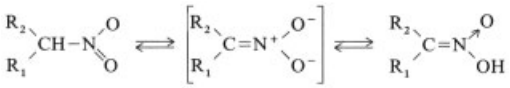
Nitro Compounds, Aliphatic

SHELDON B. MARKOFSKY, W. G. Grace & Co., Columbia, Maryland 21044, United States

1. Introduction

Aliphatic nitro compounds (RNO_2), also called nitroalkanes and nitroparaffins, are isomeric with the chemically different alkyl nitrites (RONO). As shown by the following equilibrium involving a secondary nitroalkane, the nitroalkane and nitronic acid are tautomers, sharing a common nitronate anion.

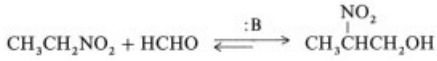


The nitroalkane is less acidic than the corresponding nitronic acid and, in most cases, the equilibrium lies far to the left. The acidity of the primary and secondary nitroalkanes is due partly to the electron-withdrawing effect of the nitro group and the resonance stability of the nitronate anion.

2. Properties

Physical Properties. The four nitroalkanes of greatest industrial significance, nitromethane [*75-52-5*], CH_3NO_2; nitroethane [*79-24-3*], $CH_3CH_2NO_2$; 1-nitropropane [*108-03-2*], $CH_3CH_2CH_2NO_2$; and 2-nitropropane [*79-46-9*], $CH_3CH(NO_2)CH_3$ are all colorless liquids when pure. Nitroalkanes are only slightly soluble in water. Due in part to its polarity, the nitro group causes a large increase in flash point and boiling point compared to the corresponding hydrocarbon. Nitroalkanes are often useful because they readily form azeotropes with many organic solvents such as alcohols, ketones, and hydrocarbons [1]. The physical properties of the four basic nitroalkanes are listed in Table 1 (see next page).

Chemical Properties. Primary and secondary nitroalkanes are excellent building blocks for the synthesis of more complex molecules, since the readily formed nitronate anion undergoes many useful condensation reactions. Especially important is the condensation of these anions with aldehydes and ketones (Henry reaction) [3–8], and the Michael reaction, in which the nitronate anion reacts with α,β-unsaturated carbonyl compounds, nitriles, esters, and other activated alkenes [9–12]. The following is an example of the Henry reaction:



A typical Michael addition is shown as follows:

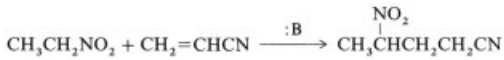


Figure 1 shows how nitroalkanes can be employed to make more complicated molecules.

The nitro group can subsequently be transformed into a variety of other functional groups, as illustrated in Figure 2. Thus, nitroalkanes allow the precise placement of these functional groups into complex structures. The chemistry depicted in Figures 1 and 2 (see next pages) is discussed in detail in [2, 13–18].

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Table 1. Physical properties of the four common nitroalkanes [2]

Property	Nitromethane	Nitroethane	1-Nitropropane	2-Nitropropane
M_r	61.041	75.068	89.095	89.095
bp (101.3 kPa), °C	101.20	114.07	131.18	120.25
Aqueous azeotrope				
bp (101.3 kPa), °C	83.59	87.22	91.63	88.55
wt % nitroalkane	76.4	71.0	63.5	70.6
mp (101.3 kPa), °C	−28.55	−89.52	−103.99	−91.32
Density, g/cm^3				
at 20 °C	1.138	1.051	1.001	0.988
at 30 °C	1.124	1.039	0.991	0.977
n_D^{20}	1.38188	1.39193	1.40160	1.39439
Vapor pressure at 25 °C, MPa	4.89	2.79	1.36	2.29
Vapor density (air = 1)	2.1	2.58	3.06	3.06
Evaporation rate (BuOAc = 1)	1.39	1.21	0.88	1.10
Evaporation number (diethyl ether = 1)	9	11	16	10
Heat of combustion, kJ/mol (liq.) at 25 °C	−709	−1363	−2017	−2001
Heat of formation, kJ/mol (liq.) at 25 °C	−113	−142	−168	−181
Heat of vaporization, kJ/mol (liq.)				
at 25 °C	38.3	41.6	43.4	41.4
at *bp*	34.4	38.0	38.5	36.8
Specific heat capacity at 25 °C, Jmol^{-1} K^{-1}	106	138.6	175.7	175.3
Solubility in water, wt %				
at 25 °C	11.1	4.7	1.5	1.7
at 70 °C	19.3	6.6	2.2	2.3
Solubility of water in nitroalkane, wt %				
at 25 °C	2.1	1.1	0.6	0.5
at 70 °C	7.6	3.0	1.7	1.6
Lower flammability, wt %	7.1	3.4	2.2	2.6
Upper flammability, wt %				11
Flash point, °C				
Tag open cup	44.4	41.1	48.9	37.8
Tag closed cup	35	30.6	35.6	27.8
Ignition temperature, °C	418	414	421	428
Critical temperature t_c, °C (calculated)	315	324	340	326
Critical pressure p_c, MPa (calculated)	6.30	4.98	4.33	4.49
Critical density ϱ_c, g/cm^3 (calculated)	0.353	0.329	0.314	0.318
Surface tension, (N/cm) × 10^{-5} at 20 °C	37.48	32.66	30.64	29.87
Viscosity, mPa · s				
at 10 °C	0.731	0.769	0.972	0.883
at 20 °C	0.647	0.677	0.844	0.770
at 30 °C	0.576	0.602	0.740	0.677
Dielectric constant, at 30 °C	35.87	28.06	23.24	25.52
pH of 0.01 M aqueous solution at 25 °C	6.4	6.0	6.0	6.2

3. Production

For more than forty years, the four principal nitroalkanes have been produced by the high-temperature vapor-phase nitration of propane [19]. The process, which employs nitric acid as the nitrating agent, is based on a free radical reaction, in which the active species is the NO_2 radical. This procedure produces a nitroalkane mixture rich in nitropropanes. The process is used by Angus Chemical Company for bulk production of nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane.

The reaction is carried out at 350 – 450 °C. At this temperature all participants in the reaction are gaseous. The reaction is fast but not too fast, so that good temperature control is still assured. The pressure is adjusted to 0.8 – 1.2 MPa, so that the reaction product leaving the reactor can be condensed without liquefying the hydrocarbon. The temperature of the exothermic reaction can be controlled in various ways:

1) By using an excess of propane to remove the heat, the molar ratio of propane to nitric acid being at least 4 : 1;

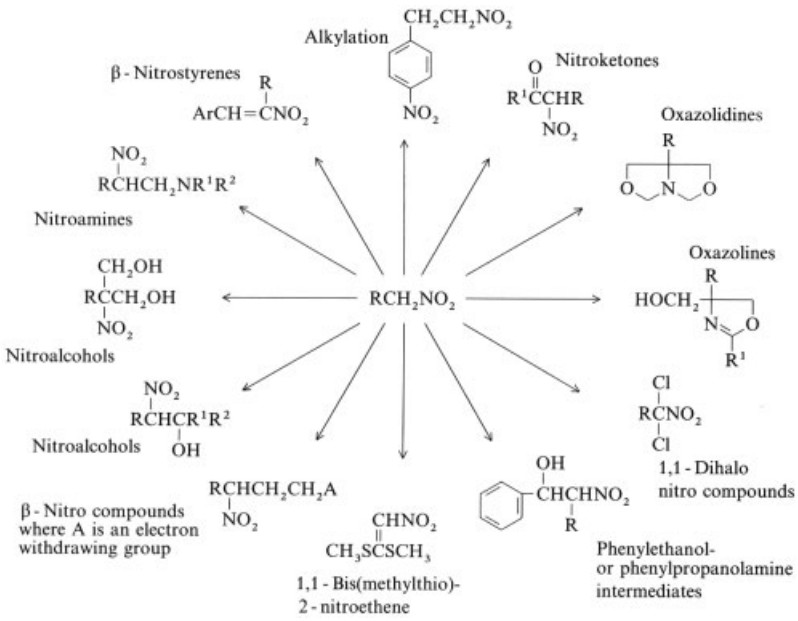


Figure 1. Building new chemicals with nitroalkanes

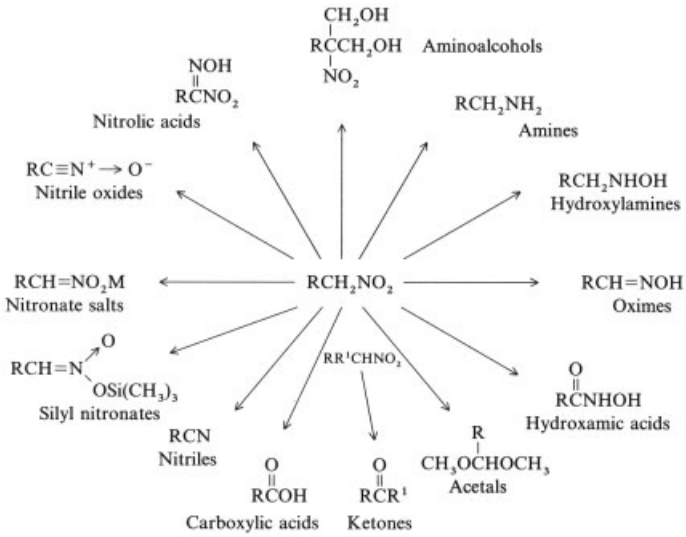


Figure 2. Functional group transformations

2) By spraying liquid nitric acid into the heated propane, the heat of reaction being used to vaporize nitric acid and to produce nearly adiabatic conditions;
3) By using 60 – 70 % nitric acid, thus producing a large volume of steam, which acts as an inert medium in the reactor; or
4) By controlling the temperature in the reactor via the residence time, the shorter the residence time the lower being the temperature. Short residence time is also important for maximum formation of nitroalkane and minimum formation of byproducts.

The vapor-phase nitration of propane by nitric acid proceeds mainly by a free radical mechanism. The decomposition of the nitric acid to ·OH and ·NO_2 or ·ONO, the postulated initiating step, requires temperatures above 350 °C.

By reaction of the OH radicals with alkanes, alkyl radicals can be formed, which then react further with NO_2 radicals to give nitroalkanes. However, the alkyl radicals can also react with HNO_3 to form nitroalkane and ·OH and in that way continue the chain. The most important side reaction of the alkyl radical is the formation of nitrite, which is unstable at the reaction temperature and decomposes to nitric oxide and an alkoxy radical.

$$R\cdot + \cdot ONO \longrightarrow RONO$$

$$RONO \longrightarrow RO\cdot + NO$$

Alkoxy radicals can decompose with cleavage of the carbon – carbon bond and formation of alkyl radicals of lower molecular weight.

$$R'CH_2O\cdot \longrightarrow R'\cdot + CH_2O$$

This can explain the formation of nitroethane and nitromethane during the nitration of propane. Other byproducts of this process are alcohols, aldehydes, ketones, and related oxygen-containing derivatives.

The conversion of nitric acid to nitroalkanes in vapor-phase nitration is less than 50 %. An improved conversion can be achieved by adding a small amount of oxygen or halogen. This is not done in the industrial process, however, since addition of oxygen promotes the formation of large amounts of oxygen-containing byproducts, whereas with halogen addition, corrosion problems or difficulties with the processing of the reaction mixture can occur.

Most of the nitric acid is converted to NO, NO_2, N_2O, and N_2; NO and NO_2 are recovered. The overall loss of nitric acid is 20 – 40 %.

Excess propane is sometimes also recovered from the reactor liquid and reused, so that about 60 – 80 % of the propane reacts to give nitroalkanes.

Rapid cooling immediately after the nitration leads to liquefaction of the nitroalkanes and the oxygen-containing byproducts. The liquid and gas phases are separated, and after propane and nitrogen oxides have been recovered from the gas phase they are returned to the reactor. Some of the byproducts, e.g., formaldehyde, are removed by separation of the aqueous phase. The low-boiling oxygen-containing byproducts such as acetaldehyde or acetone, and nitrogen-containing byproducts such as acetonitrile, can be separated as distillation first runnings from the organic phase. The nitroalkanes so obtained are subjected to a chemical washing process (to remove dissolved higher-boiling oxygen-containing impurities) and then washed with water. The remaining water is removed by passing through a drying tower, and the individual nitroalkanes are then obtained as pure products by fractional column distillation.

More recently, a number of publications have been issued describing improved methods for the syntheses of nitroalkanes [20–25]. However, in the past few years only one major new nitroalkane plant has been placed in operation, the W. R. Grace & Co. facility in Deer Park, Texas. The new Grace process employs a mixture of ethane and propane for the hot-tube, free-radical process, and uses N_2O_4 as the source of NO_2. This process produces a nitroalkane mixture richer in nitromethane and nitroethane.

4. Quality Specifications and Analysis

The specifications for the four nitroalkanes produced at the Grace plant in Texas are given in Table 2. Purity and total nitroalkane content are assayed by capillary gas chromatography; water content is measured by typical Karl Fischer procedures. The acidity is determined by dissolving

Table 2. Product specifications of the four common nitroalkanes (W. R. Grace & Co.)

Specification	Nitromethane	Nitroethane	1-Nitropropane	2-Nitropropane
Purity, wt % (min.)	97	97∗	94	94
Total nitroalkanes, wt % (min.)	99	99	99	99
Acidity, wt % acetic acid (max.)	0.1	0.1	0.2	0.1
Water, wt % (max.)	0.1	0.1	0.1	0.1
Color, APHA (max.)	20	20	20	20
Relative density at 25 °C	1.124 – 1.129	1.042 – 1.047	0.997 – 0.999	0.984 – 0.988

∗ A special grade of nitroethane is available with > 99 % purity.

the nitroalkane in methanol and titrating with dilute sodium hydroxide with bromocresol green as indicator.

5. Storage and Transportation

Nitroalkanes can be safely stored and transported, but certain precautions should be observed with respect to their shock sensitivity. It is necessary to protect nitroalkanes from extremes of temperature and pressure, e.g., fire and shock, and from chemical contamination which could further sensitize them to these extremes. Although the four commercial nitroalkanes are relatively insensitive to detonation by shock at ordinary temperatures, their sensitivity increases with increasing temperature. The tendency of the nitroalkanes toward detonation is inversely related to chain length. Nitromethane presents the most serious shock-sensitivity hazard of the four common nitroalkanes.

Adiabatic compression also poses a special problem in the handling of nitromethane. Thus, the transfer of nitromethane via pumps and piping requires special conditions designed to avoid adiabatic compression [1].

In addition, special care must be taken to avoid forming dry alkali-metal salts of the nitroalkanes, especially in the case of nitromethane. For example, in the presence of a strong base, such as sodium hydroxide, nitromethane can form the sodium salt of methazonic acid (2-nitroacetaldehyde oxime) which, when dry, is very shock sensitive and can explode. Mixtures of nitromethane and an amine and/or heavy metal oxides, such as those of silver, lead, and mercury, can lead to violent decompositions and should be avoided.

Nitromethane is packaged in 55-gallon drums to a net weight of 500 lb. The drum headspace is filled with nitrogen to exclude moisture and to reduce the hazard of adiabatic compression during transportation. The drums are thin-walled so that they rupture easily in the event of high energy impact. Nitromethane drums should not be stacked, but stored on-end in a single layer.

Nitroethane, 1-nitropropane, and 2-nitropropane are also transported in 55-gallon drums under nitrogen. However, because these nitroalkanes are not as shock sensitive as nitromethane, there are no special restrictions on stacking drums.

Nitroethane, 1-nitropropane, and 2-nitropropane are also available neat in bulk quantities transported in tank wagons or rail cars. Bulk nitromethane presents special hazards and, in the United States, may not be transported undiluted in containers having a capacity greater than 110 gallons (ca. 416 L). Nitromethane, however, can be transported in bulk when mixed with any of a variety of approved diluents. The following diluents, along with their minimum content in wt %, have been approved for the transportation of nitromethane: 1,2-butylene oxide (40 %), cyclohexanone (25 %), 1,4-dioxane (35 %), methanol (45 %), 1,1,1-trichloroethane (50 %), 1-nitropropane (48 %), and 2-nitropropane (47 %). These bulk nitromethane mixtures are safely transported by road and ocean freight. All of the nitroalkanes should be kept away from oxidizing, corrosive, or sensitizing materials.

For more details on storage and transportation procedures, refer to a nitroalkane safety guide [1].

6. Uses of Nitroalkanes and their Derivatives

6.1. Nitromethane and Derivatives

One of the most important uses for nitromethane in which it is used without chemical modification is the stabilization of halogenated hydrocarbons. For example, small amounts of nitromethane (and sometimes nitroethane and/or 1-nitropropane) are widely used in industry to form stable noncorrosive mixtures with 1,1,1-trichloroethane that are used in vapor degreasing, dry cleaning, and for cleaning semiconductors and lenses. These nitroalkanes are useful for inhibiting corrosion on the interiors of tin-plated steel cans containing water-based aerosol formulations. Nitromethane is also employed to stabilize the halogenated propellants for aerosols.

Nitromethane is frequently employed as a polar solvent for cyanoacrylate adhesives and acrylic coatings. Nitromethane is also used for cleaning electronic circuit boards; nitroethane and nitropropanes are also used for this purpose. Nitromethane alone, and in mixtures with

methanol and other nitroparaffins, is used as a fuel by professional drag racers and hobbyists. Hobbyists use the nitromethane-based fuel primarily for radio-controlled aircraft. The explosives industry utilizes nitromethane in a binary explosive formulation. The liquid (nitromethane) and solid (inorganic nitrate) ingredients are safely transported and stored separately as standard commercial products. When mixed, an explosive more energetic than 60 % dynamite is formed. There are also commercial and military applications for nitromethane in shaped charges, which are often used for targeted undersea explosions and line trenching.

Nitromethane Derivatives. *Chloropicrin* [*76-06-2*], trichloronitromethane, Cl_3CNO_2 can be prepared by the reaction of nitromethane with sodium hypochlorite. This chlorinated nitro compound is an effective fungicide and nematocidal fumigant.

Tris(hydroxymethyl)nitromethane [*126-11-4*], [2-(hydroxymethyl)-2-nitro-1,3-propanediol], $(CH_2OH)_3CNO_2$ is obtained if three moles of formaldehyde react with nitromethane via the Henry reaction. This derivative is used as a biocide.

Tris(hydroxymethyl)aminomethane [*77-86-1*], [2-amino-2-(hydroxymethyl)-1,3-propanediol], $(CH_2OH)_3CNH_2$ is prepared by reduction of tris(hydroxymethyl)nitromethane. It is used industrially as a buffer and as a component in adhesives and resins.

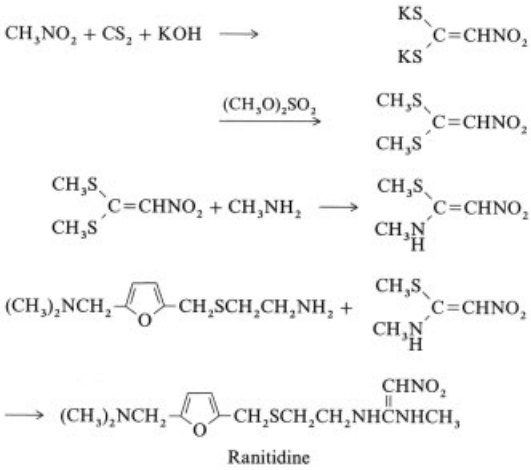
The addition of two moles of formaldehyde to nitromethane by the Henry reaction gives di(hydroxymethyl)nitromethane $(CH_2OH)_2CHNO_2$, which can be converted to the corresponding amino compound, $(CH_2OH)_2CHNH_2$ (2-amino-1,3-propanediol) [*1794-90-7*]. This amine is employed in the synthesis of the X-ray contrast agent Iopamidol [26].

The brominated product $(CH_2OH)_2CBrNO_2$ (2-bromo-2-nitro-1,3-propanediol) [*52-51-7*], which can be derived from di(hydroxymethyl) nitromethane is a widely used biocide (Bronopol).

The reaction between benzaldehyde and nitromethane does not stop at the corresponding nitroalcohol; instead, dehydration to β-nitrostyrene, $C_6H_5CH{=}CHNO_2$ [(2-nitroethenyl)-benzene] [*102-96-5*], occurs. This nitroalkene has been used as a chain transfer agent, i.e., to lower the molecular weights of polymers in their free radical initiated synthesis.

Treatment of β-nitrostyrene with bromine, followed by dehydrobromination, gives bromonitrostyrene, $C_6H_5CH{=}CBrNO_2$ [(2-bromo-2-nitroethenyl)benzene] [*7166-19-0*], which is employed as a slimicide.

An important use of nitromethane is in the synthesis of the anti-ulcer drugs Nizatidine [27] and Ranitidine [28]. A commercial route to Ranitidine is shown below [29]:



Finally, nitromethane is used in the preparation of the psychotropic agent Sulpiride [30].

6.2. Nitroethane and Derivatives

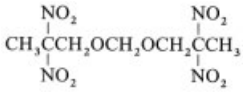
Nitroethane is employed as a solvent due to its excellent wetting properties and its ability to form azeotropes with many industrial solvents. For example, some printing inks contain nitroethane.

Nitroethane is used by the commercial blasting industry as either a fuel or sensitizer of water-based blasting agents. Nitroethane can be added to nitromethane to reduce its tendency to detonate when used as a fuel in internal combustion engines.

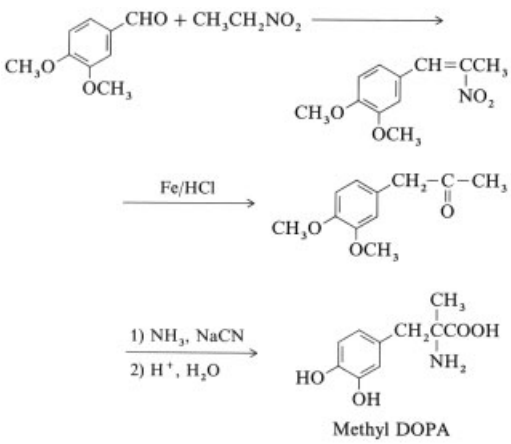
Nitroethane Derivatives. The Henry reaction between two moles of formaldehyde and nitroethane gives 2-methyl-2-nitro-1,3-propanediol [*77-49-6*], $CH_3CNO_2(CH_2OH)_2$ which is utilized as a biocide in cutting oils.

Catalytic hydrogenation of 2-methyl-2-nitro-1,3-propanediol affords the corresponding amine, 2-amino-2-methyl-1,3-propanediol [*115-69-5*]. After reaction with oleic acid, this aminoalcohol forms an oxazoline [31], which is used as a specialty cationic surfactant.

Nitroethane is used to make a plasticizer for solid rocket fuels [32]. The molecuar structure for this plasticizer is:



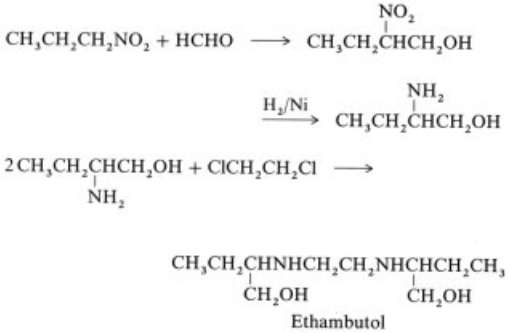
The antihypertensive drug Aldomet (methyl DOPA) is made using nitroethane. The synthesis follows the general route [33, 34]:



Methyl DOPA

6.3. 1-Nitropropane and Derivatives

Like the other basic nitroalkanes, 1-nitropropane is employed as a solvent or cosolvent.



Ethambutol

The most important use for 1-nitropropane is in the synthesis of Ethambutol, an antituberculosis drug [35].

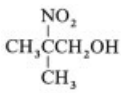
Only the D-enantiomer of 2-amino-1-butanol is used in the final synthetic step.

Relatively small quantities of 1-nitropropane are used in the preparation of biocides [36].

6.4. 2-Nitropropane and Derivatives

A major use of 2-nitropropane is as an industrial solvent. It is used in vinyl inks that are employed in printing, flexography, and photogravure. The 2-nitropropane, often mixed with alcohols, dissolves a large number of resins such as epoxy, polyurethane, polyester, vinyl, urea–formaldehyde, and phenolic. These solvent–resin mixtures are used for coatings. For example, can-coating varnishes contain the nitroalkane because of its excellent wetting properties. Other applications of these 2-nitropropane formulations are in adhesives and in electrostatic paints. Some of the properties of 2-nitropropane that make it so versatile in many of these applications are: high polarity and flash point, appropriate evaporation rate, good wetting and azeotropic properties, and satisfactory resistivity.

2-Nitropropane Derivatives. The Henry reaction of 2-nitropropane with formaldehyde yields 2-methyl-2-nitro-1-propanol (NMP) [*76-39-1*].



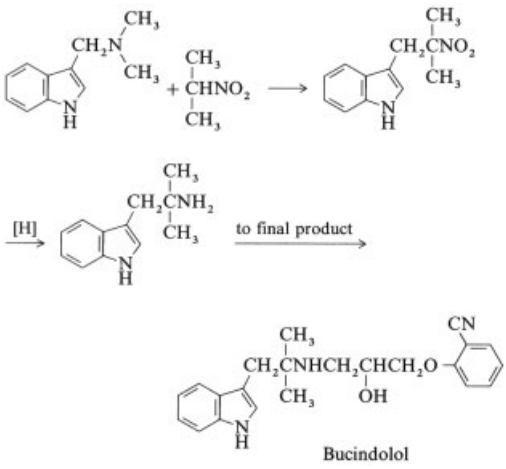
This nitroalcohol has been employed as an adhesive component to improve tire cord bonding [37].

Catalytic hydrogenation of NMP affords 2-amino-2-methyl-1-propanol (AMP) [*124-68-5*]. This aminoalcohol is a useful organic base for neutralizing and solubilizing applications. Other applications of AMP are:

1) AMP is used in toiletries, cosmetics, and in hair sprays, in which it neutralizes and solubilizes the carboxyl-containing polymers used in their formulation.
2) In conjunction with fatty acids, AMP is an excellent dispersing agent for powders and pigments, especially titanium dioxide.

3) AMP has been employed as a formaldehyde scavanger in melamine – formaldehyde, urea–formaldehyde, and phenol – formaldehyde resins.
4) AMP has also been used as a wetting agent, as an emulsifier in polishing waxes, and in textiles for permanent pleats.

Finally, 2-nitropropane has been utilized in the preparation of the experimental β-blocking drug, Bucindolol, [38–40], whose synthesis scheme shows how 2-nitropropane can be used to introduce a *tert*-butylamine functionality into a molecule:



7. Toxicology and Occupational Health

The two most important health controls for nitroalkane exposure are adequate ventilation and prevention of skin contact.

In the United States, OSHA and ACGIH have set PE's and TLV's for the nitroalkanes [41, 42]. The OSHA and ACGIH limits are shown in Table 3, together with MAK values.

Table 3. Industrial exposure limits for nitroalkanes, mL/m^3 (ppm)

Compound	PEL (OSHA)	TLV (ACGIH)	MAK
Nitromethane	100	100	100
Nitroethane	100	100	100
1-Nitropropane	25	25	25
2-Nitropropane	25	10	*

* Identified as a suspected human carcinogen; safe exposure limit has not been established.

Inhalation is the major industrial hazard of nitroalkane exposure. The reported effects of overexposure to vapors are headache, nausea, vomiting, and convulsions. Although chronic exposure to animals indicates some liver and kidney injury, no such injury has been reported in humans when exposures were maintained below the TLV levels.

Nitroalkane vapors can cause eye irritation at levels above the recommended TLVs. Since the nitroalkanes' odor detectabilities are poor, odor detection does not serve as a warning for overexposure. Therefore, prolonged exposure to vapors above the TLV necessitates the use of respirators. Such exposure may occur in operations that require entry into tanks or closed vessels and in emergency situations. Acute exposure to extremely high concentrations of 2-nitropropane vapors has resulted in serious injuries and, in some cases, death when workers were exposed in enclosed spaces without using recommended respiratory protection or adequate ventilation. For respiratory protection, supplied-air or self-contained breathing apparatus with a full facepiece should be used.

Nitroalkanes are mild skin irritants due to their solvent action but are not absorbed through the skin. Although irritation can occur from prolonged or repeated skin contact, no allergic or sensitization reactions have been reported.

The acute LD_{50} (rat, oral) of the nitroalkanes is as follows [43]:

Nitromethane	1210 ± 322 mg/kg
Nitroethane	1620 ± 193 mg/kg
1-Nitropropane	455 ± 75 mg/kg
2-Nitropropane	725 ± 160 mg/kg

The National Toxicology Program of the U.S. Department of Health and Human Services, The International Agency for Research on Cancer, and the American Conference of Governmental Industrial Hygienists list 2-nitropropane as a suspect carcinogen. The classification is based on studies in which prolonged exposure to 2-nitropropane was found to cause liver neoplasms in laboratory rats [44].

In 1979, an epidemiological study of workers exposed to 2-nitropropane was reported by the International Minerals and Chemical Corporation. The authors concluded that analysis of these data does not suggest any unusual cancer or other disease mortality pattern among this

group of workers [45]. There is no evidence that 2-nitropropane causes cancer in humans.

8. References

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