PART - I

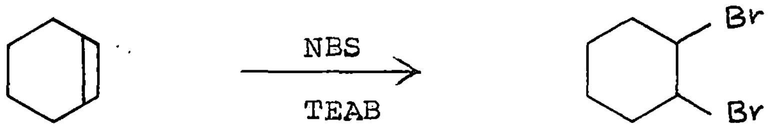
ACTION OF N-BROMOSUCCINIMIDE ON TRITERPENOIDS AND STEROIDS

CHAPTER - I

A SHORT REVIEW OF THE ACTION OF N-BROMOSUCCINIMIDE ON TRITERPENOIDS AND STEROIDS.

A well known reagent N-bromosuccinimide (NBS) has been magnificently used for allylic bromination since 1919 when Wohl[1] and then Zeigler[2] carried out the application of the reagent on allylic bromination. The reagent also reacts with olefins to add bromine at the double bond or acts as a source of hypohalous acid in the aqueous solution.

Braude et al (1952) showed that the addition reaction is catalysed by tetra alkyl ammonium salt. Thus cyclohexene in presence of tetra ethyl ammonium bromide reacts with NBS to give 1,2-dibromocyclohexane.

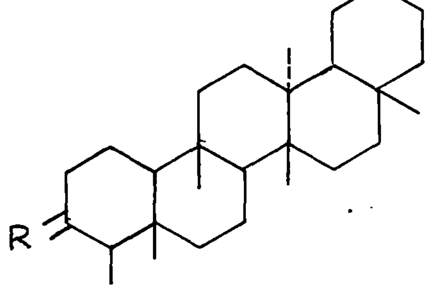


The reagent NBS is also used for the oxidation of allylic methylene to carbonyl function[1-3].

The triterpenoids and their derivatives undergo a number of rearrangement reactions with NBS and having been interested the author has also carried out some reactions of NBS on triterpenoids and in this connection it is essential to represent a short review on the basis of previous work of this type of rearrangement reactions.

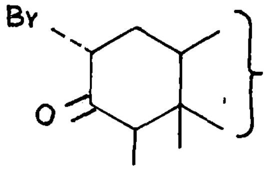
Action of NBS on friedelin and its derivatives.

Corey and Ursprung[3] have reported that friedelin 1 on direct bromination gave 2α-bromofriedelin 2 while bromination of appropriate enol benzoate gave the isomeric 4α-bromofriedelin 3. They also prepared a dibromofriedelin by the action of HBr in $CHCl_3$ which were assigned as 2α, 4α-dibromofriedelin 4 from the UV spectra. Djerassi et al[4] reported 2α, 4β-dibromofriedelin 5 by bromination of 2α-bromofriedelin 2 in acetic acid. Stevenson et al[5,6a,6b] reported that friedelan 6 when oxidised with it afforded friedel 18-ene 7.

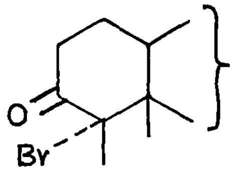


1, R = O

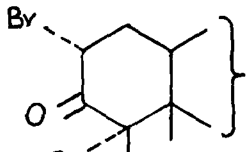
6, R = H_2



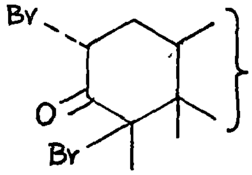
2



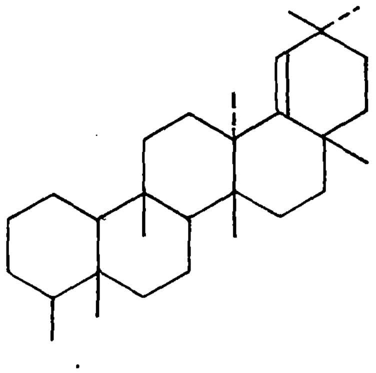
3



4

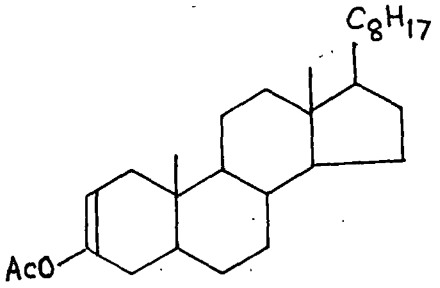


5

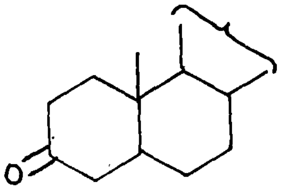


7

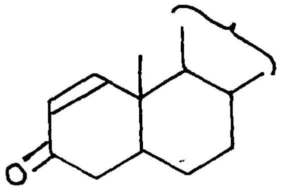
Rubin et al[7] provided an example of allylic bromination with subsequent spontaneous dehydrobromination by reaction of NBS on $\Delta^{2(3)}$-acetoxy-cholestene 8. This enol acetate of cholestanone 9 (ring A/B trans) reacted with NBS in CCl_4 to produce a mixture of Δ^{I} and Δ^{4}-cholesten-3-one (10 and 11) and 2-bromo-cholestan-3-one 12, the amount was enhanced with reaction time at the expense of 10



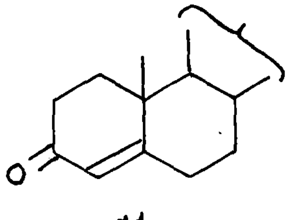
8



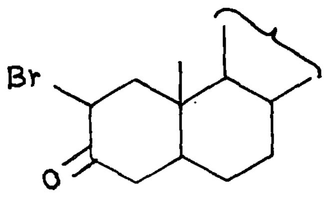
9



10

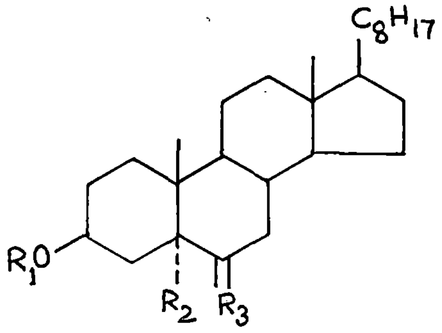


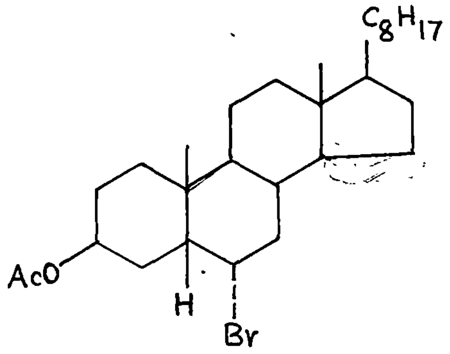
11



12

Pradhan et al[8] carried out 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 cholestan-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 spectral studies of (IR, ^{1}H NMR, Mass and ^{13}C NMR). They reported compound 15 for the first time.





15

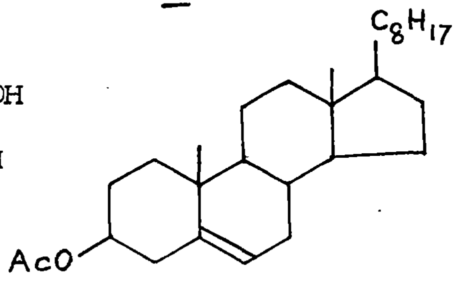
14, R_1 = Ac, R_2 = Br and R_3 = 0

16, R_1 = Ac, R_2 = OH and R_3 = 0

17, R_1 = Ac, R_2 = OH and $R_3 = {<}^{OH}_{H}$

18, R_1 = H, R_2 = OH and R_3 = 0

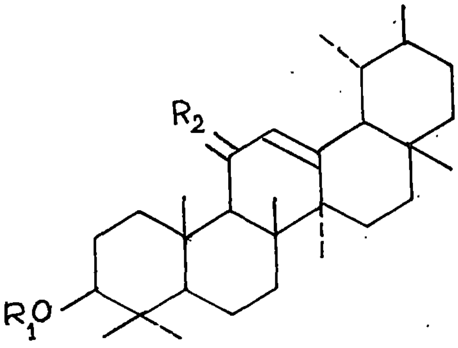
19, R_1 = H, R_2 = OH and $R_3 = {<}^{OH}_{H}$



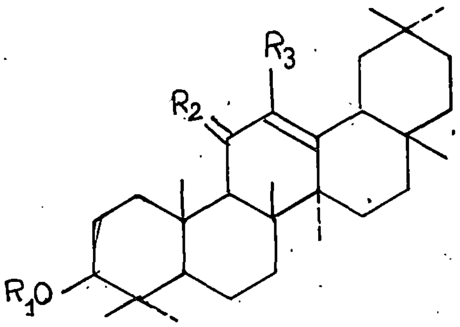
13

OXIDATION OF ALLYLIC METHYLENE TO CARBONYL GROUP:

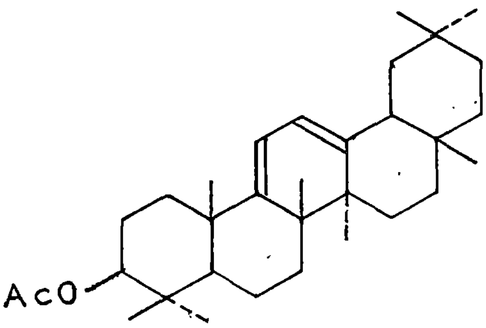
Corsano et al[9] reported the direct oxidation of allylic methylene to carbonyl group by NBS in aqueous dioxane solution. Thus 3β-acetoxy-urs-12-en-11-one 21 was obtained in about 80% yield from α-amyrin acetate 20.



20, R_1 = Ac; R_2 = H_2
21, R_1 = Ac; R_2 = 0



22, R_1 = Ac; R_2 = H_2; R_3 = H
23, R_1 = Ac; R_2 = 0; R_3 = H
24, R_1 = Ac; R_2 = $\overset{H}{\diagup}\cdots$OH; R_3 = H
25, R_1 = Ac; R_2 = $\overset{H}{\diagup}\cdots$OMe; R_3 = H
26, R_1 = Ac; R_2 = $\overset{H}{\diagup}\cdots$OAc; R_3 = H
27, R_1 = Ac; R_2 = $\overset{H}{\diagup}\cdots$OH; R_3 = Br



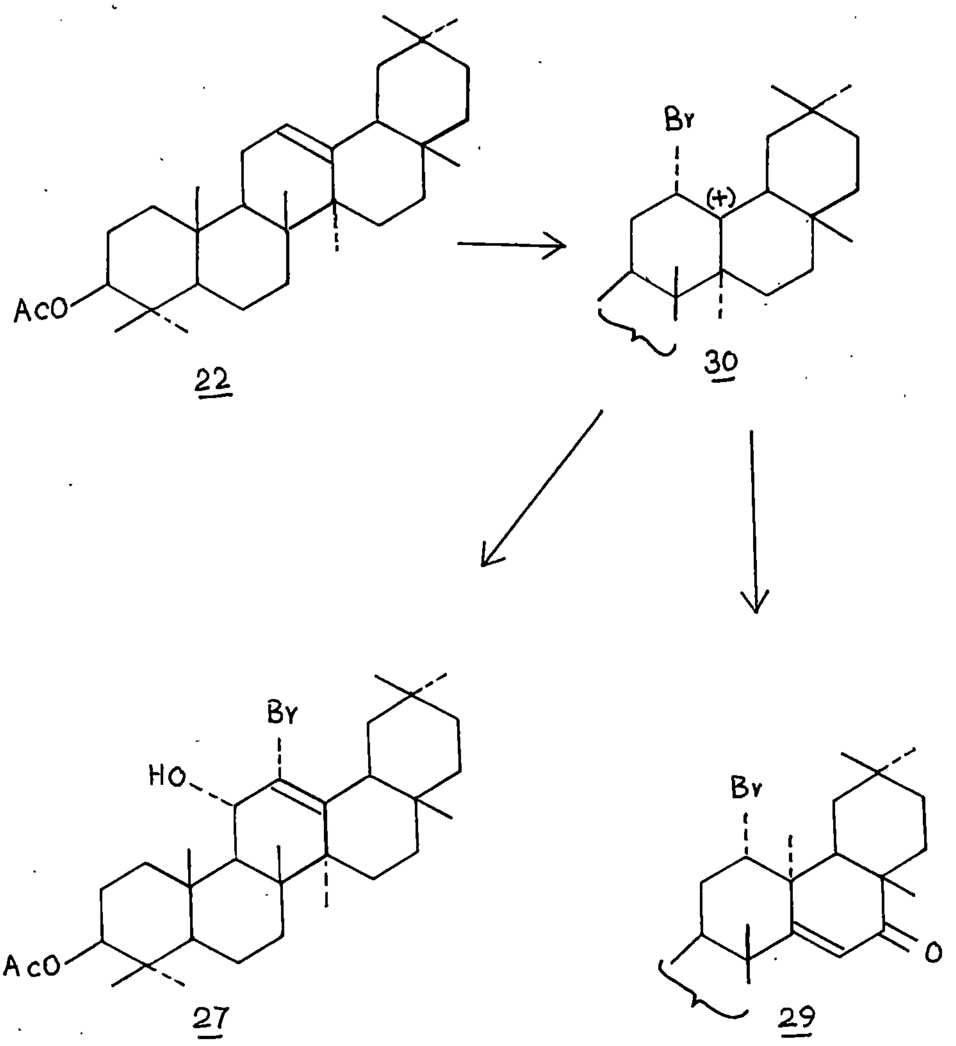
28

Finucane et al[10-11] discovered a new method for direct oxidation of allylic methylene to carbonyl functions by the action of NBS and simultaneous irradiation with visible light. They claimed that a high yield of α,β -unsaturated ketone was formed when trisubstituted olefins containing an allylic methylene group were treated with NBS in aqueous dioxane followed by irradiation with visible light.

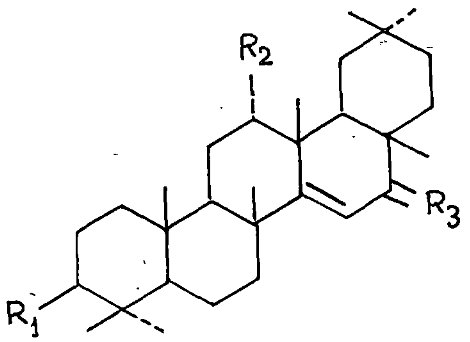
Finucane et al[10-11] treated β -amyrin acetate <u>22</u> with NBS in aqueous dioxane in a typical ambient light experiment as described by Corsano et al[9]. They isolated compounds 3β-acetoxy-olean-12-en-11-one <u>23</u>, bromo compound <u>27</u> and 3β-acetoxy-olean-12-ene-11α-ol <u>24</u>. Oxidation of compound <u>24</u> with chromium trioxide in acetone afforded <u>23</u>.

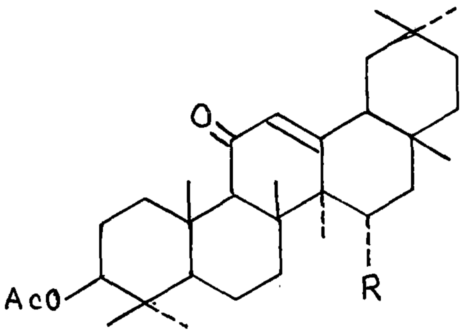
In another experiment, the products were isolated by column chromatography over alumina and thereby obtained β-amyrin acetate <u>22</u>, 3β-acetoxy-olean-12-ene-11-one <u>23</u>, a bromo compound <u>29</u> and a mixture of polar compounds. The polar fraction on elution with methanol was acetylated and on rechromatography gave 11α-methoxy-olean-12-ene-3β-yl acetate <u>25</u> together with small amount of compound <u>24</u> and olean-9(11), 12-diene-3β-yl acetate <u>28</u> and traces of 3β, 11α-diacetate <u>26</u>. The fraction 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-en-11-ol <u>27</u> and the minor fraction was identified as 12α-bromo-16-one <u>29</u>.

The formation of <u>27</u> and <u>29</u> suggested that the initial α-face attack on β-amyrin acetate <u>22</u> at C-12, would lead to a carbonium ion <u>30</u>. Elimination of a proton from C-12 followed by allylic hydroxylation would then lead the compound <u>27</u>. Alternately, migration of 14α-methyl group to C-13 and elimination of a proton from C-15, would give the compound <u>29</u> after subsequent allylic oxidation.



Thomson et al[11] carried out the oxidation of taraxeryl acetate 31 by the same manner as reported by Corsano et al[9] and got two major products whose structures were assigned as 16-oxo-taraxeryl acetate 32 and 16β-hydroxy taraxeryl acetate 33. On treatment of 33 with chromic acid in acetone gave the unsaturated ketone 32. The workers also performed the reaction on 31 by the method followed for β -amyrin acetate which resulted in the formation of 12α-bromo-taraxer-14-en-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 assigned as 11-keto-15-bromo β -amyrin acetate which in turn yielded a compound 36 which was free from halogen on treatment with Zn-dust in AcOH. Its structure was established as β -amyrenonyl acetate.

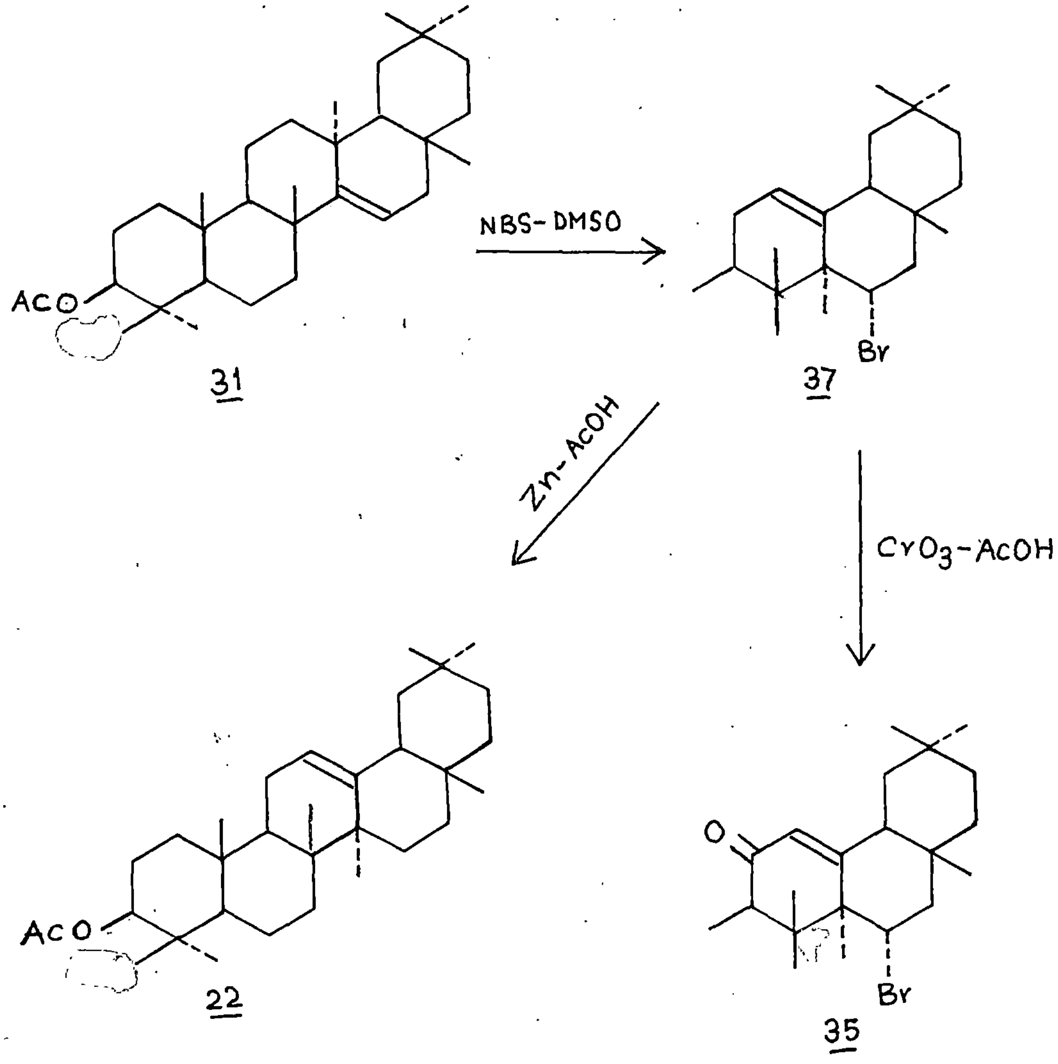




31, R_1 = OAc, R_2=H, R_3 = H_2
32, R_1 = OAc, R_2 = H, R_3 = 0
33, R_1 = OAc, R_2 = H, R_3 = $\overset{H}{\cdots}$OH
34, R_1 = OAc, R_2 = Br, R_3 = 0

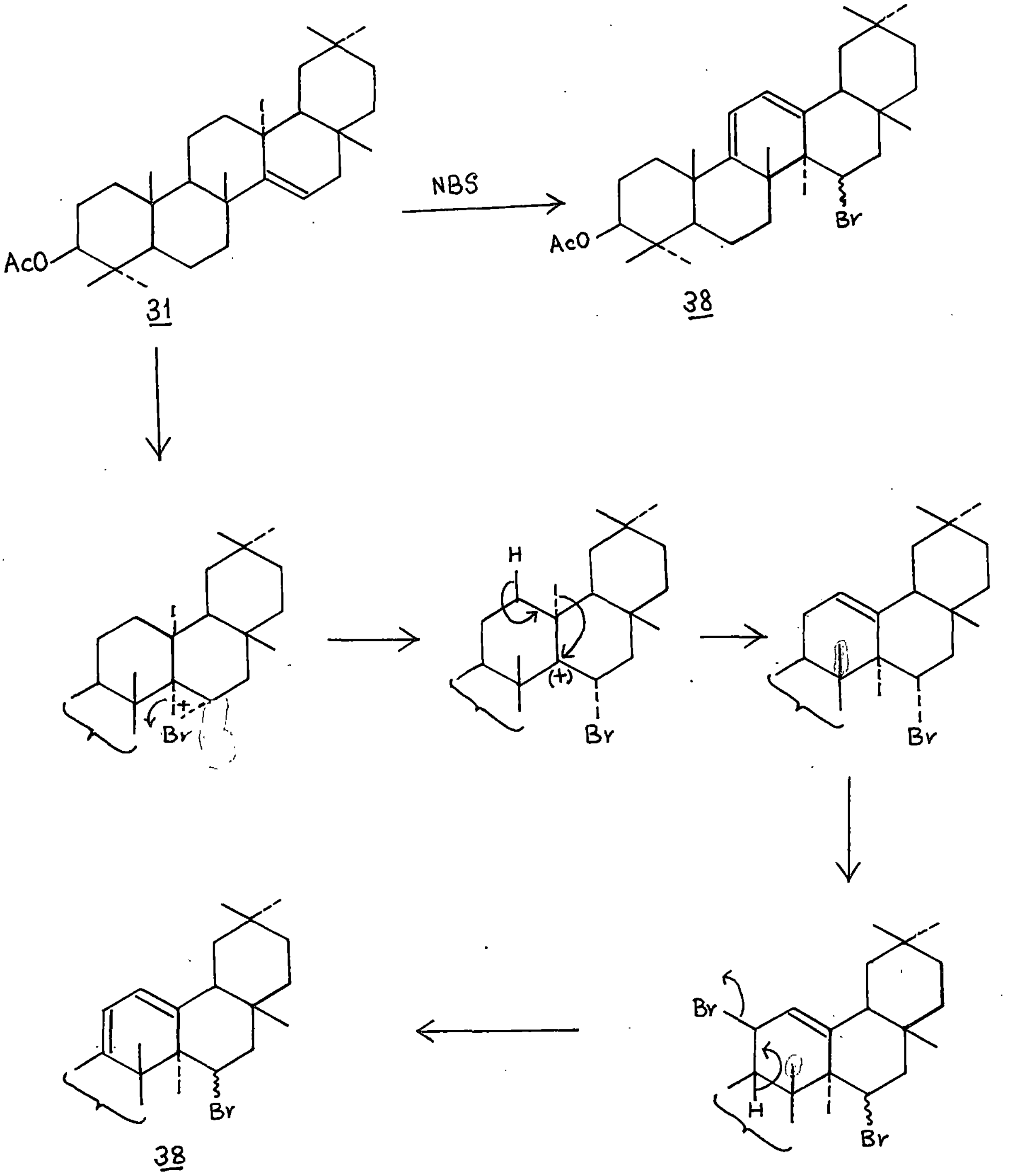
35, R = Br
36, R = H

Khastgir et al[12] carried out the oxidation of taraxeryl acetate 31 by adopting the same method due to Dalton[13] using NBS in DMSO solvent. Treatment of taraxeryl acetate 31 with aqueous DMSO in $CHCl_3$ followed by NBS while keeping in dark for several days 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 the compound 37 would be expected to have the same stereochemistry as in the case of product obtained from NBS in aqueous dioxane. The compound 37 on oxidation with CrO_3-AcOH[17] gave the compound 35 which was identical with the product obtained from the oxidation of NBS in aqueous dioxane.



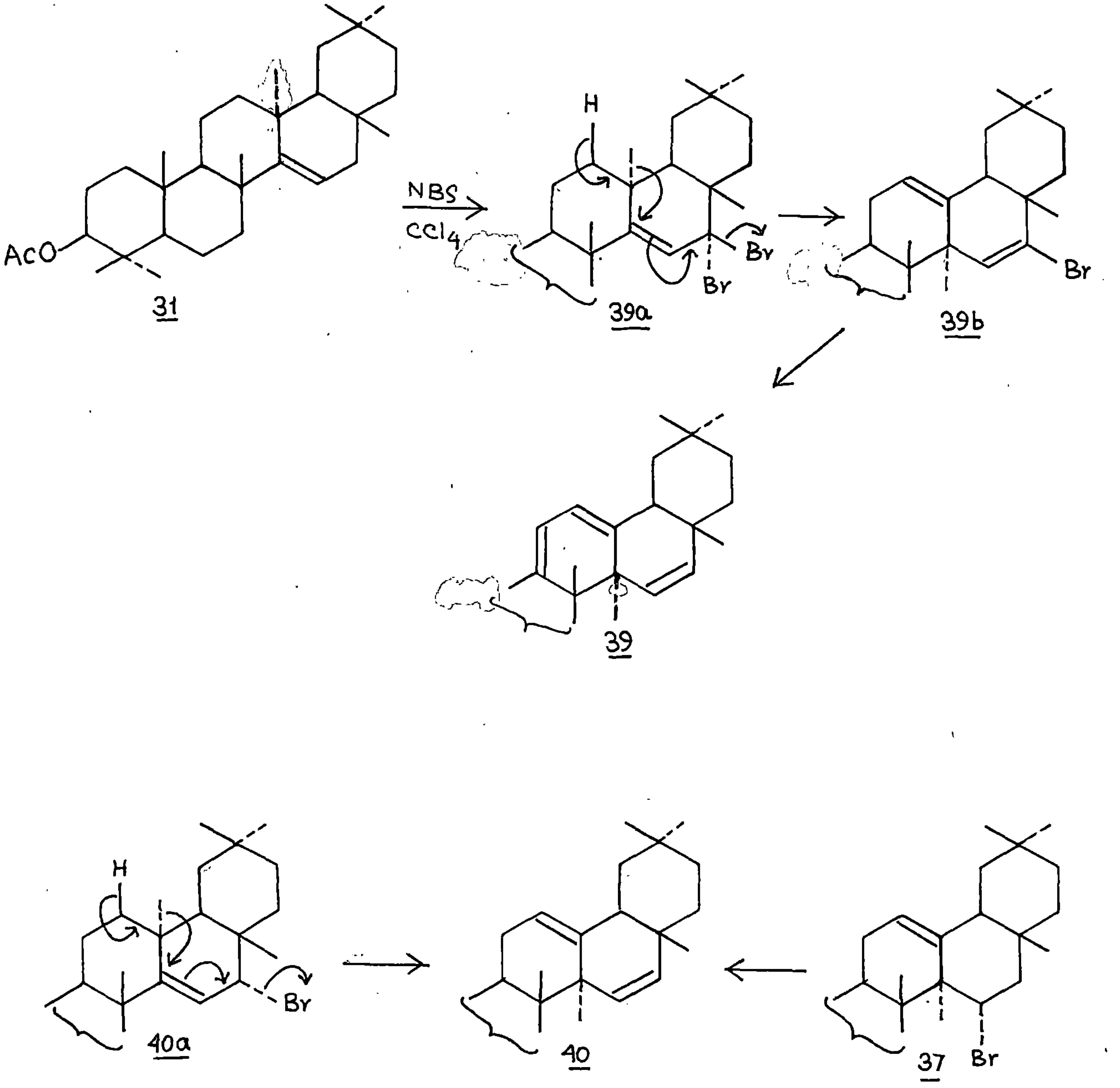
The second compound devoid of bromine was identified as 16-oxotaraxeryl acetate 32. The third product was found to be 38. The proposed mechanism for the formation of 38 has been shown as under Scheme -1:

SCHEME - 1



Khastgir et al[12] also studies the reaction of taraxeryl acetate 31 with 2-mole equivalent of NBS in CCl_4 using light for three hours and isolated a compound which was assigned by the structure 39. When the same reaction was carried out with one mole equivalent of NBS then a halogen free product was afforded of structure 40 identical to that of dehydrobromination of 37. The mechanism proposed for the formation of 39 and 40 is as shown in Scheme - II.

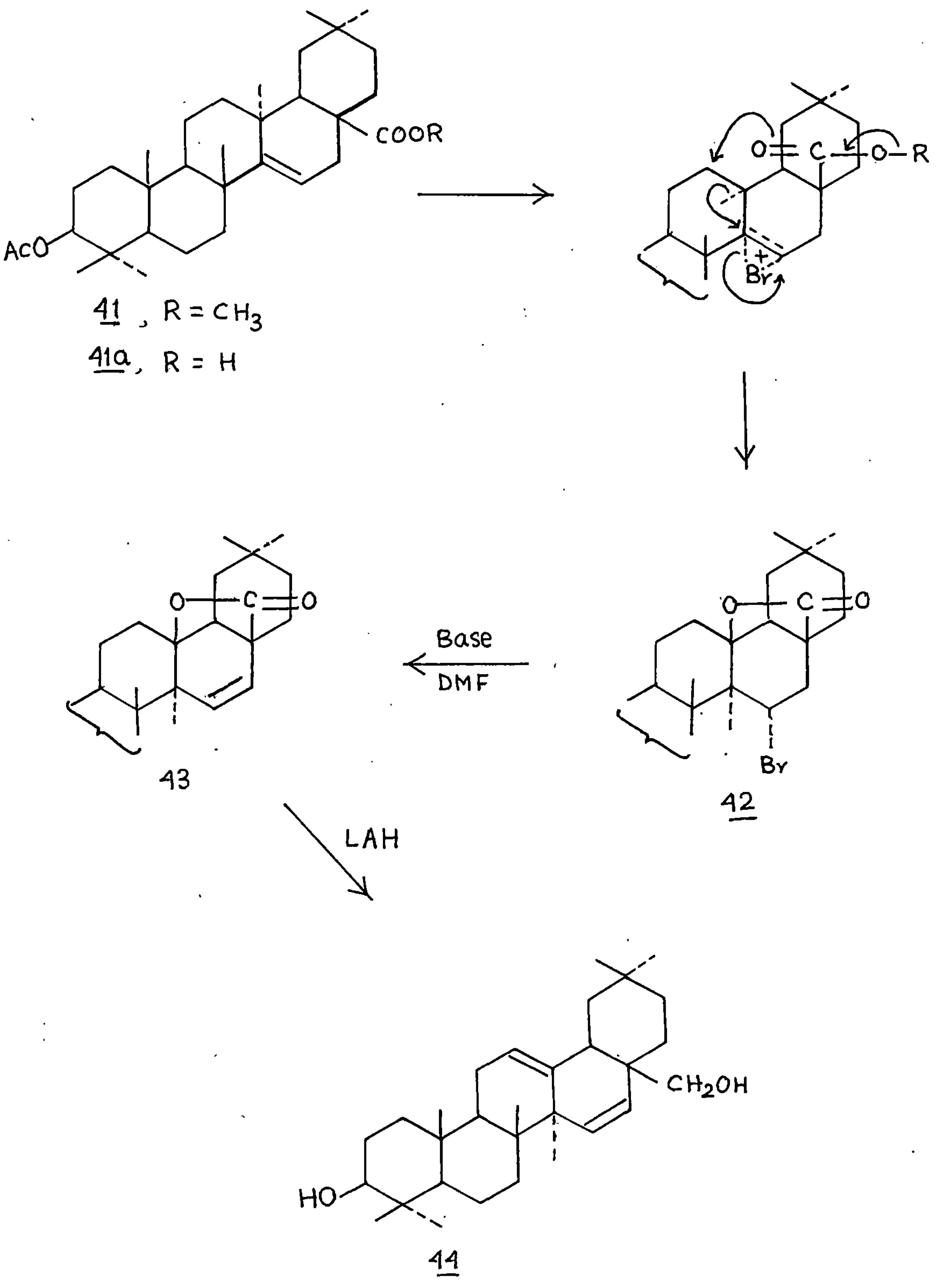
SCHEME - II



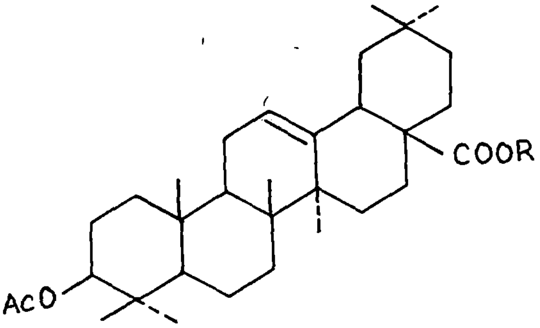
Pradhan et al[14] carried out the reaction of NBS on triterpenoid acids and esters. They studied the reaction on methyl acetyl aleuritolate 41 or its acid 41a with NBS in DMSO keeping the reaction mixture in dark for 12 hours and then isolated a bromo-lactone 42. The structure of bromo-lactone was confirmed from the fact that dehydrobromination with N,N-dimethyl aniline afforded 15(16)-dehydrolactone 43 which on reduction with lithium aluminium hydride (LAH) 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 equatorial position so as to have the minimum strain and steric interaction. The next step involved concerted migration of the C-13 methyl to C-14 position and simultaneous elimination of the methoxyl methyl or proton to form 28 $\rightarrow$ 13-olide 42. The mechanism has been shown in the following Scheme - III.

SCHEME - III

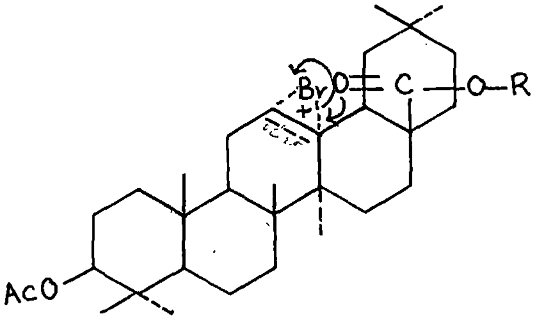

COOR
AcO
41, R = CH3
41a, R = H
O=C–O–R
Br
Base
DMF
O–C=O
Br
42
43
LAH
CH2OH
HO
44

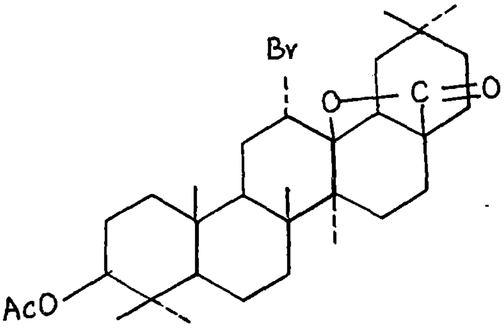
Methyl acetyl oleanolate 45a and 3β-acetyl oleanolic acid 45b under the same conditions afforded a bromolactone which was identical as 3β-acetyl-12α-bromo oleanan-28 → 13-olide[19] 46.



45a, R = CH_3

45b, R = H

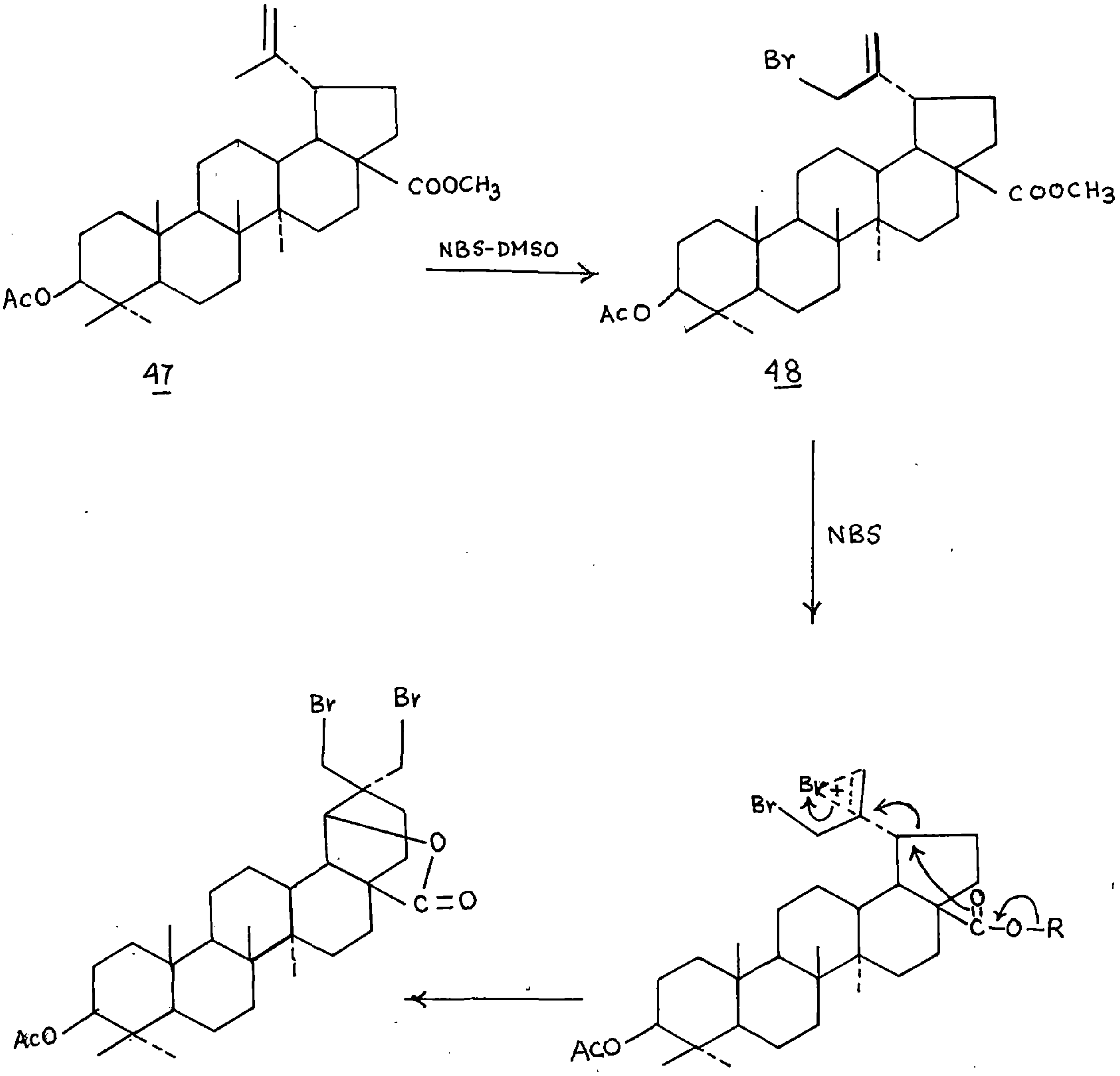




46

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 and the more polar fraction was dibromo lactone 49. The proposed mechanism of the formation of <u>48</u> and <u>49</u> has been shown in the scheme - IV.

SCHEME - IV

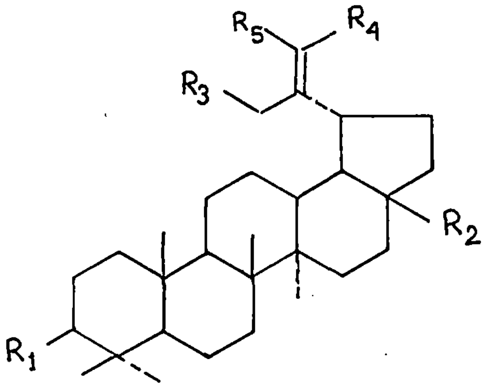


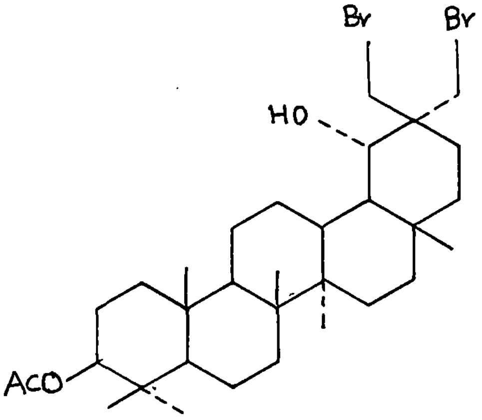
47

48

49

Recently Pradhan et al[15] reported the action of NBS on lupenyl acetate 50 in DMSO and thereby isolated four different compounds which were identified as 30-bromo lupenyl acetate 50a, 29(E-Z)-bromolupenyl acetate 50c and 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_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

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

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

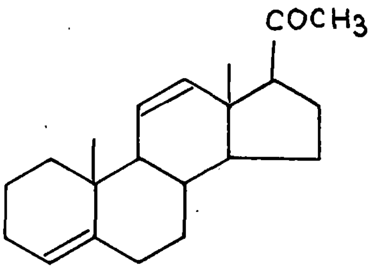
$$\text{50a} \;/(\text{50c} \;\&\; \text{50d}) \xrightarrow[\text{Water}]{\text{NBS-DMSO}} \text{50k} + \text{50l} + \text{50m}$$

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

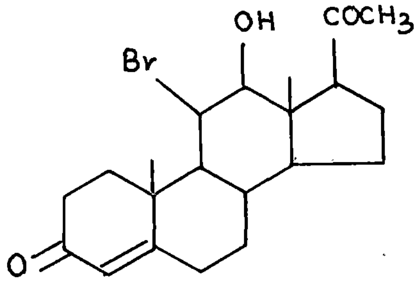
ALLYLIC HYDROXYLATION BY N-BROMOSUCCINIMIDE

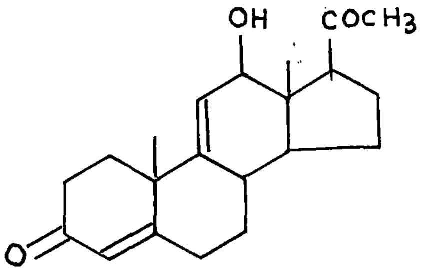
NBS may also be used for introduction of allylic hydroxyl group. The method is indirect and usually involves allylic bromination and then conversion of the resulting bromide into alcohol via the formation of formate or acetate. Thus 3-p-menthene-5-yl bromide was prepared from 3-p-menthene using NBS in $CHCl_3$ 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 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-12 α-ol-3, 20-dione[23] 53.



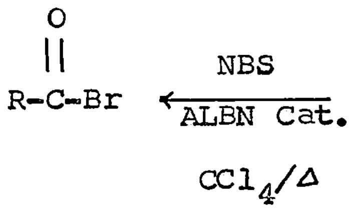
52



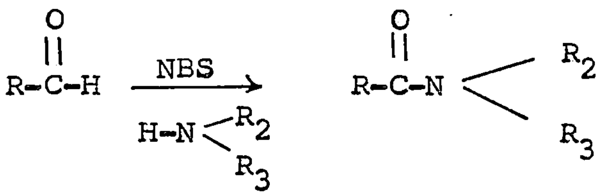


53

Most recently Marks et al[16] reported the conversion of aldehydes directly with acid bromides and amides by the action of NBS in presence of catalytic amount of ALBN as radical initiator.

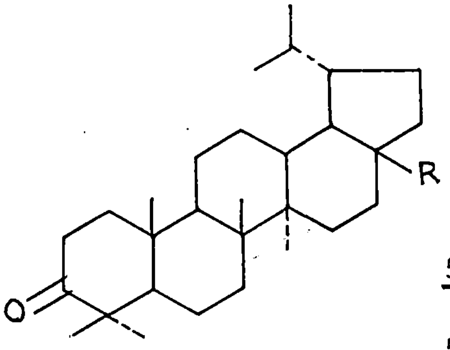


$$R{-}\overset{\overset{O}{\|}}{C}{-}Br \xleftarrow[\text{ALBN Cat.}]{\text{NBS}} \quad CCl_4/\Delta$$



$$R{-}\overset{\overset{O}{\|}}{C}{-}H \xrightarrow[\text{H-N}<^{R_2}_{R_3}]{\text{NBS}} R{-}\overset{\overset{O}{\|}}{C}{-}N<^{R_2}_{R_3}$$

Pradhan et al[17,18] have carried out extensive investigation on the reaction of NBS on 3-ketotriterpenoids mainly lupanone 54 and dihydromethyl betulinate 55 in DMSO solvent.

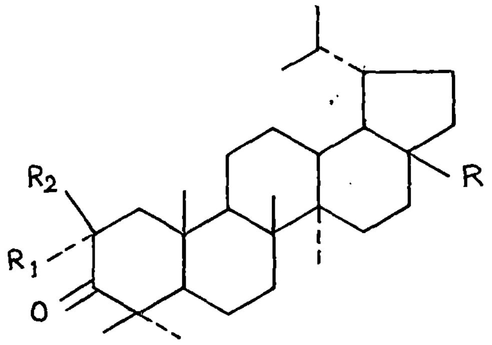


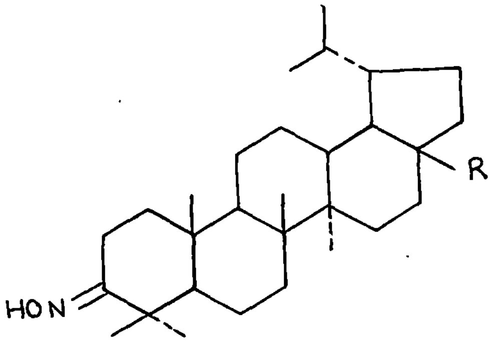
54, R = CH_3

55, R = $COOCH_3$

From lupanone 54, two bromo compounds were isolated which were identified as 2α-bromolupanone 56 and 2,2-dibromo lupanone 57 the structures of which were confirmed by spectral analysis. Similarly, compound 55 afforded 2α-bromo and 2,2-dibromo-dihydro methyl betulinate 58 and 59 respectively.

Further they have also performed the same reaction on oxime derivatives 60/61 of compounds 55/56 and reported[18] the formation of 2,2-dibromo derivatives 57/59 and 3-oximino-1(2)-ene derivatives 62/63





56, $R_1 = Br; R_2 = H; R = CH_3$

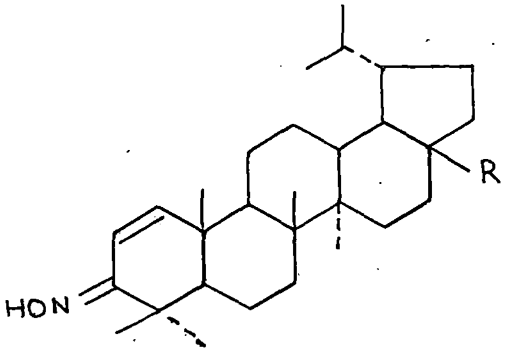
57, $R_1 = R_2 = Br; R = CH_3$

58, $R_1 = Br; R_2 = H; R = COOCH_3$

59, $R_1 = R_2 = Br; R = COOCH_3$

60, $R = CH_3$

61, $R = COOCH_3$



62, $R = CH_3$

63, $R = COOCH_3$