Kirk-Othmer Encyclopedia of Chemical Technology.

MALONIC ACID AND DERIVATIVES

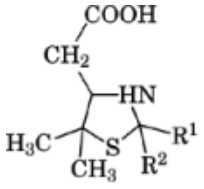
1. Malonic Acid

1.1. Physical Properties

Malonic acid, HOOC–CH_2–COOH **1**, was discovered and isolated in 1858 as a product of malic acid oxidation. The physical properties of malonic acid are listed in Table 1.

1.2. Reactions

Heating an aqueous solution of malonic acid above 70°C results in its decomposition to acetic acid and carbon dioxide. Malonic acid is a useful tool for synthesizing α-unsaturated carboxylic acids because of its ability to undergo decarboxylation and condensation with aldehydes or ketones at the methylene group. Cinnamic acids are formed from the reaction of malonic acid and benzaldehyde derivatives (1). If aliphatic aldehydes are used acrylic acids result (2). Similarly this facile decarboxylation combined with the condensation with an activated double bond yields α-substituted acetic acid derivatives. For example, 4-thiazolidine acetic acids (**2**) are readily prepared from 2,5-dihydro-1,3-thiazoles (3). A further feature of malonic acid is that it does not form an anhydride when heated with phosphorous pentoxide [1314-56-3] but rather carbon suboxide [504-64-3], [O=C=C=O], a toxic gas that reacts with water to reform malonic acid.



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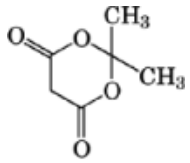

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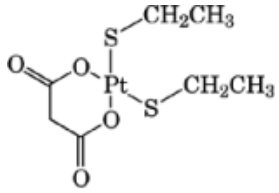
Table 1. Properties of Malonic Acid[a]

Property	Value
mol wt	104.06
melting point, °C	135 (dec)
ionization constants	
K_1	1.42×10^{-3}
K_2	2.01×10^{-6}
appearance	white crystals
solubility	
in water at 20°C	139 g/100 mL
in pyridine at 15°C	15 g/100 g

[a]Also called propanedioic acid or methanedicarboxylic acid.



(**4**)

Reactions of the carboxylic acid groups include monoesterification, diesterification, or conversion with thiols. The synthesis of mono(*tert*-butyl) malonate [40052-13-9] through condensation with *tert*-butyl alcohol [75-65-0] (4), of di-*p*-methylbenzyl malonate through condensation with *p*-methylbenzyl alcohol [589-18-4] (5), or propanebis(thioic) *S*,*S*′-diesters, $CH_2(COSR)_2$, through condensation with thiols has been reported (6). Further reactions at the carboxylic acid groups lead to ring closure. Of special interest is the synthesis of 2,2-dimethyl-1,3-dioxan-4,6-dione (**3**), commonly named Meldrum's acid [2033-24-1], through condensation with acetone [67-64-1] in the presence of acetic acid [64-19-7] and sulfuric acid [7664-93-9] (7). Malonic acid also forms acidic and neutral salts as well as double and complex salts. The platinum complexes (**4**) have been investigated as antitumor agents (8).

1.3. Preparation

The industrial production of malonic acid is much less important than that of the malonates. Malonic acid is usually produced by acid saponification of malonates (9). Further methods which have been recently investigated are the ozonolysis of cyclopentadiene [542-92-7] (10), the air oxidation of 1,3-propanediol [504-63-2] (11), or the use of microorganisms for converting nitriles into acids (12).

1.4. Economic Aspects

Malonic acid is produced by Juzen and Tateyama in Japan as well as Lonza Ltd. in Switzerland and Riedel-De Haen Ltd. in Germany. It costs around $30/kg (1993) for shipments of one to two drums.

1.5. Analytical and Test Methods

Potentiometric titration with sodium hydroxide [1310-73-2] is employed. Both equivalent points are measured, and the content is determined using the following equation:

$$\text{malonic acid, \%} = \frac{(E_2 - E_1) \times M \times 10.406}{W}$$

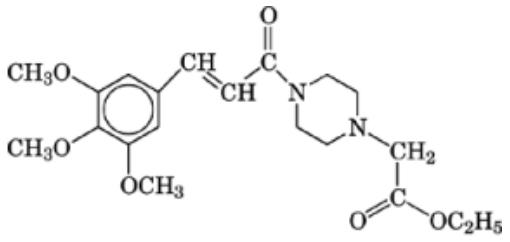
where E_1 = volume of standard NaOH at the first equivalence point, E_2 = volume of standard NaOH at the second equivalence point, M = molarity of standard NaOH solution, and W = weight of sample in grams.

1.6. Health and Safety Factors (Toxicology)

No special precautions are necessary in the handling of malonic acid beyond normal safe handling measures. Due to its acidity malonic acid is classified as a mild irritant (skin irritation, rabbits). The LD_{50} value (oral, rats) for malonic acid is 2750 mg/kg. Transport classification: RID/ADR, IMDG-Code, IATA/ICAO: not restricted.

1.7. Uses

Malonic acid is used instead of the less expensive malonates for the introduction of a CH–COOH group under mild conditions by Knoevenagel condensation and subsequent decarboxylation. The synthesis of 3,4,5-trimethoxycinnamic acid, the key intermediate for the coronary vasolidator Cinepazet maleate [50679-07-7] (**5**) involves such a pathway (13).



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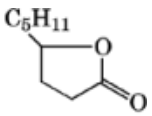


(**6**)

Knoevenagel condensation of malonic acid with heptaldehyde [111-71-7], followed by ring closure, gives the fragrance γ-nonanoic lactone [104-61-0] (**6**) (14). Beside organic synthesis, malonic acid can also be used as electrolyte additive for anodization of aluminum [7429-90-5] (15), or as additive in adhesive compositions (16).

1.8. Meldrum's Acid

Meldrum's acid [2033-24-1] (**3**) is commercially used for the production of monoesters of malonic acid and beta-keto acids (17). The chemistry of Meldrum's acid is extensively reviewed in Reference 18.

Table 2. Physical Properties of Dimethyl and Diethyl Malonate

Property	Dimethyl malonate	Diethyl malonate
other names	propanedioic acid dimethyl ester	propanedioic acid diethyl ester
appearance	colorless liquid	colorless liquid
mol wt	132.12	160.17
mp, °C	−62	−50
bp,°C[a]	181.4	199
$d^{20}{}_4$, g/mL	1.1544	1.0551
refractive index at 20°C	1.4140	1.4143
dipole moment, C·m[b]	7.97×10^{-30}	5.24×10^{-30}

[a]At 101 kPa = 1 atm·
[b]To convert C·m to debyes, multiply by 3×10^{29}.

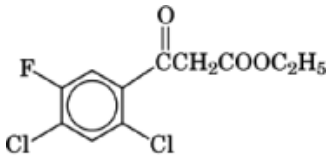
2. Malonates

2.1. Physical Properties

Industrially, the most important esters are dimethyl malonate [108-59-8] and diethyl malonate [105-53-3], whose physical properties are summarized in Table 2. Both are sparingly soluble in water (1 g/50 mL for the diethyl ester) and miscible in all proportions with ether and alcohol.

2.2. Reactions

The chemical properties of malonates are highlighted by the acidity of the methylene group ($pK_a \sim 13$) to such an extent that a proton can be easily detached by a strong base, usually alkoxides. Alkylation with 1-bromooctane [111-83-1] in the presence of sodium ethoxide [141-52-6] gives diethyl octylmalonate [1472-85-1], which can be further reduced with lithium aluminum hydride [16853-85-3], $LiAlH_4$, to yield 2-octyl-1,3-propanediol [74971-70-3] (19). The use of other starting materials which contain reactive halogen, such as 4-halo-3-methoxy-2-butenoate, gives access to 1,3-cyclopentanedione [3859-41-4] (20) upon subsequent cyclization and decarboxylation. The second hydrogen atom at the activated methylene group can be substituted analogously; thus cyclic dicarboxylic acids such as cyclopropyl-1,1-dicarboxylates (21) can be obtained starting from 1,2-dibromoethane [106-93-4]. The first ester function of the malonates is hydrolyzed much more easily than the second. This property can be used for synthesizing a large number of carboxylic acids by alkylation or acylation of a malonate followed by hydrolysis and decarboxylation of one ester group. This is the case for ethyl 2,4-dichloro-5-fluorobenzoylacetate (**7**) [86483-51-4] made through acetylation of diethyl malonate by 2,4-dichloro-5-fluorobenzoyl chloride [86393-34-2] (22).



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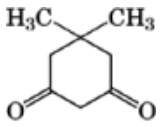

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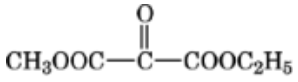

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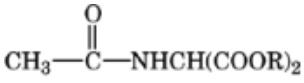


(**10**)

Further reactions on the activated methylene group involve the Knoevenagel condensation with acetones or aldehydes (23) yielding α,β-unsaturated compounds. The reaction with triethyl orthoformate [122-51-0] gives diethyl ethoxymethylenemalonate [87-13-8], $C_2H_5OCH{=}C(COOC_2H_5)_2$ (24). The Michael condensation with activated double bond containing moieties such as acrylonitrile gives the 2-(2-cyanoethyl)malonate (25). Similarly with mesityl oxide [141-79-7], dimedone [126-81-8] (**8**) is obtained upon subsequent cyclization and decarboxylation (26). The oxidation of malonates with air in the presence of a catalyst results in esters of mesoxalic acid (**9**) (27). The nitrosation with nitrous acid [7782-77-6] gives isonitromalonates, $HO{-}N{=}C(COOR)_2$, which are simultaneously acylated and hydrogenated to acetaminomalonates (**10**) (28). Besides decarboxylation and hydrogenation, the ester groups can be transesterified with *tert*-butyl alcohol [75-65-0] giving the mixed malonate, $H_5C_2OOCCH_2COOC(CH_3)_3$ (29). Finally, malonates can be converted into nitrogen-containing heterocycles, eg, pyrazolones such as, 2,4-pyrazolidinedione-1-phenyl [19933-22-3] upon reaction with phenylhydrazine [100-63-0] (30), or pyrimidines such as 2,4,6-trihydroxypyrimidine [67-52-7] upon reaction with urea [57-13-6] (31). Similarly 2-amino-4,6-dihydroxypyrimidine [56-09-7] and 4,6-dihydroxypyrimidine [1193-24-4] are obtained upon reaction with guanidine [113-00-8] (32) and formamide [75-12-7] (33), respectively.

2.3. Manufacture

2.3.1. Hydrogen Cyanide Process

This process, one of two used for the industrial production of malonates, is based on hydrogen cyanide [74-90-8] and chloroacetic acid [79-11-8]. The intermediate cyanoacetic acid [372-09-8] is esterified in the presence of a large excess of mineral acid and alcohol.

$$Cl{-}CH_2{-}COONa + NaCN \longrightarrow NC{-}CH_2{-}COONa + NaCl$$

$$NC{-}CH_2{-}COONa \xrightarrow[H_2SO_4,\ H_2O]{+ROH} ROOC{-}CH_2{-}COOR$$

A solution of sodium cyanide [143-33-9] (ca 25%) in water is heated to 65–70°C in a stainless steel reaction vessel. An aqueous solution of sodium chloroacetate [3926-62-3] is then added slowly with stirring. The temperature must not exceed 90°C. Stirring is maintained at this temperature for one hour. Particular care must be taken to ensure that the hydrogen cyanide, which is formed continuously in small amounts, is trapped and

Table 3. Malonate Production

Country	Company	Process
Europe	Hüls (Germany)	carbon monoxide process
	Lonza (Switzerland)	hydrogen cyanide process
Japan	Juzen	carbon monoxide process
	Tateyama	hydrogen cyanide process
South Korea	Korean Fertilizers	carbon monoxide process

neutralized. The solution of sodium cyanoacetate [1071-36-9] is concentrated by evaporation under vacuum and then transferred to a glass-lined reaction vessel for hydrolysis of the cyano group and esterification. The alcohol and mineral acid (weight ratio 1:2 to 1:3) are introduced in such a manner that the temperature does not rise above 60–80°C. For each mole of ester, ca 1.2 moles of alcohol are added.

Hydrochloric acid [7647-01-0], which is formed as by-product from unreacted chloroacetic acid, is fed into an absorption column. After the addition of acid and alcohol is complete, the mixture is heated at reflux for 6–8 h, whereby the intermediate malonic acid ester monoamide is hydrolyzed to a dialkyl malonate. The pure ester is obtained from the mixture of crude esters by extraction with benzene [71-43-2], toluene [108-88-3], or xylene [1330-20-7]. The organic phase is washed with dilute sodium hydroxide [1310-73-2] to remove small amounts of the monoester. The diester is then separated from solvent by distillation at atmospheric pressure, and the malonic ester obtained by redistillation under vacuum as a colorless liquid with a minimum assay of 99%. The aqueous phase contains considerable amounts of mineral acid and salts and must be treated before being fed to the waste treatment plant. The process is suitable for both the dimethyl and diethyl esters. The yield based on sodium chloroacetate is 75–85%. Various low molecular mass hydrocarbons, some of them partially chlorinated, are formed as by-products. Although a relatively simple plant is sufficient for the reaction itself, a sizeable investment is required for treatment of the wastewater and exhaust gas.

2.3.2. Carbon Monoxide Process

This process involves the insertion of carbon monoxide [630-08-0] into a chloroacetate. According to the literature (34) in the first step ethyl chloroacetate [105-39-5] reacts with carbon monoxide in ethanol [64-17-5] in the presence of dicobalt octacarbonyl [15226-74-1], $Co_2(CO)_8$, at typical temperature of 100°C under a pressure of 1800 kPa (18 bars) and at pH 5.7. Upon completion of the reaction the sodium chloride formed is separated along with the catalyst. The ethanol, as well as the low boiling point components, is distilled and the nonconverted ethyl chloroacetate recovered through distillation in a further column. The crude diethyl malonate obtained is further purified by redistillation. This process also applies for dimethyl malonate and diisopropyl malonate.

Other processes described in the literature for the production of malonates but which have not gained industrial importance are the reaction of ketene [463-51-4] with carbon monoxide in the presence of alkyl nitrite and a palladium salt as a catalyst (35) and the reaction of dichloromethane [75-09-2] with carbon monoxide in the presence of an alcohol, dicobalt octacarbonyl, and an imidazole (36).

2.4. Economic Aspects

Dimethyl and diethyl malonates are produced as shown in Table 3. Total capacity is estimated to be about 12,000 t/yr. Furthermore, producers are also reported in the People's Republic of China and in Romania. In bulk shipments, both malonates are available at ca $6/kg (1993).

2.5. Analytical and Test Methods

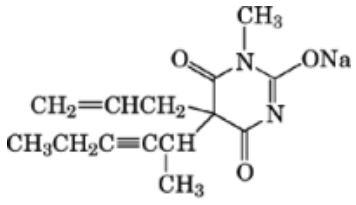
Gas chromatography is used for the quantitative analysis of malonates. Typical analysis conditions are 5% Reoplex 400 on Chromosorb G 80–100 mesh; 2 m, 0.3 cm diameter metal column; temperature for column = 120°C; detector, 150°C; and injector, 120°C. The determination of the free acid through titration and of the determination of water content according to the Karl-Fischer method are also important.

2.6. Health and Safety Factors

Dimethyl malonate and diethyl malonate do not present any specific danger of health hazard if handled with the usual precautions. Nevertheless, inhalation and skin contact should be avoided. Dimethyl malonate has a LD_{50} (oral, rats) of 4520 mg/kg and is classified as nonirritant (skin irritation, rabbits). Diethyl malonate has an LD_{50} (oral, rats) greater than 5000 mg/kg and is also classified as nonirritant (skin irritation, rabbits). Transport classification for both esters is RID/ADR: 3, IMDH-Code, IATA-ICAO: not restricted.

2.7. Uses

Dimethyl malonate and diethyl malonate have found many applications in the pharmaceutical, vitamin, agrochemical, fragrance, and dyestuff industries. Some of the many outlets in the pharmaceutical industry are the synthesis of the 5,5-disubstituted barbiturates and thiobarbituric acids such as methohexital sodium [22151-68-4] (**11**) (37) and thiopental sodium [71-73-8] (**12**) (38) (see Pharmaceuticals). Another important derivative is the vasodilatator Naftidrofuryl [31329-57-4] (**13**) obtained through condensation of 2-tetrahydrofurfuryl chloride [3003-84-7] and 1-(chloromethyl)naphthalene [86-52-2] (39). Other derivatives include the antiinflammatories phenylbutazone [50-33-9] (**14**), which is derived from the condensation of 2-(*n*-butyl)malonate with 1,2-diphenylhydrazine [122-66-7] (40), and carprofen [53716-49-7] (**15**) prepared from the Michael condensation of dimethyl methylmalonate [609-02-9] with 2-cyclohexen-1-one [930-68-7] (41) (see Analgesics, antipyretics, and antiinflammatory agents). A wide range of quinolone antibacterial agents can be prepared through condensation of an amino containing moiety with diethyl 2-ethoxymethylenemalonate (see Antibacterial agents, synthetic). Since the introduction of nalidixic acid [389-08-2] (**16**), many new compounds have been developed such as ofloxacin [82419-36-1] (**17**). Several new fluoroquinolones are reported in clinical trials (42). The anticonvulsant Vigabatrin [60643-86-9], $CH_2{=}CHCH(NH_2)CH_2CH_2COOH$ (**18**), obtained through condensation of diethyl malonate with 1,4-dichloro-2-butene [764-41-0] (43), or the antiulcer Rebamipide [90098-04-7] (**19**), whose synthesis involves the use of 2-(acetylamino)malonate (44), are examples of new pharmaceuticals recently launched.



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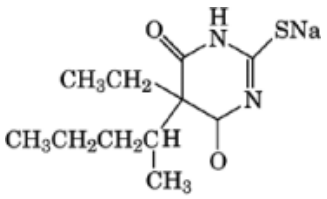

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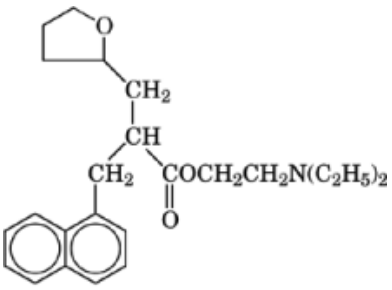

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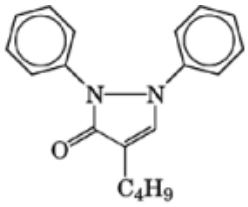

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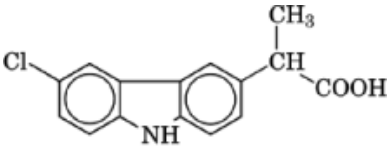

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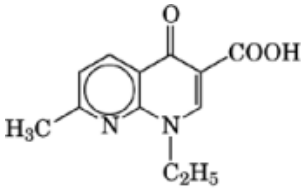

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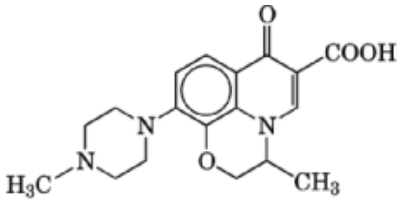

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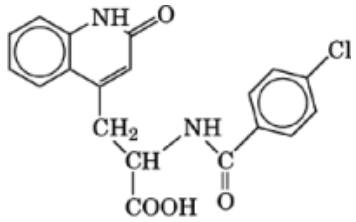
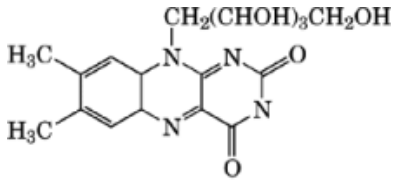


(**19**)

In the vitamins field, the synthesis of vitamin B_2 [83-88-5] (**20**) starting from barbituric acid [67-52-7] (45) is a significant outlet (see Vitamins). Since the 1970s the agrochemical industry has contributed to the increasing number of new applications for malonates. This is mainly due to the introduction of the new cyclohexanedione-type herbicides whose first steps of the respective synthesis resembles the synthetic method of dimedone (26), which is a Michael addition followed by ring closure and decarboxylation (see Herbicides). One of the first products introduced was sethoxydim [74051-80-2] (**21**) (46) which has been since been followed by other derivatives such as tralkoxydim [87820-88-0] (47). A further prominent new class has been the novel low dosage sulfonylurea herbicides deriving from 2-aminopyrimidines such as 2-amino-4-chloro-6-methoxypyrimidine [5734-64-5] and 2-amino-4,6-dimethoxypyrimidine [36315-01-2]. Whereas the former is made from the condensation of a malonate with guanidine, the latter is preferably accessible from malononitrile. Representatives of this new herbicides class are chlorimuron–ethyl [90982-32-4] (**22**) (48) and bensulfuron–methyl [83055-99-6] (**23**) (49). As of this writing more than 10 different sulfonylurea herbicides are either launched or in a late development stage. In the dyestuff industry, both the malonate derivatives barbituric acid and 2,4-dihydroquinoline [86-95-3] are used as coupling components for the CI Pigment Yellow 139 [36888-99-0] (**24**) (50) and the CI Disperse Yellow 5 [6439-53-8] (**25**) (51) (see Dyes and dye intermediates).



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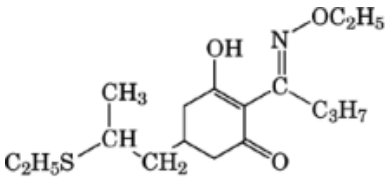

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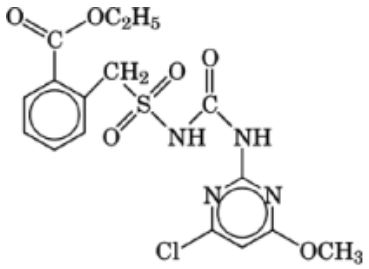

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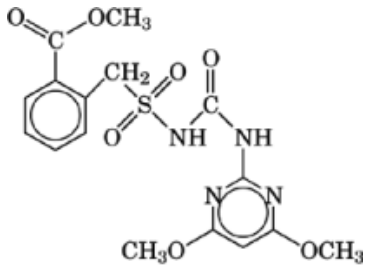

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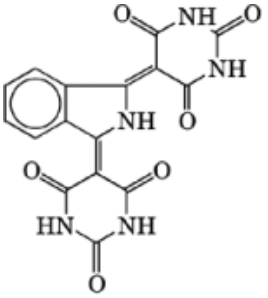

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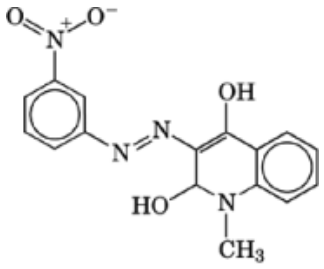
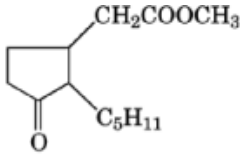


(**25**)

A commercially important outlet in the fragrance industry is the methyl dihydrojasmonate [24851-98-7] (**26**) which is made by Michael addition of a malonate to 2-pentyl-2-cyclopenten-1-one [91791-21-21-8] (52) and which is used in perfumery for blossom fragrances, particularly jasmine (see Perfumes).



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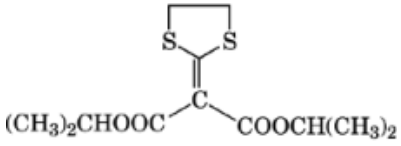


(**27**)

Malonates can also be used as blocking agents in the formulation of one-part urethanes. These systems, curable by moisture, are used, for example, for automotive windshield glazing (53) (see Urethane polymers).

2.8. Diisopropyl Malonate

This dialkyl malonate has gained industrial importance for the synthesis of the fungicide dialkyl malonate [50512-35-1] (**27**) through condensation with carbon disulfide [75-15-0] and ethylene dichloride [107-06-2] (54). Diisopropyl malonate [13195-64-7] is produced by Mitsubishi Chemical in Japan using the carbon monoxide process.

3. Cyanoacetic Acid and Cyanoacetates

3.1. Physical Properties

The physical properties of cyanoacetic acid [372-09-8], N≡C—CH_2COOH (**28**) are summarized in Table 4. The industrially most important esters are methyl cyanoacetate [105-34-0] and ethyl cyanoacetate [105-56-6]. Both esters are miscible with alcohol and ether and immiscible with water.

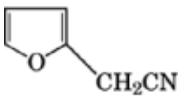
Table 4. Physical Properties of Cyanoacetic Acid, Methyl Cyanoacetate, and Ethyl Cyanoacetate

Property	Cyanoacetic acid	Methyl cyanoacetate	Ethyl cyanoacetate
other names	malonic mononitrile		
appearance	colorless crystals	colorless liquid	colorless liquid
mol wt	85.06	99.09	113.12
mp, °C	66	−22	−22
bp °C/kPa[a]	108°/1.5 kPa	203°/101 kPa	206°/101 kPa
refractive index		1.418–1.419	1.417–1.418

[a]To convert kPa to mm Hg, multiply by 7.5.

3.2. Reactions

The chemical properties of cyanoacetates are quite similar to those of the malonates. The carbonyl activity of the ester function is increased by the cyano group's tendency to withdraw electrons. Therefore, amidation with ammonia [7664-41-7] to cyanoacetamide [107-91-5] (55) or with urea to cyanoacetylurea [448-98-2] (56) proceeds very easily. An interesting reaction of cyanoacetic acid is the Knoevenagel condensation with aldehydes followed by decarboxylation which leads to substituted acrylonitriles (57) such as (**29**), or with ketones followed by decarboxylation with a shift of the double bond to give β,γ-unsaturated nitriles (58) such as (**30**) when cyclohexanone [108-94-1] is used.



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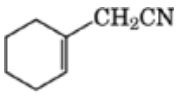


(30)

3.3. Manufacture

Cyanoacetic acid and cyanoacetates are industrially produced by the same route as the malonates starting from a sodium chloroacetate solution via a sodium cyanoacetate solution. Cyanoacetic acid is obtained by acidification of the sodium cyanoacetate solution followed by organic solvent extraction and evaporation. Cyanoacetates are obtained by acidification of the sodium cyanoacetate solution and subsequent esterification with the water formed being distilled off. Other processes reported in the literature involve the oxidation of partially oxidized propionitrile [107-12-0] (59). Higher esters of cyanoacetic acid are usually made through transesterification of methyl cyanoacetate in the presence of aluminium isopropoxide [555-31-7] as a catalyst (60).

3.4. Economic Aspects

In order to avoid the extraction and evaporation steps, most of the cyanoacetic acid derivatives are made directly from solution; therefore, only a small portion of the acid produced is traded. Cyanoacetic acid is produced by Boehringer-Ingelheim and Knoll in Germany, Juzen in Japan, as well as Hüls in the United States. When sold in tons, the price of cyanoacetic acid was ∼ $9/kg in 1993.

Methyl cyanoacetate and ethyl cyanoacetate are produced by Lonza in Switzerland and Hüls in the United States, as well as Juzen and Tateyama in Japan. The total production capacity is estimated to be in the range of 10,000 metric tons per year. The market price for both esters in bulk shipments was around $6/kg in 1993.

3.5. Analytical and Test Methods

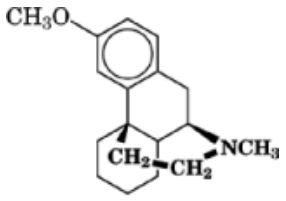
Potentiometic titration is an analytical method for cyanoacetic acid. Methyl and ethyl cyanoacetates are usually analyzed by gas chromatography using the same equipment as for the malonates but with a higher column and injector temperatures, namely 150 and 200°C, respectively.

3.6. Health and Safety Factors

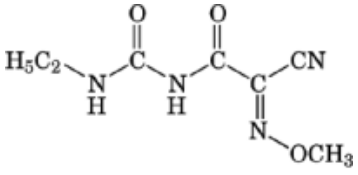
Handling of cyanoacetic acid and cyanoacetates do not present any specific danger or health hazard if handled with the usual precautions. Cyanoacetic acid is classified as a moderate irritant (skin irritation, rabbits) and has an LD_{50} (oral, rats) of 1500 mg/kg. Methyl and ethyl cyanoacetate are both classified as slight irritants (skin irritation, rabbits) and have an LD_{50} (oral, rats) of 3062 and 2820 mg/kg, respectively. Transport classification: cyanoacetic acid:RID/ADR: 8; IMDG-Code: 8; IATA/ICAO: 6.1. Methyl and ethyl cyanoacetate: RID/ADR: 6.1; IMDG-Code:6.1; IATA/ICAO: 6.1.

3.7. Uses

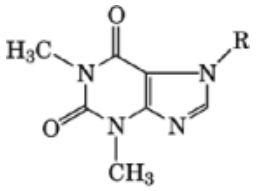
In many cases cyanoacetic acid, cyanoacetates, or cyanoacetamide can be used alternatively. The traded cyanoacetic acid is mainly intended for the synthesis of the cough remedy dextromethorphan [125-71-3] (**31**) (61) (see Expectorants, antitussives, and related agents) and of the fungicide cymoxanil [57966-95-7] (**32**) (62) (see Fungicides, agricultural).



(**31**)



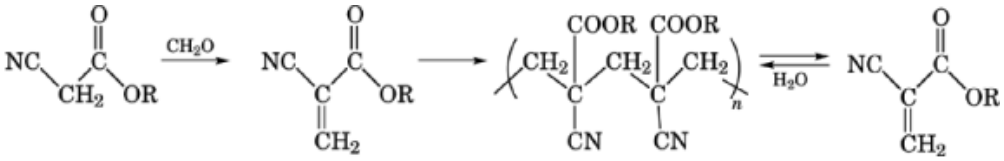
(**32**)



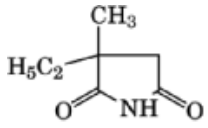
(**33**)

Otherwise cyanoacetic acid is directly converted as a solution with 1,3-dimethylurea [96-31-1] into 2-cyano-*N*,*N*′-dimethylcarbamoyl acetamide [39615-79-7] which is further upgraded into the diuretics theophylline [58-55-9] (**33** where $R = H$) and caffeine [58-08-2] (**33**, where $R = CH_3$) (63).

The largest application of methyl and ethyl cyanoacetate is the production of the cyanoacrylate adhesives widely used within the car and electronic industries. Esters of higher alcohols such as 1-butanol [71-36-3] have also gained industrial importance. Basically the Knoevenagel condensation of a cyanoacetate and formaldehyde [50-00-0] followed by nearly spontaneous dehydration gives cyanoacrylate which undergoes an immediate polymerization to polycyanoacrylate. However, this polymerization is reversible on heating and the monomer can be formed again and subsequently purposely polymerized by traces of moisture.



Otherwise cyanoacetates are widely used in the synthesis of pharmaceuticals such as the anticonvulsant ethosuximide [77-67-8] (**34**), (64) and valproic acid [99-66-1] (**35**) (65), the gout remedy allopurinol [315-30-0] (**36**) (66), or the antihypertensive amiloride [2609-46-3] (**37**) (67) (see Pharmaceuticals).



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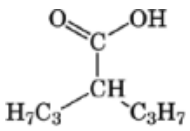
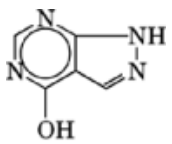
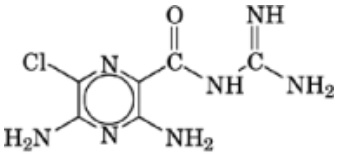


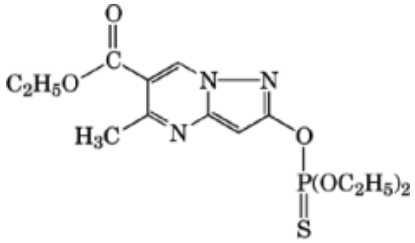
(**35**)



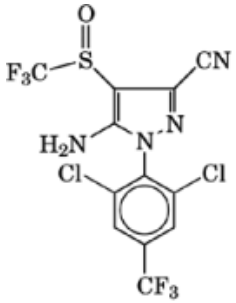
(**36**)



(**37**)

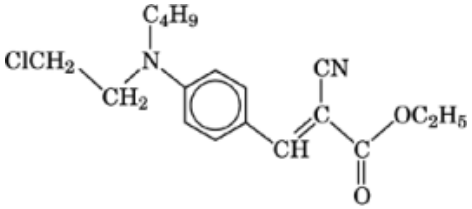


(**38**)



(**39**)

In the agrochemical field, outlets for cyanoacetates are the fungicides pyrazophos [13457-18-6] (**38**) (68) and fipronil [120068-37-3] (**39**) (69) (see Fungicides, agricultural). Cyanoacetates are also used as dye intermediates, for producing Celliton Fast Yellow 7G (**40**) (70), as well as in the synthesis of uv absorbers (71) etocrylene [5232-99-5] (**41**, R = ethyl) and octocrylene [6197-30-4] (**41**, R = 2 – ethylhexyl) (see Dyes and dye intermediates).

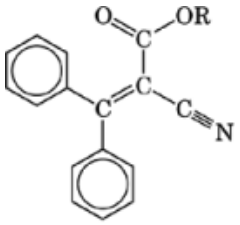


(**40**)

Table 5. Physical Properties of Malononitrile

Property	Value
other names	propanedinitrile, dicyanomethane
mol wt	66.06
appearance	white crystals
mp, °C	31
bp, °C	
at 76 kPa[a]	218–219
at 1.7 kPa[a]	108–109
$d^{35}{}_4$, g/mL	1.0494
dipole moment, 25°C, C·m[b]	1.19×10^{-29}
solubility, g/mL	
in water	0.133
in ethanol	0.40
in ether	0.20

[a]To convert kPa to mm Hg, multiply by 7.5.
[b]To convert $\mathrm{C{\cdot}m}$ to debyes, multiply by 3.0×10^{29}.



(41)

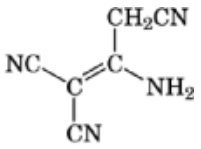
4. Malononitrile

4.1. Physical Properties

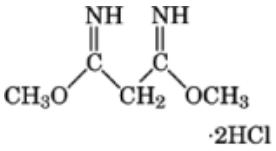
The physical properties of malononitrile [109-77-3], N≡C—CH_2C≡N (**42**) are listed in Table 5.

4.2. Reactions

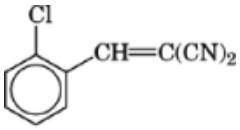
The chemistry of malononitrile is reviewed in References 72 and 73. Like malonates and cyanoacetates, the chemical properties of malononitrile are determined by two reactive centers, namely the methylene group and the two cyano functions. The high acidity of the methylene group ($pK_a \sim 11$) as compared to malonates ($pK_a \sim 13$) makes the deprotonation of malononitrile quite easy even with relatively weak base. A peculiar reaction of malononitrile is the base-catalyzed dimerization leading to 2-amino-1,1,3-tricyanopropene [868-54-2] (**43**) (74). Reaction of malononitrile at the cyanide groups without participation of the methylene group are rare. The most common one is the acid-catalyzed addition of alcohols in which one or both cyano groups are converted into the imidate group. For example (**44**) which upon ring closure gives access to 2-amino-4,6-dimethoxypyrimidine [36315-01-2] (75). Another one is the condensation with guanidine giving 2,4,6-triaminopyrimidine [1004-38-2] (76).



(**43**)

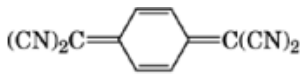


(**44**)

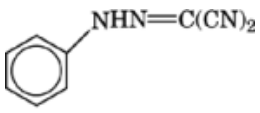


(**45**)

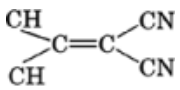
Otherwise, the main reactions at the methylene group are the dialkylation with alkyl halides (77), the acetylation with acetyl chloride which yields acetylmalononitrile [1187-11-7] (78), the Knoevenagel condensation, as well as the condensation with triethyl orthoformate, gives ethoxymethylenemalononitrile [123-06-8], $C_2H_5O{-}CH{=}C(CN)_2$ (79). In the Knoevenagel condensation, aliphatic aldehydes with α-hydrogen atoms usually lead to further condensation products. In the case of aromatic aldehydes this problem does not exist and dicyanostyryl compounds such as (**45**) can easily be made (80). Condensation with 1,4-cyclohexandione [637-88-7] gives 7,7,8,8-tetracyanoquinodimethane [1518-16-7] (**46**) upon further dehydrogenation (81).



(**46**)



(**47**)



(**48**)

Nitrogen derivatives such as 2-aminomalononitrile [5181-05-5] and phenylazomalononitrile [6017-21-6] (**47**) are obtained through nitrosation followed by reduction (82) and condensation with benzenediazonium (83), respectively. Halogen derivatives of interest are the dibromomalononitrile [1885-23-0] which is isolated

in the form of a stable complex with potassium bromide [7758-02-3]. This complex can be debrominated to give tetracyanoethylene [670-54-2] (**48**) (84).

4.3. Manufacture

Malononitrile can be produced batchwise by elimination of water from cyanoacetamide [107-91-5] with phosphorous pentachloride [10026-13-8] (85). It is now produced continuously starting from cyanogen chloride [506-77-4] and acetonitrile [75-05-8]. The reaction takes place at temperatures above 700°C, the reaction products are malononitrile, excess acetonitrile, hydrochloric acid, and small amounts of maleic acid [110-16-7], succinic acid [110-15-6], and fumaric acid [110-17-8]. The products leaving the reactor are immediately cooled to 40–80°C, and gaseous hydrogen chloride is simultaneously separated, fed into a washer, and recovered as dilute hydrochloric acid. Excess acetonitrile is removed by a combination of vacuum distillation and thin-film evaporation. The recovered acetonitrile contains very little hydrogen chloride and can be recycled without risk of corrosion.

Removal of maleic and fumaric acids from the crude malononitrile by fractional distillation is impractical because the boiling points differ only slightly. The impurities are therefore converted into high boiling compounds in a conventional reactor by means of a Diels-Alder reaction with a 1,3-diene. The volatile and nonvolatile by-products are finally removed by two vacuum distillations. The by-products are burned. The yield of malononitrile amounts to 66% based on cyanogen chloride or acetonitrile.

Other processes recently reported in the literature are the gas-phase reaction of lactonitrile [78-97-7] with ammonia and oxygen in the presence of molybdenum catalyst (86), or the vapor-phase reaction of dimethyl malonate with ammonia in the presence of dehydration catalyst (87).

4.4. Economic Aspects

Malononitrile of minimum 99% purity was available as a solidified melt for ca $30/kg in 1993 for ton quantities. Malononitrile is produced by Lonza Ltd. (Switzerland) using the cyanogen chloride process.

4.5. Analytical and Test Method

Gas chromatography is appropriate for the quantitiative analysis of malononitrile. Typical analysis conditions are 3% Reoplex 400 on Chromosorb G 80–100 mesh; 2 m, 2 mm diameter column; temperature for column = 60 − 180°C; injector, 200°C; and detector, 200°C. The solidification point is usually measured also.

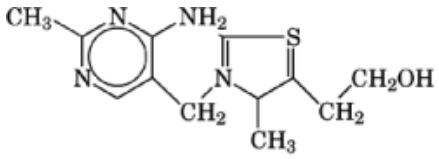
4.6. Health and Safety Factors

Malononitrile is usually available as a solidified melt in plastic-lined drums. Remelting has to be done carefully because spontaneous decomposition can occur at elevated temperatures, particularly above 100°C, in the presence of impurities such as alkalies, ammonium, and zinc salts. Melting should be carried out by means of a water bath and only shortly before use. Occupational exposure to malononitrile mainly occurs by inhalation of vapors and absorption through the skin. Malononitrile has a recommended workplace exposure limit of 8 mg/m^3, an LD_{50} (oral, rats) of 13.9 mg/kg, and is classified as slight irritant (skin irritation, rabbits). Transport classification: RID/ADR: 61, IMDG-Code: 6.1, IATA/ICAO: 6.1.

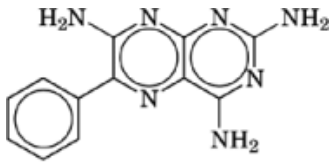
4.7. Uses

Malononitrile is extensively used in the life science industry, especially for the synthesis of *N*-containing heterocycles. The synthesis of thiamine or vitamin B_1 [59-43-8] (**49**) from ethoxymethylenemalononitrile [123-06-8] through 4-amino-5-cyano-2-methylpyrimidine [698-29-3] (88) still represents an important outlet for malonon-

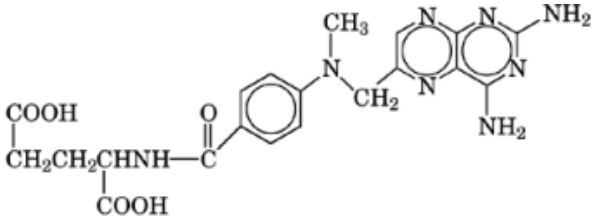
itrile. The introduction of several new highly active sulfonylurea herbicides such as (**23**) based on 2-amino-4,6-dimethoxypyrimidine has also opened an industrial outlet for malononitrile. Further life science products of industrial importance are the diuretic triamterene [396-01-0] (**50**) (89) (see Diuretic agents) and the antineoplastic methotrexate [59-05-2] (**51**) (90), both deriving from 2,4,6-triaminopyrimidine, or the antihypertensive minoxidil [38304-91-5] (**52**) made via ethyl *N*,2-dicyanoacetamidate [53557-77-0], $NCCH_2C(NCN)OC_2H_5$ (91).



(**49**)



(**50**)



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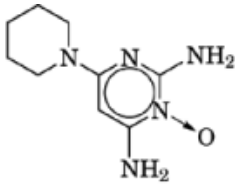
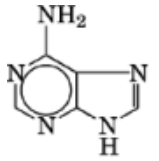
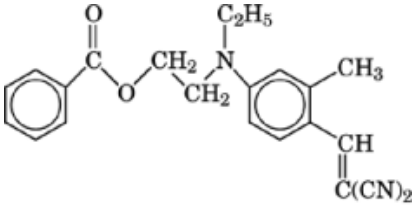


(**52**)

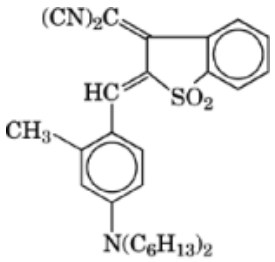
Another compound of interest is adenine [73-24-5] or 6-aminopurine (**53**) derived from phenylazomalononitrile (92). The introduction of the dicyanostyryl moiety has led to the industrialization of several methine dyes such as the CI Disperse Yellow [6684-20-4] (**54**) (93). The CI Disperse Blue 354 [74239-96-6] (**55**) also represents a new class of aminoarylneutrocyanine dyes with a brilliant blue shade (94). The dimer of malononitrile is also used for the synthesis of new dyes (95).



(53)



(54)



(55)

Other miscellaneous applications of malononitrile are the synthesis of 7,7,8,8-tetracyanoquinodimethane (**46**) which is a powerful electron acceptor in the formation of charge-transfer complexes which are of interest because of their conductivity of electricity (96), as well as of 2-chlorobenzylidene malononitrile [2698-41-1] (**45**) also known as CS-gas, which is a safe lachrymatory chemical used for self-defense devices (97).

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