PART-II

ACTION OF N-BROMOSUCCINIMIDE ON PENTACYCLIC TRITERPENOIDS OF LUPANE AND FRIEDELANE SKELETON IN DIMETHYL SULFOXIDE.

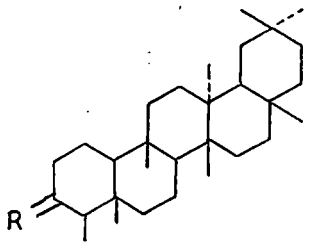
CHAPTER-I

A SHORT REVIEW OF REACTIONS OF N-BROMOSUCCINIMIDE.

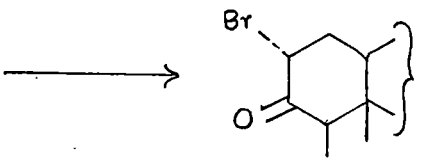
The reagent N-bromo-succinimide(NBS) has been extensively used as an allylic brominating agent since 1919, when Wohl[1] and then Zeigler[2] made a detailed study in this field. The reagent also reacts with olefins to add bromine atom at the double bond and also used for oxidation of allylic methylene to carbonyl functions[3-5] . Triterpenoids undergo a variety of rearrangement reactions with NBS. The author have carried out some reactions of NBS on triterpenoids and it is necessary to give a brief discussion on the previous works of this type of rearrangement reactions.

ALLYLIC BROMINATION AND RELATED REACTIONS:

Corey and Ursprung[6] have reported that friedlin-1 on direct bromination gave 2α-bromofriedlin 2 and bromination of appropriate enol benzoate gave the isomeric 4α-bromofriedlin 3 . They have also prepared a dibromofriedlin 4 by reaction with HBr in $CHCl_3$, which they assigned as 2α, 4α-dibromofriedlin from UV spectra. Djerassi et al[7] reported the formation of 2α,4β-dibromofriedlin 5 by bromination of 2α-bromofriedlin 2 in acetic acid. Stevenson et al[8,9] reported that friedelane 6 was oxidised to friedel 18-ene 7.



1. R=O
6. R=H$_2$



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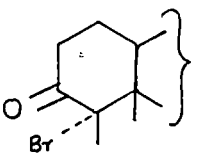

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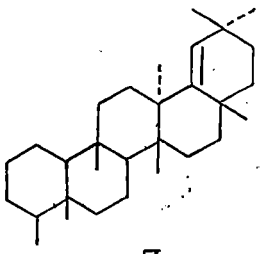

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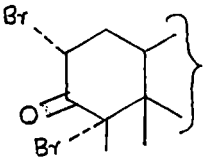

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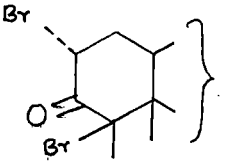
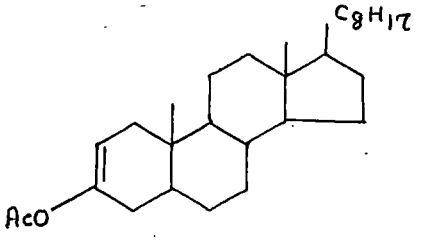


5.

Rubin et al[10] provided an example of allylic bromination with subsequent spontaneous dehydrobromination by reaction of NBS with Δ^2-3-acetoxy-cholestene **8** . This enol actate of cholestanone **9** (ring A/B trans) reacted with NBS in CCl_4 to give a mixture of Δ^1 and Δ^4-cholesten-3-one, **10** and **11** and 2-bromo-cholestan-3-one **12**, the amount of which increased with reaction time at the expense of **10** .



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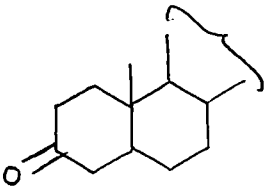

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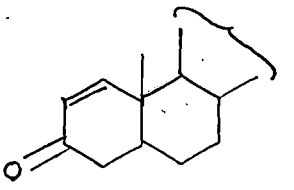

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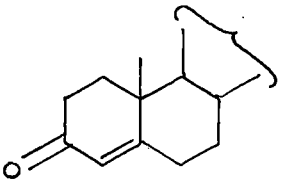

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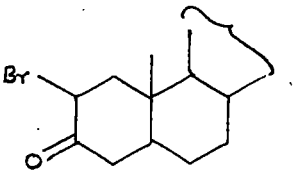

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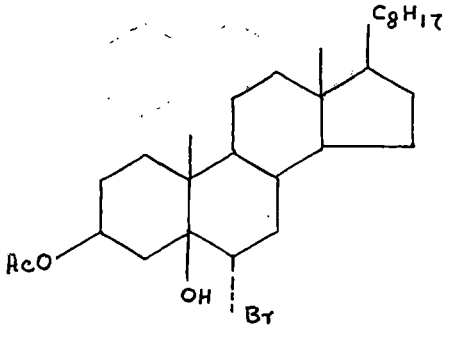
Pradhan et al[11] studied the action of NBS on cholesteryl acetate **13** in dimethyl sulfoxide(DMSO) solvent and isolated six different compounds which were identified as 5α-bromo-6-keto cholestan-3β-yl acetate **14**, 6α-bromo-5β-hydroxy coprostan-3β-yl acetate **15**, 5α-hydroxy-6-keto cholestan-3β-yl acetate **16**, 5α,6β-dihydroxy cholestan-3β-yl acetate **17**, 3β,5α-dihydroxy cholestan-6-one **18** and cholestan-3β,5α,6β triol **19** by chemical and spectral (IR, ^{1}H NMR, Mass and ^{13}C NMR) studies. They reported compound **15** for the first time



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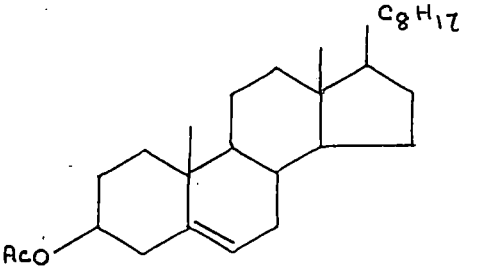

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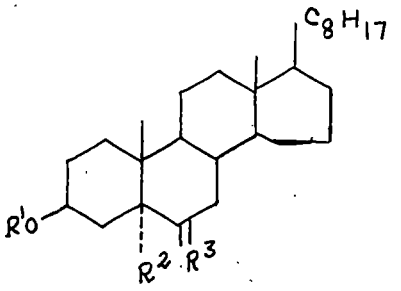


14, R^1 = Ac, R^2= Br and R^3= O.

16, R^1= Ac, R^2= OH and R^3= O.

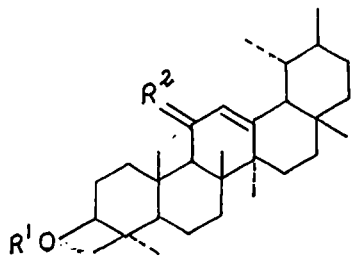
17, R^1= Ac, R^2= OH and R^3=  .

18, R^1= H, R^2= OH and R^3 = O.

19, R^1= H, R^2= OH and R^3 =  .

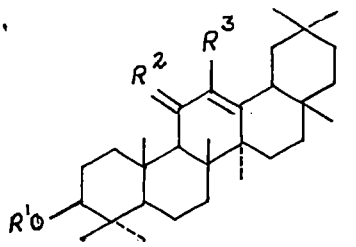
OXIDATION OF ALLYLIC METHYLENE TO CARBONYL GROUP:

Corsano et al[12] reported direct oxidation of the allylic methylene to carbonyl group with NBS in aqueous dioxane solution. Thus 3β-acetoxy-urs-12-ene-11-one **21** was formed in 80% yield from α-amyrin acetate **20**



20, R^1= Ac; R^2= H.

21, R^1= Ac; R^2 = O.



22, R^1= Ac; R^2= H_2; R^3= H

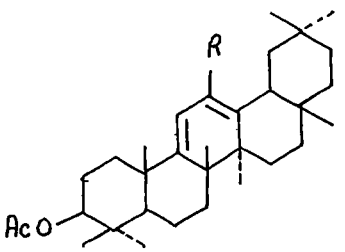
23, R^1= Ac; R^2= O; R^3 = H

24 R^1= Ac; R^2= OH; R^3= H

25, R^1 = Ac; R^2= OMe; R^3= H

26, R^1= Ac; R^2= OAc; R^3= H

27, R^1= Ac; R^2= OH; R^3= Br.

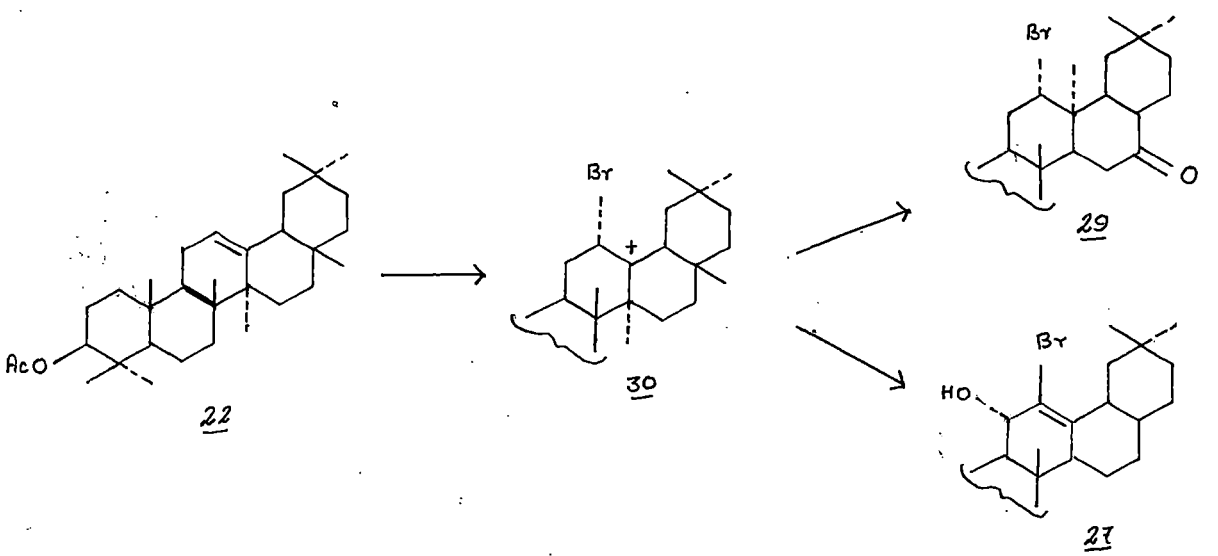


28, R=H.

Finucane et al[13,14] reported an improved method for the direct oxidation of the allylic methylene to carbonyl functions by the action of NBS and simultaneous irradiation with 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 ketone were formed in high yield. Finucane et al treated β-amyrin acetate 22 with NBS in aqueous dioxane in a typical ambient light experiment as described by Corsano et al[12]. They isolated starting material, 3β-acetoxy-olean-12-ene-11-one, bromo compound and 3β-acetoxy- olean-12-ene-11α-ol, 24. Oxidation of the latter 24 with chromium trioxide in acetone afforded 3β-acetoxy--olean-12-ene-11-one 23.

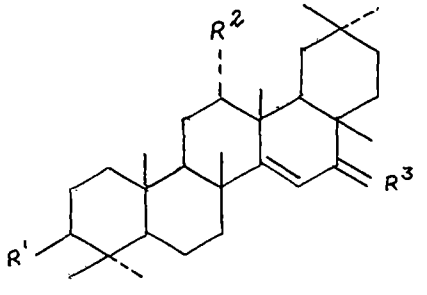
In another experiment,the products were isolated by chromatography over alumina and yielded β-amyrin acetate 22, 3β-acetoxy-olean-12-ene-11-one 23,bromo compound and polar material. The polar fraction on elution with methanol was acetylated and on rechromatography gave 11α-methoxy-olean-12-ene-3β-yl acetate 25 together with smaller amount of 11α-ol 24, and olean-9(11), 12-diene-3β-yl acetate 28 and trace of 3β,11α-diacetate 26. The fractions containing bromo compounds was resolved by chromatography over alumina and fractionally crystallised into two components. the major product was identified as 3β-acetoxy 12-bromo olean-12 ene-11-ol 27,the minor component of the mixture of bromo compound was identified as 12α-bromo-16-one 29. The mechanism proposed for the formation of 27 and 29 suggested that the initial α-face attack on β-amyrin acetate 22 at C-12,would lead to a carbonium ion 30. Elimination of a proton from C-12 followed by allylic hydroxylation would than lead to 27. Alternatively, migration of 14α-methyl group to C-13, elimination of a proton from C-15,and subsequently allylic oxidation would give 29.

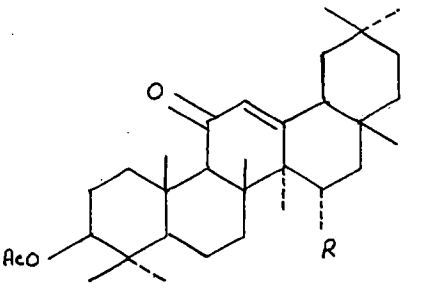


22 30 29 27

Thomson et al[14] carried out oxidation of taraxeryl acetate 31 by following the method of Corsano et al[12] and obtained two major products to which the assigned structure of 16-oxo taraxeryl acetate 32 and 16β-hydroxy taraxeryl acetate 33.
Treatement of 33 with chromic acid in acetone gave the unsaturated ketone 32. The workers also carried out the reaction on 31 by the method described for β-amyrin acetate,which resulted in the formation of 12α-bromo-taraxer-14-ene-16-one 34.

Oxidation of taraxeryl acetate with NBS in aqueous dioxane[13] for 5 hours in presence of $CaCO_3$ in visible light gave a compound 35 the structure of which was established as 11-keto-15-bromo β- amyrin acetate,which in turn yielded a halogen free compound 36 on treatment with Zn-dust in AcOH. Its structure was established as β-amyrenonyl acetate.

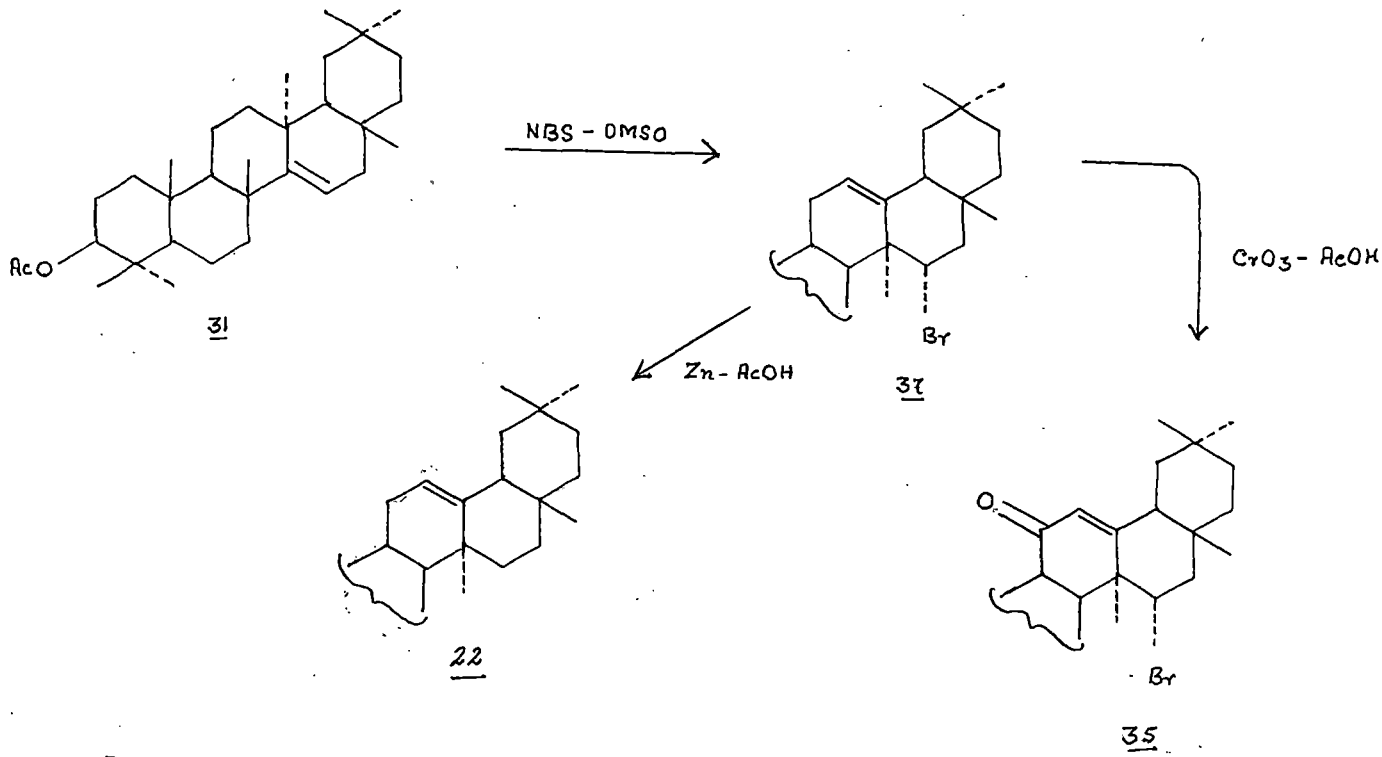




31, R^1= OAc; R^2= H; R^3= H_2
32, R^1=OAc; R^2= H; R^3= O.
33, R^1= OAc; R^2=H; R^3= 
34, R^1= OAc; R^2 = Br; R^3= O

35, R= Br
36, R= H

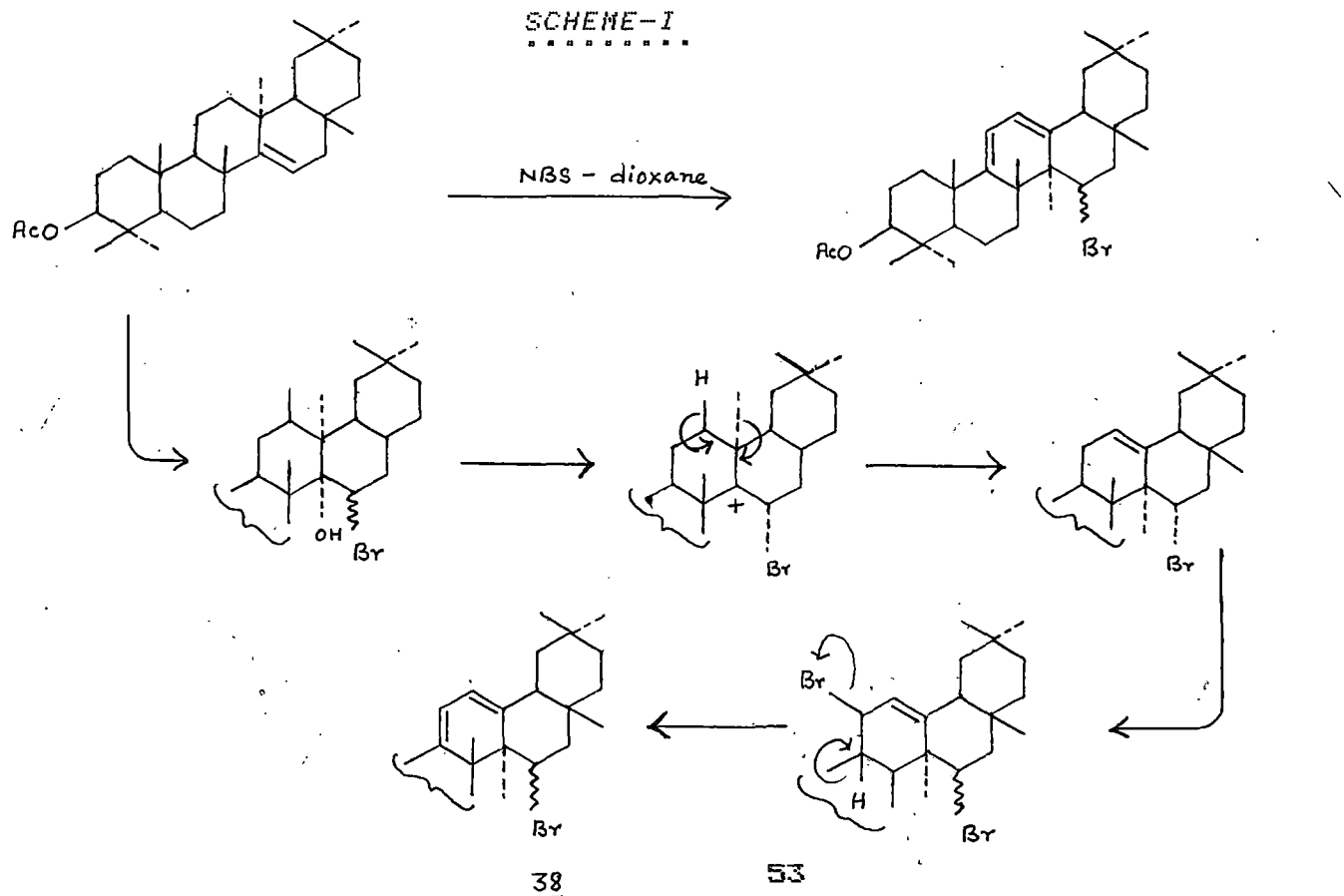
Khastgir et al[15] carried out the oxidation of taraxeryl acetate 31 by the method of Dalton[16] using NBS in DMSO solvent. Treatment of taraxeryl acetate 31 with aqueous DMSO in $CHCl_3$ and NBS in dark afforded a solid 37. The compound 37 on treatment with Zn-acetic acid yielded β-amyrin acetate 22. The Br-atom at 15 position of 37 would be expected to have the same stereochemistry as in the case of product from NBS aqueous dioxane oxidation method. Compound 37 on oxidation with CrO_3-AcOH[17] gave 35 identical with the product obtained from NBS aqueous dioxane oxidation method.



31 37 22 35

The second compound devoid of bromine was identified as 16- oxo taraxeryl acetate 32. The third product was found to be 38. The mechanism for the formation 38 was proposed as in scheme-I.

SCHEME-I

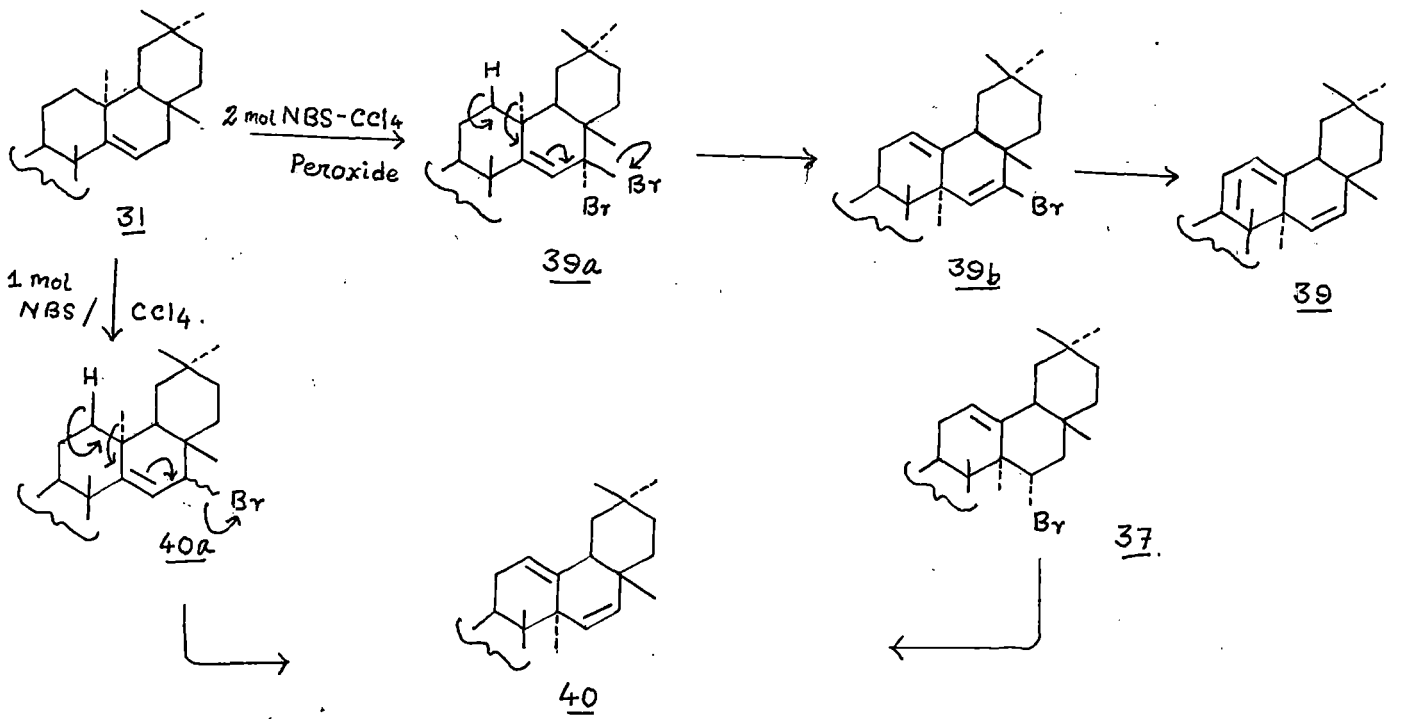


38 53

Khastgir et al[15] also studied the reaction of taraxeryl acetate 31 with 2-moles equivalent of NBS in CCl_4 using light for three hours and isolated a product, which was assigned the structure 39. When the same reaction was carried out with one mole equivalent of NBS, it afforded a halogen free product of structure 40, identical to that obtained by dehydrobromination of 37.

The mechanism for the formation of 40 and 39 was proposed in scheme -II.

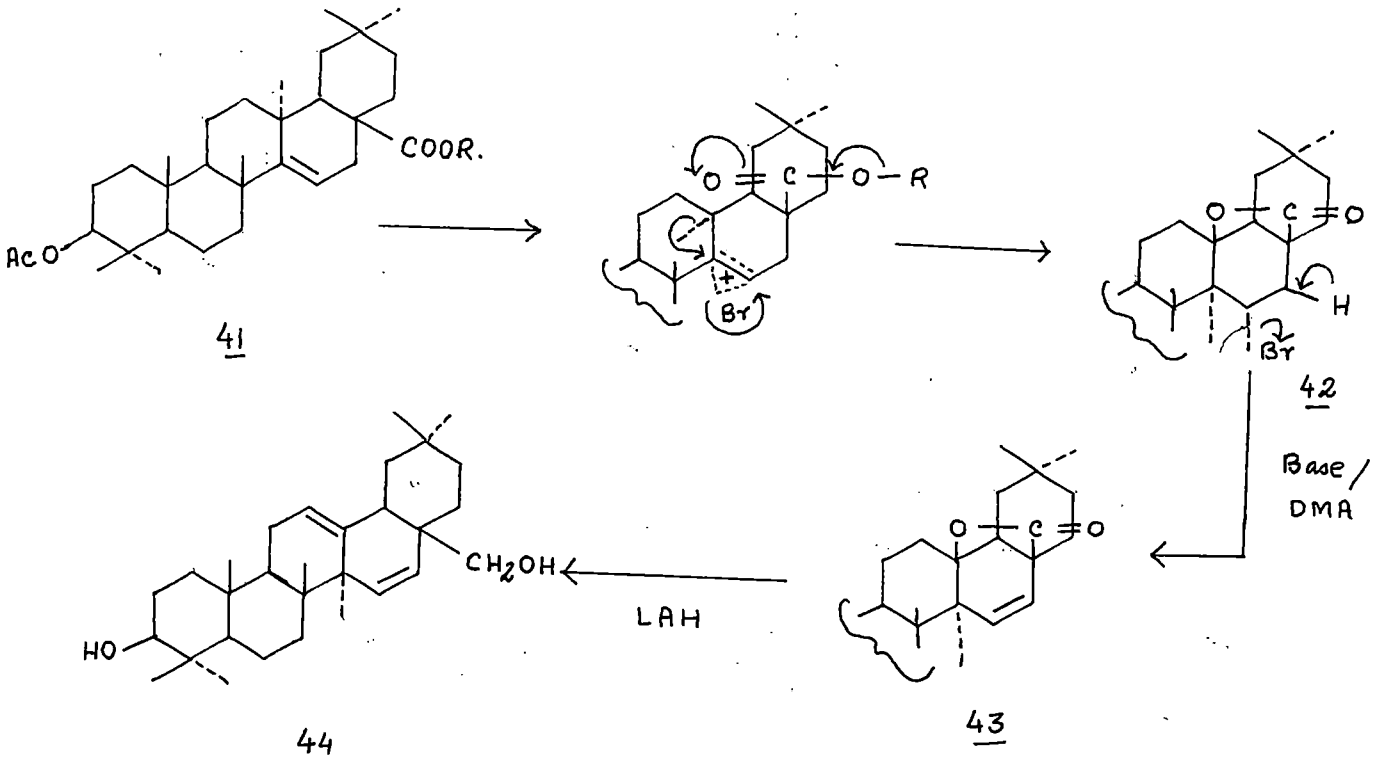
SCHEME-II



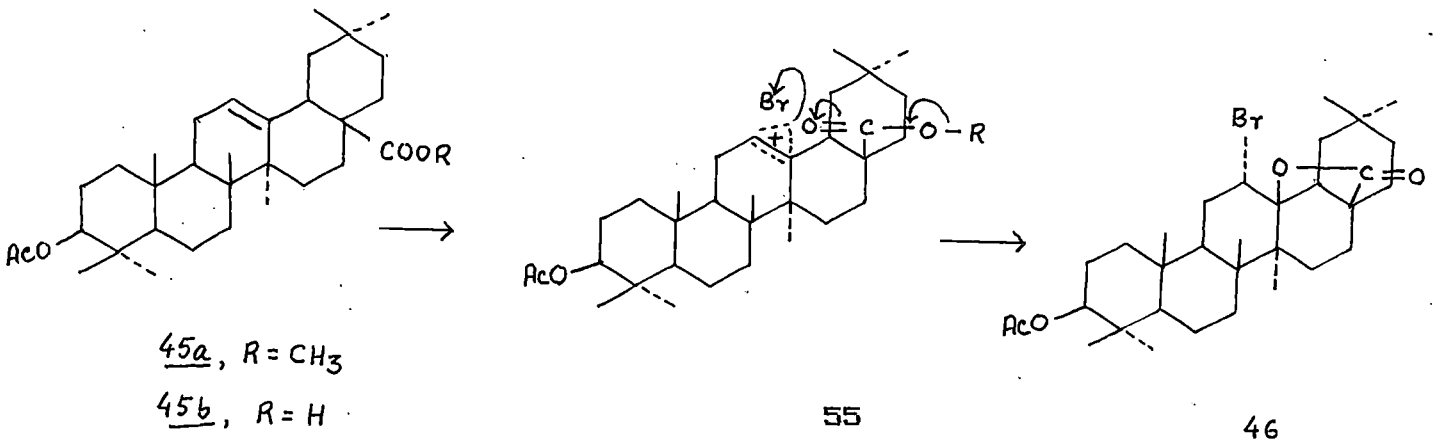
Pradhan et al[18] carried out the reaction of NBS on triterpenoid acids and esters. They studied the reactions of methyl acetyl aleuritolate 41 with NBS in DMSO in the dark for 12 hours and isolated a bromo-lactone 42. The structure of the bromo-lactone was confirmed from the fact that dehydrobromination with dimethyl aniline afforded 15,16-dehydrolactone 43 which on LAH reduction furnished aegiceradiol 44.

The mechanism of formation of **42** involved the attack of bromonium ion from NBS in DMSO at the double bond. Bromine being a bulky atom ultimately assumed the equitorial 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 **42**. The mechanism is shown in the following scheme-III

SCHEME-III



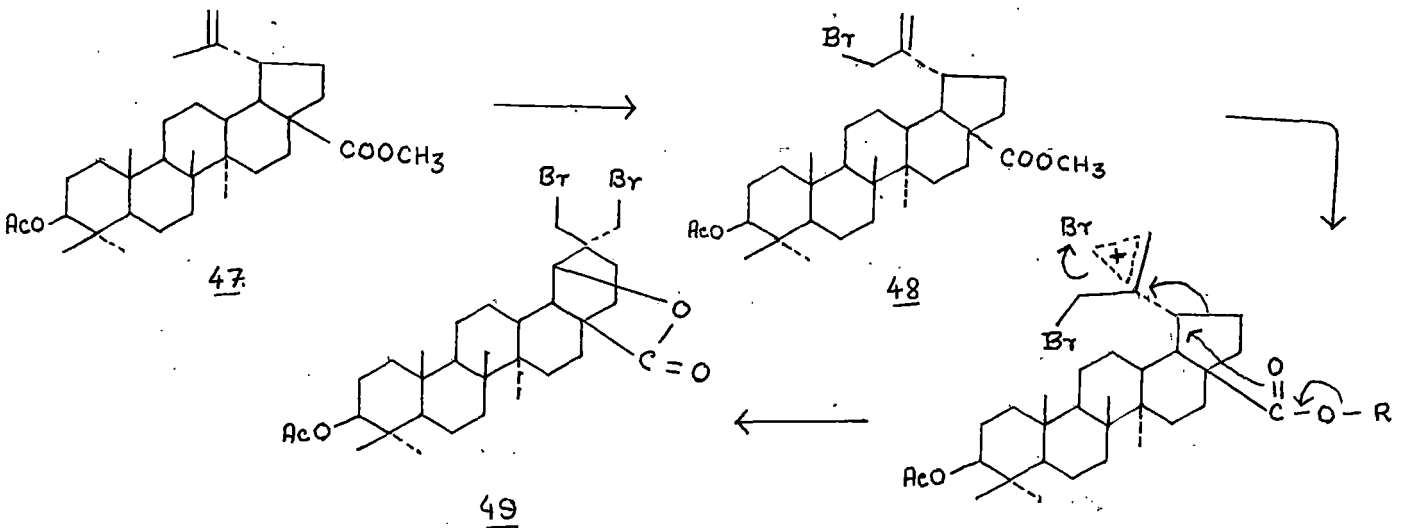
Methyl acetyl oleanolate **45a** and 3β-acetyl oleanolic acid **45b** under the same condition afforded the bromolactone **46** which was found to be identical with 12α-bromo oleanan-28 → 13-olide.[19]



Methyl 3β-acetyl betulinate **47** on similar reaction with NBS in DMSO afforded two different bromo compounds. The less polar one was identified as methyl 30-bromo-3β-acetyl betulinate **48**. The more polar fraction was dibromo-lactone **49**.

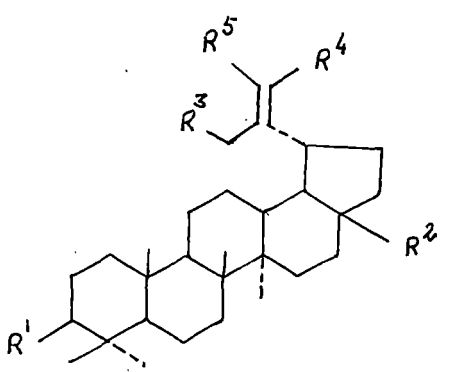
The proposed mechanism of formation of **48** and **49** is shown below in the scheme-IV.

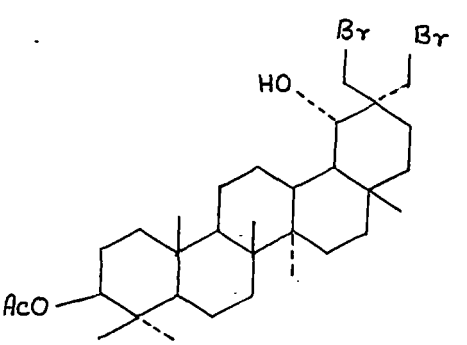
SCHEME-IV



47 48 49

Recently Pradhan et al[20] reported the action of NBS on lupenyl acetate **50** in DMSO and isolated four different compounds which were 30-bromo lupenyl acetate **50a**, 29(E-Z)-bromo lupenyl acetates **50c** & **50d** and 29,30-dibromo 18-iso-oleanan-19α-hydroxy 3β-yl acetate **51**.





51.

50, R^1 = OAc; R^2 = CH_3; R^3 = R^4 = R^5 = H
50a, R^1 = OAc; R^2 = CH_3; R^3 = Br; R^4 = R^5 = H
50c, R^1 = OAc; R^2 = CH_3; R^4 = Br; R^3 = R^5 = H
50d, R^1 = OAc; R^2 = CH_3; R^5 = Br; R^3 = R^4 = H

Compound **50a** and mixture of **50c** & **50d** with NBS in DMSO containing water afforded 30-oxo lupeol **50k** and 20(E-Z)-bromo lupeol **50l** & **50m** respectively.

$$\underline{50a} \;/\; (\underline{50c} \;\&\; \underline{50d}) \xrightarrow[\text{water}]{\text{NBS-DMSO}} \underline{50k} + \underline{50l} + \underline{50m}$$

50k, $R^1 = OH$; $R^2 = CH_3$; $R^3 = O$; $R^4 = R^5 = H$
50l, $R^1 = OH$; $R^2 = CH_3$; $R^5 = Br$; $R^3 = R^4 = H$
50m, $R^1 = OH$; $R^2 = CH_3$; $R^4 = Br$; $R^3 = R^5 = H$

Compound **50a** on alumina afforded 30-hydroxy lupenyl acetate **50h** and 30-hydroxy lupeol **50i**

50h, $R^1 = OAc$; $R^2 = CH_3$; $R^3 = OH$; $R^4 = R^5 = H$
50i, $R^1 = R^3 = OH$; $R^2 = CH_3$; $R^4 = R^5 = H$

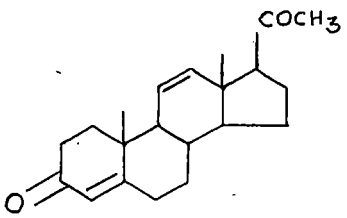
(A detailed report of this investigation has been published in Indian Journal of Chemistry, 1991, pages 32-37, a reprint of which is enclosed in appendix-1.)

ALLYLIC HYDROXYLATION BY N-BROMOSUCCINIMIDE

The NBS may be used for the introduction of allylic hydroxyl group. The method is indirect and usually involves allylic bromination and conversion of the resulting bromide into alcohol via the formation of formate or acetate. Thus 3-p menthene 5-yl bromide was prepared from 3-p methene using NBS in $CHCl_3$ and 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 3-p menthene 5-ol[21].

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[22]. An example of hydroxylation of steroids is illustrated by the transformation of 11-dihydro progesterone 52 to give $\Delta^{4-9(11)}$ pregenadien 12α-ol 3,20 dione[23] 53.



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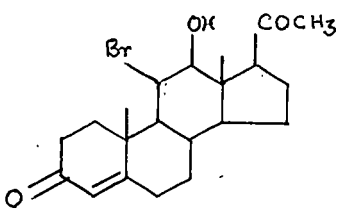

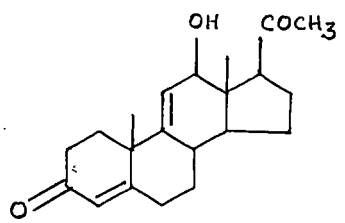

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Recently Marks et al[24] reported the conversion of aldehydes directly into acid bromides and amides by action of NBS in presence of catalytic amount of AIBN as radical initiator.