THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

FOURTEENTH EDITION

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Cystatin B. [99194-04-4] Stefin B; CPI-B; NCPI; neutral cysteine proteinase inhibitor. Broadly distributed in human cells and tissues; general cytosolic inhibitor to protect against leakage of lysosomal enzymes. Mutations in the cystatin B gene have been associated with progressive myoclonus epilepsy. Isoln from human spleen: M. Järvinen, A. Rinne, *Biochim. Biophys. Acta* **708**, 210 (1982); from human liver: G. D. J. Green *et al., Biochem. J.* **218**, 939 (1984). Review of role in Unverricht-Lundborg disease: A.-E. Lehesjoki, *EMBO J.* **22**, 3473-3478 (2003). Mature human form is a single chain, non-glycosylated peptide containing 98 amino acid residues; mol wt 11.2 kDa. Isoelectric point: 5.6-6.3.

Cystatin C. [91448-99-6] Post-γ-globulin; γ-CSF; γ-trace. Found ubiquitously in vertebrates; major extracellular cysteine peptidase inhibitor in mammals. Isoln from human CSF: J. Clausen, *Proc. Soc. Exp. Biol. Med.* **107**, 170 (1961); from urine of patients with renal dysfunction: E. A. Butler, F. V. Flynn, *J. Clin. Pathol.* **14**, 172 (1961). Identification as a cystatin: A. J. Barrett *et al., Biochem. Biophys. Res. Commun.* **120**, 631 (1984). Review of biochemistry and clinical role: M. Mussap, M. Plebani, *Crit. Rev. Clin. Lab. Sci.* **41**, 467-550 (2004); of efficacy as biomarker for glomerular filtration rate: G. Filler *et al., Clin. Biochem.* **38**, 1-8 (2005). Clinical evaluation to predict risk of cardiovascular events in elderly patients: M. G. Shlipak *et al., N. Engl. J. Med.* **352**, 2049 (2005). Mature human form is a single chain, non-glycosylated peptide containing 120 amino acid residues; mol wt 13.3 kDa. Isoelectric point: 9.3. Electrophoretic mobility: γ_3 (agarose gel electrophoresis at pH 8.6). $E^{1\%}_{1cm}$ 9.1 (280 nm). Conc in plasma of healthy adults: 0.8 to 1.2 mg/l.

THERAP CAT: Cystatin C as diagnostic aid (renal function).

2779. Cysteamine. [60-23-1] 2-Aminoethanethiol; mercaptamine; β-mercaptoethylamine; 2-aminoethyl mercaptan; thioethanolamine; decarboxycysteine; MEA; mercamine; L-1573; Becaptan; Lambratene (formerly). C_2H_7NS; mol wt 77.15. C 31.14%, H 9.15%, N 18.16%, S 41.56%. $HSCH_2CH_2NH_2$. A sulfhydryl compound with a variety of biological effects. Prepn: Gabriel, Leupold, *Ber.* **31,** 2837 (1898); Knorr, Rössler, *ibid.* **36,** 1281 (1903); Mills, Jr., Bogart, *J. Am. Chem. Soc.* **62,** 1173 (1940); Wenker, *ibid.* **57,** 2328 (1935); D. A. Shirley, *Preparation of Organic Intermediates* (Wiley, New York, 1951) p 189. Use in treatment of paracetamol (acetaminophen) poisoning: L. F. Prescott *et al., Lancet* **2,** 109 (1976); A. L. Harris, *Br. Med. J.* **284,** 825 (1982). Effects in nephropathic cystinosis: M. Yudkoff *et al., N. Engl. J. Med.* **304,** 141 (1981). Radioprotective effects: R. P. Bird, *Radiat. Res.* **72,** 290 (1980); C. J. Koch, R. L. Howell, *ibid.* **87,** 265 (1981). Cysteamine has been shown to be a duodenal ulcerogen in rats: H. Selye, S. Szabo, *Nature* **244,** 458 (1973); S. Szabo, *Am. J. Pathol.* **93,** 273 (1978); P. Kirkegaard *et al., Scand. J. Gastroenterol.* **15,** 621 (1980). *Review:* S. Szabo, *Lab. Invest.* **51,** 121 (1984). It has also been found to deplete somatostatin concentration: S. Szabo, S. Reichlein, *Endocrinology* **109,** 2255 (1981); S. M. Sagar *et al., J. Neurosci.* **2,** 225 (1982). In pituitary tissue, cysteamine is a potent depletor of prolactin concentrations *in vivo* and *in vitro:* W. J. Millard *et al., Science* **217,** 452 (1982). Toxicity studies: E. Beccari *et al., Arzneim.-Forsch.* **5,** 421 (1955); D. L. Klayman *et al., J. Med. Chem.* **12,** 510 (1969); P. K. Srivastava, L. Field, *ibid.* **18,** 798 (1975).

Crystals by sublimation *in vacuo*. Disagreeable odor. mp 97-98.5°. Oxidizes to cystamine on standing in air. Freely sol in water, alkaline reaction. LD_{50} in mice (mg/kg): 625 orally; 250 i.p. (Klayman); (Srivastava, Field).

Hydrochloride. $C_2H_7NS.HCl$. Crystals from alc, mp 70.2-70.7°. Sol in water, alcohol. LD_{50} (cg/kg): 23.19 i.p. in rats; 14.95 i.v. in rabbits (Beccari).

USE: Experimentally as a radioprotective agent and to produce acute and chronic duodenal ulcers in rats.

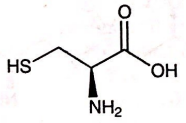
THERAP CAT: Antidote to acetaminophen.

2780. Cysteic Acid. [13100-82-8] 3-Sulfoalanine; α-amino-β-sulfopropionic acid. $C_3H_7NO_5S$; mol wt 169.16. C 21.30%, H 4.17%, N 8.28%, O 47.29%, S 18.96%. $HOOCCH(NH_2)CH_2SO_3H$. Has been isolated from human hair oxidized with permanganate: Lissizin, *Z. Physiol. Chem.* **173,** 309 (1928). Occurs normally in the outer part of the sheep's fleece, where the wool is exposed to light and weather: Martin, Synge, *Adv. Protein Chem.* **2,** 3 (1945). Prepd from cystine or cysteine by oxidation with bromine in water: Friedmann, *Beitr. Chem. Physiol. Pathol.* **3,** 25, 38; Gortner, Hoffman, *J. Biol. Chem.* **72,** 435 (1927).

L-Form. Octahedra or needles from dil alc (also forms a monohydrate, prismatic needles). When anhydr, dec 260°. $[\alpha]^{20}_D$ +8.66° (1.85 g in 25 ml). pKa_1 (25°): 1.89; pKa_2 8.7; pKb about 12.7. Soluble in water. Insol in alcohol.

DL-Form. Crystals, dec 245°.

2781. Cysteine. [52-90-4] L-Cysteine; Cys; C; β-mercaptoalanine; (*R*)-2-amino-3-mercaptopropanoic acid; 2-amino-3-mercaptopropionic acid; α-amino-β-thiolpropionic acid; half-cystine; thioserine. $C_3H_7NO_2S$; mol wt 121.16. C 29.74%, H 5.82%, N 11.56%, O 26.41%, S 26.47%. A non-essential amino acid in human development. Readily oxides to form a dimeric amino acid, cystine, *q.v.*, in which the two Cys are linked via a disulfide bridge, a common structural feature in proteins. Early chemistry and biochemistry: *Amino Acids and Proteins,* D. M. Greenberg, Ed. (Charles C. Thomas, Springfield, IL, 1951) 950 pp., *passim*; J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids* **vol 1-3** (John Wiley and Sons, Inc., New York, 1961) pp. 1879-1928, *passim.* Simple synthesis of racemic cysteine: V. J. Martens *et al., Angew. Chem. Int. Ed.* **20,** 668 (1981). Determn in proteins: J. G. Hoogerheide, C. M. Campbell, *Anal. Biochem.* **201,** 146 (1992); D. Atherton *et al., ibid.* **212,** 98 (1993). Review of biosynthesis: N. M. Kredich *et al., Ciba Found. Symp.* (Netherlands) **72,** 87-99 (1980). Review of transport in mammalian cells: S. Bannai, *Biochim. Biophys. Acta* **779,** 289-306 (1984). Review of effects on acrylonitrile toxicity: D. E. Nerland *et al., Drug Metab. Rev.* **20,** 233-246 (1989). Review of thermodynamics and kinetics: T. R. Ralph *et al., J. Electroanal. Chem.* **375,** 1-15 (1994); of electrosynthesis: *eidem, ibid.* 17-27. Review of role in chemo- and radioprotectant strategies: J. C. Roberts, *Amino Acids* **8,** 113-124 (1995).



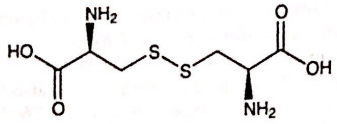
Crystals. $[\alpha]^{25}_D$ +6.5° (5*N* HCl); $[\alpha]^{25}_D$ +13.0° (glacial acetic acid). pK_1 1.71; pK_2 8.33; pK_3 10.78. Absorption spectrum: Abderhalden, Rossner, *Z. Physiol. Chem.* **178,** 160 (1928). Freely sol in water, alcohol, acetic acid, ammonia water. Insol in ether, acetone, ethyl acetate, benzene, carbon disulfide, carbon tetrachloride. In neutral or slightly alkaline aq solns it is oxidized to cystine by air. More stable in acidic solns.

Hydrochloride. [52-89-1] $C_3H_7NO_2S.HCl$. Crystals, dec 175-178°. $[\alpha]^{25}_D$ +5.0° (5*N* HCl); $[\alpha]^{25}_D$ +10.0° (glacial acetic acid). Sol in water, alcohol, acetone; the aq soln is acid. *Keep tightly closed.* Decomposes and oxidizes slowly; hygroscopic.

USE: As dough conditioner.

THERAP CAT (VET): Has been used as a detoxicant.

2782. Cystine. [56-89-3] L-Cystine; [*R*-(*R**,*R**)]-3,3′-dithiobis[2-aminopropanoic acid]; dicysteine; β,β′-dithiodialanine; α-diamino-β-dithiolactic acid; β,β′-diamino-β,β′-dicarboxydiethyl disulfide; bis(β-amino-β-carboxyethyl) disulfide; Gelucystine. $C_6H_{12}N_2O_4S_2$; mol wt 240.30. C 29.99%, H 5.03%, N 11.66%, O 26.63%, S 26.69%. Non-essential amino acid for human development. Formed by the dimerization of two cysteines, *q.v.* through the sulfur. These disulfide bridges occur both within and between polypeptides; often found in extracellular proteins. First amino acid described in 1810 by Wollaston. Isoln from horn hydrolysate: K. A. H. Mörner, *Z. Physiol. Chem.* **28,** 595 (1899). Early chemistry and biochemistry: *Amino Acids and Proteins,* D. M. Greenberg, Ed. (Charles C. Thomas, Springfield, IL, 1951) 950 pp. *passim*; J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids* **vols 1-3** (John Wiley and Sons, Inc., New York, 1961) pp. 1879-1928, *passim.* Distribution in protein: R. C. Fahey *et al., J. Mol. Evol.* **10,** 155 (1977). Review of lysosomal transport including pathophysiology: W. Gahl in *Pathophysiol. Lysosomal Transp.*, J. G. Thoene, Ed. (CRC Press, Boca Raton, FL, 1992) pp 45-71. Review of thermodynamics and kinetics: T. R. Ralph *et al., J. Electroanal. Chem.* **375,** 1-15 (1994); of electrosynthesis: *eidem, ibid.* 17-27.



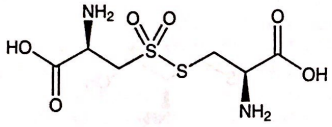
Hexagonal tablets from water, dec 260-261° (sealed tube). $[\alpha]_D^{20}$ −223.4° (1.0*N* HCl). pK_1 1; pK_2 2.1; pK_3 8.02; pK_4 8.71 at 35°. Soly in water (g/l) at 25°: 0.112; at 50°: 0.239; at 75°: 0.523; at 100°: 1.142. Quite sol in aq solns below pH 2 or above pH 8. Soly curves: Sano, *Biochem. Z.* **168,** 14 (1926). Insol in alc. Absorption spectrum: Marchlewski, Nowotonowna, *Bull. Soc. Chim. Fr.* [4] **39,** 163, 166 (1926).

D-Form. [349-46-2] Crystals. $[\alpha]_D^{20}$ +223° (1.0*N* HCl). Soly in water at 25°: 0.057 g/l.

DL-Form. [923-32-0] Crystals. Soly in water at 25°: 0.057 g/l.

***meso*-Form.** [6020-39-9] Crystals. Soly in water: 0.056 g/l.

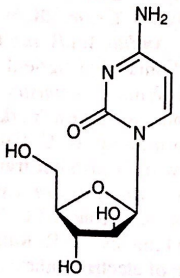
2783. L-Cystine *S,S*-Dioxide. [30452-69-8] 2-Amino-2-carboxyethyl 2-amino-2-carboxyethanethiosulfonate; L-cystine thiosulfonate; sacysyl-cysteine. $C_6H_{12}N_2O_6S_2$; mol wt 272.30. C 26.47%, H 4.44%, N 10.29%, O 35.25%, S 23.55%. Oxidation product of cystine. Prepn: G. Toennies, T. F. Lavine, *J. Biol. Chem.* **113,** 571 (1936); R. Emilozzi, L. Pichat, *Bull. Soc. Chim. Fr.* **1959,** 1887. Orignally thought to be a mixture of two isomers, cystine *S,S*-dioxide and ***cystine S,S'-dioxide***: G. E. Utzinger, *Experientia* **17,** 374 (1961). Elucidaton of structures: G. Axelson *et al., Spectrochim. Acta* **23A,** 2015 (1967); L. D. Setiawan *et al., Surf. Interface Anal.* **7,** 188 (1985). Use in determn of sulfite: T. Ubuka *et al., Anal. Biochem.* **126,** 273 (1982); *idem et al., ibid.* **140,** 449 (1984).



Solid, relatively unstable in aqueous solns; disproportionates to cystine and cysteine sulfinic acid.

USE: In detection of sulfites and thiosulfate.

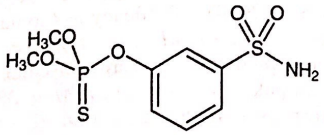
2784. Cytarabine. [147-94-4] 4-Amino-1-β-D-arabinofuranosyl-2(1*H*)-pyrimidinone; 1-β-D-arabinofuranosylcytosine; Ara-C; β-cytosine arabinoside; aracytidine; CHX-3311; U-19920; Alexan; Aracytine; Cytosar; Depocyte; Udicil. $C_9H_{13}N_3O_5$; mol wt 243.22. C 44.44%, H 5.39%, N 17.28%, O 32.89%. Nucleoside analog; converted by cellular kinases into the active metabolite, ***AraCTP***. Prepn: J. H. Hunter, **US 3116282** (1963 to Upjohn); T. Y. Shen *et al., J. Org. Chem.* **30,** 835 (1965). NMR soln structure of Ara-C within a DNA dodecamer: B. I. Schweitzer *et al., Biochemistry* **33,** 11460 (1994). Crystal structure of complex with human topoisomerase I: J. E. Chrencik *et al., J. Biol. Chem.* **278,** 12461 (2003). Clinical pharmacology and toxicology: R. C. Donehower *et al., Cancer Treat. Rep.* **70,** 1059 (1986). Symposium on clinical pharmacology, pharmacokinetics and efficacy in leukemia: *Scand. J. Haematol.* **36,** Suppl. 44, 1-74 (1986). Review of development of a high dose treatment for acute myeloid leukemia: R. L. Capizzi, *Invest. New Drugs* **14,** 249-256 (1996); of cellular metabolism and mechanism of action: S. Grant, *Adv. Cancer Res.* **72,** 197-233 (1998).



Crystals from ethanol, mp 212-213°. $[\alpha]_D^{24}$ +153° (c = 0.5 in water). uv max at pH 2: 281.0, 212.5 nm (ε 13171, 10230); at pH 12: 272.5 nm (ε 9259).

THERAP CAT: Antineoplastic.

2785. Cythioate. [115-93-5] Phosphorothioic acid *O*-[4-(aminosulfonyl)phenyl] *O,O*-dimethyl ester; phosphorothioic acid *O,O*-dimethyl ester *O*-ester with *p*-hydroxybenzenesulfonamide; *O,O*-dimethyl *O*-*p*-sulfamoylphenylphosphorothioate; CL-26691; ENT-25640; Proban. $C_8H_{12}NO_5PS_2$; mol wt 297.29. C 32.32%, H 4.07%, N 4.71%, O 26.91%, P 10.42%, S 21.57%. Prepn: G. Berkelhammer, **US 3005004** and R. I. Hewitt, G. Berkelhammer, US **3179560** (1961, 1965 to Am. Cyanamid). Pharmacodynamics: H. G. Smith, R. L. Goulding, *J. Econ. Entomol.* **63,** 1640 (1970). Efficacy as ectoparasiticide: C. P. Doval, I. Gupta, *Indian Vet. J.* **55,** 890 (1978); P. M. Bowen, N. J. Caldwell, *Vet. Med. Small Anim. Clin.* **77,** 79 (1982). Toxicity data: E. E. Kenaga, W. E. Allison, *Bull. Entomol. Soc. Am.* **15,** 85 (1969).

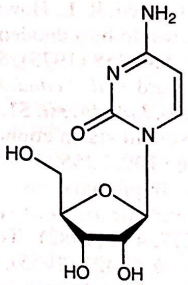


Crystals, mp 70-71°. n_D^{25} 1.5346. LD_{50} orally in rats: 160 mg/kg (Kenaga, Allison).

USE: Insecticide.

THERAP CAT (VET): Ectoparasiticide.

2786. Cytidine. [65-46-3] 4-Amino-1-β-D-ribofuranosyl-2-(1*H*)-pyrimidinone; cytosine riboside; 1-β-D-ribofuranosylcytosine. $C_9H_{13}N_3O_5$; mol wt 243.22. C 44.44%, H 5.39%, N 17.28%, O 32.89%. Constituent of nucleic acids. Isoln from yeast nucleic acid: Levene, Jacobs, *Ber.* **43,** 3154 (1910); Levene, La Forge, *ibid.* **45,** 608 (1912). Sepn from other nucleosides by ion-exchange chromatography: Cohn in Chargaff-Davidson, *The Nucleic Acids* **vol. I** (New York, 1955) p 211. Synthesis: Howard *et al., J. Chem. Soc.* **1947,** 1052. Crystal structure: Furberg *et al., Acta Crystallogr.* **18,** 313 (1965). *Review: Basic Principles in Nucleic Acid Chemistry* **vol. 1,** P. O. P. Ts'o, Ed. (Academic Press, New York, 1974) *passim.*



Long needles from 90% ethanol, dec 220-230°. $[\alpha]_D^{25}$ +31° (c = 0.7 in water). Freely sol in water, less sol in alcohol. pK (amino, cationic) 4.22; pK (sugar, anionic) 12.5. uv max (pH 8.2): 271 nm (ε 9100); (pH 2.2): 280 nm (ε 13400), Voet *et al., Biopolymers* **1,** 193 (1963).

Sulfate. $(C_9H_{13}N_3O_5)_2.H_2SO_4$. Long prismatic needles, mp 224-225° (dec with effervescence). $[\alpha]_{589}^{25}$ +34°; $[\alpha]_{546}^{25}$ +43°.

2787. 2'-Cytidylic Acid. [85-94-9] Cytidine-2'-monophosphate; cytidylic acid *a*; 2'-cytidinephosphoric acid; cytidine-2'-phosphate; 2'-cytosylic acid; 2'-CMP. $C_9H_{14}N_3O_8P$; mol wt 323.20. C 33.45%, H 4.37%, N 13.00%, O 39.60%, P 9.58%. Ribonuclease inhibitor. Prepn from yeast ribonucleic acid: Cohn, Carter, *J. Am. Chem. Soc.* **72,** 2606 (1950); Loring *et al., J. Biol. Chem.* **196,** 807 (1952); by phosphorylation of $N^6,O^{3'},O^{5'}$-tribenzoylcytidine: Rammler, Khorana, *J. Am. Chem. Soc.* **84,** 3112 (1962). Crystal structure and conformation of the trihydrate: Kartha *et al., Science* **179,** 495 (1973). *Reviews: See* Cytidine.