THE MERCK INDEX

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THIRTEENTH EDITION

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AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

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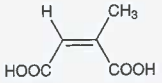
radiation: Langendorff, Koch, *Strahlentherapie* **106,** 451 (1958); Braun *et al., ibid.* **108,** 262 (1959), *C.A.* **52,** 18841h (1958); **53,** 17325e (1959).

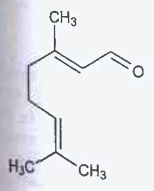
THERAP CAT: In treatment of hepatic disorders.

2345. Citraconic Acid. [498-23-7] (*Z*)-2-Methyl-2-butenedioic acid; methylmaleic acid. $C_5H_6O_4$; mol wt 130.10. C 46.16%, H 4.65%, O 49.19%. Obtained by carefully heating citric acid at about 175°. Production of citraconic anhydride from itaconic acid: Humphrey, **US 2966498** (1960 to Pfizer). Toxicity study: P. M. Jenner *et al., Food Cosmet. Toxicol.* **2,** 327 (1964).

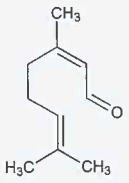


Hygroscopic monoclinic crystals; characteristic odor. d 1.62. mp ~90° (dec). Freely sol in water, alc, ether, slightly in chloroform. Practically insol in benzene, petr ether. LD_{50} in rats, mice (mg/kg): 1320, 2260 orally (Jenner).

2346. Citral. [5392-40-5] 3,7-Dimethyl-2,6-octadienal. $C_{10}H_{16}O$; mol wt 152.23. C 78.90%, H 10.59%, O 10.51%. Constituent of many commercial oils such as lemon grass, verbena, lemon, and orange. Citral from natural sources is a 2:1 mixture of two geometric isomers geranial and neral. Isoln from lemongrass: F. W. Semmler, *Ber.* **23,** 2965 (1890); F. D. Dodge, *Am. Chem. J.* **12,** 553 (1890). Separation of isomers: Y. R. Naves, *Bull. Soc. Chim. France* **1952,** 521. IR determn in lemon and orange oils: P. L. Mahia *et al., Food Chem.* **46,** 193 (1993). Stability in food emulsions and beverages: E. J. Freeburg *et al., Perfumer Flavorist* **19**(4), 23 (1994). Review of toxicity: D. L. J. Opdyke, *Food Cosmet. Toxicol.* **17,** 259-266 (1979); of reaction chemistry: R. K. Baslas, B. Gupta, *Ind. Perfum.* **32,** 266-272 (1988). Comprehensive reviews: J. L. Simonsen, *The Terpenes,* **vol. I,** 83-100 (1947); P. Z. Bedoukian, *Perfumery and Flavoring Synthetics* (Allured Publishing Corporation, Wheaton, IL, 3rd ed., 1986) pp 106-117.



Geranial



Neral

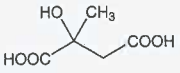
Mobile pale yellow liquid having a strong lemon-like odor. d_{25}^{25} 0.885-0.891. n_D^{20} 1.4860-1.4900. Flash point: 99.5°C (208°F). LD_{50} orally in rats: 4.96 g/kg (Opdyke).

Geranial. [141-27-5] Trans-citral; citral a. Light oily liquid with strong lemon odor. $bp_{2.6}$ 92-93°. d_4^{20} 0.8888. n_D^{20} 1.4898. Practically insol in water. Miscible with alc, ether, benzyl benzoate, diethyl phthalate, glycerol, propylene glycol, mineral oil, essential oils.

Neral. [106-26-3] *cis*-Citral; citral b. Light oily liquid with a lemon odor not as intense but sweeter than gerianal. $bp_{2.6}$ 91-92°. d_4^{20} 0.8860. n_D^{20} 1.4869. Solubilities same as gerianal.

USES: In the synthesis of vitamin A, ionone and methylionone. As a flavor and in perfumery for its citrus effect.

2347. Citramalic Acid. [2306-22-1] 2-Hydroxy-2-methylbutanedioic acid; 2-methylmalic acid; 2-hydroxy-2-methylsuccinic acid; α-hydroxypyrotartaric acid. $C_5H_8O_5$; mol wt 148.11. C 40.55%, H 5.44%, O 54.01%. Enzymatic synthesis: Barker, Blair, *Biochem. Prepns.* **9,** 21 (1962). Chemical synthesis: Barker, *ibid.* 25; J. B. Wilkes, R. G. Wall, *J. Org. Chem.* 45, 247 (1980). Stereoselective synthesis: E. G. J. Staring *et al., Rec. Trav. Chim.* **105,** 374 (1986).

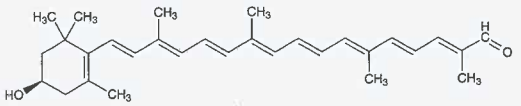


***dl*-Form.** Deliquescent monoclinic prisms from ethyl acetate + petr ether, mp 117°. Sublimes. Freely sol in water, acetone. Sol in ethyl acetate, ether. Practically insol in petr ether, benzene.

***d*-Form.** Crystals, mp 112.2-112.8°. $[\alpha]_D^{22}$ +23.6° (c = 3 in H_2O).

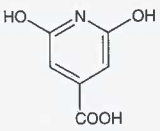
***l*-Form.** Crystals, mp 112-113°. $[\alpha]_D^{20}$ −23.4° (c = 3 in H_2O).

2348. β-Citraurin. [650-69-1] 3-Hydroxy-8′-apo-β,ψ-carotenal; citraurin. $C_{30}H_{40}O_2$; mol wt 432.64. C 83.28%, H 9.32%, O 7.40%. Carotenoid pigment found only in orange peel. Isoln by chromatography: Zechmeister, Tuzson, *Ber.* **69,** 1878 (1936); **70,** 1966 (1937). The peels from 100 kilos of oranges yield about 35 mg. Structure: Zechmeister, Tuzson, *loc. cit.;* Karrer, Solmssen, *Helv. Chim. Acta* **20,** 682 (1937); Karrer *et al., ibid.* 1020; Zechmeister, v. Cholnoky, *Ann.* **530,** 291 (1937); Karrer *et al., Helv. Chim. Acta* **21,** 445 (1938). Abs config: Bartlett *et al., J. Chem. Soc. (C)* **1969,** 2527. Synthesis: H. Pfander *et al., Helv. Chim. Acta* **63,** 1377 (1980).



Thin orange or yellow-colored plates from benzene + petr ether, mp 147°. Absorption max (benzene): 497, 467 nm. Freely sol in acetone, ethanol, ether, benzene, and carbon disulfide. Sparingly sol in petr ether.

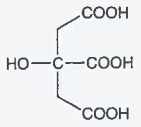
2349. Citrazinic Acid. [99-11-6] 1,2-Dihydro-6-hydroxy-2-oxo-4-pyridinecarboxylic acid; 2,6-dihydroxyisonicotinic acid; 2,6-dihydroxy-4-pyridinecarboxylic acid. $C_6H_5NO_4$; mol wt 155.11. C 46.46%, H 3.25%, N 9.03%, O 41.26%. Prepn from citric acid with aq NH_3 at 140-160° under pressure: Bavley, Hamilton, **US 2729647** (1956 to Pfizer). Purification: Bavley *et al.,* **US 2738352** (1956 to Pfizer).



Yellowish powder with a greenish tinge; carbonizes above 300° without melting. Ultrapure material which is white or colorless, has been prepared. Almost insol in water; slightly sol in hot HCl; sol in alkali hydroxide or carbonate solns. Alkaline solns turn blue on standing.

2350. Citric Acid. [77-92-9] 2-Hydroxy-1,2,3-propanetricarboxylic acid; β-hydroxytricarballylic acid. $C_6H_8O_7$; mol wt 192.12. C 37.51%, H 4.20%, O 58.29%. Widely distributed in plants and in animal tissues and fluids. Produced by mycological fermentation on an industrial scale using crude sugar solns, such as molasses and strains of *Aspergillus niger: See* review by Von Loesecke, *Chem. & Eng. News* **23,** 1952 (1945); Schweiger, **US 2970084** (1961 to Miles Labs.); *Faith, Keyes & Clark's Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 275-279. Also extracted from citrus fruits (lemon juice contains 5 to 8%) and from pineapple waste. *Reviews:* Wilson, *Chem. & Met. Eng.* **29,** 787 (1923); Browne, *Ind. Eng. Chem.* **13,** 81 (1921); Warneford, Hardy, *ibid.* **17,** 1283 (1925); E. F. Bouchard, E. G. Merritt in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 6** (Wiley-Interscience, New York, 3rd ed., 1979) pp 150-

179. Toxicity: Gruber, Halbeisen, *J. Pharmacol. Exp. Ther.* **94,** 65 (1948).



Anhydr form, mp 153°. Crystals are monoclinic holohedra and crystallize from hot concd aq soln. d 1.665. At 25°, pK_1 3.128; pK_2 4.761; pK_3 6.396, Bates, Pinching, *J. Am. Chem. Soc.* **71,** 1274 (1949). Soly in water: 54.0% w/w at 10°; 59.2% at 20°; 64.3% at 30°; 68.6% at 40°; 70.9% at 50°; 73.5% at 60°; 76.2% at 70°; 78.8% at 80°; 81.4% at 90°; 84.0% at 100°.

Monohydrate. Orthorhombic crystals from cold aq solns. Pleasant, sour taste. d 1.542. Monohydrate crystals lose water of crystn in dry air or when heated at about 40 to 50°, slightly deliquescent in moist air. Softens at 75°. mp ~ 100°. pH of 0.1*N* soln = 2.2. Densities of aqueous soln (15°/15°): 10% = 1.0392; 20% = 1.0805; 30% = 1.1244; 40% = 1.1709; 50% = 1.2204; 60% = 1.2738. Soly in g/100 g satd soln: ether 2.17; chloroform 0.007; amyl alcohol 15.43; amyl acetate 5.98; ethyl acetate 5.28. Soly at 19° in g/100 g solvent: methanol 197; propanol 62.8. LD_{50} i.p. in rats: 975 mg/kg (Gruber, Halbeisen).

Pharmaceutical Incompatibilities: Potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, sulfides. Dilute aq solns may ferment on standing.

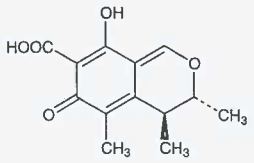
Barium salt heptahydrate. Barium citrate. $C_{12}H_{10}Ba_3O_{14}.7H_2O$. Powder. Loses all H_2O at 150°. Sol in 1750 parts water; freely sol in dil HCl or HNO_3; practically insol in alcohol.

Ethyl ester. Ethyl citrate; triethyl citrate. $C_{12}H_{20}O_7$. Bitter, oily liq. d^{20} 1.137. bp_{760} 294°; $bp_{1.0}$ 127°. Viscosity at 25°: 35.2 cps. Pour pt ~10°. n_D^{20} 1.4455. Soly: water ~6.9%; peanut oil 0.8%. Misc with alc, ether.

USE: Acidulant in beverages, confectionery, effervescent salts, in pharmaceutical syrups, elixirs, in effervescent powders and tablets, to adjust the pH of foods and as synergistic antioxidant, in processing cheese. Used in beverages, jellies, jams, preserves and candy to provide tartness. In the manuf of alkyd resins; in esterified form as plasticizer, foam inhibitor. In the manuf of citric acid salts. As sequestering agent to remove trace metals. As mordant to brighten colors; in electroplating; in special inks; in analytical chemistry for determining citrate-soluble P_2O_5; as reagent for albumin, mucin, glucose, bile pigments.

THERAP CAT: Component of anticoagulant citrate solns (citrate dextrose soln; citrate phosphate dextrose soln; citric acid syrup).

2351. Citrinin. [518-75-2] (3*R*,4*S*)-4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid; Antimycin. $C_{13}H_{14}O_5$; mol wt 250.25. C 62.39%, H 5.64%, O 31.97%. Antibiotic substance produced by a white spore aspergillus which has been placed under the species name *Aspergillus niveus* (Thorn and Raper). Also produced in small quantities by *Penicillium citrinum:* Hetherington, Raistrick, *Trans. Roy. Soc. London* **B220,** 269 (1931); Raistrick, Smith, *Chem. & Ind (London)* **60,** 828 (1941); Timonin, *Science* **96,** 494 (1942); Timonin, Rovatt, *Can. J. Pub. Health* **35,** 80 (1944). Identity with antimycin: Haese, *Arch. Pharm.* **296,** 227 (1963). Structure: Brown *et al., J. Chem. Soc.* **1949,** 867; Warren *et al., J. Am. Chem. Soc.* **79,** 3812 (1957); Kovac *et al., Nature* **190,** 1104 (1961). Synthesis: Cartwright *et al., J. Chem. Soc.* **1949,** 1563; J. A. Barber *et al., J. Chem. Soc. Perkin Trans. I* **1986,** 2101. Stereochemistry: Cram, *J. Am. Chem. Soc.* **72,** 1001 (1950); Mehta, Whalley, *J. Chem. Soc.* **1963,** 3777; Mathieson, Whalley, *ibid.* **1964,** 4640. Physical characteristics and toxicity: Nagai *et al., Chem. Zentr.* **1958,** 8088, *C.A.* **55,** 1914 (1961). Crystal and molecular structure: Rodig, *Chem. Commun.* **1971,** 1553. Biosynthesis: J. Barber *et al., J. Chem. Soc. Perkin Trans. I* **1981,** 2577; L. Colombo *et al., ibid.* 2594. Physicochemical data: A. E. Pohland *et al., Pure Appl. Chem.* **54,** 2219 (1982). Toxicology: A. M. Ambrose, F. De Eds, *J. Pharmacol. Exp. Ther.* **88,** 173 (1946). *Review:* Saito *et al.*, "Yellowed Rice Toxins" in *Microbial Toxins,* A. Ciegler, S. Kadis, A. Ajl, Eds. (Academic Press, New York, 1971) **vol. VI,** pp 357-367.

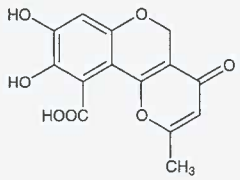


Lemon-yellow needles from alcohol, dec 175°. $[\alpha]_D^{18}$ −37.4° (c = 1.15 in alc.). uv max: 250, 331 nm ($E_{1cm}^{1\%}$ 370, 418). Strong acid. Practically insol in water. Sol in alcohol, dioxane, dilute alkali. Solns change color with changes in pH, from lemon-yellow at pH 4.6 to cherry-red at pH 9.9. *Poisonous!* LD_{50} in mice, rats (mg/kg): 35, 67 i.p. (Ambrose, De Eds).

Methyl citrinin. $C_{14}H_{16}O_5$. Plates from benzene, dec 139°. $[\alpha]_D^{18}$ +217.1° (c = 0.38 in acetone). uv max: 260, 334 nm ($E_{1cm}^{1\%}$ 520, 151.6). Sol in hot alcohol; moderately sol in chloroform. Practically insol in petr ether.

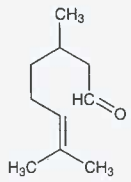
Dihydrocitrinin. $C_{13}H_{16}O_5$. Prisms from benzene, dec 171°. $[\alpha]_D^{18}$ −18.8° (c = 4.148 in chloroform). uv max: 260, 330 nm ($E_{1cm}^{1\%}$ 400, 100). Sol in alcohol, acetone, chloroform; sparingly sol in benzene, petr ether.

2352. Citromycetin. [478-60-4] 8,9-Dihydroxy-2-methyl-4-oxo-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-10-carboxylic acid; frequentic acid. $C_{14}H_{10}O_7$; mol wt 290.22. C 57.94%, H 3.47%, O 38.59%. Antibiotic substance produced by *Penicillium frequentans* Westling and *P. vesiculosum* Bainier and by *Citromyces* spp: Hetherington, Raistrick, *Phil. Trans. Roy. Soc. London, Ser. B,* **220,** 209 (1931); Grove, Brian, *Nature* **167,** 995 (1951). Structure: Robertson *et al., J. Chem. Soc.* **1951,** 2013. Biosynthesis: Birch *et al., ibid.* **1958,** 4576; Money, *Nature* **199,** 592 (1963). Total synthesis: M. Yamauchi *et al., J. Chem. Soc. Perkin Trans. I* **1987,** 395.



Dihydrate. Yellow crystals, effervescence at 155°, dec 290-300° (considerable antecedent blackening). Freely sol in ethanol; readily sol in aq sodium carbonate soln; sparingly sol in water, chloroform. Insol in benzene, hexane. Stable to acid and alkali at 100°.

2353. Citronellal. [106-23-0] 3,7-Dimethyl-6-octenal. $C_{10}H_{18}O$; mol wt 154.25. C 77.87%, H 11.76%, O 10.37%. Chief constituent of citronella oil; also found in many other volatile oils, such as lemon, lemon grass, melissa: Tiemann, *Ber.* **32,** 834 (1899); Spoon, *Chem. Weekbl.* **54,** 236 (1958). Structure: Naves, *Bull. Soc. Chim. France* **1951,** 505; Eschinazi, *J. Org. Chem.* **26,** 3072 (1961).



Liquid. bp_1 47°. n_D^{20} 1.4460. $[\alpha]_D^{25}$ +11.50°. d 0.848-0.856. Soluble in alcohols; very slightly sol in water.