Part III

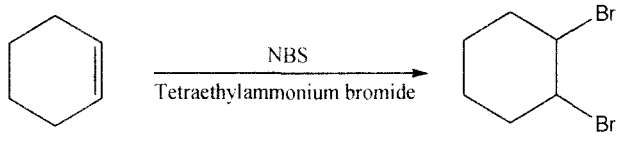
STUDIES ON THE ACTION OF *N*-BROMOSUCCINIMIDE IN DIMETHYL SULPHOXIDE ON MONOTERPENOIDS

CHAPTER I

A SHORT REVIEW ON THE ACTION OF *N*-BROMOSUCCINIMIDE ON TERPENOIDS

It has been found that triterpenoids undergo a 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 (NBS). As we have carried out some reactions of NBS it is felt necessary to give a brief account of the previous works on the oxidative transformation with the help of this reagent.

NBS has been in use for allylic bromination since 1919, when Wohl and then Zeigler made detailed studies on application of the reagent for allylic bromination. The reagent also reacts with olefins to add bromine to the double bond or acts as a source of hypohalous acid in aqueous solution. Braude et al. (1952) have shown that the addition reaction is catalysed by tetraalkylammonium salts e.g. cyclohexene in the presence of tetraethylammonium bromide forms mainly 1,2-dibromocyclohexane.

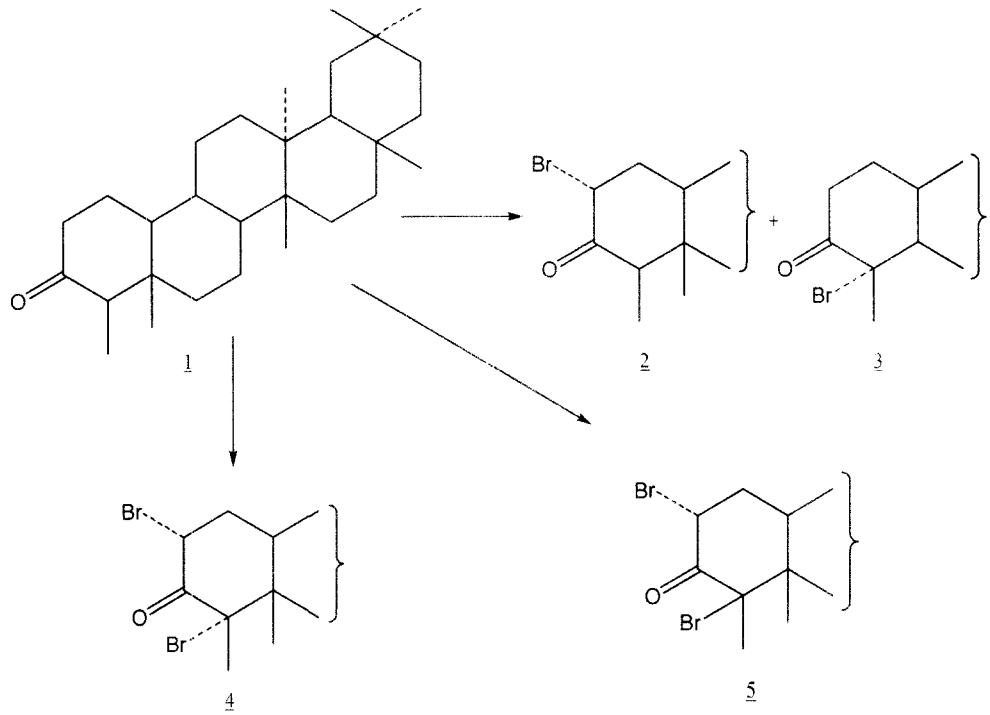


The reagent is also in extensive use since 1969 as an effective reagent for the oxidation of allylic methylene to carbonyl functionality [1-3]. Many reviews have appeared on the action of NBS; of them (a) Djerassi [4] and (b) Homer and Wenkelman [5] for allylic bromination and (c) Filler [6] on bromination and oxidation reactions are worth mentioning.

Action of NBS on friedelin and its derivatives:

Corey and Ursprung [7] 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-dibromofriedelin from the UV absorption at 332 nm. Djerassi et al. [8] 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.



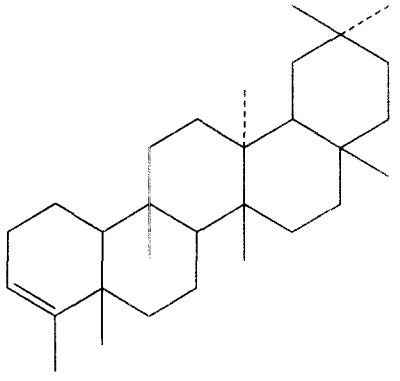
1 2 3 4 5

Takahashi and Ourrison [9] 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 [10-11] 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, $[\alpha]_D$ $+92^0$ was unstable

in chloroform/hydrobromic acid, the presumed equilibrium mixture $[\alpha]_D$ -75^0, being formed after 24 hours. 2α-bromofriedelin 2 also gave the same result on similar equilibration.

For obtaining dibromofriedelin, since this route was unsuccessful, 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 TNM 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 8 [12-13], it was assumed that 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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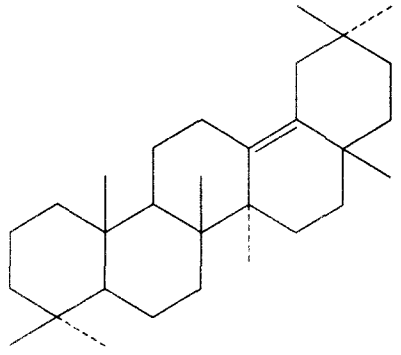

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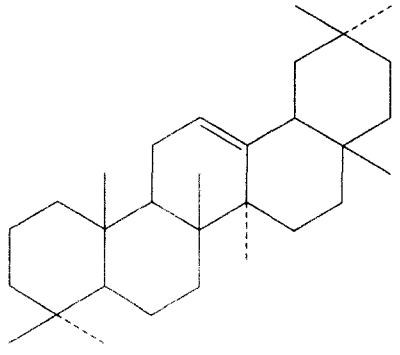

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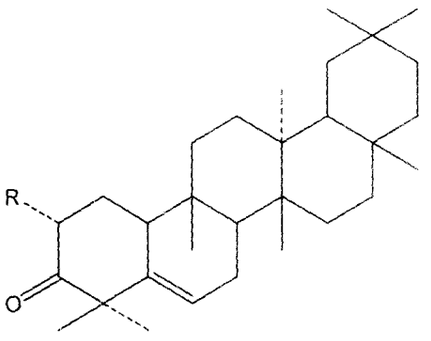
A precedent for such a rearrangement was provided by the action of silver acetate on 4α-bromofriedelin 3 to yield a product 7 which was shown to be a mixture [14] of alnus-5-enone 9 (R = H) and alnus-5(10)-enone 10 (R = H). The probability that the unsaturated bromoketone derived from 2 could be represented as 2-bromo-alnus-enone 9 (R = Br) 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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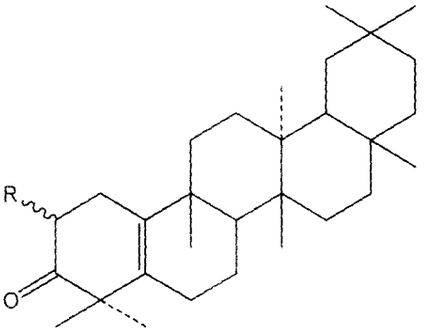

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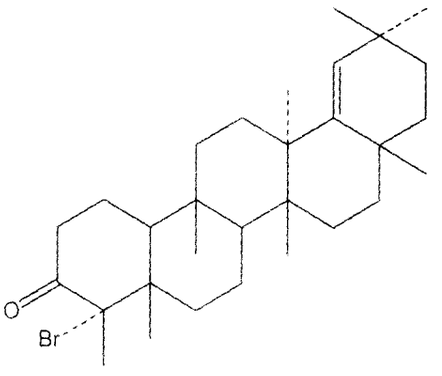
Treatment of 4α-bromofriedelin 3 with NBS gave an isomeric nonconjugated axial bromo substituted ketone 11 $C_{30}H_{47}OBr$ which on dehydrobromination gave the identical ketone $C_{30}H_{48}O$, 12. Lithium aluminium hydride reduction of 12a gave an alcohol 12c and on Huang-Minlon reduction gave the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



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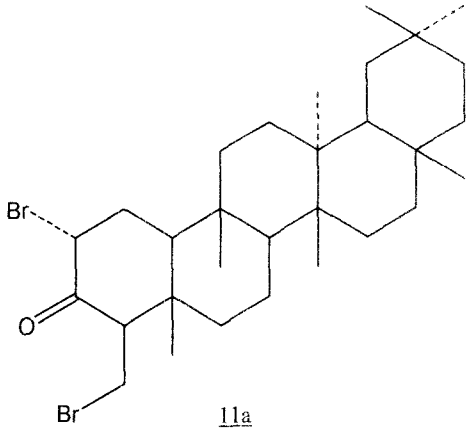
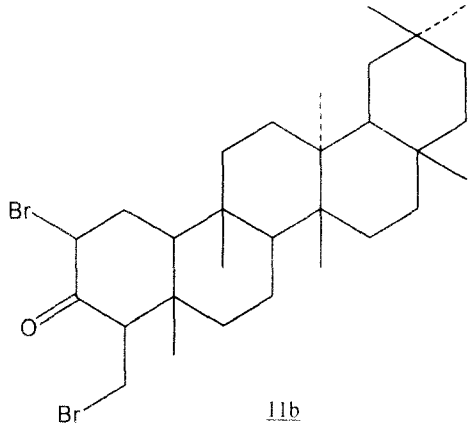
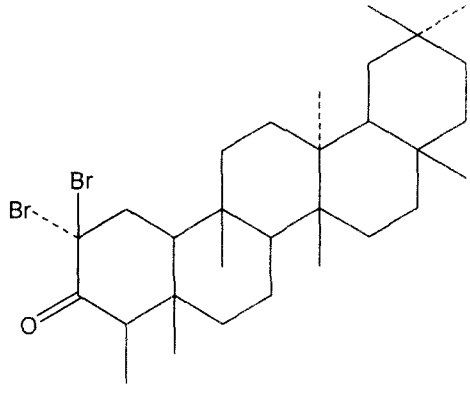
Pradhan et al. [15] studied the reaction of NBS in DMSO on friedelin 1 and observed that it gave a mixture of five products. They designated the compounds as 2α, 23-dibromofriedelin 11a, 2β,23-dibromofriedelin 11b, 2α-bromofriedelin 2, 2,2-dibromofriedelin 11c and 2,3-diketo friedelin 11d.



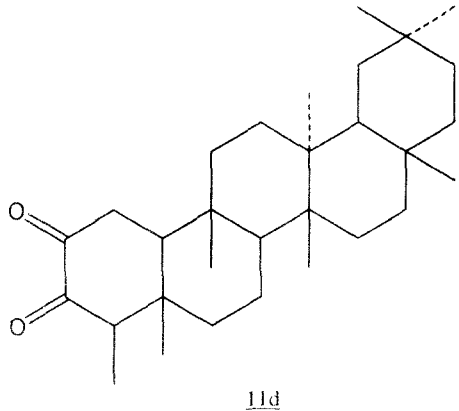
11a



11b



11c



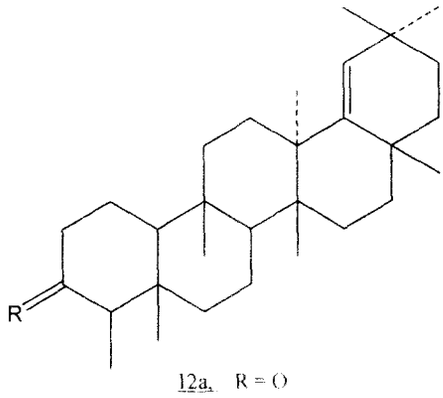
11d

Action of NBS on saturated hydrocarbon friedelane [9,15] 14 was also examined and they isolated an unsaturated hydrocarbon 12b identical in all respect with that obtained from Huang-Minlon reduction of 12a. This fact suggested that the products obtained by the action of NBS on ketones 2 and 3 were ethylenic nonconjugated 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 12b, 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 [16-17] comparable to the Δ^{12}-trisubstituted ethylenic linkage in β-amyrin series. The terminal UV absorption of 12a, 12b and 12c indicated that the double bond was trisubstituted. The resistance of hydrogenation of 12b further suggested that the ethylenic system was not disubstituted and the friedelin skeleton does not permit the existence of a tetrasubstituted double bond. ^{1}H NMR spectrum of the ketone 12a showed a singlet which was attributed to an olefinic proton not conjugated with carbonyl group. The location of double bond on bromoketones 2, 3 and hydrocarbon 12b 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 was not located in ring A and B, though there had been much work on the synthetic application of allylic compounds [18].

Comparatively little was known about the action of NBS on saturated systems. It has been proved that cyclohexane [19-20] and cycloheptane [20] yield cycloalkyl bromide with NBS under certain condition and decalin gave a tetrabromooctahydronaphthalene [21] which can also be obtained from probable intermediate 9,10- octalin.

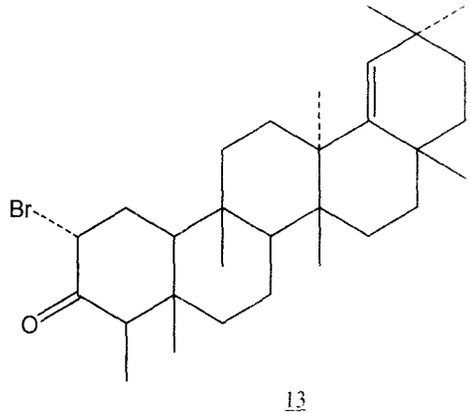
Cason et al. [22] have also drawn attention to the fact that NBS is not a reagent of general applicability for the α-bromination of saturated ester due to the selective attack on hydrogen at the tertiary carbon at either sites of the molecule. In these experiments the workers established that in friedelin 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 by its 1,3-diaxial blocking effects to approaching succinimide radical.



12a, R = O

12b, R = H_2

12c, R = OH



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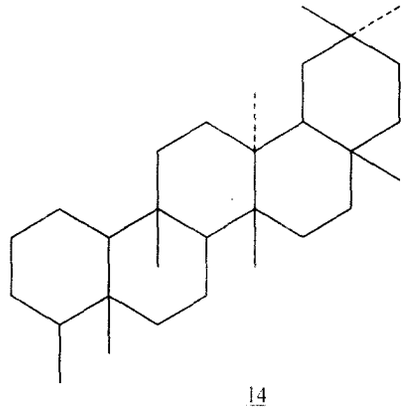

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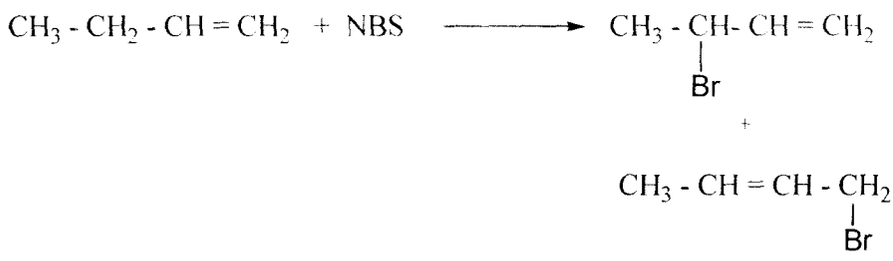
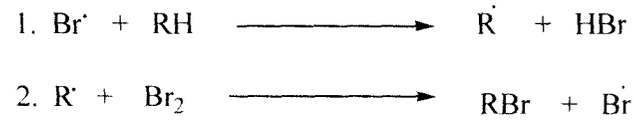
Bromination and NBS oxidation of saturated hydrocarbon, friedelane:

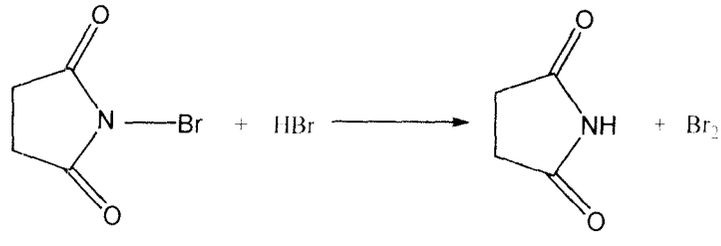
Olefin may be halogenated in the allylic position by a number of reagents. Nevertheless, NBS is by far the most common among them. An initiator usually peroxide is needed with this reagent. The reaction is quite specific at allylic position and the yields are usually good. However, in the case of unsymmetrical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



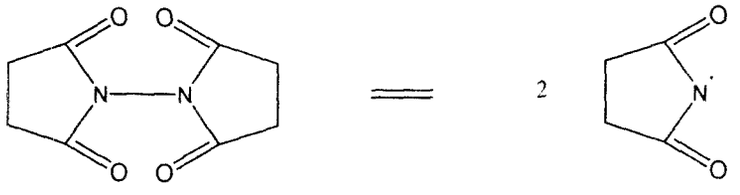
When a double bond has two different α-positions (e.g. $CH_3 - CH = CH - CH_2 - CH_3$) then a secondary position is substituted more readily than the primary one. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary position have been performed [18]. That the mechanism of allylic bromination is of the free radical type was demonstrated by Douben and McCoy [18]. 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 indicator 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:



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

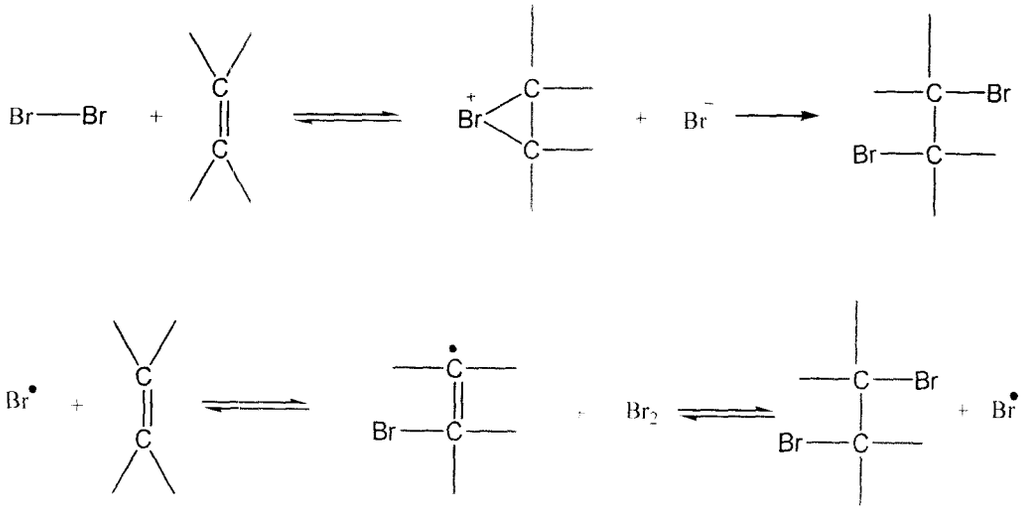


The formation of NBS is therefore to provide a source of Br_2 in a low steady state concentration and then use up the HBr liberated in step-1 [23-24]. Previously it was supposed that the abstracting species was the succinimide radical 15 but there is no much evidence that this species is involved in the reaction and is probably not even formed. The main evidence is that NBS and bromine show similar selectivity [25-28] which would not be the case if a different species was abstracting in each case [29] and that 15 has proved itself to be a much less stable species that was originally thought, since its dimer 16 show no tendency to dissociate [30-31].



16 15

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 attached to the substrate, whether the addition is electrophilic or free radical.



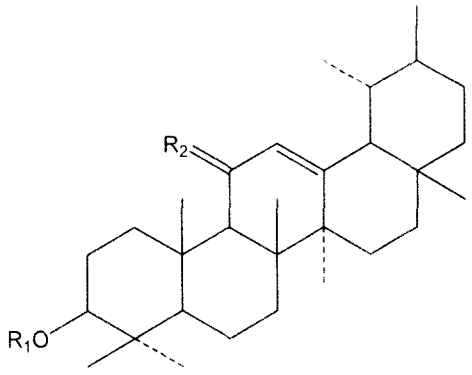
The other bromine atom comes from another bromine molecule. If the concentration of bromine is sufficiently low, there will not be a high probability that the proper species will be in the vicinity once the intermediate forms and the equilibrium will lie to the left. That is why the rate of addition is slow so that the allylic substitution goes to completion successfully. If this is true then it should be possible to brominates an olefin in the allylic position without completion 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 is demonstrated by McGrath et al. [32].

Stevenson et al. [9, 15] reported that when the saturated hydrocarbon friedelane 14 was oxidized by NBS, friedel-18-one, 12b was obtained. In order to explain, the function of NBS was to provide molecular bromine; this is compared with the action of bromine on 14 in carbon tetrachloride solution.

A solution of bromine in carbon tetrachloride was added to friedelane 14, the colour of bromine being discharged and the reaction mixture was worked up in the usual way [9]. Friedel-18-ene 12b 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 [9] in the bromination of 3-keto 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.

Oxidation of allylic methylene to carbonyl group by NBS:

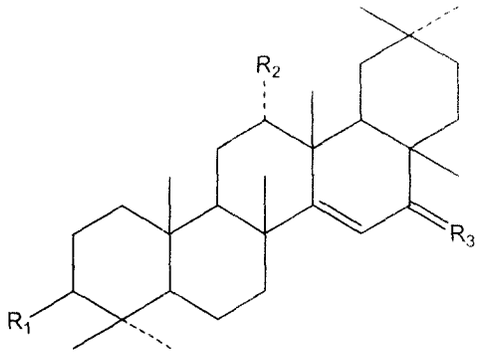
NBS is in wide use since 1969 as an effective reagent for oxidation of allylic methelenes to carbonyl function. Corsano et al. [38] reported the formation of 3β-acetoxy-urs-12-ene-11-one 18 in 80% yields by direct oxidation of α-amyrin acetate 17 with NBS in aqueous dioxin solution.

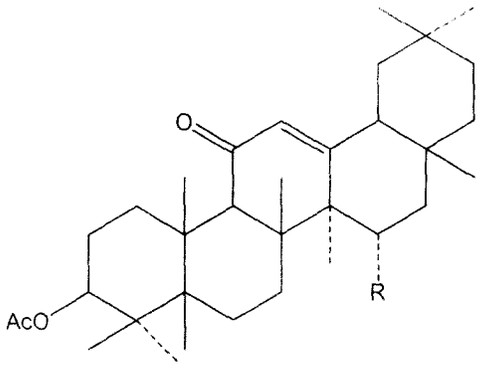


17 R_1 = Ac, R_2 = H

18 R_1 = Ac, R_2 = O

Thomson et al. [39] carried out oxidation of taraxeryl acetate 19 by the method of Corsano et al. [38] and obtained two major products to which they assigned the structure of 16-oxo-taraxeryl acetate 20 (Ca 30%) and 16β-hydroxytaraxeryl acetate 21 (Ca 30%). Treatment of 21 with chromic acid in acetone gave the unsaturated ketone 20. These authors also carried out the oxidation on 19 by the method described for β-amyrin acetate, which resulted in the formation of 12α-bromo-taraxer-12-en-16-one 22. Oxidation of taraxeryl acetate in aqueous dioxane for five and half hours in presence of $CaCO_3$ in visible light gave a compound 23, the structure of which was established as 11-keto-15-bromo-β-amyrin acetate, which in turn gave a halogen free compound 24 on treatment with Zn dust in acetic acid. Its structure was established as β-amyrenonyl acetate 24.





19, R_1 = OAc, R_2 = H, R_3 = H_2

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

21, R_1 = OAc, R_2 = H, R_3 = β-OH, α-H

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

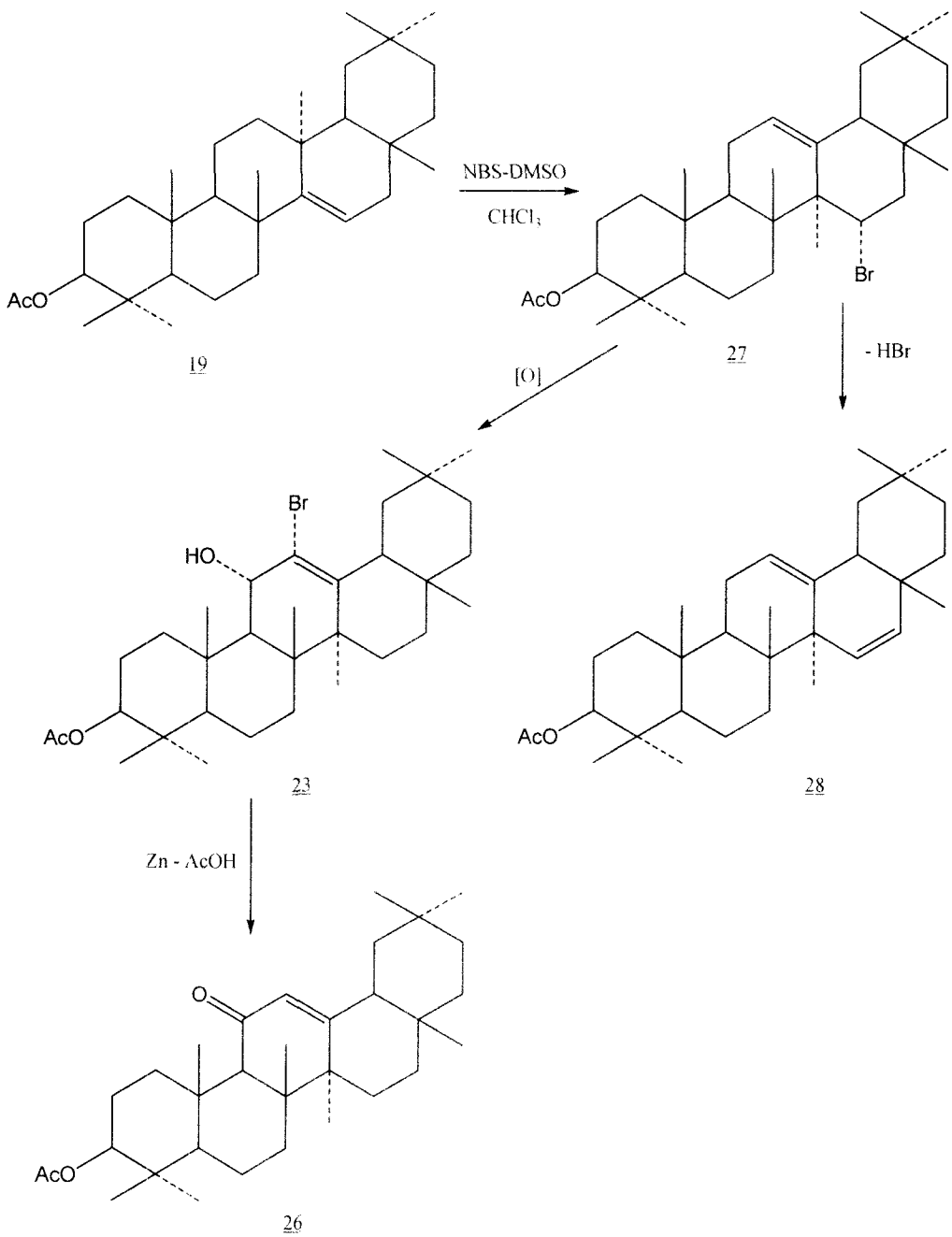
23, R = Br

24, R = H

Khastgir et al. [41] repeated the oxidation study of taraxeryl acetate 19 with NBS in aqueous dioxane according to the method of Finucane and Thomson [39-40] but the products isolated were quite different from those reported by Finucane et al. [37]. Khastgir et al. [41] observed that taraxeryl acetate 19 on oxidation with NBS in aqueous dioxine gave a mixture of two compounds which were separated by chromatography over alumina column followed by crystallization.

The first solid $C_{32}H_{49}O_3Br$, m.p. 238-40^{0}C obtained on elution with petroleum ether in a column was characterized as 15-bromo-β-amyrenonyl acetate 25. Its structure was proved by the following 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-amyrin acetate [42]. Khastgir also tried to prepare the 15-bromo compound 27 by a suitable method. They carried out the oxidation of taraxeryl acetate 19 by the method of Dalton and Jones [43] using NBS in dimethyl sulphoxide solvent [44]. Taraxeryl acetate 19 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^{0}C, showing no UV absorption between 220-300 nm. From IR, NMR and mass spectra the structure of 15-bromo-compound was assigned to be 25. The bromine atom at 15 positions of 34 would be expected to have the same stereochemistry as in the case of product from NBS

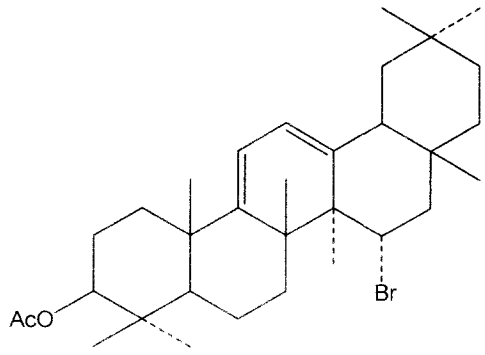
aqueous dioxane oxidation. Compound 25 on oxidation with CrO_3-AcOH [38] gave 23, m.p. 238-40^{0}C identical with the product obtained from NBS aqueous dioxane method.



Dehydrobromination of 27 with KOAc in acetic acid at 130^0C for 4 hours gave a product $C_{32}H_{50}O_2$, m.p. 199-200^0C. The same compound was obtained when 27 was refluxed with dimethylaniline for six hours. The structure 28 was proposed to it.

The second compound $C_{32}H_{50}O_3$, m.p. 280-82^0C being obtained on elution with petroleum ether: ethyl acetate (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 8.85, 2.10, 4.5 ppm) suggested that the product was 16-oxo-taraxeryl acetate 20, also its m.p. was different from that recorded by Finucane and Thomson [39-40].

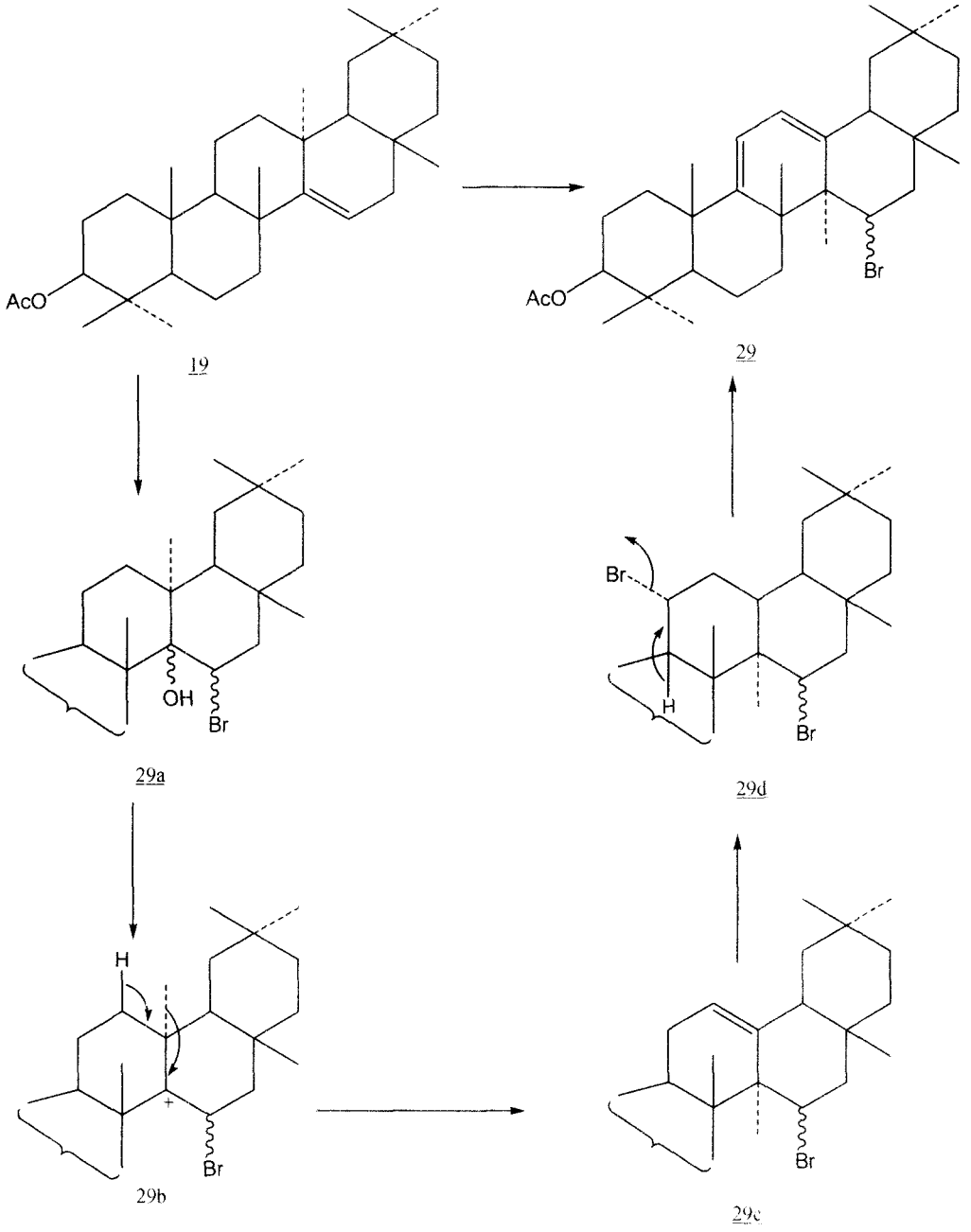
The third product having molecular formula $C_{32}H_{49}O_2Br$, m.p. 176-78^0C showed UV maxima at 276 nm indicating the presence of homoanular diene. NMR spectrum of the compound showed peaks at 5.34 and 5.85 ppm for one proton each attributed to the protons in a homoannular diene system in which both the double bonds are trisubstituted. Besides this, the spectrum showed sharp signals at 2.08 (-$OCOCH_3$) and multipletes at 4.6 (-C<u>H</u>-O-$COCH_3$) ppm on the basis of those evidences, the compound was assigned the structure 29.



29

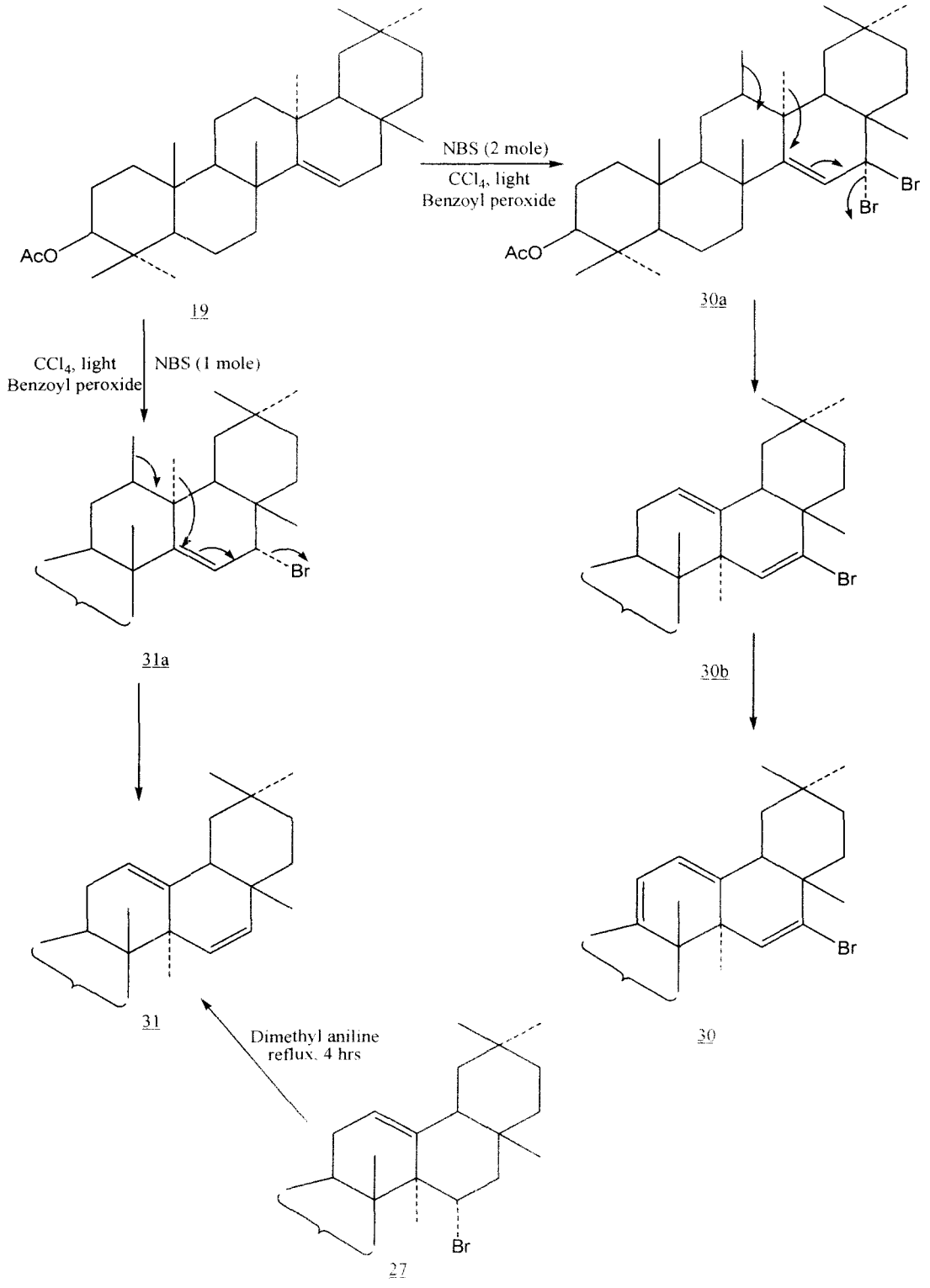
The mechanism for the formation of 29 from 19 was suggested as shown in the following Scheme-I.

Scheme-I



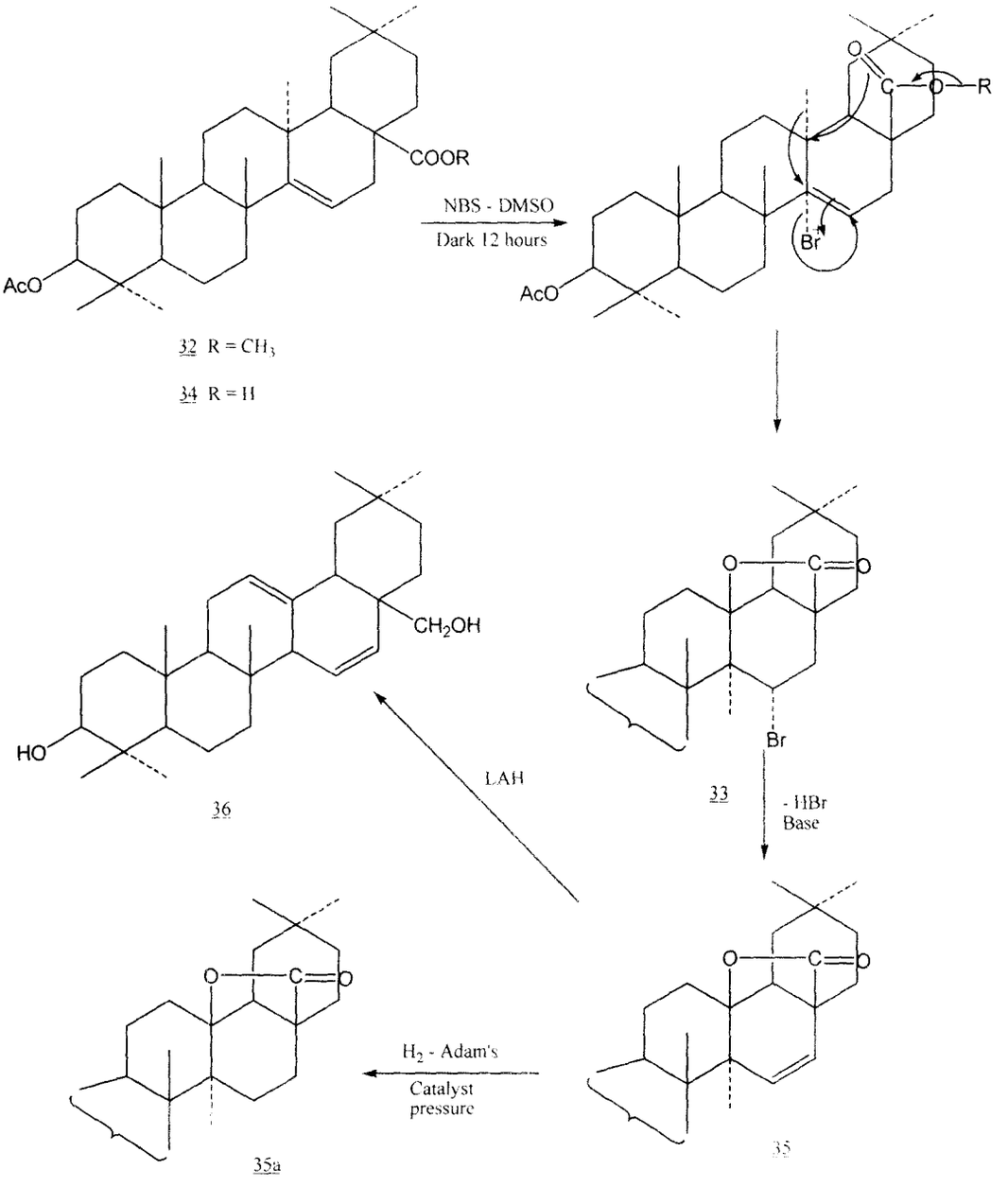
Khastgir et al. [41] also studied the reaction of taraxeryl acetate 19 with 2 moles equivalent of NBS in CCl_4 and benzoyl peroxide in the presence of visible light for about 3 hours and isolated a product which was assigned the structure 31, identical with that compound obtained by the dehydrobromination of 27. The mechanism proposed for the formation of 30 and 31 can be represented in the following scheme-II.

Scheme-II

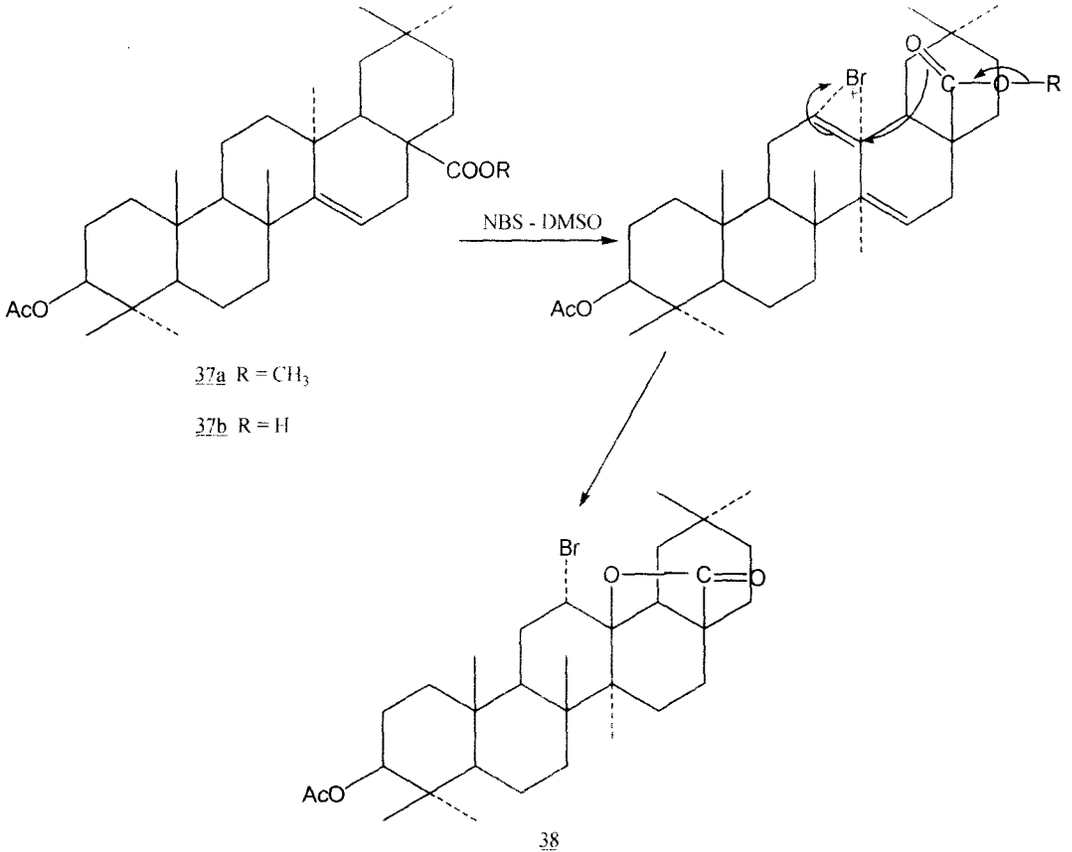

NBS (2 mole)
CCl_4, light
Benzoyl peroxide
AcO
Br
Br
19
30a
CCl_4, light
Benzoyl peroxide
NBS (1 mole)
Br
31a
Br
30b
Br
31
30
Dimethyl aniline
reflux, 4 hrs
Br
27

Pradhan et al. [47] examined the action of NBS on triterpene acids and esters in dimethyl suphoxide. They studied the reaction on acetyl methyl aleuritolate [43-45] 32 with NBS in dimethyl sulfoxide in dark for 12 hrs and isolated a bromo lactone 33. The structure of the bromolactone 33 was established from the fact that on dehydrobromination with dimethy aniline it afforded 15(16)-dehydrolactone 35, which on LAH reduction furnished aegiceradiol [46] 36 $C_{30}H_{48}O_2$, m.p. 235-36^{0}C, identical (mixed m.p., Co-IR) with an authentic sample. Compound 35 on catalytic hydrogenation over Adam's catalyst in acetic acid under pressure afforded 3β-acetyl oleanan-28 → 13-olide [47] 35a. Pradhan et al also isolated the same bromolactone 42 on repetition of the reaction on acetyl aleuritolic acid 34 [43-45].

They suggested that the mechanism of the formation of bromolactone 33 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 33.



Acetyl methyl oleanolate 37a and 3β-acetyl oleanolic acid 37b under the same condition with NBS in DMSO gave the same bromolactone 38 which was found to be identical with 3β-acetyl-12α-bromo-oleanan-28 → 13-olide [48-49].



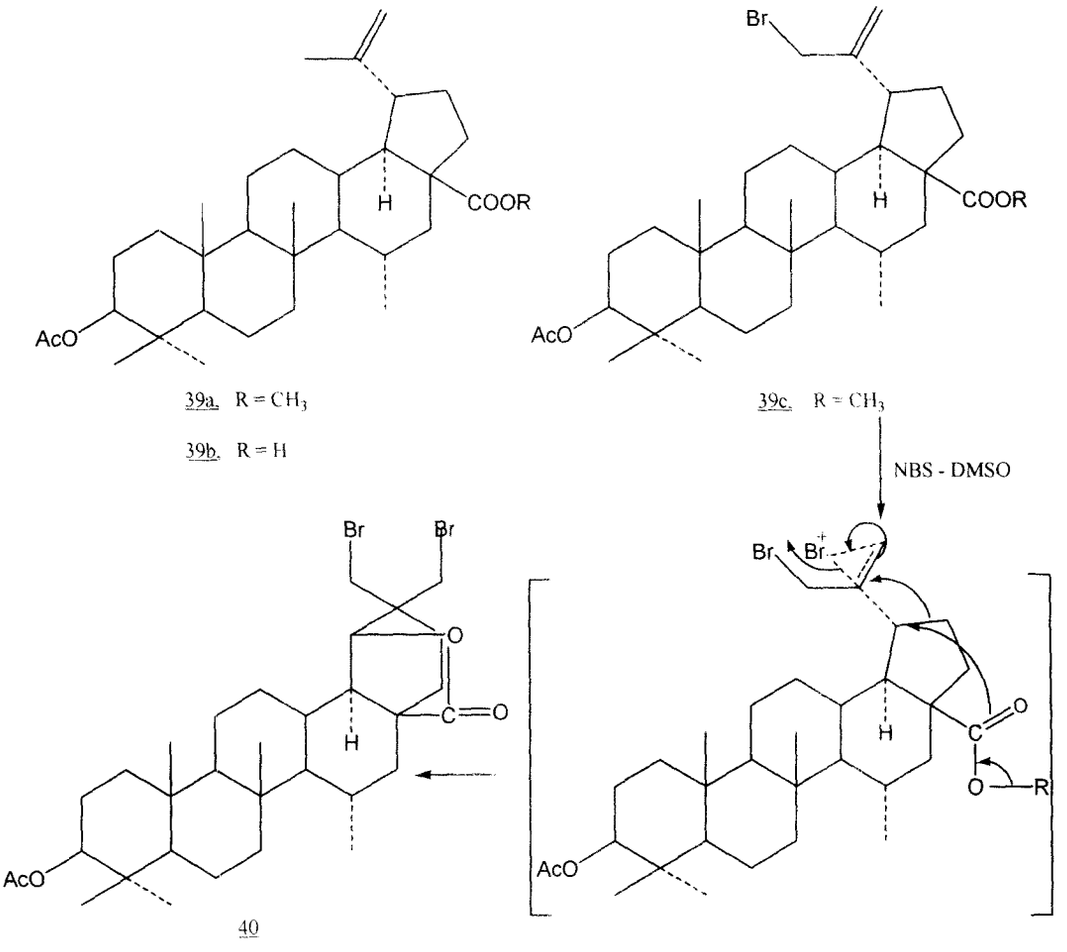
37a R = CH_3

37b R = H

38

Pradhan et al. [47] also carried out the reaction on 3β-acetyl methyl betulinate [50] 39a under similar conditions with NBS in DMSO. Two different bromo compounds were separated by chromatography. The less polar one. $C_{33}H_{51}O_4Br$, m.p. 235-36^{0}C $[\alpha]_D$ +42.55^0 was identified as methyl-30-bromo-3β-acetyl betulinate 39c. The structure was supported by IR, ^{1}H NMR data. The more polar fraction (10%) isolated was dibromolactone 40, having molecular formula $C_{32}H_{48}O_4Br_2$, m.p. 303-4^{0}C. The structure of this dibromolactone 40 was arrived at from the studies of mass, CD, IR, ^{1}H NMR and ^{13}C NMR values. The structure of 40 was further confirmed by some reactions. The compound 40 could not be dehydrobrominated with dimethylaniline, but on debromination with Raney Nickel-hydrogen gave a compound having the formula $C_{32}H_{50}O_4$, m.p.> 360^{0}C 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-dibrmo-18α-oleanan 28 → 19β-olide. The proposed mechanism of formation of 40 is shown in the following scheme-III.

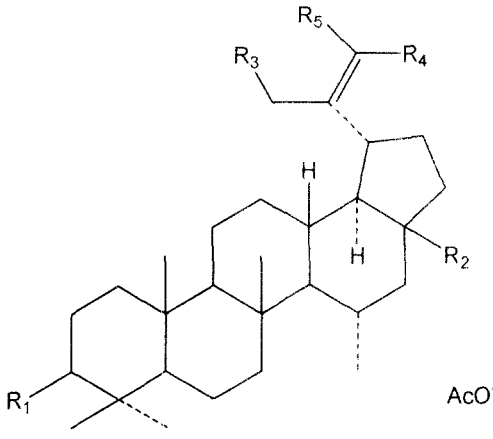
Scheme III

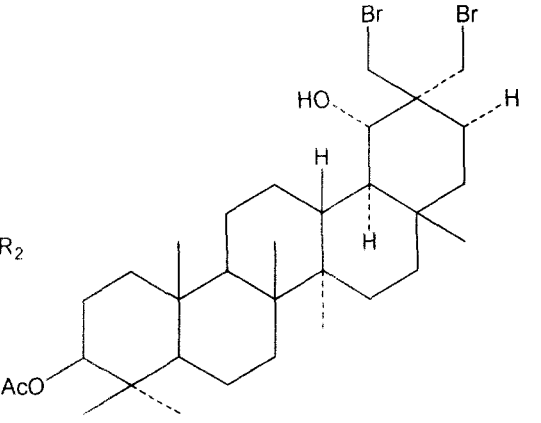


Pradhan et al. [47] also reported that 3β-acetyl betulinic acid 39b furnished dibromolactone 49 on similar treatment with NBS in DMSO.

They [50] also studied the reaction on lupenyl acetate 41 with NBS in DMSO. The compounds formed were identified as 30-bromolupenyl acetate 41a, 29-(E-Z)-bromolupenyl acetates 41c and 41d and 29,30-dibromo-18-iso-oleanan-19α-hydroxy 3β-yl acetate 41i. Further treatment of 41a and a mixture of 41c and 41d with NBS in DMSO containing water afforded 30-oxo-lupeol 41b and 20-(E-Z)-bromolupeol 50e

and 41f respectively: compound 41a on alumina column afforded 30-hydroxylupenyl acetate 41g and 30-hydroxylupeol 41h.





41i

41, R_1 = OAc, R_2 = CH_3, R_3 = R_4 = R_5 = H

41a, R_1 = OAc, R_2 = CH_3, R_3 = Br, R_4 = R_5 = H

41b, R_1 = OH, R_2 = CH_3, R_3 = O, R_4 = R_5 = H

41c, R_1 = OAc, R_2 = CH_3, R_3 = R_5 = H, R_4 = Br

41d, R_1 = OAc, R_2 = CH_3, R_3 = R_4 = H, R_5 = Br

41e, R_1 = OH, R_2 = CH_3, R_3 = R_4 = H, R_5 = Br

41f, R_1 = OH, R_2 = CH_3, R_3 = R_5 = H, R_4 = Br

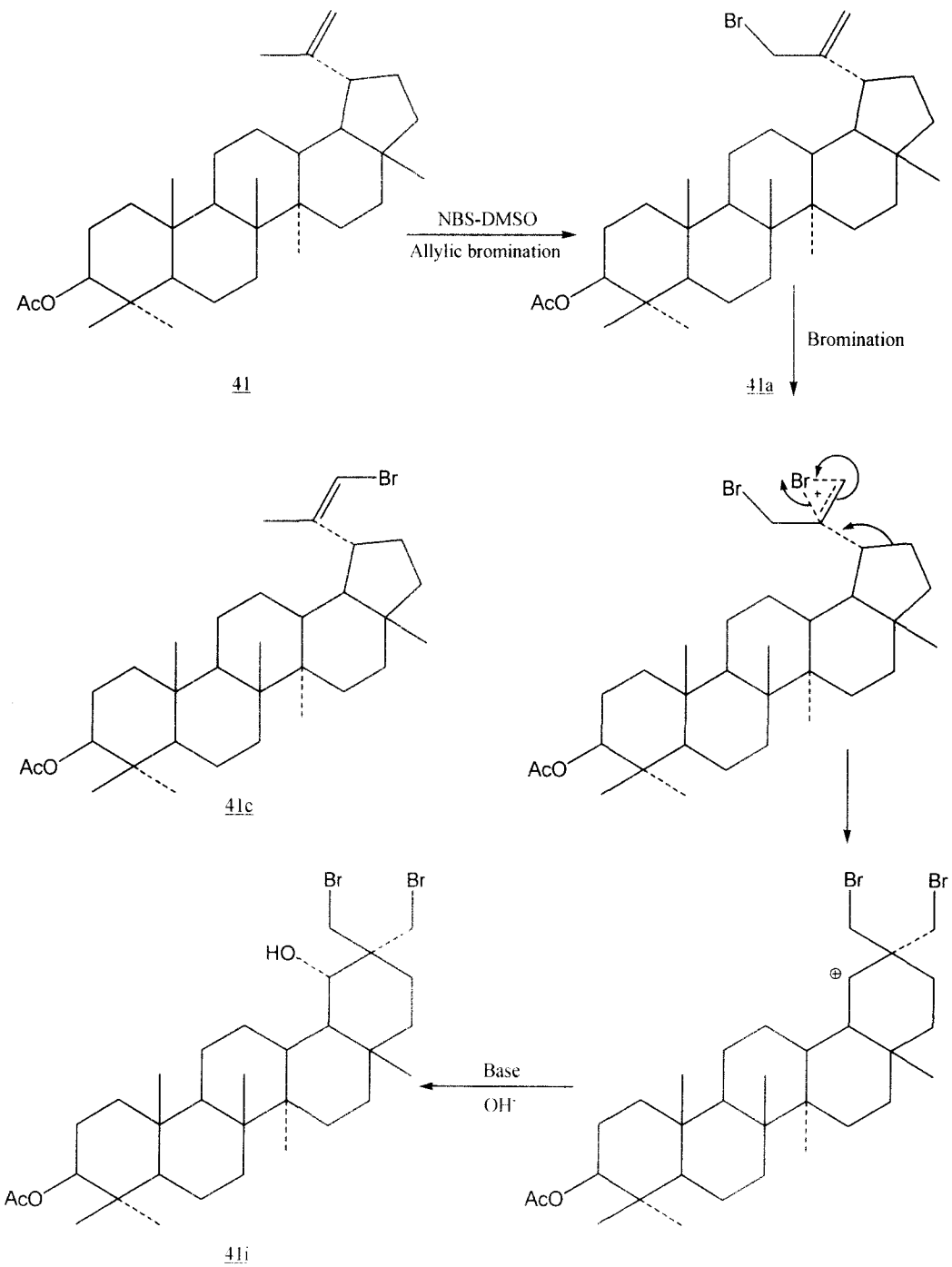
41g, R_1 = OAc, R_2 = CH_3, R_3 = OH, R_4 = R_5 = H

41h R_1 = R_3 = OH, R_2 = CH_3, R_4 = R_5 = H

Appearance of doublet at 4.01 ppm in ^{1}H NMR spectrum was the most confusing feature of this compound 41i because it was expected to give a singlet if the hydroxyl group is situated at C-19 position. So the most likely position of the location of this hydroxyl group could be C-21 which would then explain the appearance of this doublet at 4.01 ppm. In order to make an unambiguous decision on the structure of the compound 41i, two derivatives viz. keto 41j and acetate 41k had been prepared. The structure of dibromohydroxy compound 41i was confirmed from the ^{1}H NMR of keto- and acetate.

The formation of dibromohydroxy compound 41i has been proposed to take place by the following rearrangement of lupane system to oleanane system. The mechanism proposed has been represented in scheme IV.

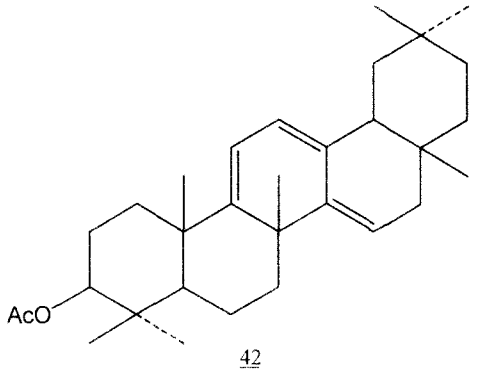
Scheme IV



41 41a 41c 41i

Anjaneyulu et al. [51] in their attempt to prepare mariladiol from taraxeryl acetate 19 applied the reaction of NBS on taraxeryl acetate 19 in aqueous dioxane by the method of Finucane and Thomson [39]. A mixture of four compounds were obtained two of which were identified as 30 and 35 by physical means. The third compound 42, $C_{32}H_{48}O_2$ (M^+ 486) contained two double bonds conjugated in a homoannular diene system as indicated by the UV absorption at 280 nm (€ = 6200). The PMR spectrum exhibited two singlets at 5.5 and 5.29 ppm each integrating for two protons. The former value was attributed to the homoannular-9(11),12-diene system and the latter two protons at C-15 and C-16. Based on these spectral data the structure of compound 42 was assigned as 3β-acetoxy-oleana-9(11),12,15-triene.

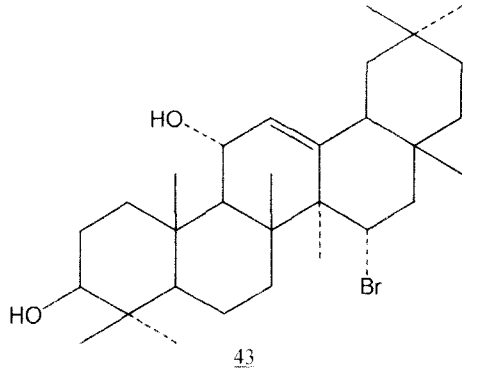
The fourth compound crystallized from chloroform-methanol mixture was characterized as 3β-ol of 42.



42

To prepare 3β-acetoxy-oleana-9(11),12,15-triene 42 they [51] planed to convert 15-bromo-β-amyrenonyl acetate 25 into 15-bromo-olean-12-en-3,11-diol which on dehydration with acetic anhydride [52] followed by dehydrohalogenation would give 42. Reduction of 25 with LAH gave epimeric diols. The major diol was separated by fractional crystallization 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 the 11α-hydroxy group [39, 53].

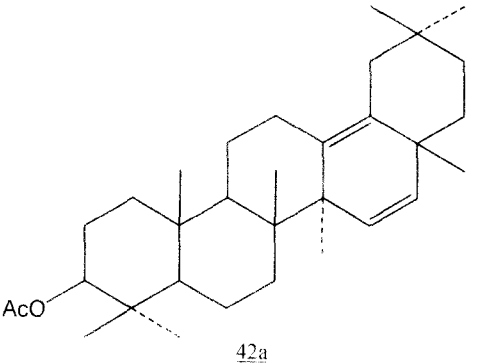
Thus the structure of major diol was assigned as 15-bromo-olean-12-en-3β,11α-diol 43.



43

Further support of this structure was provided by PMR spectrum.

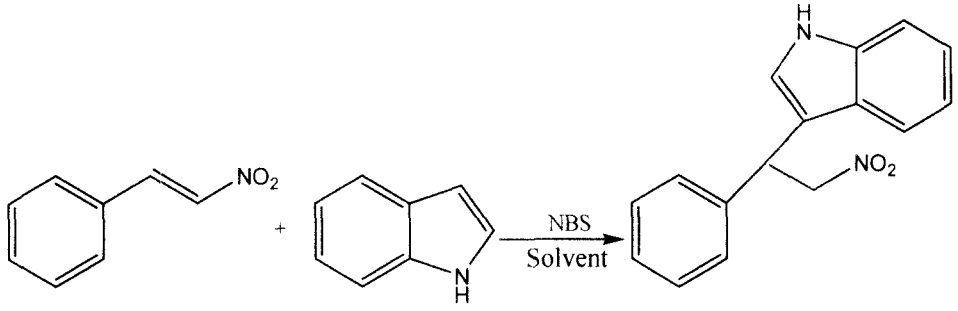
The remaining diol mixture after acetylation with Ac_2O/Py gave a product which was analysed for $C_{32}H_{49}O_2Br$. From the UV spectrum (λ_{max} MeOH 277 nm) and NMR data (5.5, 4.7 ppm) the structure of this compound was assigned as 3β-acetoxy-15-bromo-oleana-8(11),12-diene 29. Dehydrohalogenation of 27 with *N,N*-dimethylaniline gave a compound which was found to be identical in all respects with 42. They attempted to prepare 16β-acetoxy-taraxeryl from taraxeryl-acetate following the method of Barton et al. [54]. They isolated a compound characterized as 3β-acetoxy-oleana-13(18),15-diene 42a along with 16β-acetoxy taraxeryl acetate and 16-oxo-taraxeryl acetate.



42a

Yao et al. [55] reported NBS as a mild source of bromine and widely used in the presence of a catalytic amount of free-radical initiators for benzylic and allylic brominations with high regioselectivity. In many instances, NBS have been used as an

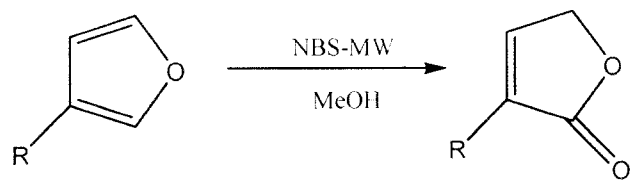
activator in stereoselective glycosidation, protection and deprotection of ketals or THP ethers and in the synthesis of diindolylalkanes. It is also widely employed as a mild oxidant as well as for oxidative cyclizations. Recently, they have reported synthesis of 1,5-benzodiazepine derivatives catalyzed by NBS under mild conditions. In continuation of their research work on nitroolefins, they have developed a new route for the synthesis of 3-alkylated indoles 45 via Friedel-Crafts alkylation of indole 44 with β-nitrostyrene, catalyzed by NBS.



44 45

Iranpoor et al. [56] reported a novel catalytic and selective protocol for the deprotection of *S,S*- and *S,O*-acetals and ketals in the presence of their *O,O*-analogs. In this method, *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (TABCO), trichlorocyanuric acid (TCCA) as sources of electrophilic halogens and also bromine are used in a catalytic cycle in the presence of DMSO.

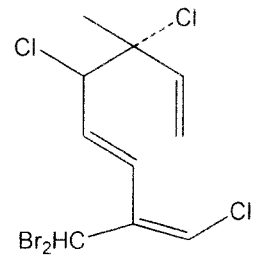
Gopalakrishnan et al. [57] reported the oxidation of the furan ring into a butyrolactone in a similar type of limonoid, gedunin, was effected using the oxidant, *N*-bromosuccinimide and resulted in a poor yield and took a long time for completion. In recent years, the use of microwave and ultrasound irradiation in organic reactions has increased due to shorter reaction times, higher yields and operational simplicity. In the present study, the possibility of applying microwave and ultrasound irradiation to carry out selective oxidation of the furan ring in triterpenoids has been explored.



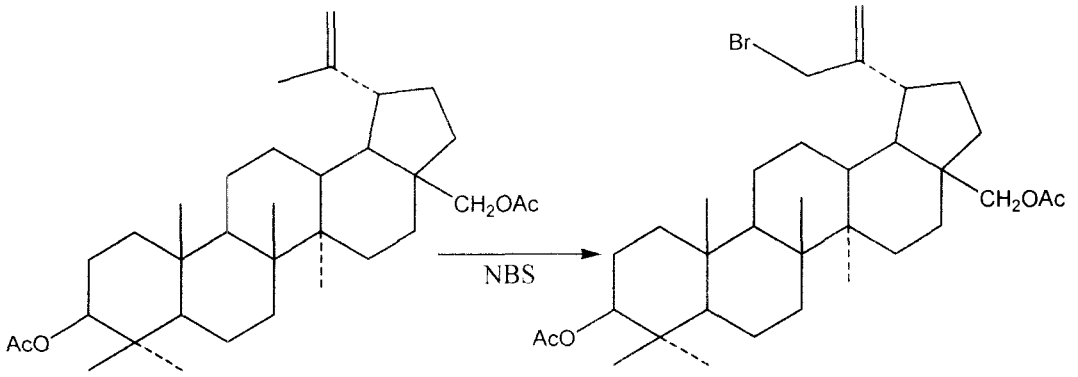
Ardashov et al. [58] reported that reaction of NBS with (-)-verbenone and (+) trans-verbenol in presence of water, unusual products were obtained where the compound having an oxabicyclo [3.2.1] octane skeleton but containing different numbers of bromine atom in their molecules.

Rao et al. [59] reported that isoxazole derivative of the methyl ester of glycyrrhetinic acid reacted with NBS and catalytic amount of AIBN in chloroform under the influence of tungsten lamp to give a bromo compound. The bromo derivative then was treated with a base to give cyanoenone.

Imperato et al. [60] reported the isolation of some new monoterpenoids from *Aplysia limacine* and further halogenation on them gave cyclic halogenated monoterpenoids.



Flekhter et al. [61] reported allylic bromination of 3,28-di-O-acetylbetulin 46 with NBS in CCl_4 in 72% yield to give 30-bromobetulin acetate 47.



46 47

Wang et al. [62] reported six new different products on reaction of acetyllycoctonie derived from lycoctonine from the roots of *Delphinium potaninii* in *t*-BuOH with NBS. It is emphasized that the varieties and yields of the products in this reaction depended greatly upon reaction conditions and the types of substrate. Oxidation involving the nitrogen atom of the C_{19}-diterpenoid alkaloids with various oxidants such as $KMnO_4$, OsO_4, CrO_3, Ag_2O, *m*-CPBA, etc. has been reported but there have been no prior reports on the preparation of the imines starting from these alkaloids with NBS. In the previous works on modification of C_{19}-diterpenoid alkaloids, they reported the reaction of the aconitine-type alkaloids 3-acetylpseudaconine, 3,13-diacetylyunaconitine, 3-acetylyunaconitine with NBS to give the *N*-deethyl and/or the imine derivatives. In addition, it was found that the varieties and yields of the resultants were greatly dependant upon the reaction conditions.

Ungur et al. [63] acetylated geranyllinalool under standard conditions to geranyllinalyl acetate, which was isomerized with $[PdCl_2(MeCN)_2]$ to the mixture of (2E)- and (2Z)-geranylgeranyl acetates. This mixture was then treated with NBS followed by K_2CO_3 according to the procedure of Van Tamelen and Curphey to provide the mixture of compounds (E)-14,15-epoxygeranylgeraniol and (Z)-14,15-epoxygeranylgeraniol.

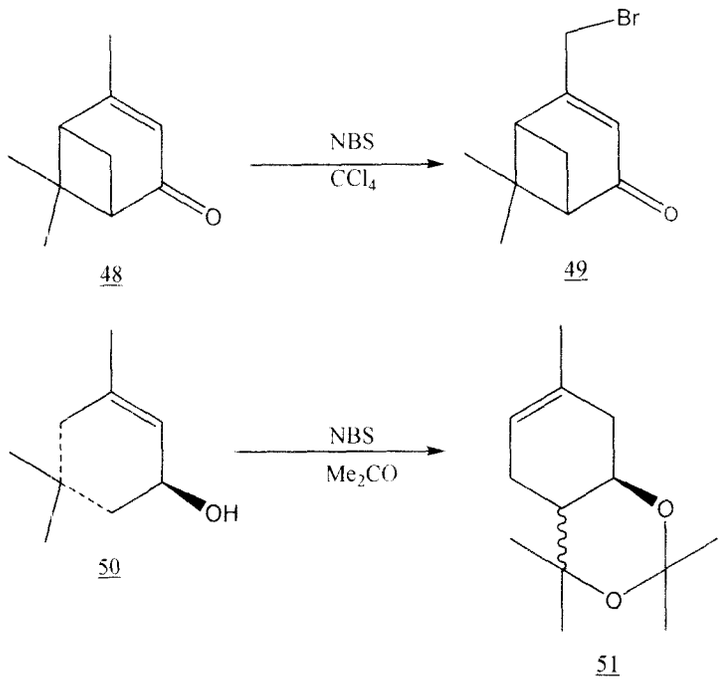
Wang et al. [64] also reported that norditerpenoid and diterpenoid alkaloids are a group of highly oxygenated and complex natural products. They not only have important pharmacological activities such as analgesic, local anesthetic, anti-

inflammatory and antiarrhythmetic, but also may set off a lot of interesting chemical reactions. In order to search for higher activity, low-toxicity compounds and conversion of the skeletons, they carried out the structural modification of the aconitine-type norditerpenoid alkaloids. In this case, the *N*-deethylation was one of the most common reactions by oxidizing reagents such as NBS.

Alves et al. [65] isolated a diterpenoid eremanthine from *Schistosoma mansoni*. They further extended the reaction of eremanthine with *N*-bromosuccinimide in dioxane containing 20% of water and the formation of an ether linkage between the C-4 and C-10 positions was possible only if the five- and seven-membered rings were *cis*-fused.

Roberts et al. [66] reported that α-pinene reacted with NBS to give complex mixtures of brominated and bromine-free compounds, among which verbenyl bromide, bornyl bromide, mirtenyl bromide, *p*-cymene, and probably fenchyl bromide were identified.

Ardashov et al. [67] showed that the reaction of verbenone 48 with NBS in carbon tetrachloride is accompanied by allylic bromination with formation of compound 49 in which the pinane skeleton was conserved. On the other hand, (–)-*trans*-verbenol [(–)-50] reacted with NBS in acetone to give *O,O'*-isopropylidene derivative of bromo-substituted diol with a *p*-menthane skeleton 51. The reaction of *cis*-verbenol with NBS followed an analogous pattern. The reactions of (–)-verbenone [(–)-48] and (+)-*trans* verbenol [(+)-50] with *N*-bromosuccinimide in the presence of water and found that these reactions led to the products whose structure differed considerably from the structure of compounds 49 and 51 obtained previously by reactions of (–)-48 and (+)-50 with NBS under different conditions.



48 49

50 51

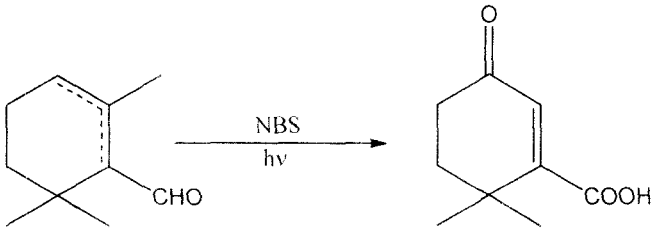
Yusubov et al. [68] reported the controlled introduction of halogen substituents into the structure of naturally occurring monoterpenes which provided an entry into a plethora of important synthetic intermediates and other practically useful products. Numerous examples of bromination, chlorination, and iodination of carvone, pinene, limonene, citral, camphen, pulegone and other terpenes and terpenoids have been reported in the literature. The most common and best investigated reaction is the bromination of terpenes using *N*-bromosuccinimide and other brominating reagents. In contrast, the chemoselective introduction of chlorine or iodine into a terpene structure represents a challenging problem. Several examples of a relatively selective chlorination of terpenoids with hypochlorous acid, *tert*-butylhypochlorite, or nitrosyl chloride were reported in the literature. Iodination of terpenes has previously been achieved by using iodine or *N*-iodosuccinimide.

Sawant et al. [69] reported cembranoids as natural diterpenes with 14-membered macrocyclic rings. The simplest natural cembranoid, (+)-cembrene, was isolated from pine oleoresin. Sarcophytols A and B are known cembranoids that inhibit tumor promotion. Sarcophine is a related cembranoid isolated from the Red Sea soft coral *Sarcophyton glaucum*. Sarcophine and its bioconversion products and

semisynthetic derivatives are reported to possess cancer chemopreventive activity. Oxymercuration-demercuration of sarcophine using $Hg(OAc)_2$ and $NaBH_4$ afforded four new rearranged and hydroxylated products. Bromination of sarcophine with *N*-bromosuccinimide (NBS) furnished two new brominated and rearranged products. Reaction with iodine gave the known iso-sarcophinone and (+)-sarcophytoxin B. Structure elucidation was based on a combination of transition state modeling, molecular dynamics, mechanistic considerations, and 2D-NMR data. The antiproliferative activity of the new products is also reported.

Raldugin et al. [70] reported the reaction of the diterpene hydrocarbene with NBS in aqueous acetone takes place as the addition of the elements of hypobromus acid, leading to the addition products at the C_4-double bond-5(R) and 5(S)-bromoisocembrols and 5(R)-bromo-4-epiisocembrol. At the same time, products of the bromination of cembrane-18 and 5-bromo cembrenes are formed.

Sierra et al. [71] reported that α- and β-cyclocitrals 52 could be converted, in one step, into the keto acid 53 by *hν*/NBS and a base in aqueous dioxane.

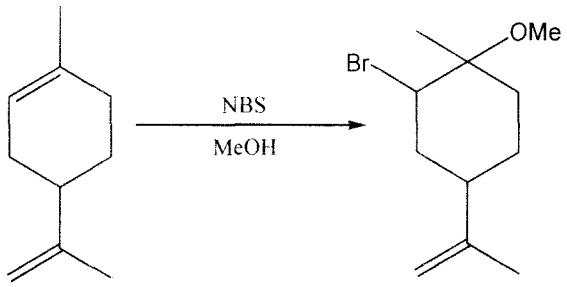


52 53

Mattos et al. [72] reported the reaction of (S)-α-terpineol with equimolar NBS in aqueous acetonitrile produced (1R,2R,4S)-2-bromo-4-(2-hydroxypropan-2-yl)-1-methylcyclohexanol in 75% isolated yield, along with minor amount of (1R,4S,5S)-4-bromo-4,7,7-trimethyl-6-oxabiclo[3.2.1]octane and (1R,4S,6R)-6-bromo-1,3,3-trimethyl-oxabiclo[2.2.2]octane. On the other hand, the reaction performed in anhydrous acetonitrile produced the two bicyclic bromoethers as the unique products in

88% combined yield. Similar results were obtained with the reaction performed in aqueous THF (bromohydrin, bicyclic bromoethers and cis α-terpinol oxide, derived from the bromohydrin formed) and in dry dichloromethane (only the bicyclic bromoethers formed in 50% combined yield).

Thomas et al. [73] reported the synthesis of 55 from (+) limonene 62 by treating it with NBS in methanol. In their work, it was interesting to note that between the two nonconjugated double donds, in 54; the double bond in the ring was affected leaving the vinylic one intact.



54 55

Hence, versatile applications of NBS mostly in triterpenoid skeletons are quite obvious from the litereature. However, limited reports on the investigation of NBS in DMSO solvent on monoterpenoids have encouraged the author to study the influence of this useful oxidizing agent on some monoterpenoids taking camphor as a model compound. In addition the author has further extended the reaction on oxime derivative of camphor. The following is the details of the present investigation.

CHAPTER II

STUDIES ON THE ACTION OF *N*-BROMOSUCCINIMIDE IN DIMETHYL SULFOXIDE ON CAMPHOR

Treatment of camphor (56) with NBS in DMSO:

Camphor 56 (3 g) was dissolved in $CHCl_3$ (150 mL) and DMSO (75 mL). To this solution NBS (3.5 g) was added in small lots and kept in dark for 6 hrs. The solution was extracted with chloroform and made free of DMSO by repeated washing with water. The residue obtained after removal of solvent was chromatographed over silica gel. Compound A was isolated and was then purified by crystallizations from chloroform and methanol.

Characterization of compound A:

Compound A m.p. 155-60^{0}C gave an intense green flame in Beilstein test showing the presence of bromine in A. It gave no colouration with TNM. Elemental analysis indicated the molecular formula $C_{10}H_{14}OBr_2$ which was supported by the existence of three ion peaks (Fig. 4) at 308, 310 and 312 in the ratio of 1:2:1 providing the presence of two bromine atoms in compound A. Its IR spectrum (Fig. 1) showed a peak at 1743 cm^{-1} for the carbonyl stretching vibration. This is further substantiated by ^{1}H and ^{13}C NMR spectrum. Its ^{1}H NMR spectrum (Fig. 2) showed at 0.913 ppm (broad multiplet, 6H for two geminal methyls at C_7), 1.939 ppm (m, 3H, for $-CH_3$ at C_1), 1.371 ppm (m, 2H, for C_6-2H), 1.684 ppm (m, 2H for C_5 -2H) and 2.343 ppm (m, 1H at C_4). Its ^{13}C NMR spectrum (Fig. 3) showed 9.26 ppm (C_{10}), 19.78 ppm (C_8, C_9), and 46.78 ppm (very low intensity must be due to quaternary carbon at C_7), 29.91 ppm (C_6), 27.05 ppm (C_5), 43.03 ppm (for low intensity quaternary carbon at C_3) and 43.29 ppm (C_4). Peaks for carbonyl carbon appeared at 210 ppm with very low intensity which may be due to the low relaxation time as well as for the quadruple effect. Thus from the above result the structure for compound A was assigned as 3,3-dibromocamphor 57.

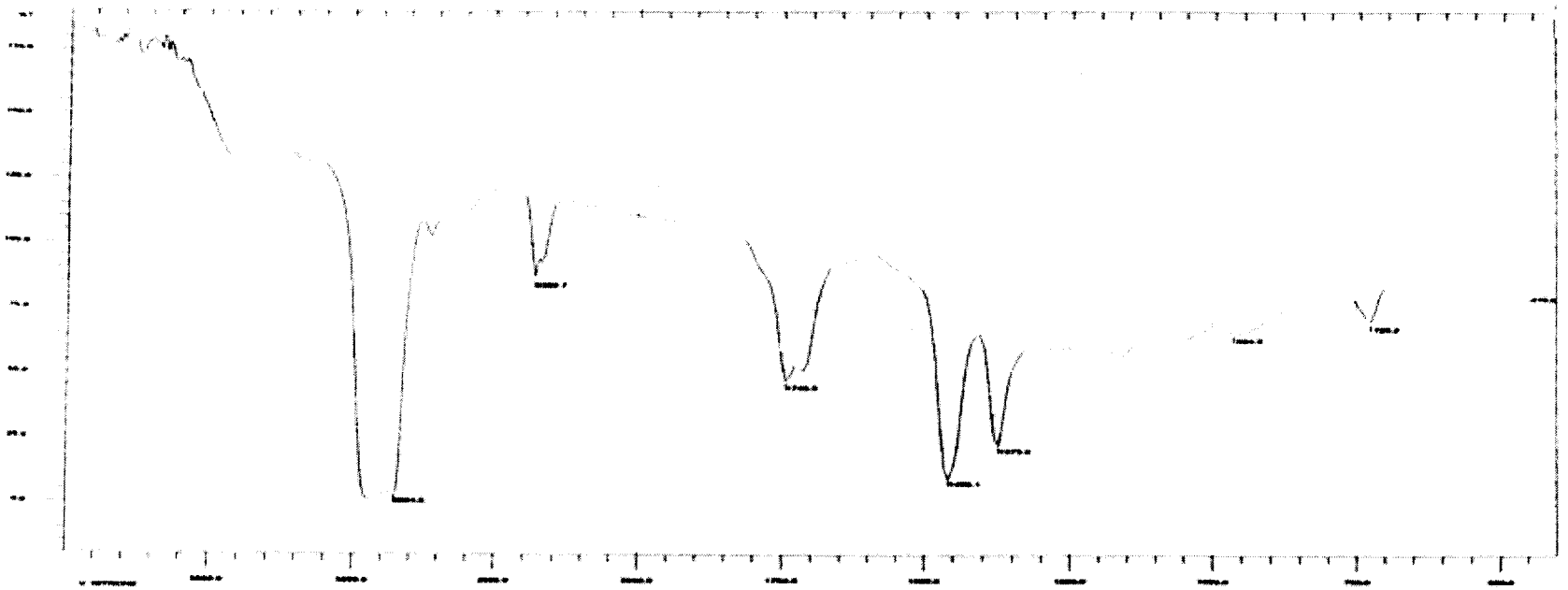


Fig. 1: IR spectrum of 3,3-dibromocamphor

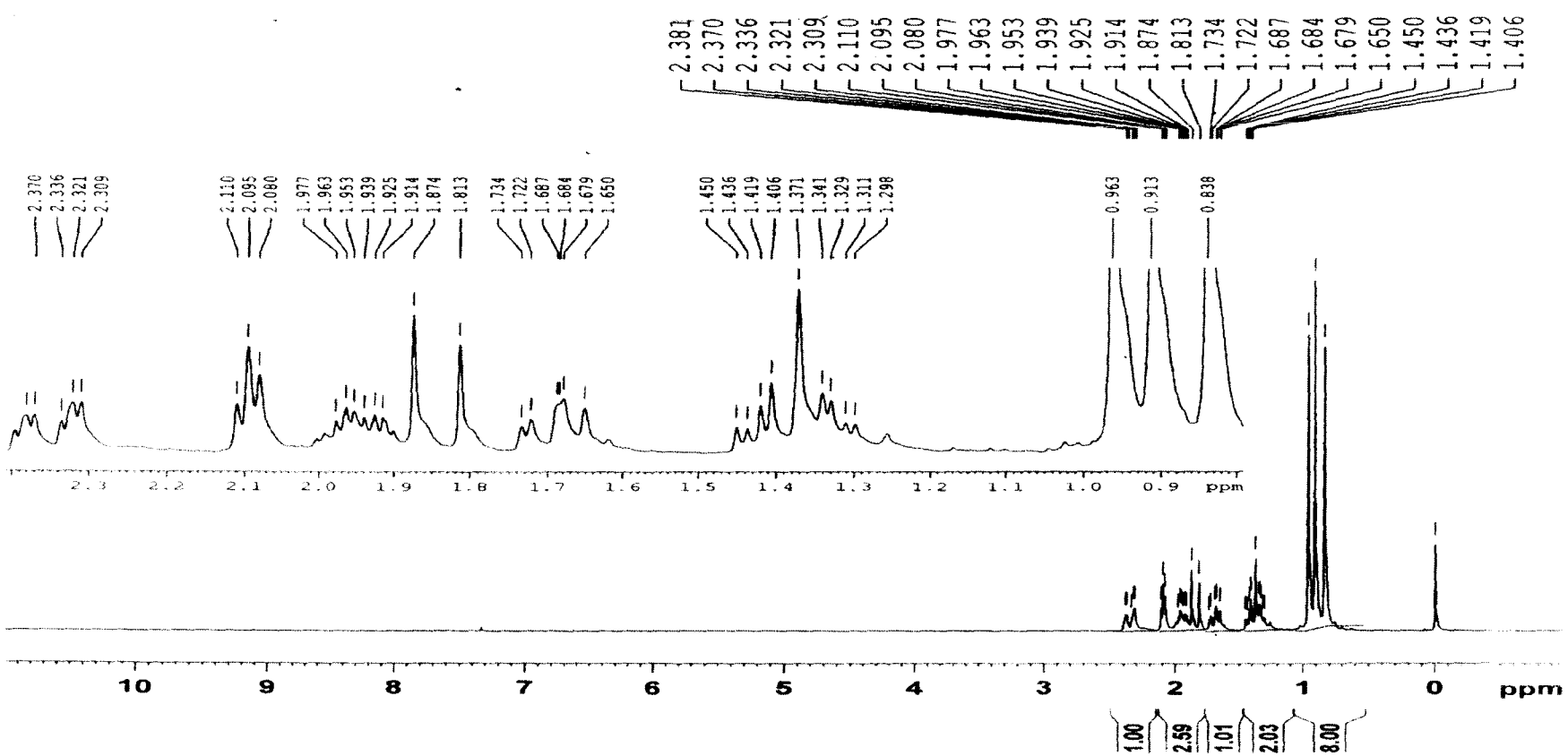


Fig. 2: ^{1}H NMR spectrum of 3,3-dibromocamphor

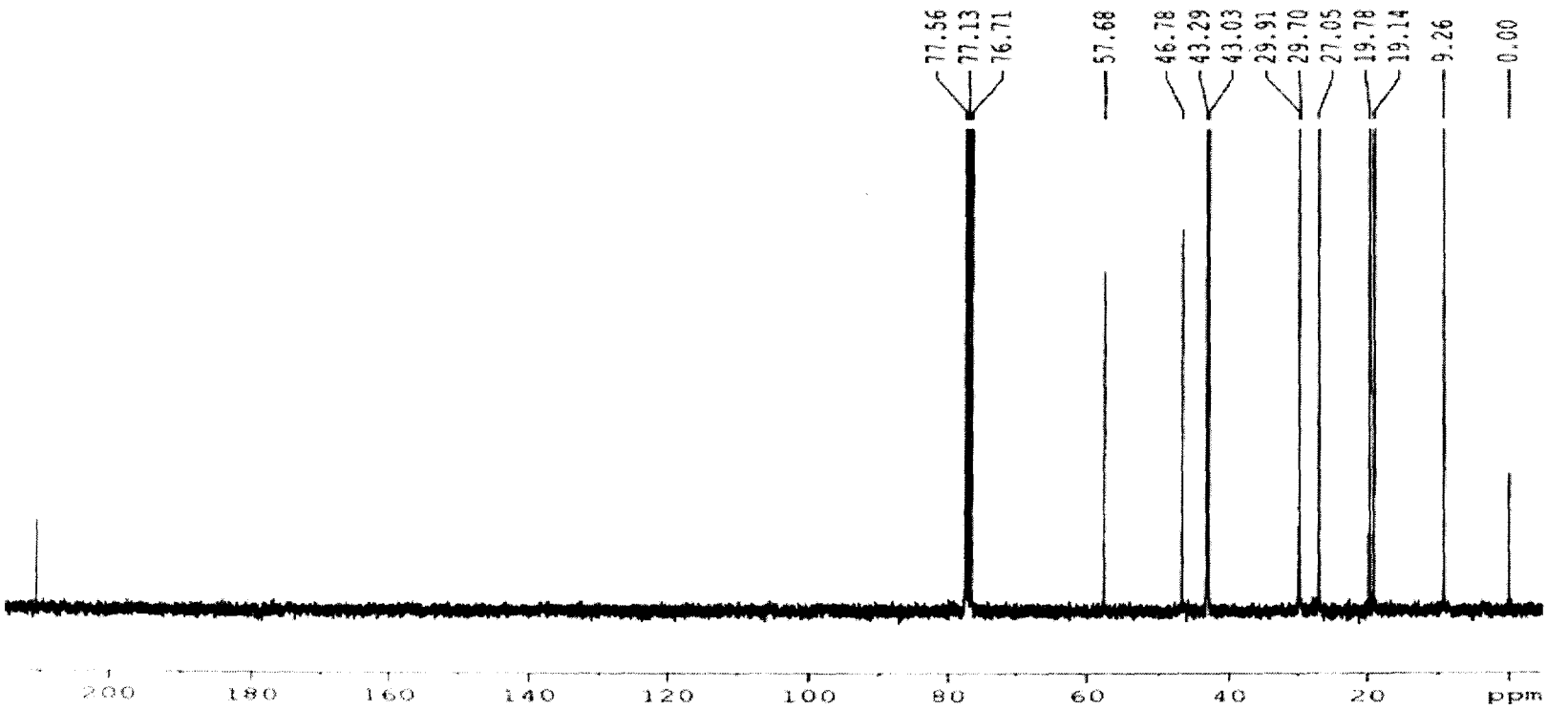


Fig. 3: ^{13}C NMR spectrum of 3,3-dibromocamphor

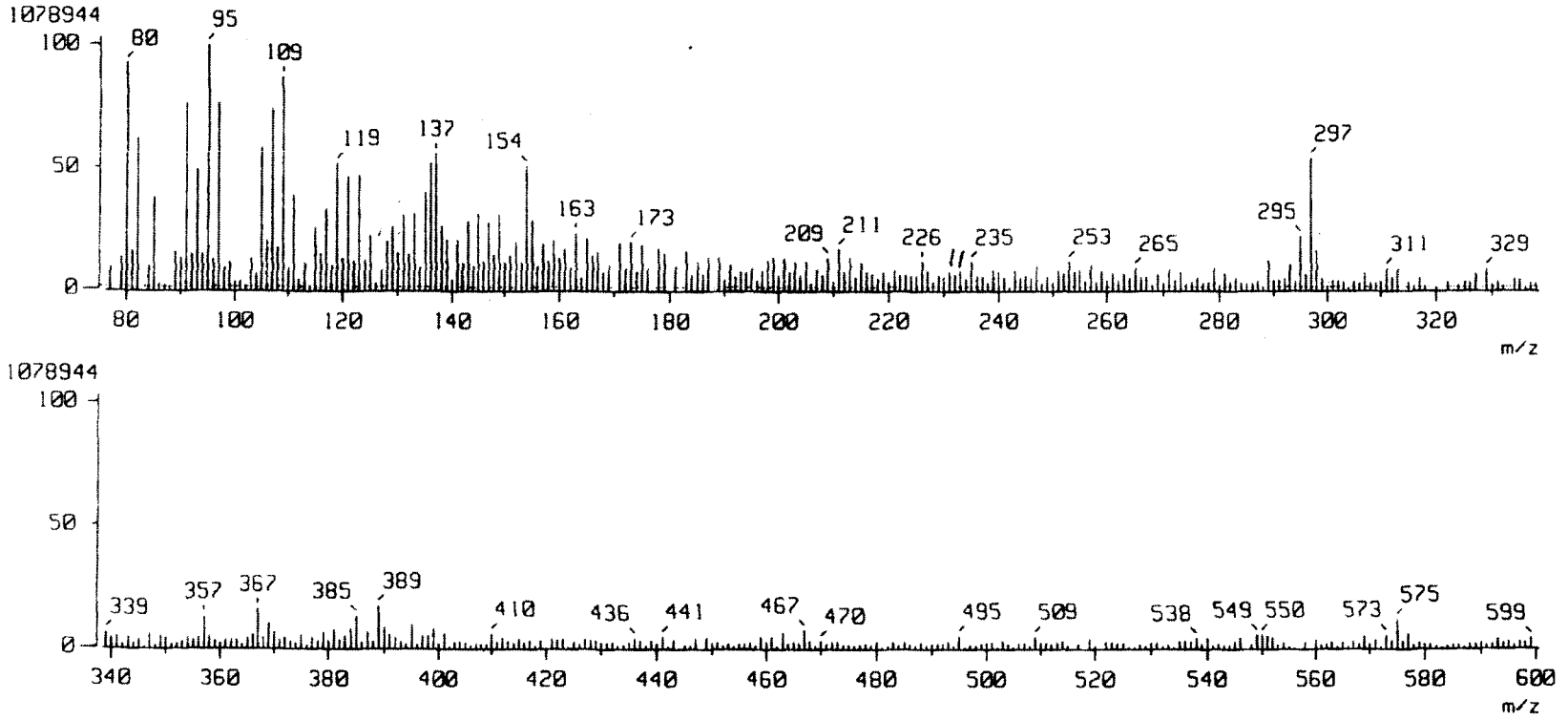
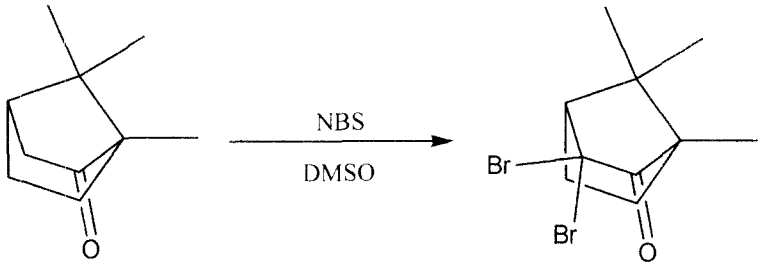


Fig. 4: Mass spectrum of 3,3-dibromocamphor



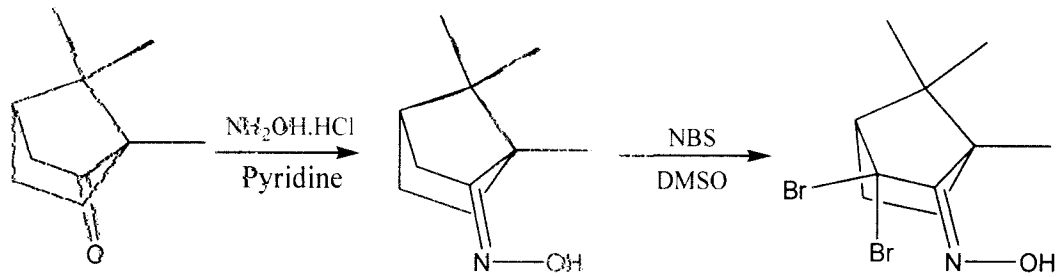
56 57

Studies on the action of NBS-DMSO on camphor oxime (58): Isolation of 3,3-dibromocamphor oxime (59)

The oxime of camphor is likely a candidate for the allylic oxidation with NBS. Oxime derivative of camphor 58, m.p. 115-19^{0}C, [74] was prepared by treatment of $NH_2OH.HCl$ in presence of small amount of pyridine with camphor (see experimental). The oxime 58 was then subjected to the reaction of NBS in DMSO as performed in the previous occasions. The product obtained after usual method was separated by chromatography. The product obtained was compound B.

Compound B was purified by crystallization from chloroform-methanol, had the m.p. 100-105^{0}C. It showed green flame in Beilstein test but developed no colouration with TNM. Elemental analysis indicated the molecular formula as $C_{10}H_{15}ONBr_2$ which was supported by the existence of three ion peaks at [Fig. 8] m/z 323, 325 and 327 in the ratio of 1:2:1 providing the presence of two bromine atoms. The other important peaks appeared at m/z 309, 311 and 313 $[M-N]^+$; 281 $[M-C(CH_3)_2]^+$; 267, 265, 251, 221, 207, 178, 163 and 147 (base peak). Its IR spectrum [Fig. 5] showed a broad peak at 3300-3400 cm^{-1} and other peaks at 1170, 948.9 and 725.2 cm^{-1}. Its ^{1}H NMR spectrum (Fig. 6) showed three clear identifiable signals which are those from the methyl groups, of which one singlet at 0.95 ppm (C_{10}) and two singlet at 0.78 and 0.84 ppm (for C_8 and C_9 respectively). The remaining protons have resonance signals between 1.0 and 3.0 ppm from TMS and these overlap badly to spin-spin splitting. A broad signal for the proton of =N-OH group in between 7.0 to 9.0 ppm from TMS. Its ^{13}C NMR spectrum (Fig. 7) showed 10 peaks of which 10.09 ppm (C_{10}), 17.51 ppm and 18.43 ppm (C_8 and C_9), 26.23 ppm (C_5), 31.59 ppm (C_6), 47.29 ppm (C_3), 50.83 ppm

(C_4), 32.10 ppm (low intensity due to quaternary carbon at C_7) and 42.69 ppm (low intensity due to the quaternary carbon at C_1). Peaks for C_2 quaternary carbon was appeared at 168 ppm. Thus from the above result the compound B assigned as 3,3-dibromocamphor oxime 4.



56 58 59

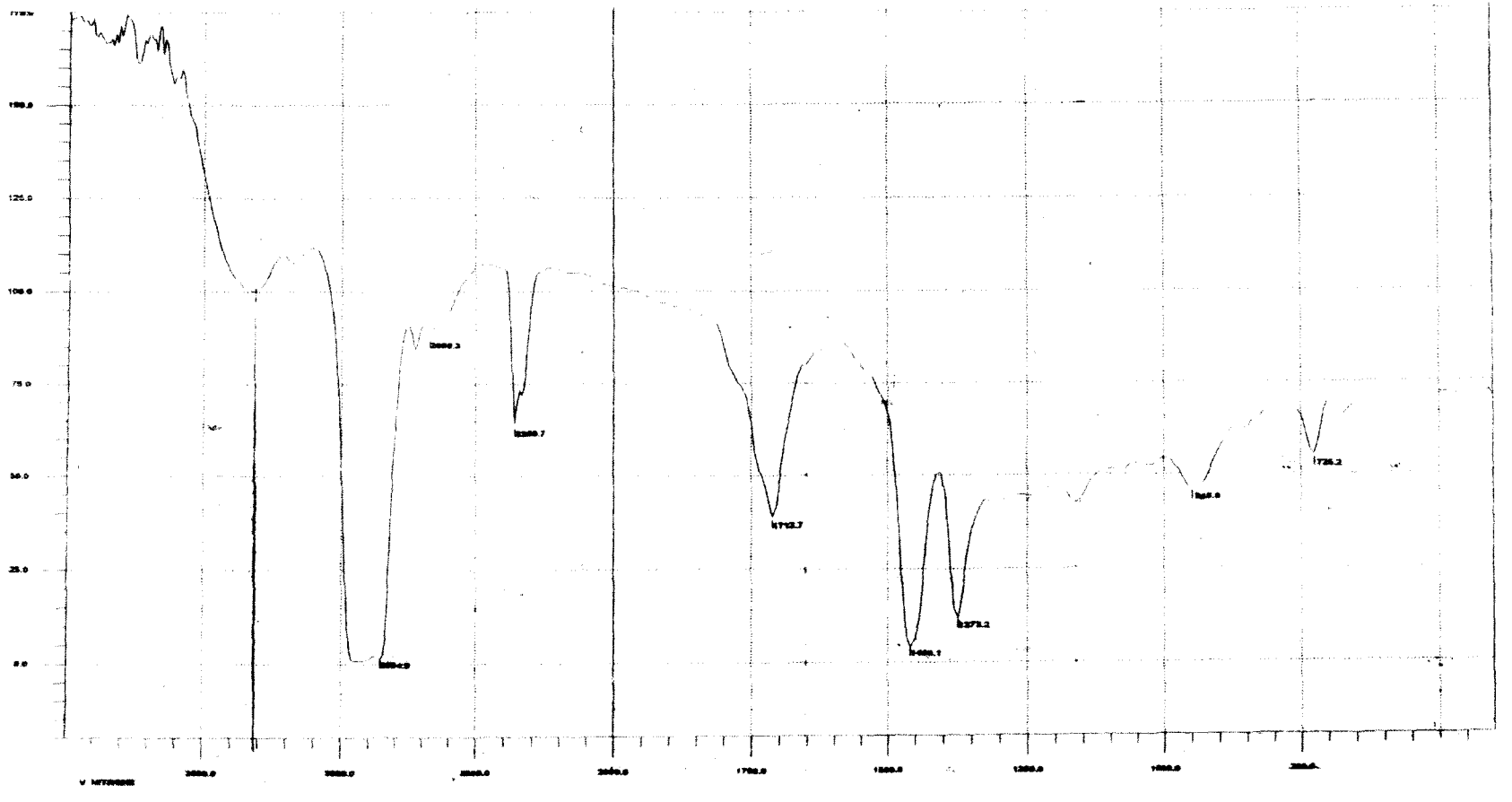


Fig. 5: IR spectrum of 3,3-dibromocamphor oxime

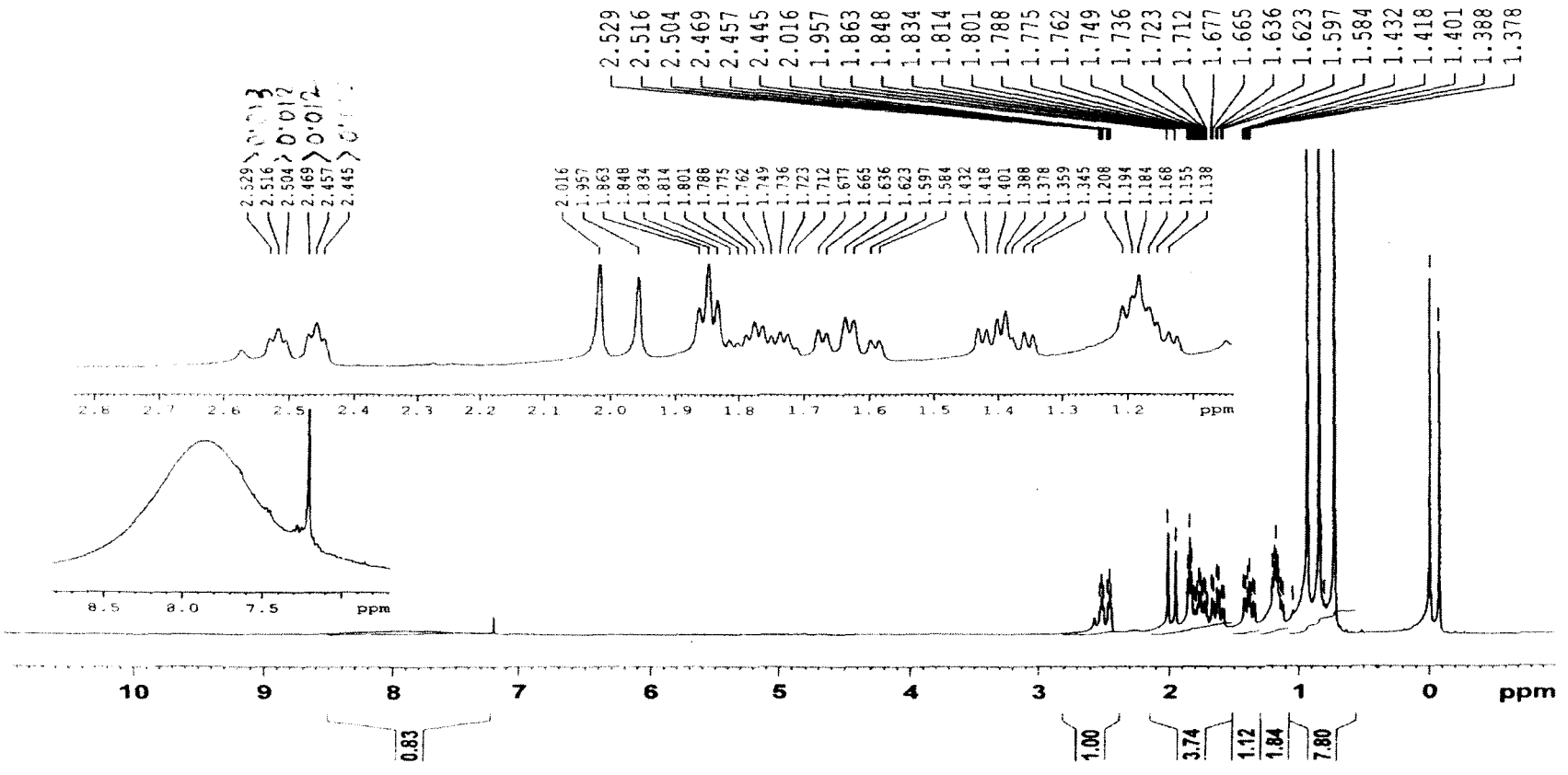


Fig. 6: ^{1}H NMR spectrum of 3,3-dibromocamphor oxime

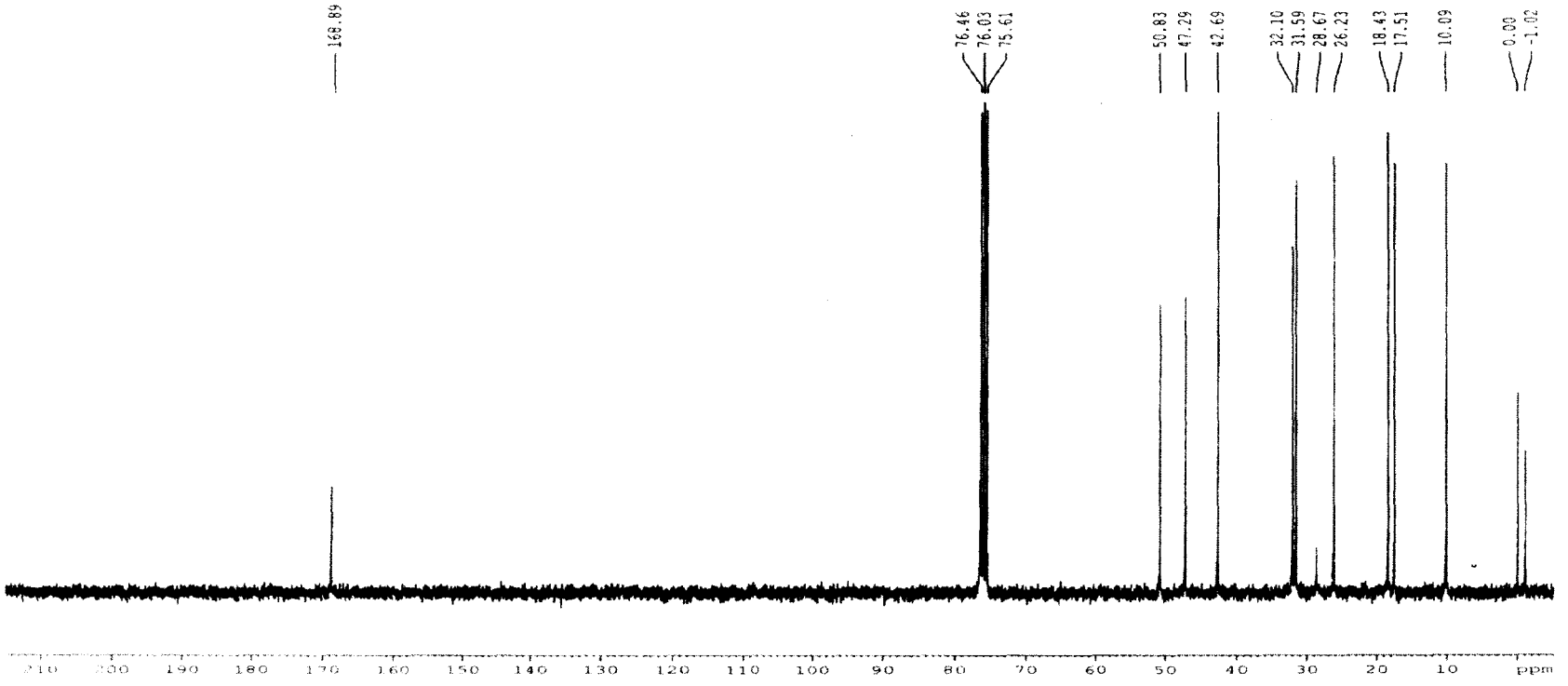


Fig. 7: ^{13}C NMR spectrum of 3,3-dibromocamphor oxime

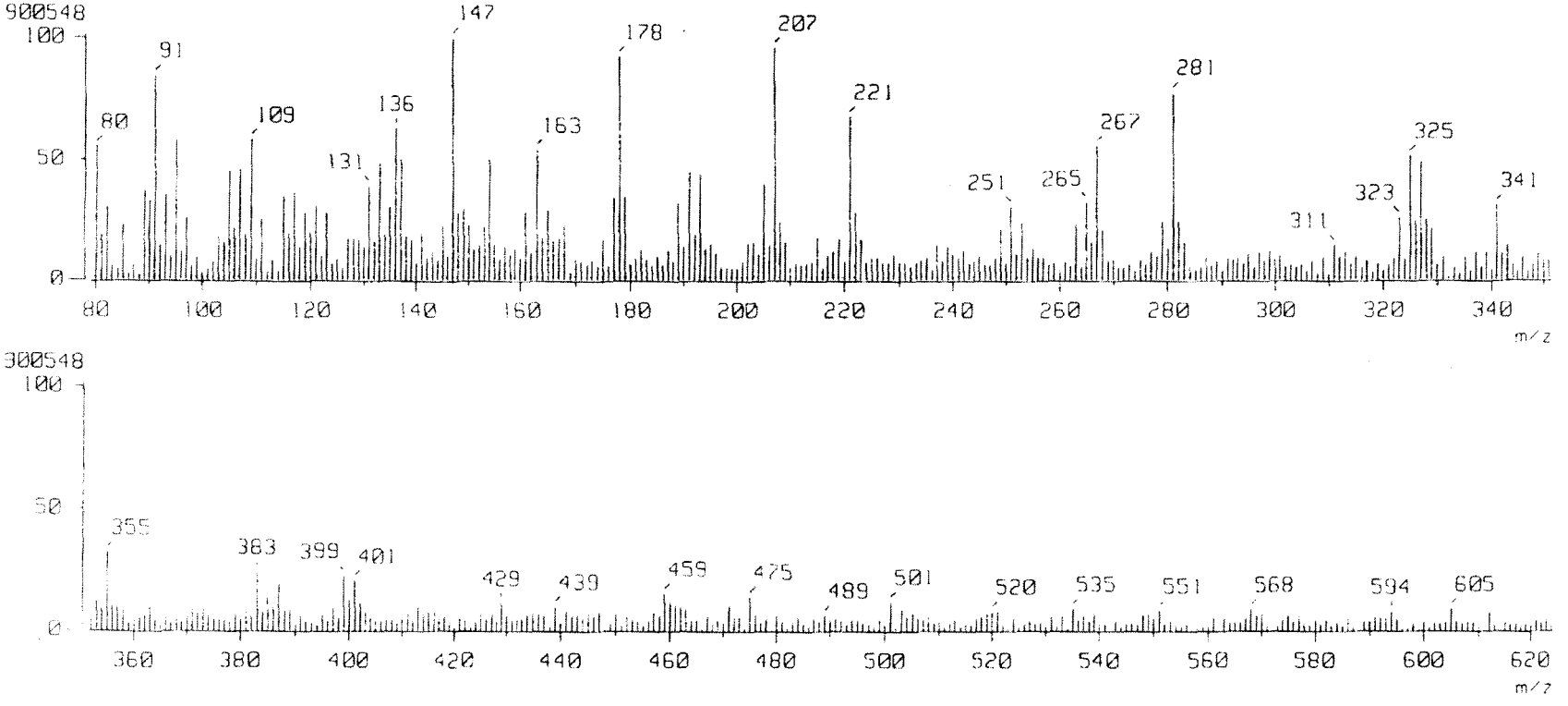


Fig. 8: Mass spectrum of 3,3-dibromocamphor oxime

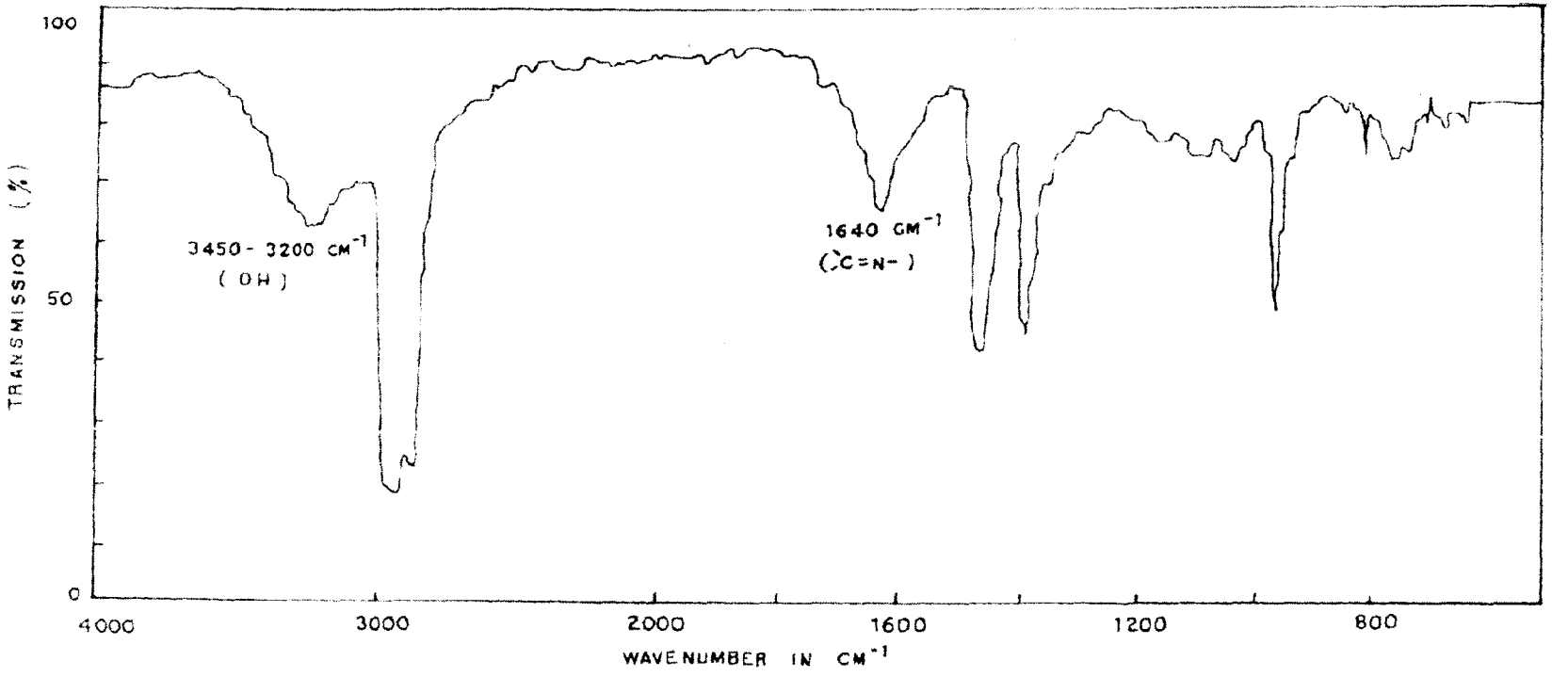


Fig. 9: IR spectrum of camphor oxime

CHAPTER III

EXPERIMENTAL & REFERENCES

Melting points are uncorrected. Petroleum ether used during the investigation had the b.p. 60-80^{0}C. IR spectra were taken in nujol or on KBr on Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on 300 MHz Bruker avance FT-NMR spectrometers using $CDCl_3$ solution containing TMS as reference. ^{13}C NMR spectra were recorded on 300 MHz Bruker avance FT-NMR spectrometer using $CDCl_3$ solution containing TMS as reference. Mass spectra were recorded on JEOL-AccuToF JMS-T100LC spectrometer. All the rotations were taken in $CHCl_3$ solution. Column chromatography was performed over silica gel (60-120 mesh, BDH). TLC was performed on chromatoplate of silica gel G (Glaxo and BDH) and the spots were located by exposing to iodine vapour.

Treatment of camphor (56) wth *N*-bromosuccinimide: Formation of 3,3-dibromo camphor (57)

A solution of 56 (3 g) in chloroform (150 mL) was mixed with dimethyl sulphoxide (75 mL). *N*-bromosuccinimide (3.5 g) was then added to it in small lots in order to keep the temperature of the reaction mixture below 25^{0}C and the mixture kept in dark for 10 days. It was extracted with chloroform and washed several times with water, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue (2.8 g) was chromatographed over silica gel column, developed with petroleum ether and eluted with the following solvents (Table 1).

Table 1

Eluent	Fractions 50 mL each	Residue On evaporation	m.p. after crystallization
Petroleum ether	1	oil	--
Pet. ether +ethyl acetate (80:20)	2-7	Solid	154-56^{0}C

Further elution with more polar solvents did not afford any solid material.

Examination of fractions 2-7 (Table 1) : Isolation of 3,3-dibromo camphor

The fractions 2-7 (Table 1) showed homogeneity on TLC were combined (0.8 g) and crystallized from a mixture of chloroform and methanol. The crystallization afforded crystals of compound, m.p. 155-60^{0}C. It showed positive Beilstein test for halogen and was found identical with 3,3-dibromo camphor 57 (mixed m.p., Co-IR and Co-TLC).

Analysis report	%C	%H
Found	38.60	04.50
Calculated for $C_{10}H_{14}OBr_2$	38.30	04.70

IR: ν_{max}^{Nujol} 1743 (CO), 1180 cm^{-1} Fig. 1

^{1}H NMR ($CDCl_3$): 0.913 ppm (broad multiplet, 6H for two geminal methyl at C_7). 1.939 ppm (m, 3H, for $-CH_3$ at C_1), 1.371 ppm (m, 2H, for C_6-2H), 1.684 ppm (m, 2H for C_5 -2H) and 2.343 ppm (m, 1H at C_4). Fig. 2

^{13}C NMR ($CDCl_3$): 9.26 ppm (C_{10}); 19.14 ppm and 19.78 ppm (C_8 and C_9), 46.78 (C_7), 29.91 ppm (C_6), 27.05 ppm (C_5), 43.29 ppm (C_4), 43.03 ppm (C_3), 210 ppm (carbonyl carbon), and 57.68 ppm (C_1) Fig. 3

Mass: m/z 308, 310 and 312 (1:2:1) 298, 297, 295, 154. Fig. 4

Preparation of oxime derivative of camphor

To a solution of camphor (3 g) dissolved in pyridine (30 mL) was added hydroxylamine hydrochloride (3 g) and ethanol (150 mL). The mixture was then refluxed on water bath for 4 hours. It was then cooled and poured over ice-cold water when white solid separated out. It was washed with water filtered through suction and dried. The dried mass was crystallized several times with chloroform-methanol mixture when camphor oxime 58 m.p. 118-119^{0}C (Lit. [74] m.p. 115-19^{0}C) was obtained.

IR: ν_{max}^{Nujol} 3450-3200, 1640, cm^{-1}. Fig. 9

Treatment of camphor oxime (58) with *N*-bromosuccinimide: Formation of 3,3-dibromocamphor oxime (59)

A solution of camphor oxime 58 (2 g) in chloroform (100 mL) was mixed with dimethyl sulphoxide (50 mL). *N*-bromosuccinimide (2 g) was then added to it in small lots in order to keep the temperature of the reaction mixture below 25^{0}C and the mixture kept in dark for 10 days. The residue (1.75 g) obtained after usual work up and therefore chromatographed over silica gel column. The chromatogram was developed with petroleum ether and eluted with the following solvents (Table 2).

Table 2

Eluent	Fractions 50 mL each	Residue On evaporation	m.p. after crystallization
Petroleum ether	1-2	Nil	--
Pet. ether +ethyl acetate (80:20)	3-10	Nil	--
Pet. ether +ethyl acetate (60:40)	11-14	Solid	98-99^{0}C

Further elution with more polar solvents did not afford any solid material.

Examination of fractions 11-14 (Table 2): Isolation of 3,3-dibromocamphor oxime

The fractions 11-14 (Table 2) showed homogeneity on TLC and were combined (0.8g), crystallized from a mixture of chloroform and methanol. The crystallization afforded crystals of compound, m.p. 100-105^{0}C. It showed positive Beilstein test for halogen and was found identical with 3,3-dibromocamphor oxime 59 (mixed m.p., Co-IR and Co-TLC).

Analysis report	%C	%H
Found	35.65	04.81
Calculated for $C_{10}H_{15}ONBr_2$	35.71	04.73

IR: ν_{max}^{Nujol} 3300-3400 cm^{-1} and other peaks at 1170, 948.9 and 725.2 cm^{-1}. Fig. 5

^{1}H NMR ($CDCl_3$):	0.95 ppm (C_{10}), 0.78 ppm and 0.84 ppm (for C_8 and C_9). The reaming protons have resonance singnals between 1.0 and 3.0 ppm from TMS and they overlaps badly thanks to spin-spin splitting. A broad singnal for the proton of =N-OH group in between 7.0 to 9.0 ppm from TMS.	Fig. 6
^{13}C NMR ($CDCl_3$):	10.09 ppm (C_{10}), 17.51 and 18.43 ppm (C_8, C_9), 26.23 ppm (C_5), 31.59 ppm (C_6), 47.29 ppm (C_3), 50.83 ppm (C4), 32.10 ppm (C_7), 42.69 ppm (C_1) and peak for C_2 quaternary carbon appeared at 168 ppm.	Fig. 7
Mass:	m/z 323, 325 and 327 in the ratio of 1:2:1 (two bromine atoms) 309, 311, 313 $[M-N]^+$; 281 $[M-C(CH_3)_2]^+$; 267, 265, 251, 221, 207, 178, 163 and 147 (base peak).	Fig. 8

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