinc dust and acetic acid, a halogen free compound was isolated and was found to be identical with an authentic sample of β-amyrenonyl acetate[41] 51, prepared by CrO_3 - AcOH oxidation of β-amyrin acetate. Khastgir also tried to prepare the 15-bromo-compound 52 by a suitable method. They carried out the oxidation of taraxeryl acetate 44 by the method of Dalton and Jones[42] using NBS in dimethyl sulphoxide solvent[43]. Taraxeryl acetate 44 on treatment with aqueous dimethyl sulphoxide in chloroform and NBS in dark afforded a solid $C_{32}H_{51}O_2Br$, m.p. 180-82°, showing no uv absorption between 220-300 nm. From IR, NMR and mass spectra the structure of 15-bromo-compound was assigned to be 52. The bromine atom at 15 position of 52 would be expected to have the same

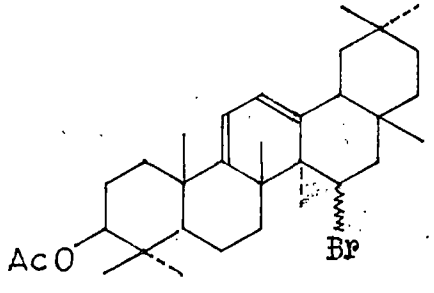
stereochemistry as in the case of product from NBS-aqueous dioxane oxidation method. Compound 52 on oxidation with CrO_3-AcOH[41] gave 50, m.p. 238-40° identical with the product obtained from NBS - aqueous dioxane method.



Dehydrobromination of 52 with KOAc in acetic acid at 130° for 4 hours gave a product $C_{32}H_{50}O_2$, m.p. 199-200°. The same compound was obtained when 52 was refluxed with dimethylaniline for six hours. The structure 53 was proposed to it.

The second compound $C_{32}H_{50}O_3$, m.p. 280-82° being obtained on elution with petroleum ether : benzene (4:1) mixture was devoid of bromine. UV (λ_{max} 245 nm), IR (peaks at 1730, 1680, 1250 cm^{-1}), mass peak (M^+ 482) and NMR spectrum (peaks at δ 5.85, 2.10, 4.5 ppm) suggested that the product was 16-oxo-taraxeryl acetate 45, although its m.p. was different from that recorded by Finucane and Thomson[39].

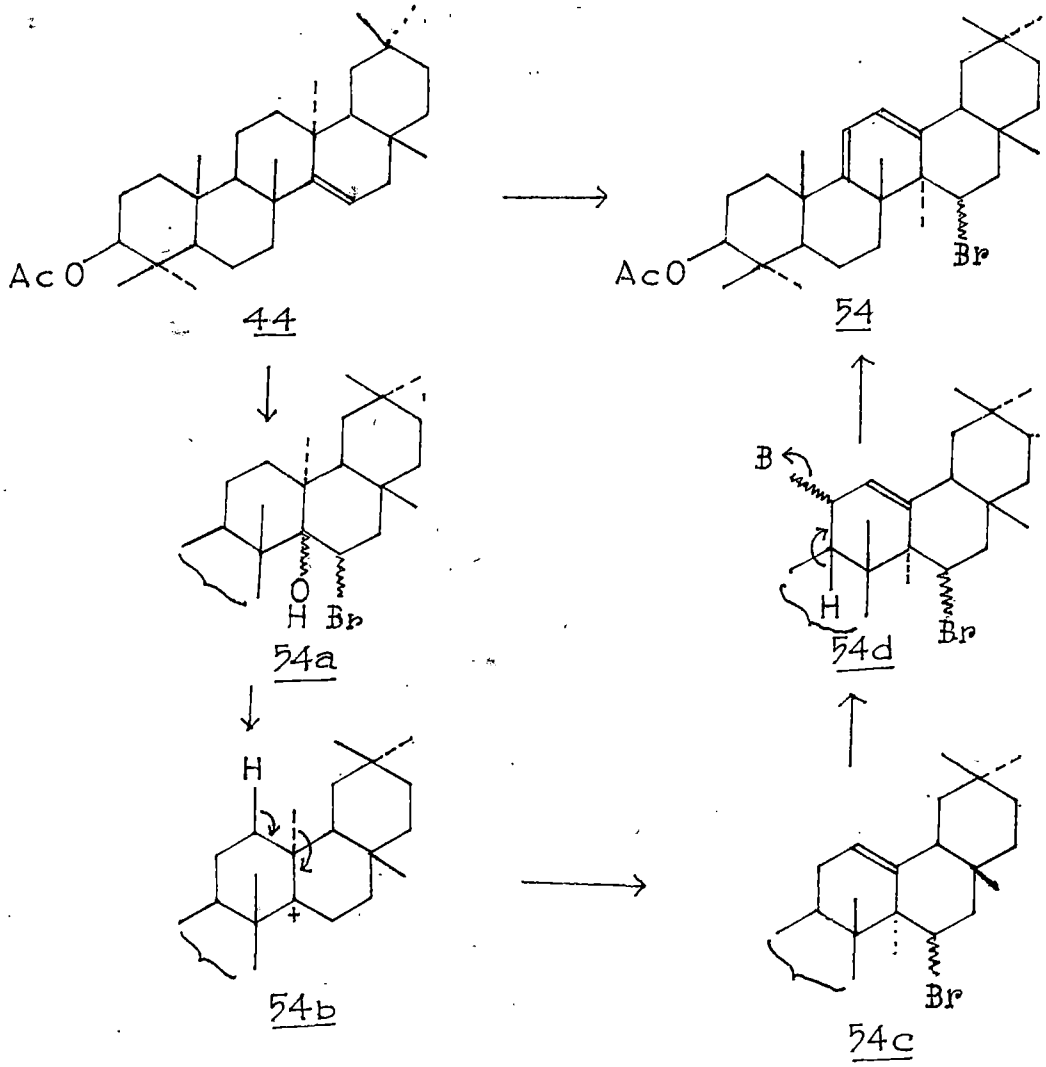
The third product having molecular formula $C_{32}H_{49}O_2Br$, m.p. 176-78° showed uv maxima at 276 nm indicating the presence of homoanular diene. NMR spectrum of the compound showed peaks at δ 5.34 and 5.85 ppm for one proton each attributable to the protons in a homoanular diene system in which both the double bonds are trisubstituted. Besides this, the spectrum showed sharp signals at 2.08 (-O.CO.CH_3) and multiplets at 4.6 (-CH.O.$COCH_3$) ppm. On the basis of those evidences, the compound was assigned the structure 54.



54

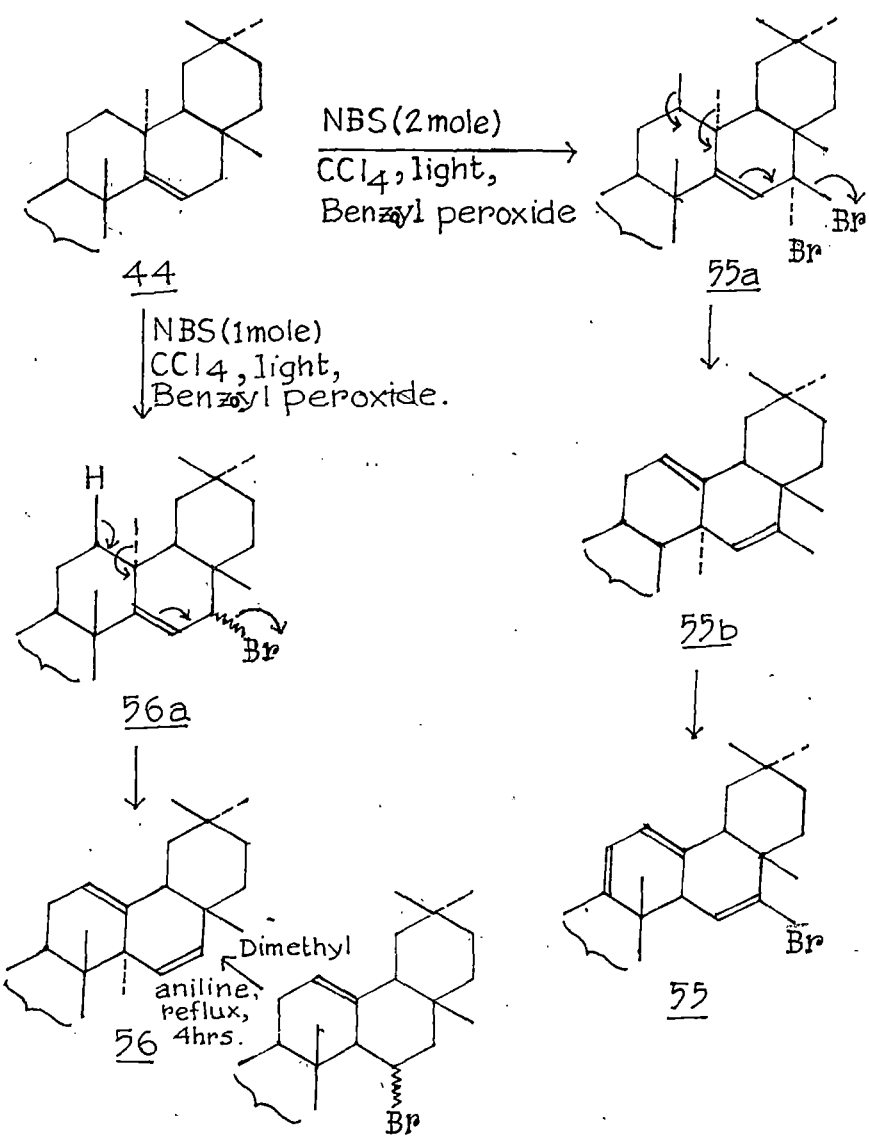
The mechanism for the formation of 54 from 44 was suggested as shown in the following Scheme I.

Scheme - I



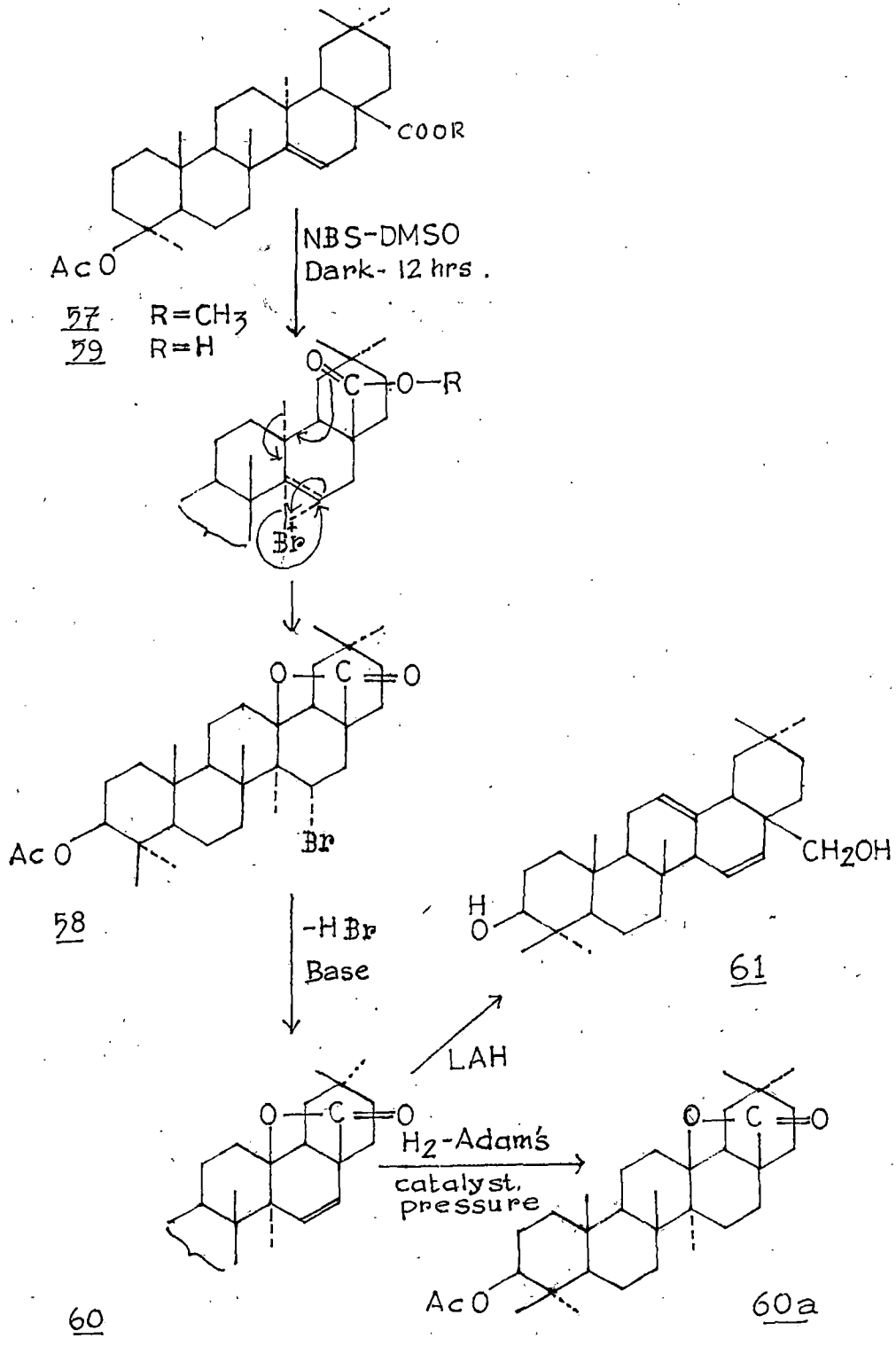
Khastgir et al[40] also studied the reaction of taraxeryl acetate 44 with 2 moles equivalent of NBS in CCl_4 and benzoyl peroxide in the presence of visible light for about 3 hours and isolated a product which was assigned the structure 56, identical with that compound obtained by the dehydrobromination of 52. The mechanism proposed for the formation of 55 and 56 can be represented in the following Scheme - II.

Scheme - II

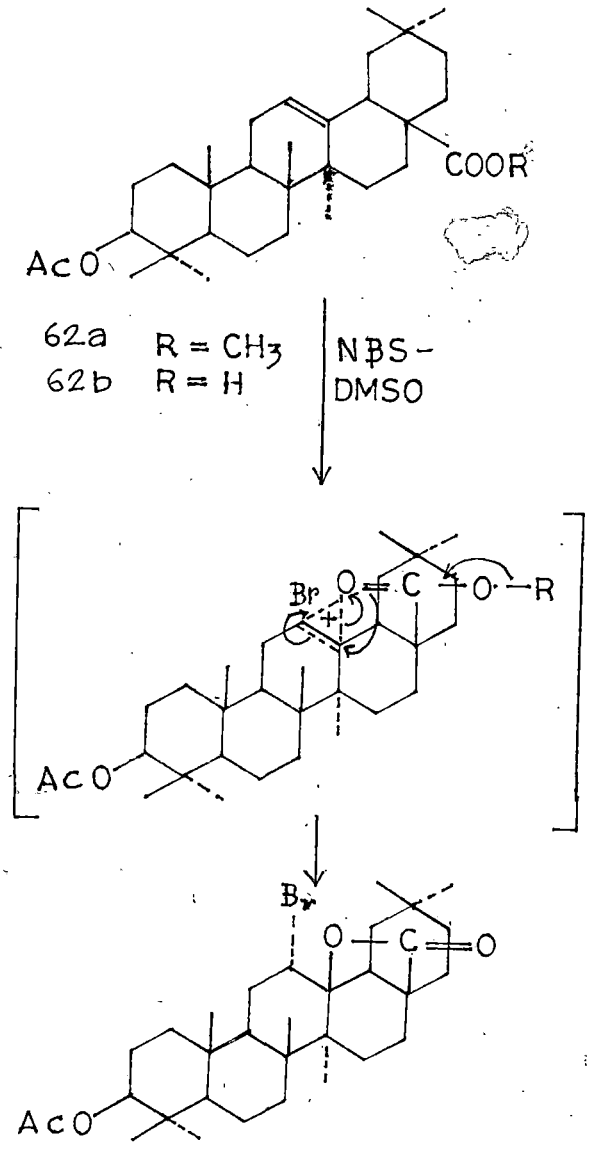


Pradhan et al[44] examined the action of NBS on triterpene acids and esters in dimethyl sulphoxide. They studied the reaction on acetyl methyl aleuritolate[42] 57 with NBS in dimethyl sulphoxide in dark for 12 hours and isolated a bromo lactone 58. The structure of the bromolactone 58 was established from the fact that on dehydrobromination with dimethylaniline it afforded 15, 16 dehydrolactoce 60, which on LAH reduction furnished aegiceradiol[43] 61, $C_{30}H_{48}O_2$, m.p. 235-6°, identical (mmp, CO-IR) with an authentic sample. Compound 60 on catalytic hydrogenation over Adam's catalyst in acetic acid under pressure afforded 3β-acetyl oleanan-28⟶13-olide[44] 60a. Pradhan et al also isolated the same bromolactone 58 on repeatation of the reaction on acetyl aleuritolic acid[42] 59.

They suggested that the mechanism of the formation of bromolactone 58 probably involved the attack of the bromonium ion from NBS in DMSO at the double bond. Bromine being a bulky atom ultimately assumed the equatorial position so as to have the minimum strain and steric interaction. The next step involved concerted migration of the C-13 methyl to the C-14 position and elimination of the methoxy methyl to form the 28⟶13 olide 58.


COOR
AcO
NBS-DMSO
Dark- 12 hrs.
57 R=CH3
59 R=H
O
C
O—R
Br
O—C=O
AcO
Br
58
-HBr
Base
LAH
CH2OH
H
O
61
O—C=O
H2-Adam's
catalyst,
pressure
AcO
60
60a

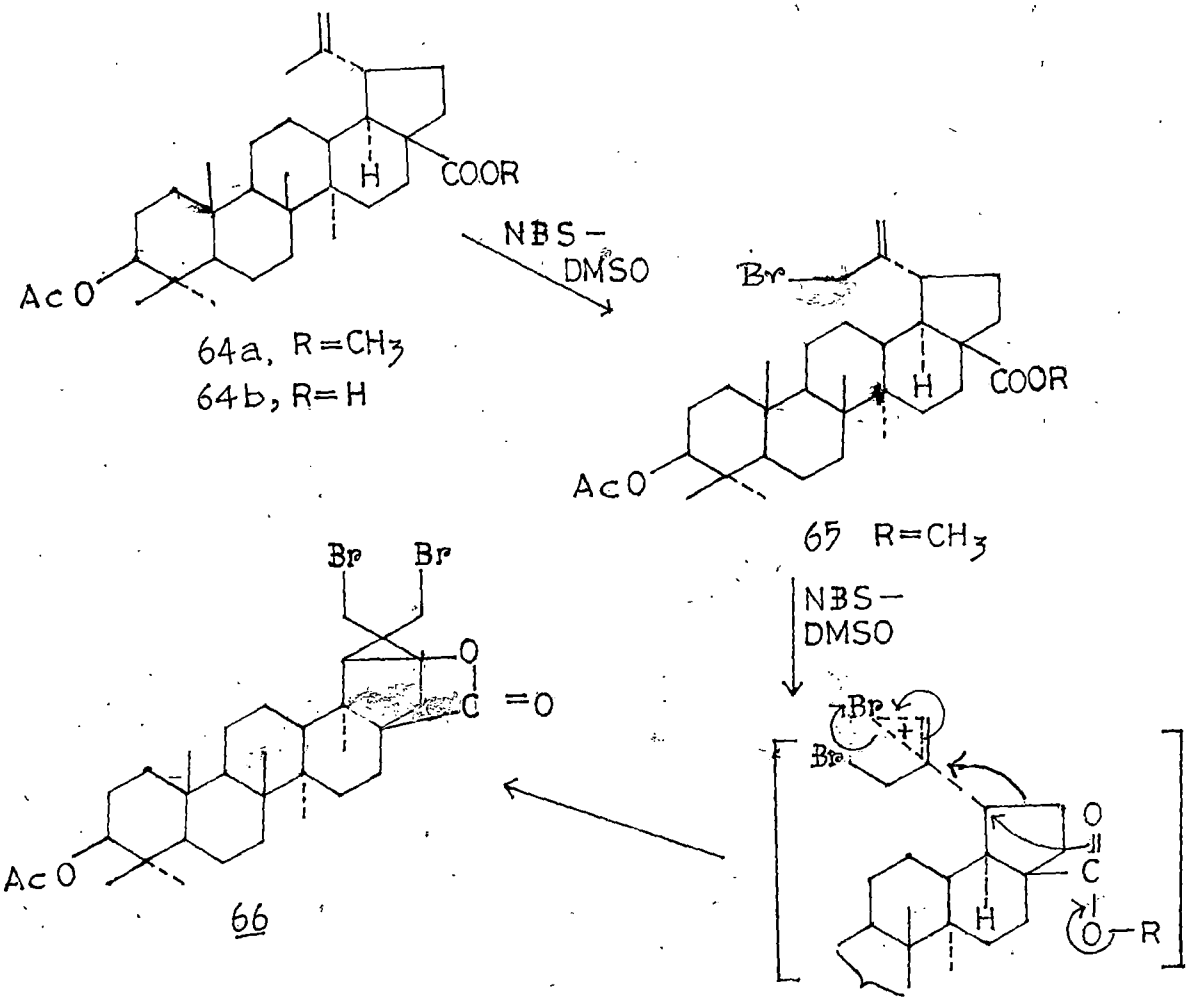
Acetyl methyl oleanolate 62a and 3β-acetyl oleanolic acid 62b under the same condition with NBS in DMSO gave the same bromolactone 63 which was found to be identical with 3β-acetyl-12α-bromo-oleanan-28 ⟶ 13 olide[48].



63

Pradhan et al also carried the reaction on 3β-acetyl methyl betulinate[49] 64a under similar condition with NBS in DMSO. Two different bromo compounds were separated by chromatography. The less polar one, $C_{33}H_{51}O_4Br$, m.p. 235-6°, $[\alpha]_D$ +42.55° was identified as methyl-30-bromo-3β-acetyl betulinate 65. This structure was supported by IR, ^1H NMR data. The more polar fraction (10%) isolated was dibromolactone 66, having molecular formula $C_{32}H_{48}O_4Br_2$, m.p. 303-4°. The structure of this dibromo lactone 66 was arrived at from the studies of mass, CD, IR, ^1H NMR and ^{13}C NMR values. The structure of 66 was further confirmed by some reactions. The compound 66 could not be dehydrobrominated with dimethyl aniline, but on debromination with Raney Nickal - hydrogen gave a compound having the formula $C_{32}H_{50}O_4$, m.p. >360° and was found to be identical with 3β-acetyl oleanan-28 ⟶ 19β-olide. On the basis of these observations the dibromolactone has been assigned the structure 3β-acetyl-29, 30-dibromo-18α, oleanan 28⟶ 19β-olide. The proposed mechanism of formation of 66 is shown in the following Scheme - III.

Scheme - III



64a, R=CH_3
64b, R=H

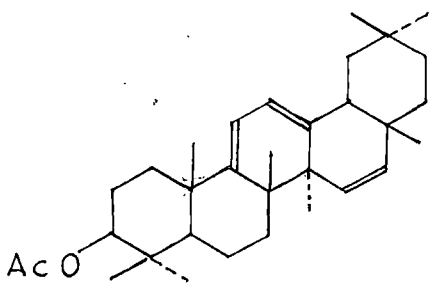
65 R=CH_3

66

Pradhan et al[44] also reported that 3β-acetyl betulinic acid 64b also furnished dibromolactone 66 on similar treatment with NBS in DMSO.

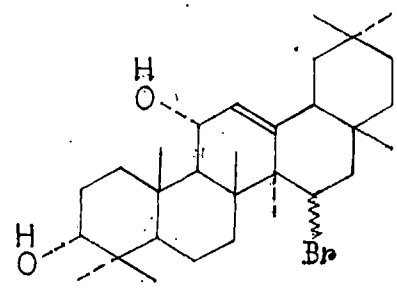
Anjaneyulu et al[50] in their attempt to prepare maniladiol from taraxeryl acetate 44 applied the reaction of NBS on taraxeryl acetate 44 in aqueous dioxane by the method of Finucane and Thomson[38]. A mixture of four compounds was obtained two of which were identified as 55 and 60 by physical means. The third compound 67, $C_{32}H_{48}O_2$ (M^+ 486) contained two double bonds conjugative in a homoanular diene system as indicated by the uv absorption at 280 nm (ϵ=6200). The PMR spectrum exhibited two singlets at δ 5.5 and 5.29 each integrating for two protons. The former value was attributed to the homoannular -9(11), 12-diene system and the latter to protons at C-15 and C-16. Based on these spectral data the structure of compound 67 was assigned 3β-acetoxy-oleana-9(11), 12, 15 triene.

The fourth compound crystallised from chloroform-methanol mixture was characterised as 3β-ol of 67.



67

To prepare 3β-acetoxy-oleana-9(11), 12, 15 triene 67 they[50] planned to convert 15-bromo β-amyrenonyl acetate 50 into 15-bromo-olean-12-en-3, 11 diol which on dehydration with acetic anhydride[51] followed by dehydrohalogenation would give 67. Reduction of 50 with LAH gave epimeric diols. The major diol was separated by fractional crystallisation from hexane. This on acetylation at room temperature gave a major product found to be a diacetate. The ready formation of diacetate is attributed to the unhindered nature of 11α-hydroxyl[39,51]. Thus the structure of major diol was assigned as 15-bromo-olean-12-en-3β, 11α-diol 68.



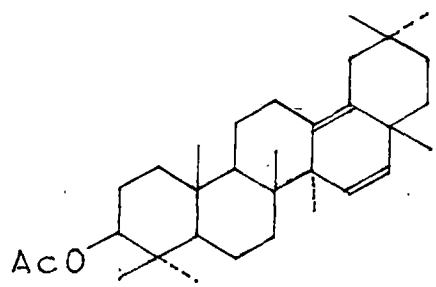
68

Further support of this structure was provided by PMR spectrum.

The remaining diol mixture after acetylation with Ac_2O/Py gave a product which was analysed for $C_{32}H_{49}O_2Br$. From the uv spectrum (λ_{max} MeOH 277 nm) and NMR data (δ 5.5, 4.7 ppm) the structure of this compound was assigned as 3β-acetoxy-15-bromo-oleana-9(11), 12 diene 54. Dehydrohalogenation of 54 with

N,N dimethyl aniline gave a compound which was found to be identical in all respect with 67.

They attempted to prepare 16β-acetoxy-taraxeryl from taraxeryl-acetate following the method of Barton et al[52]. They isolated a compound characterised as 3β-acetoxy oleana-13(18), 15-diene 67a along with 16β-acetoxy taraxeryl acetate and 16-oxo-taraxeryl acetate.



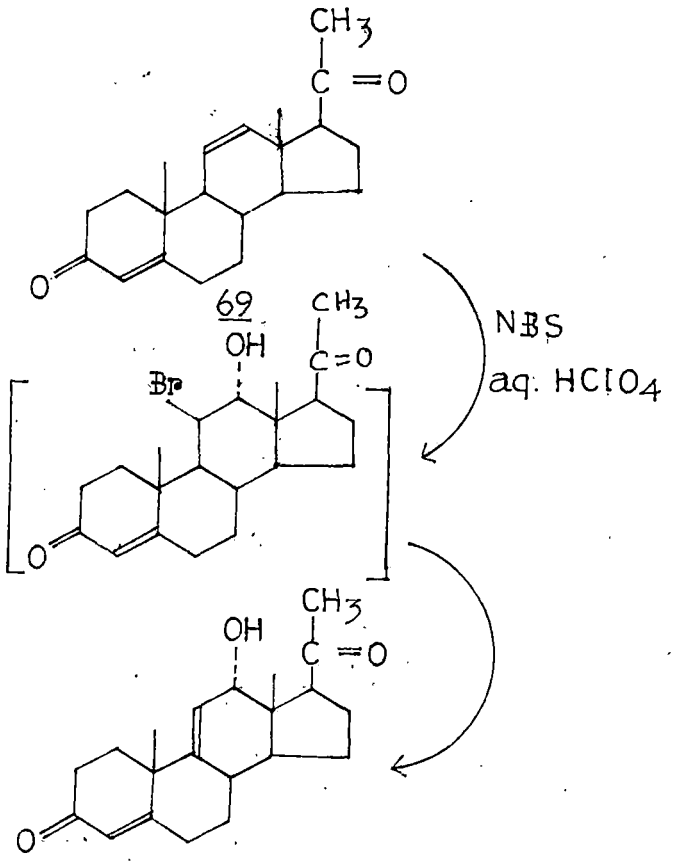
67a

Allylic hydroxylation by NBS

N-bromosuccinimide may be used to introduce an allylic hydroxyl group in a compound. The method is indirect and generally involves allylic bromination and the conversion of the resulting bromide into alcohol via the formation of formate and acetate. Thus, 3β-menthene-5 yl bromide was prepared from 3β-menthene using NBS in $CHCl_3$ in the presence of uv light. The bromide was converted to 3-p-menthene-5 yl formate by sodium formate and the crude ester on treatment with methanolic sodium carbonate gave dl-trans-3p-menthene 5-ol[53].

A mixture of cis-(38%) and trans-(62%) cyclodecene formed the bromide, which on reaction with silver acetate in glacial acetic acid gave the crude acetate from which 2-cyclodecen-1-ol was obtained on treatment with methanolic hydroxide.[54]

An example of the hydroxylation of steroids is illustrated by the transformation of 11-dihydro progesterone 69 to give $\Delta^{4,9(11)}$ pregenadien-12α-ol-3, 20-dione[55] 70.



70