

## CHARACTERIZATIONS IN STUDYING THE EFFECT OF ACID REAGENT ON THE REARRANGEMENT REACTION OF CAMPHOROXIME PRODUCING DIFFERENT RATIOS OF THE $\alpha$ : $\beta$ -CAMPHOLENE NITRILES

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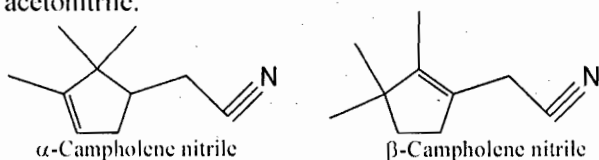
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### Abstract

There are two major steps in the synthesis of pleasant fragrant  $\alpha$ - and  $\beta$ - campholene nitriles from camphor. The first is the reaction of hydroxylamine with camphor to give the camphoroxime, which rearranges in the presence of acid during the second step to give either  $\alpha$ - or  $\beta$ - or both  $\alpha\beta$ - campholene nitriles. The nature of the acid determines the type of isomer(s) formed and the amount of each isomer in the product. This paper reports the rearrangement products of camphoroxime using HI,  $\text{PCl}_5$ ,  $\text{HNO}_3$  and  $\text{CH}_3\text{COOH}$  acids, which are rarely used in literature. Also  $\text{H}_2\text{SO}_4$ ,  $\text{HNO}_3$ , HI,  $\text{PCl}_5$  and  $\text{H}_3\text{PO}_4$  were found to give very high yields (79% and above) of the fragrant campholene nitriles, while organic acid catalysts gave campholene nitriles in very low yields (<5%).

### 1. Introduction

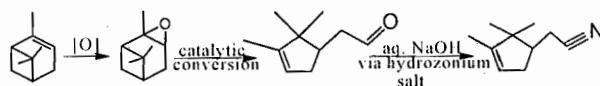
Campholene nitriles ( $\text{C}_{10}\text{H}_{15}\text{N}$ ) are monoterpenes that have high economic importance as aroma and cosmetic enhancing fragrant chemical compounds. They have found very wide applications in aroma and perfumery industries. Campholene nitriles are also referred to as campholenitriles, and they exist in  $\alpha$ - and  $\beta$ - isomeric forms. The  $\alpha$ -isomer is 2, 2, 3-trimethyl-3-cyclopentene-1-acetonitrile, while the  $\beta$ -isomer is 2, 3, 3-trimethyl-1-cyclopentene-1-acetonitrile.



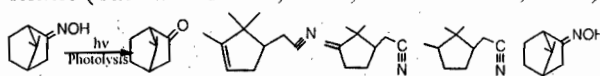
Campholene nitriles are stable in applications as well as safe on skin and environment (Brunke, 1993). Their odours range from fresh resinous to woody sandalwood (Brunke and Klein, 1982). Campholene nitriles and their derivatives are referred to with a variety of trade names like cantryl in Dragoco, sandalwood, samsara, bacdanol brahmanol, sandalore, sandrano and polysantol. Natural occurrence of compounds having structures similar to campholenes are reported as components of essential oils like juniperberry, *J.communis* (Thomas, 1972), physiologically and pharmacologically active compounds (Nomura *et al.*, 1996; Pirisino *et al.*, 1980; Soloduchko and Zabza, 1979).

The high demand and economic importance of aroma compounds like campholene nitriles which are obtained in very low yields from natural sources, necessitates its synthesis, for better yields, at lower cost and cheaper rate (Bauchbauer *et al.*, 1983; Tyman, 1983; Moronkola *et al.*, 2004; Gream *et al.*, 2006). Meyer (1883) and Leuckart (1887) starting from camphor first attempted the synthesis of campholene nitrile (Pawlenski, 1903), while Tiemann (1896) was the first to elucidate and assign the structure. Campholene nitriles are now synthesized by a number of ways; some of the routes are illustrated below:

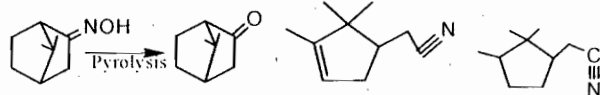
1. Epoxidation of  $\alpha$ -pinene, which is catalytically, converted to campholene aldehyde and on treatment with aqueous NaOH through its hydrazone salt form mainly the  $\alpha$ -campholene nitrile (Smith and Walker, 1962).



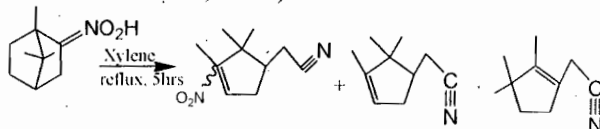
2. Photolytic reaction of camphoroxime gave  $\alpha$ -campholene nitrile as one of the five compounds formed.  $\alpha$ -Campholene nitrile is the second fraction in the chromatographic separation. The other four compounds formed are camphor, iso- $\alpha$ -campholenitrile,  $\alpha$ -campholanitrile and unreacted oxime (Sato and Obase, 1967; Winters *et al.*, 1971).



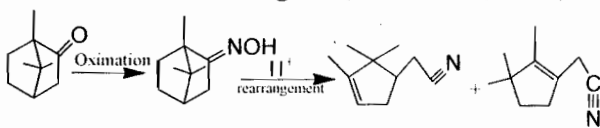
3. Pyrolytic reaction of camphoroxime gave  $\alpha$ -campholene nitrile and two other products, camphor and  $\alpha$ -campholanonitrile. (Sato and Obase, 1967).



4. Thermolysis of camphor-nitrimine gave nitronitriles in high yields (38%), along with the  $\alpha$ - (20%) and  $\beta$ - (14%) campholene nitriles (Winters *et al.*, 1971; Buchi and Wuest, 1979).



5. Acid-catalyzed rearrangement of camphoroxime (formed from oximation of camphor), in a form of Beckmann fission to form mixtures of  $\alpha$ - and  $\beta$ -campholene nitriles in different ratios, depending on the nature of acidic reagent (Nazir *et al.*, 1965).



This method is the most preferred, most likely because of the easy accessibility and cheap precursor of camphor. Action of acidic reagents such as  $\text{H}_2\text{SO}_4$  (Pirisino and Sparatore, 1968; Conley and Ghosh, 1971),  $\text{SOCl}_2$  (Pawlenski, 1903),  $\text{HCl}$  (Pirisino and Sparatore, 1968; Kozlov and Pekh, 1982) and  $\text{P}_2\text{O}_5$  (Nazir *et al.*, 1965), have been investigated in the conversion of camphoroxime to campholene nitriles.  $\alpha$ -Campholene nitrile is the main product in the conversion of camphoroxime when  $\text{P}_2\text{O}_5$  and concentrated  $\text{H}_2\text{SO}_4$  were the acidic catalysts [Nazir *et al.*, 1967; Pirisino and Sparatore, 1968; Brieskorn and Hemmer, 1976]. As the  $\text{H}_2\text{SO}_4$  become more dilute,  $\beta$ -campholene nitrile was also formed in appreciable amount (Pirisino and Sparatore, 1968). Concentrated  $\text{HCl}$  catalyzed rearrangement of camphoroxime to yield mainly  $\beta$ -campholene nitrile (Nazir *et al.*, 1965). Dehydration occurred as side reaction in the rearrangement of camphoroxime to nitriles with strong acids like  $\text{H}_2\text{SO}_4$  and *p*-toluene sulphonyl chloride (Nazir *et al.*, 1965; Pirisino and Sparatore, 1968). The rearrangement reaction in the second step mimics to some extent Beckmann's (Nazir *et al.*, 1965 & 1967; Conley and Ghosh, 1971) in the involvement of change of the actual carbon-skeleton of camphoroxime compared to the structure of the final campholene nitrile formed. Beckmann rearrangement is characterized by stereochemical interchange of the group anti- to the  $\text{OH}$  on  $\text{C}=\text{N}$  i.e. it is a stereochemical intramolecular exchange of the anti-group in the rearrangement reaction.

In the synthesis of campholene nitriles, studies using organic acids like  $\text{CH}_3\text{COOH}$  and inorganic acids like  $\text{HI}$ ,  $\text{PCl}_5$  and  $\text{HNO}_3$  in the rearrangement

reactions of camphoroxime are rare in literature. This paper reports the use of modern spectroscopic data to characterize and quantify products of the synthesis of  $\alpha$ - and  $\beta$ -campholene nitriles from rearrangement of camphoroxime.

## 2. Materials and Methods

General experimental procedure:

Melting point was determined on Gallenkamp melting point apparatus. Refractive indices were taken on Hilger and Watts Refractometer. IR spectra were recorded on ATI Mattson Genesis series FTIR TM in  $\text{CCl}_4$ , which was corrected for, and a Bruker IFS 25 FTIR instrument, ran neat on  $\text{NaCl}$  cells.

UV spectra were taken on a UV-160A, UV-visible recording Shimadzu spectrophotometer (stabilizer-volt Ace Type IB, solvent was hexane) and Hewlett Packard 8452 a single beam spectrophotometer. Quartz cells of 1 cm cell path were used and solvents were absolute ethanol and hexane.

$^1\text{H}$  NMR spectra were recorded at 200 MHz on Varian XL200 and 300 MHz on Bruker AC-300 NMR spectrometers.  $^{13}\text{C}$  NMR spectra were recorded on AC-300 spectrometer. Proton-carbon-fluorine-phosphorus [HCFP] probe was used and NMR was conducted at room temperature. All NMR spectra were recorded in  $\text{CDCl}_3$  and chemical shifts were reported in ppm downfield of TMS as internal standard. The residual solvent signals at 7.24 ppm and 77.0 ppm for  $\text{CDCl}_3$  were also used as internal reference standards. The NMR absorptions were quoted in  $\delta$  units.

Low-resolution electron ionization mass spectra (LREIMS) were acquired at 70 eV using VG Trio 1 quadrupole mass spectrometer equipped with a direct inlet probe. High-resolution electron ionization mass spectra (HREIMS) were produced using VG ZAB-HF double focusing mass spectrometer.

Syntheses and purifications were monitored with thin layer chromatography (TLC). Chromatograms were on pre-coated TLC aluminium plates of silica gel, and prepared TLC plates of 15 cm by 10 cm. The TLC plates were prepared by spreading aqueous slurry of Merck Silica gel G on glass plates. The plates were activated at 110  $^\circ\text{C}$  for 1 hr. Spotted plates were developed in different solvent systems such as hexane / ethylethanoate / trichloromethane / benzene / methanol. Positions of each component in the compound mixtures were visualized by exposure to iodine vapour in iodine tank for 5 to 10 minutes. Reference compounds were supplied by flavour division of Haarmann and Reimer in Holzminden, Germany. Products of the syntheses were purified and isolated by vacuum liquid chromatography. TLC grade silica gel (60 mesh) and sintered glass filter funnel of porosity 3 with ground glass joints were used in the VLC adapting the method of Coll and Bowden, 1986.

Synthesis of camphoroxime:

40 g (0.58 mol) of hydroxylamine hydrochloride [NH<sub>2</sub>OH.HCl], 40 ml of pyridine and 400 ml (95%) ethanol were added to 40 g (0.26 mol) camphor and refluxed for 2 hrs with antibumping granules. Excess alcohol was distilled off under reduced pressure. Content was placed in an ice bath and 400 ml distilled water was added while stirring until white precipitate of camphoroxime was formed. It was filtered under suction and recrystallized in distilled ethanol (160 ml). The pure solution was left for 48 hrs, after which needle-like pure oxime crystallized out. Crystals were filtered by suction and dried in a dessicator in 90% (wt) yield. M.pt 116-117 °C (Lit. M.pt is 115-119 °C). Rearrangement of camphoroxime to α- and β-campholene nitriles:

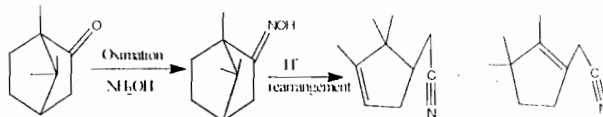
Camphoroxime was added to each of the acidic reagents H<sub>2</sub>SO<sub>4</sub>, HI, PCl<sub>5</sub>, H<sub>3</sub>PO<sub>4</sub>, HNO<sub>3</sub>, SOCl<sub>2</sub> and CH<sub>3</sub>COOH in a ratio of 1:2 of oxime:acid. The oxime and each acid were refluxed for 60 mins. Reaction mixture was added to ice and 150 ml distilled water. Oily product was extracted with diethyl ether (100 ml) three times. Extract was neutralized with saturated NaHCO<sub>3</sub> and was washed with distilled water. The ether was dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was distilled off under vacuum leaving the campholene nitrile.

Pure campholene nitriles were eluted with 90% hexane in chloroform by vacuum liquid chromatography on TLC grade silica gel (60 mesh) using the sintered glass of porosity 3 (Coll and Bowden, 1986). Different yields of campholene nitriles were obtained from each acid.

3. Results and Discussion

α- and β- campholene nitriles were synthesized from camphoroxime (M.pt = 116-117 °C), which was obtained from camphor in 90.2 % yield by modified methods of Nazir *et al.*, 1965; Conley and Ghosh,

1971, and Brieskorn and Hemmer, 1976. Synthesis of camphoroxime involved an initial nucleophilic addition of the nitrogen on the hydroxylamine to the carbon of the carbonyl on camphor, followed by the elimination of water to yield the camphoroxime. Structure of the camphoroxime synthesized was confirmed by spectroscopy (IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and MS) (see Fig.1 & Table 1).

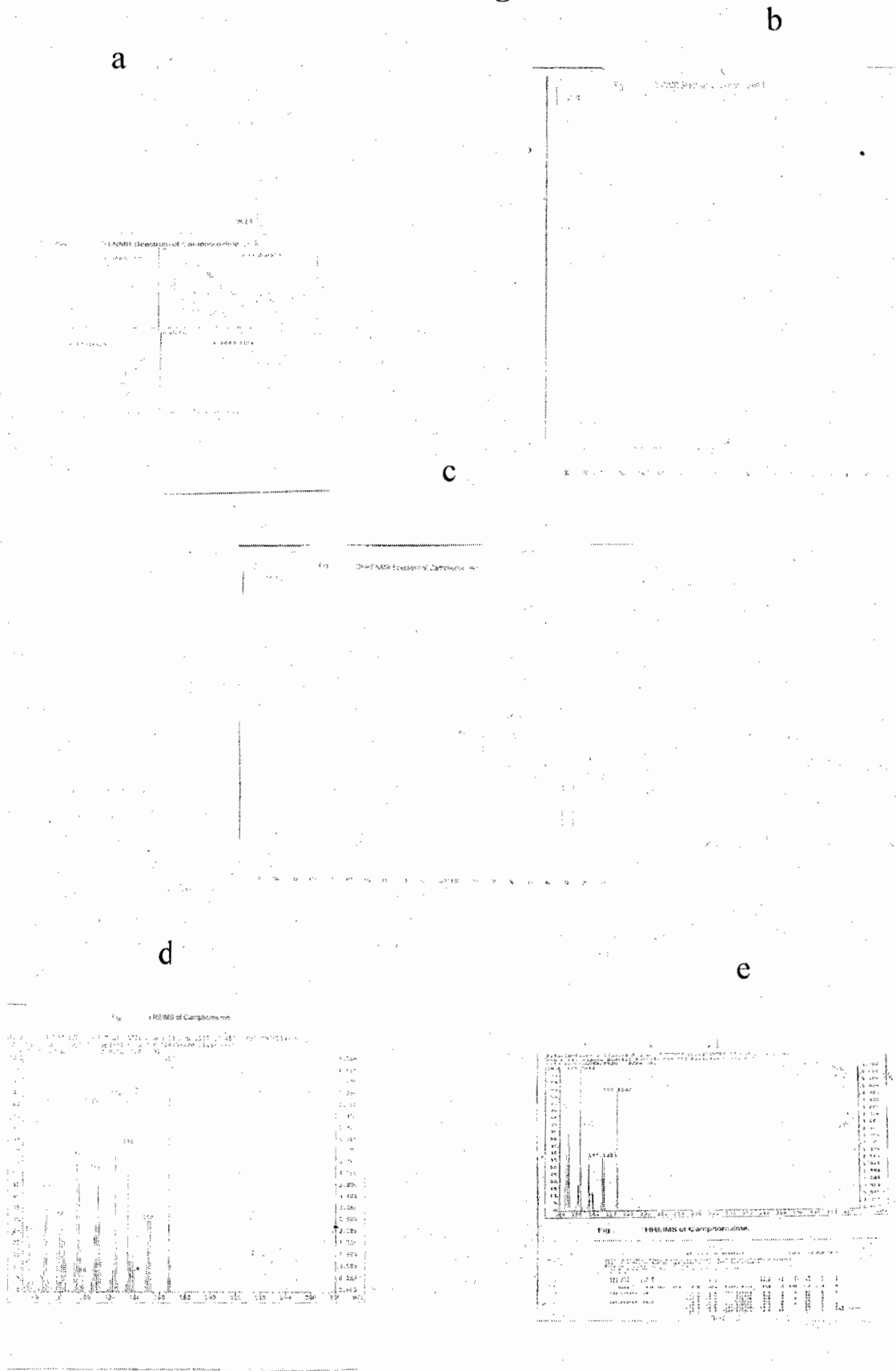


The IR spectrum agreed with that in the literature (Nazir *et al.*, 1965; Sato and Obase, 1967). <sup>1</sup>H NMR of the three methylene(3 -CH<sub>2</sub>) groups on C-3, 5, 6 appear as doublets and multiplets between δ 2.0-1.18 because of geminal and vicinal couplings between the protons. <sup>1</sup>H NMR spectrum of prepared oxime agreed with its structure. <sup>13</sup>C NMR spectrum indicated the occurrence of ten carbon atoms, which agrees with structure of camphoroxime. DEPT-NMR showed the three methyl C-8, 9, 10 pointing up in the high field region of the spectrum, likewise it showed the three methylene C-3, 5, 6 pointing down between δ 33-27, and methane C-4 absorbed at δ 43.61. However the quaternary C-1, 2, 7 were not visible in the DEPT-NMR since only carbon atoms carrying hydrogen (CH<sub>3</sub>, CH<sub>2</sub> & CH) are observed in DEPT spectrum. HREIMS of oxime indicated mass of 167.1282, which is close to that calculated for C<sub>10</sub>H<sub>17</sub>NO (167.1310), and gave a double bond equivalence (DBE) of 3.0 accounted for by the two rings and one carbon-nitrogen double bond (C=N). Loss of C=N-OH from oxime give the base peak at m/z 124.0644 on the HREIMS. The mass spectrum is consistent with the structure of camphoroxime. The camphoroxime was subsequently used in the syntheses of campholene nitriles CN<sub>1</sub>-CN<sub>7</sub>.

Table 1: Spectra data of synthesized camphoroxime

Technique	Values
IR (cm <sup>-1</sup> )	3360 (OH), 2852, 2926, 1463, 721 & 1375 (CH <sub>2</sub> & CH <sub>3</sub> ), 1641 & 1691 (C=N).
<sup>1</sup> H-NMR [δ(ppm)]	0.73, 0.85 & 0.94 (3CH <sub>3</sub> , s), 2.0[CH <sub>2</sub> , d], 1.85, 1.75, 1.63, 1.39 & 1.18 (2CH <sub>2</sub> , m), 2.5 (CH, dt), 9.5 (OH, bs)
<sup>13</sup> C and DEPT-NMR [δ(ppm)]	169.4 (C=NOH), 10.99, 18.43 & 19.34 (3CH <sub>3</sub> ), 27.2, 32.5 & 32.9 (3CH <sub>2</sub> ), 43.61 (CH), 51.66 & 48.14 (2C <sub>q</sub> ).
MS: HREIMS & LREIMS (m/z)	167.1282(100%) [M <sup>+</sup> ], 124.0644(85%) [M-2(CH <sub>3</sub> ) <sub>2</sub> -H] <sup>+</sup> , 134(64%) [M-CH <sub>3</sub> -H <sub>2</sub> O] <sup>+</sup> , 93(59%), 108(53%), 110(49%), 150(30%) [M-OH] <sup>+</sup> , 152(30%) [M-CH <sub>3</sub> ] <sup>+</sup> , 136(15%) [M-NOH] <sup>+</sup> , 122(10%) [M-3CH <sub>3</sub> ] <sup>+</sup>

**Fig.1**



The camphoroxime prepared were acid-catalyzed to campholene nitriles using seven different acids. The yields are presented in Table 2.

Conversion of the camphoroxime to nitriles is an acid catalyzed rearrangement reaction similar to the Beckmann type. The acidic reagents successfully effected the syntheses but in different yields of the campholene nitriles, which were purified by vacuum liquid chromatography (VLC). Use of the organic acid catalyst ethanoic acid gave very low yield of campholene nitrile (2.12%), though it is rarely reported in literature. The other six acids produced high yields of the campholene nitriles (53 to 95.6%, Table 2). TLC analyses show the campholene nitriles at  $R_f = 0.5$  (in 1:1 hexane:CHCl<sub>3</sub>) and  $R_f = 0.77$  (in CHCl<sub>3</sub>). Synthesized campholene nitriles were characterized by IR, UV, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS.

Spectral Data of the Campholene Nitriles (CN<sub>1</sub>-CN<sub>6</sub>) Synthesized

IR and UV:

The IR results agree with the literature values reported for  $\alpha$ - and  $\beta$ -campholene nitriles (Nazir *et al.*, 1965; Sato and Obase, 1967). The absorptions displayed in the UV are as stated in Table 3.

<sup>1</sup>H, and <sup>13</sup>C NMR of synthesized campholene nitriles: The <sup>1</sup>H-NMR of CN<sub>1</sub> (Fig. 2) from action of conc. H<sub>2</sub>SO<sub>4</sub> on oxime show that  $\alpha$ - isomer is the major product. This agrees with the literature report of Pirisino and Sparatore, 1968; Brieskorn and Hemmer, 1976. Olefinic proton on C-4 of the  $\alpha$ - isomer in CN<sub>1</sub> was observed as multiplet at  $\delta$  7.3. Methylene protons on C-7 are represented as 2H multiplet at  $\delta$  3.2 while the protons on C-5 resonate as multiplet at  $\delta$  2.1 ( $J = 2.8$  Hz) due to vicinal and geminal couplings. The

multiplet at  $\delta$  2.7 is for the methane proton on C-1 of the  $\alpha$ - isomer. Methyl protons show signals at  $\delta$  0.9,  $\delta$  1.0 and  $\delta$  1.3. The multiplet absorption at  $\delta$  1.8 indicate that some of  $\beta$ -campholene nitrile is also synthesized in CN<sub>1</sub>, hence the catalytic effect of conc. H<sub>2</sub>SO<sub>4</sub> on camphoroxime produces mostly  $\alpha$ -campholene nitrile and some  $\beta$ -campholene nitrile.

<sup>1</sup>H NMR of the campholene nitrile, CN<sub>2</sub>, formed from the reaction of acidic reagent HI on camphoroxime is presented in Fig. 2. The absorptions show that CN<sub>2</sub> is a mixture of  $\alpha$ - and  $\beta$ -campholene nitriles. Multiplets at  $\delta$  2.1 and  $\delta$  2.35 are for the absorptions of the ring methylene protons in the  $\beta$ -isomer. Olefinic protons on C-4 of the  $\alpha$ -isomer are responsible for the multiplet at  $\delta$  7.3. Methylene protons on C-7 show signal at  $\delta$  3.2 while multiplets at  $\delta$  2.7 is for the methine-proton on C-1 of the  $\alpha$ - isomer. Protons on the three-methyl groups resonate at  $\delta$  1.0, 1.3 and 1.55.

Expanded <sup>1</sup>H NMR, <sup>13</sup>C NMR and DEPT-NMR of CN<sub>5</sub> are shown in Fig. 3 a & b. CN<sub>5</sub> is the campholene nitrile formed from the action of HNO<sub>3</sub> on camphoroxime, which is rarely used in literature. The geminal methyl protons appear as 3H singlets at  $\delta$  0.85 and  $\delta$  0.96. The third methyl protons resonate at the lower field  $\delta$  1.42 as 3H singlet, which is more deshielded. <sup>13</sup>C NMR spectrum indicates the three methyl carbons show signals at  $\delta$  12.21, 20.26 & 20.34. These were also confirmed by the DEPT spectrum pointing downwards at  $\delta$  25-40, which indicates more of the  $\beta$ -campholene nitrile is formed when HNO<sub>3</sub> is used as acidic reagent on camphoroxime. Absence of the vinylic (olefinic) proton confirm that the major isomer formed in CN<sub>5</sub>

**Table 2:** Acids used and Yields of Campholene nitriles synthesized with the RI and TLC ( $R_f$ ) results.

Acid used*	Campholene nitrile formed	% Yield**	Refractive Index (RI)
H <sub>2</sub> SO <sub>4</sub>	CN <sub>1</sub>	95.57	1.490
HI	CN <sub>2</sub>	84.31	1.565
PCl <sub>5</sub>	CN <sub>3</sub>	83.75	1.484
H <sub>3</sub> PO <sub>3</sub>	CN <sub>4</sub>	79.66	1.468
HNO <sub>3</sub>	CN <sub>5</sub>	92.13	1.491
SOCl <sub>2</sub>	CN <sub>6</sub>	53.15	1.554
CH <sub>3</sub> COOH	CN <sub>7</sub>	2.12	1.473

\*The acid reagent which catalyzed syntheses of campholene nitriles from camphoroxime in a form of Beckmann rearrangement reaction.

\*\*Percentage yield of campholene nitriles synthesized after purification by VLC.

$R_f$ (CHCl<sub>3</sub>) 0.77; (C<sub>6</sub>H<sub>14</sub>:CHCl<sub>3</sub> 1:1) 0.5

**Table 3:** IR and UV Spectral Data of Synthesized Campholene Nitriles [CN<sub>1</sub>-CN<sub>6</sub>]

IR absorption bands(cm <sup>-1</sup> ) & functional group	UV absorptions
2240-2255(m) C $\equiv$ N <sub>stretch</sub>	$\lambda_{max}$ (nm) in Hex: 283(1.5), 265(0.5), 240(1.55)
2800-2950(s) C - H <sub>stretch</sub>	
1600(w-m) C = C <sub>stretch</sub>	$\lambda_{max}$ (nm) in EtOH: 250(2.1), 230(2.8), 220(2.7)
700-900 C - H <sub>def</sub> with overtone bands<2000	

The IR results agree with the literature values reported for  $\alpha$ - and  $\beta$ -campholene nitriles (Nazir *et al.*, 1965; Sato and Obase, 1967) The UV absorptions are as shown above.

Fig.2

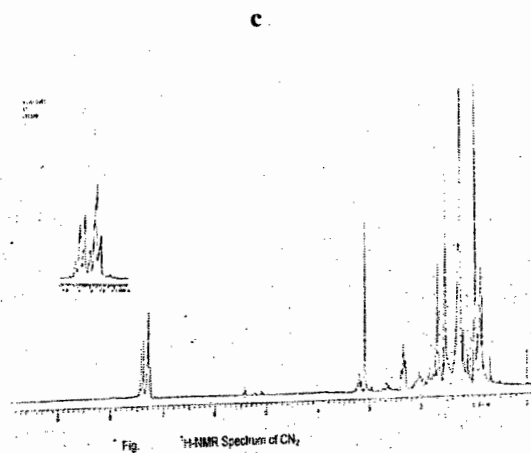
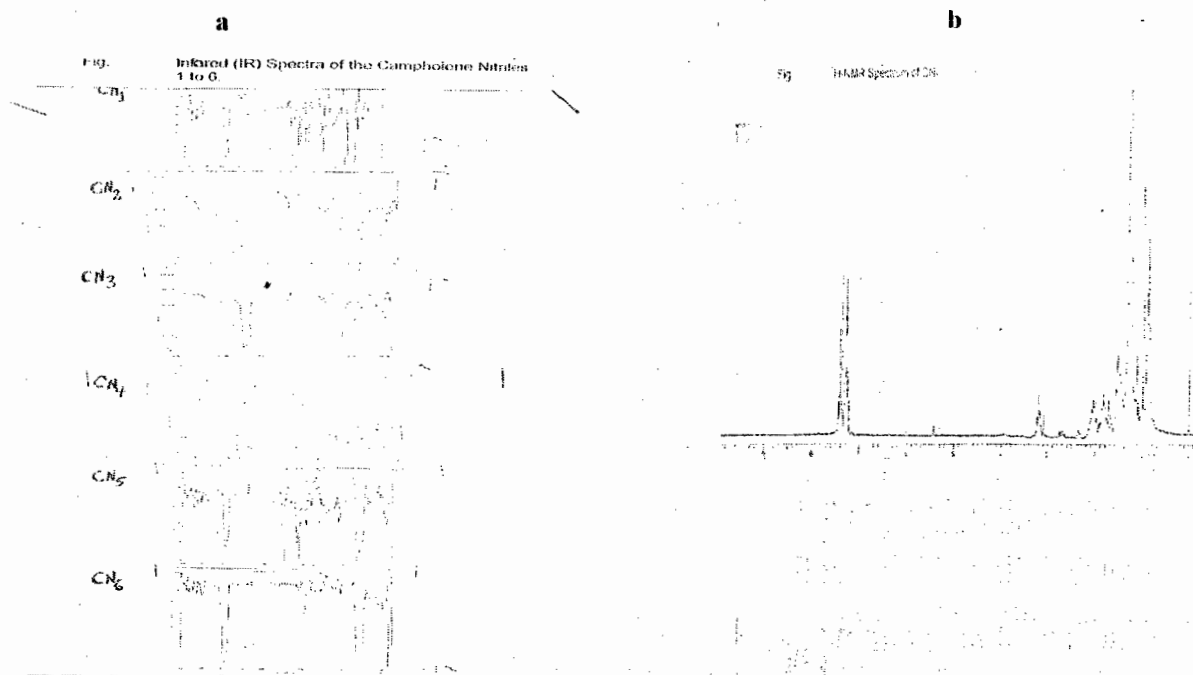
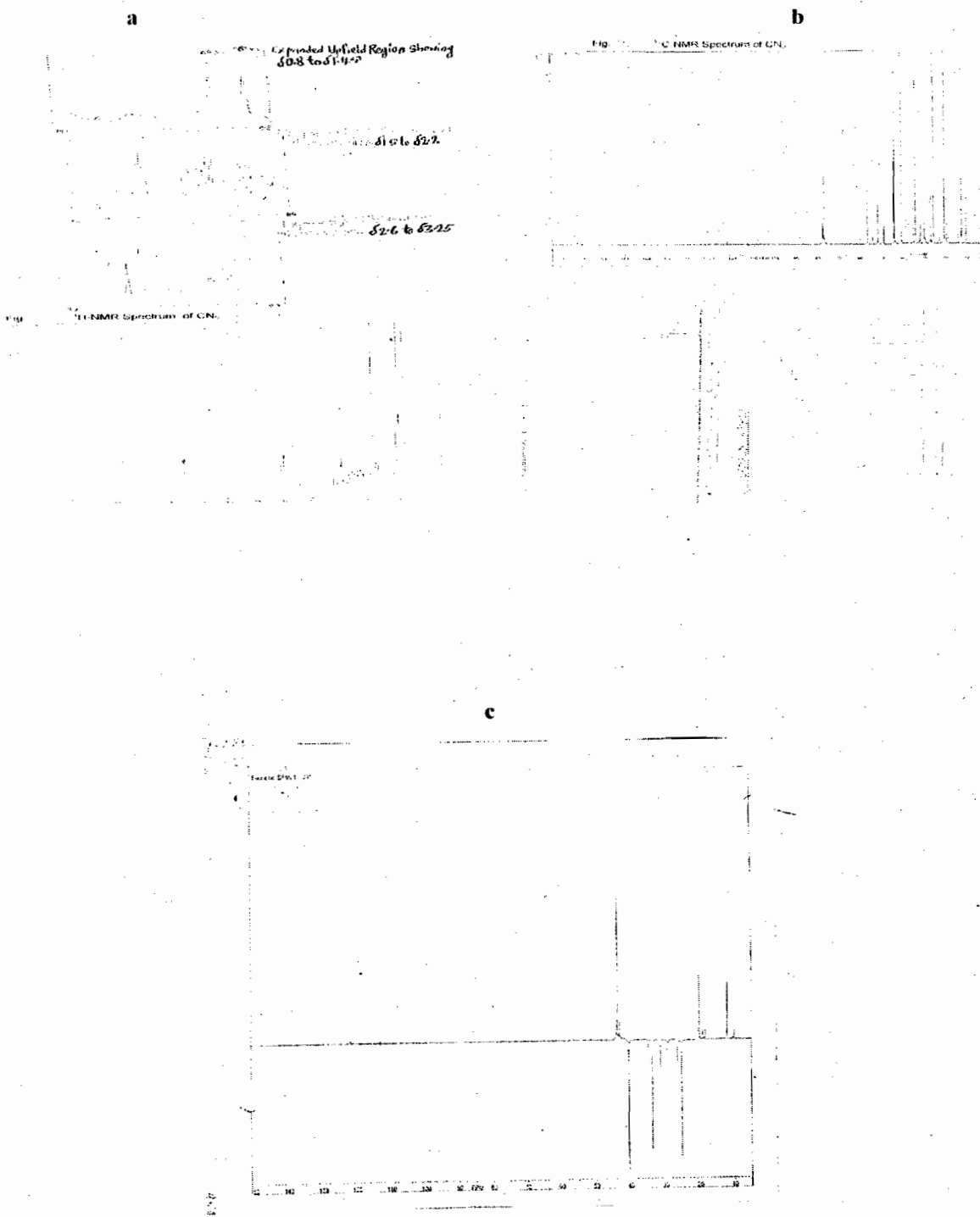
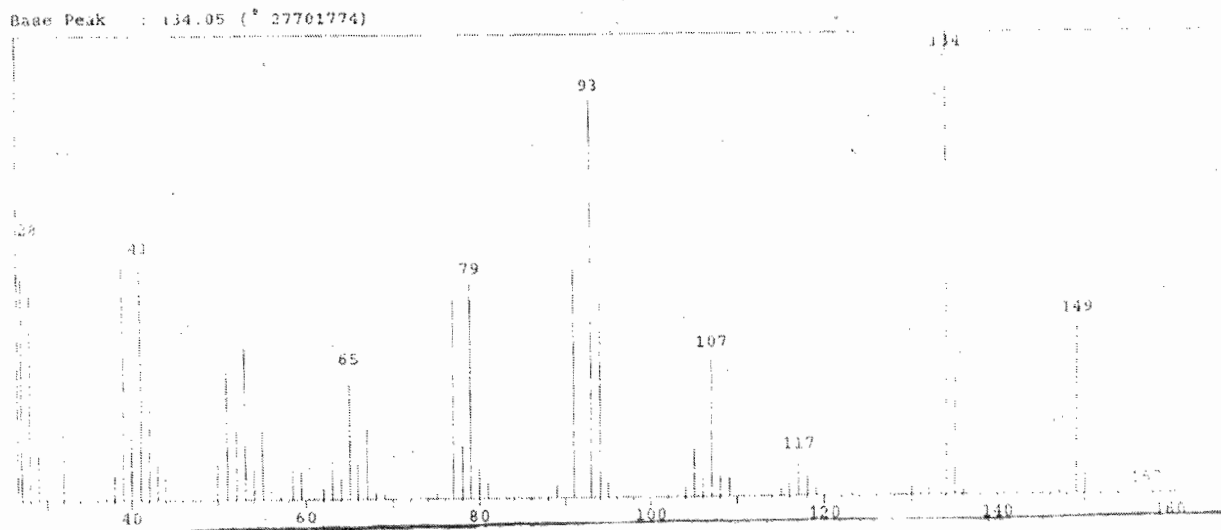


Fig.3



**Fig.4:** Mass Spectrum of Campholene nitrile in  $CN_1$ 

is  $\beta$ -campholene nitrile. The three methylene protons on C-4, 5, 7 resonate as doublets, triplets and multiplets at  $\delta$  1.65, 1.81, 1.98, 2.1, 2.72 and 3.04 which were caused by both geminal and vicinal couplings between the protons. Methylene carbons show signals at  $\delta$  25.41 (C-4),  $\delta$  33.83 (C-5) and  $\delta$  40.57 (C-7) on the  $^{13}C$  NMR spectrum. The  $^{13}C$  NMR decouple signals of methyl, methylene and methine-carbons so that signal appears as a single line.  $CH_3$  is a quartet,  $CH_2$  is a triplet and  $CH$  is a doublet. Quarternary carbon atoms C-1, 2, 3, 6 were observed at  $\delta$  128.8 (C-1),  $\delta$  128.7 (C-2),  $\delta$  56.46 (C-3), and  $\delta$  189.4 (C-6), which are singlets. The quarternary carbon atoms are not visible in the DEPT spectrum. Absorptions of C-1 and C-2 are close because the two carbon atoms are in the same chemical environment, and the signals were not very intense since the carbon atoms were not bonded directly to any H atom. Hence no coupling which usually contribute to the strong signals observed in  $^{13}C$  NMR of  $CH_3(q)$ ,  $CH_2(t)$  and  $CH(d)$ . Occurrence of little  $\alpha$ -isomer is responsible for the strong methine-carbon signal at  $\delta$  43.87, which also appeared on the DEPT spectrum.

MS of campholene nitrile:

The mass spectrum of each of  $CN_1$ - $CN_6$  had the molecular ion  $[M^+]$  at  $m/z$  149, which corresponds to the molecular weight as predicted by Sato and Obase, 1967. Mass spectrum of  $CN_1$  is given in Fig. 4, other important fragments in the spectrum are at  $m/z$  134 [b.pk:  $M-CH_3$ ] $^+$ , 150  $[M+1]^+$ , 135  $[M-N]^+$ , 109  $[M-CH_2CN]^+$  and 93  $[M-2CH_3-CN]^+$ . The spectra results are the same as those of literature (Brunke, 1993; Brieskorn and Hemmer, 1976; Conley and Ghosh, 1971).

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