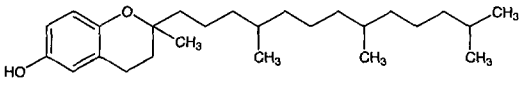
mechanism of action: H. Ito, *Expert Opin. Ther. Targets* **8**, 287-294 (2004).

THERAP CAT: Anti-inflammatory.

9494. Tocol. [119-98-2] 3,4-Dihydro-2-methyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; 2-methyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 2-methyl-2-phytyl-6-chromanol; 6-hydroxy-2-methyl-2-phytylchroman; 2-methyl-2-phytyl-6-hydroxychroman. $C_{26}H_{44}O_2$; mol wt 388.63. C 80.35%, H 11.41%, O 8.23%. Synthesis by the condensation of hydroquinone and phytol in the presence of anhydr formic acid: Pendse, Karrer, *Helv. Chim. Acta* **40**, 1837 (1957). Antioxidant activity of tocol and its methyl derivs: Olcott, van der Veen, *Lipids* **3**, 331 (1968).

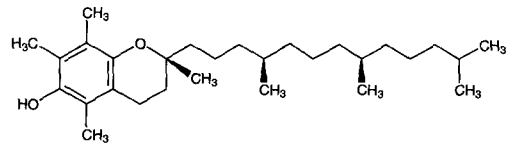


Colorless, viscous oil. $bp_{0.001}$ 165-175°.

Acetate. $C_{28}H_{46}O_3$. Viscous oil. $bp_{0.001}$ 180-185°.

USE: Antioxidant.

9495. α-Tocopherol. [59-02-9] (2*R*)-3,4-Dihydro-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-1-benzopyran-6-ol; (+)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol; *R,R,R*-α-tocopherol; *d*-α-tocopherol; 5,7,8-trimethyltocol; Optovit; Tocovital. $C_{29}H_{50}O_2$; mol wt 430.71. C 80.87%, H 11.70%, O 7.43%. Most bioactive of the naturally occurring forms of vitamin E, *q.v.* Richest sources are green vegetables, grains, and oils, particularly palm, safflower and sunflower oils. Isoln from wheat germ: H. M. Evans *et al., J. Biol. Chem.* **113,** 319 (1936). Structure: E. Fernholz, *J. Am. Chem. Soc.* **59,** 1154 (1937); **60,** 700 (1938). Synthesis of *dl*-form: P. Karrer *et al., Helv. Chim. Acta* **21,** 520, 820 (1938); F. Bergel *et al., J. Chem. Soc.* **1938,** 1382. Distillation from vegetable oils and prepn of esters: J. G. Baxter *et al., J. Am. Chem. Soc.* 918 (1943). Prepn of crystalline natural form: C. D. Robeson, *ibid.* 1660; of crystalline acetate: *idem, ibid.* **64**, 1487 (1942). Abs config of natural α-tocopherol: H. Mayer *et al., Helv. Chim. Acta* **46,** 963 (1963). Stereoselective synthesis: K.-K. Chan *et al., J. Org. Chem.* **43**, 3435 (1978). Total synthesis of all 8 stereoisomers: N. Cohen *et al., Helv. Chim. Acta* **64**, 1158 (1981). Clinical trial in Alzheimer's disease: M. Sano *et al., N. Engl. J. Med.* **336**, 1216 (1997); to improve immune function in healthy elderly: S. N. Meydani *et al., J. Am. Med. Assoc.* **277**, 1380 (1997). Review of bioavailability from vitamin E supplements: M. G. Traber, *BioFactors* **10**, 115-120 (1999). Review of clinical trials in heart disease: W. A. Pryor, *Free Radical Biol. Med.* **28**, 141-164 (2000).



Transparent needles, mp 2.5-3.5°. $[\alpha]_{546.1}^{25}$ −3.0° (benzene); $[\alpha]_{546.1}^{25}$ +0.32° (ethanol).

Acetate. [58-95-7] Spondyvit. $C_{31}H_{52}O_3$; mol wt 472.74. Light yellow oil. Crystallized at −30° as needle-like crystals, mp 26.5-27.5°. $[\alpha]_D^{25}$ +0.25° (c = 10 in chloroform); $[\alpha]_D^{25}$ +3.2° (in ethanol).

Succinate. [4345-03-3] *d*-α-Tocopheryl acid succinate; Tocovite. Needles from petr ether, mp 76-77°. uv max (ethanol): 286 nm ($E_{1cm}^{1\%}$ 38.5). Practically insol in water.

***dl*-α-Tocopherol.** [10191-41-0] *all-rac*-α-Tocopherol. Equimolar mixture of all four racemates. Slightly viscous, pale yellow oil. d_4^{25} 0.950; $bp_{0.1}$ 200-220°; n_D^{25} 1.5045. uv max: 294 nm ($E_{1cm}^{1\%}$ 71). Practically insol in water. Freely sol in oils, fats, acetone, alcohol, chloroform, ether, other fat solvents. Stable to heat and alkalies in the absence of oxygen. Not affected by acids up to 100°. Slowly oxidized by atm oxygen, rapidly by ferric and silver salts. Gradually darkens on exposure to light.

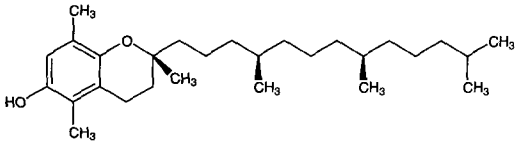
***dl*-α-Tocopherol acetate.** [52225-20-4] *dl*-α-Tocopheryl acetate; Detulin; Ephynal; Eusovit; Evion. Comprehensive description: B. C. Rudy, B. Z. Senkowski, *Anal. Profiles Drug Subs.* **3,** 111-126 (1974). Pale yellow, viscous liquid. mp −27.5°. $d_4^{21.3}$ 0.9533. $bp_{0.01}$ 184°; $bp_{0.025}$ 194°; $bp_{0.3}$ 224°. n_D^{20} 1.4950-1.4972. uv max (cyclohexane): 285.5 nm. Practically insol in water. Freely sol in acetone, chloroform, ether. Less readily sol in alc.

USE: As an antioxidant in vegetable oils and shortening.

THERAP CAT: Vitamin E supplement.

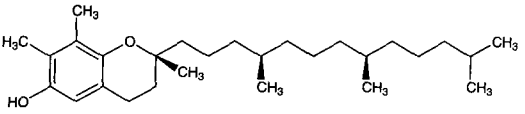
THERAP CAT (VET): Vitamin E supplement.

9496. β-Tocopherol. [16698-35-4]; [148-03-8] (*dl*-form). (2*R*)-3,4-Dihydro-2,5,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-1-benzopyran-6-ol; (+)-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 5,8-dimethyltocol; cumotocopherol; neotocopherol; *p*-xylotocopherol. $C_{28}H_{48}O_2$; mol wt 416.68. C 80.71%, H 11.61%, O 7.68%. One of the naturally occurring forms of vitamin E, *q.v.* Is biologically less active than α-tocopherol. May be separated by fractional crystn: Emerson *et al., Science* **83,** 421 (1936); *J. Biol. Chem.* **113,** 319 (1936); Baxter *et al., J. Am. Chem. Soc.* **65,** 918 (1943).



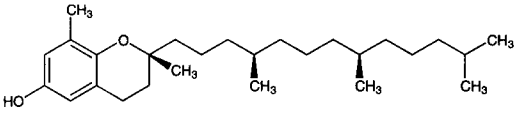
Pale yellow, viscous oil. $bp_{0.1}$ 200-210°. $[\alpha]_{546.1}^{25}$ +2.9° (c = 7.15 in ethanol). uv max: 297 nm ($E_{1cm}^{1\%}$ 87.6). Insol in water. Freely sol in oils, fats, acetone, alcohol, chloroform, ether, other fat solvents. Very stable to heat and alkalies. Slowly oxidized by atmospheric oxygen, rapidly by ferric and silver salts. Gradually darkens on exposure to light.

9497. γ-Tocopherol. [54-28-4]; [7616-22-0] (*dl*-form). (2*R*)-3,4-Dihydro-2,7,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-1-benzopyran-6-ol; (+)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; (*R,R,R*)-γ-tocopherol; 7,8-dimethyltocol; *o*-xylotocopherol. $C_{28}H_{48}O_2$; mol wt 416.68. C 80.71%, H 11.61%, O 7.68%. One of the naturally occurring forms of vitamin E, *q.v.* Most abundant tocopherol in soybean and corn oils. Isoln by fractional crystn: Emerson *et al., Science* **83,** 421 (1936); *J. Biol. Chem.* **113,** 319 (1936); J. G. Baxter *et al., J. Am. Chem. Soc.* **65,** 918 (1943). Prepn of crystalline natural form: C. D. Robeson, *J. Am. Chem. Soc.* **65**, 1660 (1943). Comparison of bioactivity with α-tocopherol, *q.v.*: J. G. Bieri, R. P. Evarts, *J. Nutr.* **104**, 850 (1974). Protective effects vs reactive nitrogen oxide species: R. V. Cooney *et al., Proc. Natl. Acad. Sci. USA* **90**, 1771 (1993); S. Christen *et al., ibid.* **94**, 3217 (1997). HPLC determn in serum: A. Sobczak *et al., J. Chromatogr. B* **730**, 265 (1999). Review of bioavailability, metabolism, and activity: Q. Jiang *et al., Am. J. Clin. Nutr.* **74**, 714-722 (2001).



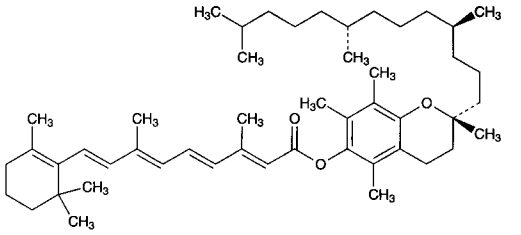
Pale yellow, viscous oil. Has been crystallized as transparent needles, mp −3 to −2°. $bp_{0.1}$ 200-210°. $[\alpha]_{546.1}^{25}$ −2.4° (c = 8.59 in benzene); $[\alpha]_{546.1}^{25}$ +2.2° (c = 9.32 in ethanol). uv max: 298 nm ($E_{1cm}^{1\%}$ 92.8). Insol in water. Freely sol in oils, fats, acetone, alcohol, chloroform, ether, other fat solvents. Very stable to heat and alkalies. Slowly oxidized by atmospheric oxygen, rapidly by ferric and silver salts. Gradually darkens on exposure to light.

9498. δ-Tocopherol. [119-13-1] (2*R*)-3,4-Dihydro-2,8-dimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-1-benzopyran-6-ol; 8-methyltocol. $C_{27}H_{46}O_2$; mol wt 402.65. C 80.54%, H 11.52%, O 7.95%. One of the naturally occurring forms of vitamin E, *q.v.* Isoln from soybean oil: Stern *et al., J. Am. Chem. Soc.* **69,** 869 (1947). Synthesis: Green *et al., J. Chem. Soc.* **1959,** 3374; **GB 900085** (1961 to Hoffmann-La Roche).



Pale yellow, viscous oil. $[\alpha]_{546}^{25}$ +3.4° (c = 15.5 in alc); $[\alpha]_{546}^{25}$ +1.1° (c = 10.9 in benzene). uv max: 298 nm ($E_{1cm}^{1\%}$ 91.2).

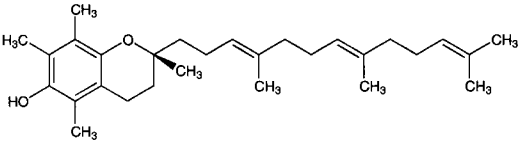
9499. Tocoretinate. [40516-48-1] Retinoic acid *rel*-(2*R*)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-1-benzopyran-6-yl ester; (±)-(2*R**)-2,5,7,8-tetramethyl-2-[(4*R**,8*R**)-4,8,12-trimethyltridecyl]-6-chromanyl retinoate; tretinoin tocoferil; DL-α-tocopheryl retinoate; L-300; N-021; Olcenon. $C_{49}H_{76}O_3$; mol wt 713.13. C 82.53%, H 10.74%, O 6.73%. Wound healing agent that stimulates proliferation of normal skin fibroblasts. Prepn: H. Fukawa, K. Tanaka, **JP Kokai 73 00469**; *eidem*, **US 3878202** (1973, 1975 both to Nisshin Flour Milling Co.). Pharmacology: K. Sakyo *et al., Oyo Yakuri* **43,** 111 (1992), *C.A.* **116,** 228223z (1992). Pharmacokinetics: T. Nakazawa *et al., ibid.* 205, *C.A.* **117,** 19823 (1993). Mechanism of action study: N. Kawamura *et al., Dig. Dis. Sci.* **39,** 2191 (1994). Clinical evaluation in skin ulcers: T. Doi, *Skin Res.* **36,** 384 (1994); K. Nakagawa *et al., ibid.* 209. Acute toxicity study: Y. Harada *et al., Oyo Yakuri* **43,** 227 (1992), *C.A.* **117,** 20721 (1992).



Light yellow oil. uv max (ethanol): 365 nm ($E_{1cm}^{1\%}$ 642). LD_{50} in mice (mg/kg): >1000 i.v.; >2000 orally (Fukawa, 1975).

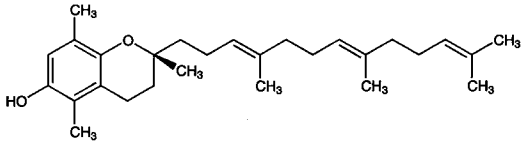
THERAP CAT: Vulnerary.

9500. α-Tocotrienol. [58864-81-6]; [1721-51-3] (unspecified stereo). (2*R*)-3,4-Dihydro-2,5,7,8-tetramethyl-2-[(3*E*,7*E*)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-2*H*-1-benzopyran-6-ol; 2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-3,7,11-tridecatrienyl)-6-chromanol; ζ_1-tocopherol. $C_{29}H_{44}O_2$; mol wt 424.66. C 82.02%, H 10.44%, O 7.54%. One of the naturally occurring forms of vitamin E, *q.v.* Isoln from wheat bran: Green *et al., J. Sci. Food Agric.* **6,** 274 (1955); Green *et al., Chem. Ind. (London)* **1960,** 73. Structure: Green *et al., J. Chem. Soc.* **1959,** 3362. Attempt at synthesis: McHale *et al., ibid.* **1963,** 784. *Review:* M. Kofler *et al.*, "Physicochemical Properties and Assay of the Tocopherols" in R. S. Harris, I. G. Wood, *Vitam. Horm.* **20,** 407-439 (1962). Synthesis of all-*trans*-form: Schudel *et al., Helv. Chim. Acta* **46,** 2517 (1963).



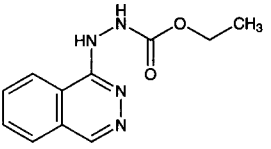
uv max (ethanol): 292.5 nm ($E_{1cm}^{1\%}$ 91).

9501. β-Tocotrienol. [490-23-3] (2*R*)-3,4-Dihydro-2,5,8-trimethyl-2-[(3*E*,7*E*)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-2*H*-1-benzopyran-6-ol; 2,5,8-trimethyl-2-(4,8,12-trimethyltrideca-3,7,11-trienyl)chroman-6-ol; 5-methyltocol; ε-tocopherol. $C_{28}H_{42}O_2$; mol wt 410.63. C 81.90%, H 10.31%, O 7.79%. One of the naturally occurring forms of vitamin E, *q.v.* Isoln from wheat germ oil and from bran: Eggitt, Ward, *J. Sci. Food Agric.* **4,** 569 (1953); Eggitt, Norris, *ibid.* **6,** 689 (1955); **7,** 496 (1956). Structure: Green *et al., J. Chem. Soc.* **1959,** 3362; *Chem. Ind. (London)* **1960,** 73; McHale *et al., J. Chem. Soc.* **1963,** 784. Synthesis: Schudel *et al., Helv. Chim. Acta* **46,** 2517 (1963).



Pale yellow oil. uv max (ethanol): 296 nm ($E_{1cm}^{1\%}$ 87).

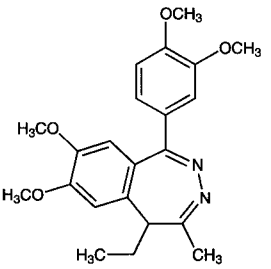
9502. Todralazine. [14679-73-3] 2-(1-Phthalazinyl)hydrazinecarboxylic acid ethyl ester; 3-(1-phthalazinyl)carbazic acid ethyl ester; N^1-carbethoxy-N^2-phthalazinehydrazine; carboethoxyphthalazinohydrazine; ecarazine. $C_{11}H_{12}N_4O_2$; mol wt 232.24. C 56.89%, H 5.21%, N 24.12%, O 13.78%. Prepn: S. Biniecki *et al., Bull. Acad. Pol. Sci. Ser. Sci.* **6,** 227 (1958), *C.A.* **52,** 18424g (1958); *eidem*, **BE 647722**; *eidem*, **US 3591588** (1964, 1971 both to Polfa). Spectrofluorometric determn in plasma: A. Ishii, T. Deguchi, *Chem. Pharm. Bull.* **26,** 2241 (1978). Pharmacological study: M. Filczewski, E. Boguka, *Pol. J. Pharmacol. Pharm.* **31,** 127 (1979), *C.A.* **91,** 204508 (1979). Absorption, distribution, excretion in rats and humans: A. Ishii *et al., Oyo Yakuri* **18,** 61 (1979), *C.A.* **92,** 104012 (1980). Clinical study: W. Reiterer, H. Czitober, *Arzneim.-Forsch.* **27,** 2163 (1977). Toxicity study: F. Parravincini *et al., Farmaco Ed. Sci.* **34,** 299 (1979).



Hydrochloride. [3778-76-5] CEPH; BT-621; Apiracohl; Apercor; Apride; Atapren; Binazin; Illcut; Propat. $C_{11}H_{12}N_4O_2$.HCl; mol wt 268.70. LD_{50} i.p. in mice: 500 mg/kg (Parravincini).

THERAP CAT: Antihypertensive.

9503. Tofisopam. [22345-47-7] 1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine; EGYT-341; Grandaxin; Seriel. $C_{22}H_{26}N_2O_4$; mol wt 382.45. C 69.09%, H 6.85%, N 7.32%, O 16.73%. The first 5*H*-2,3-benzodiazepine. Prepn: J. Korosi *et al.*, **HU 155572** (1969 to Pharm. Res. Inst.), *C.A.* **70,** 115026a (1969); **GB 1202579** corresp to **US 3736315** (1970, 1973 both to EGYT); J. Korosi, T. Lang, *Ber.* **107,** 3883 (1974). Synthesis and conformation: *eidem, Ther. Hung.* **23,** 132 (1975). FT ^{13}C NMR study: A. Neszmelyi *et al., Ber.* **107,** 3894 (1974). Pharmacology: L. Petocz, I. Kosoczky, *Ther. Hung.* **23,** 134 (1975). Human pharmacokinetics: S. Ronai *et al., ibid.* 139. Comparative efficacy: H. L. Goldberg, R. J. Finnerty, *Am. J. Psychiatry* **136,** 196 (1979).



Colorless to light cream cryst powder from isopropyl alcohol, mp 156-157°. uv max (methanol): 310, 272, 239 nm (ε 16100, 11200, 26300).

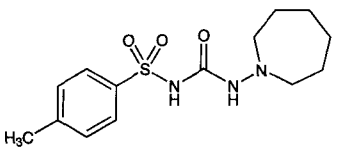
THERAP CAT: Anxiolytic.

9504. Tolan. [501-65-5] 1,1′-(1,2-Ethynediyl)bisbenzene; diphenylacetylene; diphenylethyne. $C_{14}H_{10}$; mol wt 178.23. C 94.34%, H 5.66%. $C_6H_5C{\equiv}CC_6H_5$. Prepd by the oxidation of benzil dihydrazone with mercuric oxide: Schlenk, Bergmann, *Ann.* **463,** 76 (1928); by dehydrohalogenation of stilbene dibromide: Söderbäck, *Ann.* **443,** 161 (1925); Smith, Hoehn, *J. Am. Chem.*

Soc. **63,** 1180 (1941); Smith, Falkof, *Org. Synth.* **coll. vol. III,** 350 (1955). Improved procedure: L. F. Fieser, *Experiments in Organic Chemistry* (Boston, 3rd ed., 1955) p 181.

Monoclinic, pseudo-rhombic rods or large spears from 95% ethanol. mp 60-61° (also reported as 62.5°). bp_{760} 300°; bp_{19} 170°. Dipole moment 0.3. Specific heat at 20°: 0.297. uv max: 216, 221, 269, 272, 279, 288, 297 nm (ε 20600, 20300, 23450, 25200, 33000, 23250, 29400). Insol in water. Freely sol in ether, hot alcohol.

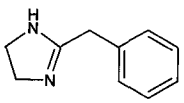
9505. Tolazamide. [1156-19-0] *N*-[[(Hexahydro-1*H*-azepin-1-yl)amino]carbonyl]-4-methylbenzenesulfonamide; 1-(hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolylsulfonyl)urea; *N*-(*p*-toluenesulfonyl)-*N'*-hexamethyleniminourea; tolazolamide; U-17835; Tolanase. $C_{14}H_{21}N_3O_3S$; mol wt 311.40. C 54.00%, H 6.80%, N 13.49%, O 15.41%, S 10.30%. Prepn: J. B. Wright, **GB 887886** (1962 to Upjohn); J. B. Wright, R. E. Willette, *J. Med. Pharm. Chem.* **5,** 815 (1962). Pharmacology: W. E. Dulin *et al., Proc. Soc. Exp. Biol. Med.* **107,** 245 (1961). Mode of action study: Marshall *et al., Metab. Clin. Exp.* **19,** 1046 (1970). Clinical experience and review of early literature: Balodimos, Marble, *Curr. Ther. Res.* **13,** 6-12 (1971). Clinical bioavailability and pharmacokinetics: P. G. Welling *et al., J. Pharm. Sci.* **71,** 1259 (1982). Structural studies: C. H. Koo *et al., Arch. Pharmacal Res.* **11,** 74 (1988). HPLC determn in serum: B. J. Starkey *et al., J. Liq. Chromatogr.* **12,** 1889 (1989). Comprehensive description: J. K. Lee *et al., Anal. Profiles Drug Subs. Excip.* **22,** 489-516 (1993).



Crystals, mp 170-173°. Very slightly sol in water; slightly sol in alcohol; sol in acetone; freely sol in chloroform. pKa (25°): 3.6, pKa (37.5°): 5.68. LD_{50} in rats, mice (mg/kg): >5000 orally, 2239 i.p. (Dulin).

THERAP CAT: Antidiabetic.

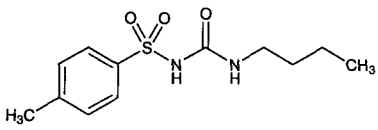
9506. Tolazoline. [59-98-3] 4,5-Dihydro-2-(phenylmethyl)-1*H*-imidazole; 2-benzyl-2-imidazoline; 2-benzyl-2-iminazoline; benzazoline; 2-benzyl-4,5-imidazoline; phenylmethylimidazoline. $C_{10}H_{12}N_2$; mol wt 160.22. C 74.96%, H 7.55%, N 17.48%. α-Adrenergic blocker. Prepn: Sonn, **US 2161938** (1939 to Ciba). HPLC determn in serum: L. M. L. Todesco *et al., Ther. Drug Monit.* **9,** 78 (1987). Review of pharmacology and clinical use: R. M. Ward, *Clin. Perinatol.* **11,** 703-713 (1984).



Hydrochloride. [59-97-2] Lambral; Priscol; Priscoline; Vaso-Dilatan. $C_{10}H_{12}N_2.HCl$; mol wt 196.68. Bitter crystals, mp 174°. Freely sol in water, alcohol; sol in chloroform; very slightly sol in ether, ethyl acetate. pH of 2.5% soln 4.9-5.3.

THERAP CAT: Vasodilator (peripheral).

9507. Tolbutamide. [64-77-7] *N*-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide; 1-butyl-3-(*p*-tolylsulfonyl)urea; tolylsulfonylbutylurea; 3-(*p*-tolyl-4-sulfonyl)-1-butylurea; *N*-*n*-butyl-*N'*-tosylurea; *N'*-4-methylbenzenesulfonyl-*N''*-butylurea; *N*-(sulfonyl-*p*-methylbenzene)-*N'*-*n*-butylurea; D-860; U-2043; Artosin; Diaben; Dolipol; Mobenol; Orabet; Orinase; Oterben; Pramidex; Rastinon. $C_{12}H_{18}N_2O_3S$; mol wt 270.35. C 53.31%, H 6.71%, N 10.36%, O 17.75%, S 11.86%. Description: Ehrhart, *Naturwissenschaften* **43,** 93 (1956). Prepn: **GB 808071**; Aumüller, Herr, **DE 1066575** (both 1959 to Hoechst); Ruschig *et al.,* **US 2968158** (1961 to Upjohn). Comprehensive description: W. F. Beyer, E. H. Jensen, *Anal. Profiles Drug Subs.* **3,** 513-543 (1974).



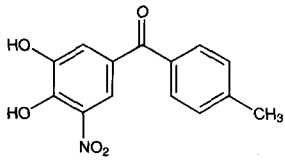
Crystals, mp 128.5-129.5°.

Sodium salt. [473-41-6] $C_{12}H_{17}N_2NaO_3S$. mp 130-133°. Tetrahydrate, mp 41-43°.

THERAP CAT: Antidiabetic.

THERAP CAT (VET): Hypoglycemic agent.

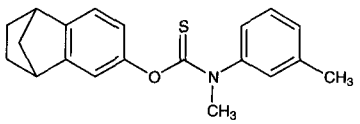
9508. Tolcapone. [134308-13-7] (3,4-Dihydroxy-5-nitrophenyl)(4-methylphenyl)methanone; 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone; Ro-40-7592; Tasmar. $C_{14}H_{11}NO_5$; mol wt 273.24. C 61.54%, H 4.06%, N 5.13%, O 29.28%. Orally active inhibitor of central and peripheral catechol-*O*-methyltransferase (COMT). Prepn: K. Bernauer *et al.,* **EP 237929**; *eidem,* **US 5236952** (1987, 1993 both to Hoffmann-La Roche). Pharmacology: G. Zürcher *et al., Adv. Neurol.* **53,** 497 (1990). HPLC determn in plasma: U. Timm, R. Erdin, *J. Chromatogr.* **593,** 63 (1992). Clinical pharmacokinetics: J. Dingemanse *et al., Clin. Pharmacol. Ther.* **57,** 508 (1995). Clinical evaluation as adjunct to levodopa: P. Limousin *et al., Clin. Neuropharmacol.* **18,** 258 (1995). Review of pharmacology and clinical experience: G. M. Keating, K. A. Lyseng-Williamson, *CNS Drugs* **19,** 165-184 (2005); of safety and efficacy: N. Borges, *Expert Opin. Drug Saf.* **4,** 69-73 (2005).



Crystals from methylene chloride, mp 146-148°.

THERAP CAT: Antiparkinsonian.

9509. Tolciclate. [50838-36-3] Methyl(3-methylphenyl)-carbamothioic acid *O*-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl) ester; *O*-(1,4-methano-1,2,3,4-tetrahydro-6-naphthyl)-*N*-methyl-*N*-(*m*-tolyl)thiocarbamate; KC-9147; Fungifos; Kilmicen; Tolmicen. $C_{20}H_{21}NOS$; mol wt 323.45. C 74.27%, H 6.54%, N 4.33%, O 4.95%, S 9.91%. Topical antimycotic agent with high liposolubility. Prepn: P. Melloni *et al.,* **DE 2313845** corresp to **US 3855263** (1973, 1974 both to Carlo Erba). *In vitro* and *in vivo* study: I. deCarneri *et al., Arzneim.-Forsch.* **26,** 769 (1976). Antimycotic studies: A. Bianchi *et al., Antimicrob. Agents Chemother.* **12,** 429 (1977). Clinical studies in dermatomycosis: L. C. Cucé *et al., J. Int. Med. Res.* **8,** 144 (1980); C. Intini *et al., Pharmatherapeutica* **2,** 439 (1980).

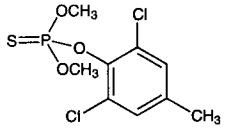


White cryst powder from isopropanol, mp 92-94°. Practically insol in water. Soly (mg/ml): 14.9 in *n*-hexane; 23.9 in *n*-octanol. LD_{50} in mice, rats, dogs (mg/kg): 4000, 6000, 5000 orally (deCarneri).

THERAP CAT: Antifungal.

9510. Tolclofos-methyl. [57018-04-9] *O*-(2,6-Dichloro-4-methylphenyl)phosphorothioic acid *O,O*-dimethyl ester; *O*-(2,6-dichloro-*p*-tolyl) *O,O*-dimethyl phosphorothioate; tolclophos-methyl; S-3349; Rizolex. $C_9H_{11}Cl_2O_3PS$; mol wt 301.13. C 35.90%, H 3.68%, Cl 23.55%, O 15.94%, P 10.29%, S 10.65%. Organophosphorus fungicide; inhibits phospholipid biosynthesis. Prepn: T. Kato *et al.,* **DE 2501040**; **GB 1467561** (1975, 1977 both to Sumitomo). Properties and biological activity: S. Ohtsuki, A. Fujinami, *Jpn. Pestic. Inf.* **41,** 21 (1982). Synthesis: M. Sasaki *et al., J.*

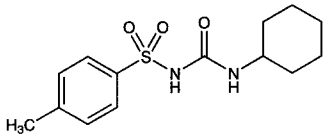
Pestic. Sci. **9,** 737 (1984). Mode of action: S. Nakamura, T. Kato, *ibid.* 725; P. Leroux *et al., Pestic. Sci.* **36,** 255 (1992). GC determn in soil, lettuce: M. Gennari *et al., J. AOAC Int.* **80,** 1298 (1997). Control of bottom rot on lettuce: J. R. Coley-Smith *et al., Plant Pathol.* **40,** 359 (1991).



White crystals from methanol, mp 79-79.5°. Vapor pressure at 20°: 4.27×10^{-4} mm Hg. Soly at 23°: water 0.3-0.4 ppm. Easily sol in xylene, acetone, cyclohexanone, chloroform. LD_{50} in male, female rats, male, female mice (mg/kg): ~5000, ~5000, 3500, 3600 orally; all >5000 dermally; ~5000, 4900, 1070, 1260 i.p.; all >5000 s.c. (Ohtsuki, Fujinami).

USE: Agricultural fungicide.

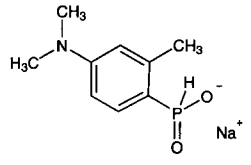
9511. Tolcyclamide. [664-95-9] *N*-[(Cyclohexylamino)carbonyl]-4-methylbenzenesulfonamide; 1-cyclohexyl-3-*p*-tolylsulfonylurea; tolhexamide; glycyclamide; cyclamide; K-386; Diaboral. $C_{14}H_{20}N_2O_3S$; mol wt 296.39. C 56.73%, H 6.80%, N 9.45%, O 16.19%, S 10.82%. Prepn: Logemann, Artini, *Ber.* **90,** 2527 (1957).



Crystals from trichloroethylene, mp 174-176°.

THERAP CAT: Antidiabetic.

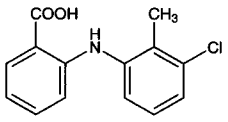
9512. Toldimfos Sodium. [575-75-7] (4-Dimethylamino-*o*-tolyl)phosphonous acid sodium salt; sodium (4-dimethylamino-*o*-tolyl)phosphonate; *p*-dimethylamino-*o*-toluenephosphonous acid sodium salt; Foston; Tonofosfan. $C_9H_{13}NNaO_2P$; mol wt 221.17. C 48.87%, H 5.92%, N 6.33%, Na 10.39%, O 14.47%, P 14.00%. Prepd from *N,N*-dimethyl-*m*-toluidine and phosphorus trichloride: Benda, Schmidt, **DE 397813** (1924 to Cassella), *Frdl.* **14,** 1409.



Trihydrate. [5787-63-3] Scales, needles, or prisms from alc. Freely sol in cold water, hot alcohol.

THERAP CAT (VET): Phosphorus source.

9513. Tolfenamic Acid. [13710-19-5] 2-[(3-Chloro-2-methylphenyl)amino]benzoic acid; *N*-(3-chloro-*o*-tolyl)anthranilic acid; *N*-(2-methyl-3-chlorophenyl)anthranilic acid; GEA-6414; Clotam; Tolfedine; Tolfine. $C_{14}H_{12}ClNO_2$; mol wt 261.70. C 64.25%, H 4.62%, Cl 13.55%, N 5.35%, O 12.23%. Deriv of anthranilic acid, related structurally to mefenamic and flufenamic acids, *q.q.v.* Prepn: **NL 6600251** (1966 to Gea A/S), *C.A.* **66,** 2377 (1967); R. A. Scherrer, F. W. Short, **US 3313848** (1967 to Parke, Davis). Inhibition of prostaglandin biosynthesis: I. B. Linden *et al., Scand. J. Rheumatol.* **5,** 129 (1976). HPLC determn: F. Nielsen-Kudsk, *Acta Pharmacol. Toxicol.* **47,** 267 (1980). Metabolism: T. Kuninaka *et al., Yakugaku Zasshi* **101,** 232 (1981), *C.A.* **95,** 168 (1981). Human pharmacokinetics: P. Pentikaeinen *et al., Eur. J. Clin. Pharmacol.* **19,** 359 (1981). Pharmacological studies: S. Yamashita *et al., Toho Igakkai Zasshi* **28,** 76-105 (1981), *C.A.* **95,** 16183, 180846 (1981). Clinical study: V. Rejholec *et al., Scand. J. Rheumatol.* **Suppl. 33,** 50 (1980); **Suppl. 36,** 1 (1980).

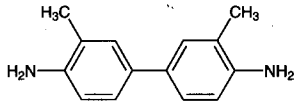


Crystals from abs ethanol, mp 207-207.5°.

THERAP CAT: Anti-inflammatory; analgesic.

THERAP CAT (VET): Anti-inflammatory.

9514. *o*-Tolidine. [119-93-7] 3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diamine; 3,3'-dimethylbenzidine; 4,4'-diamino-3,3'-dimethylbiphenyl. $C_{14}H_{16}N_2$; mol wt 212.29. C 79.21%, H 7.60%, N 13.20%. Made by alkaline reduction of *o*-nitrotoluene with zinc, and subsequent rearrangement of the *o*-hydrazotoluene formed, by boiling with HCl: Van Loon, *Chem. Weekbl.* **5,** 689 (1907). *See also* Schultz *et al., Ann.* **352,** 111 (1907). Crystal and molecular structure: Chawdhury *et al., Acta Crystallogr.* **B24,** 1222 (1968). Metabolism: Dieteren, *Arch. Environ. Health* **12,** 30 (1966). Carcinogenic activity: Pliss, Zebenzhinskii, *J. Natl. Cancer Inst.* **45,** 283 (1970).



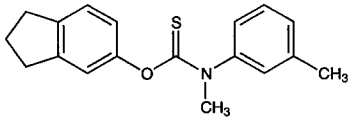
White to reddish crystals or cryst powder. mp 129-131°. Slightly sol in water; sol in alcohol, ether, dil acids. *Keep well closed and protected from light.*

Sulfate. $C_{14}H_{16}N_2.H_2SO_4$. White to gray mass. Slightly sol in water, alcohol; sol in dil acids.

Caution: Potential symptoms of overexposure to *o*-tolidine are irritation of eyes and nose. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 310. *o*-Tolidine is reasonably anticipated to be a human carcinogen: *Report on Carcinogens, Eleventh Edition* (PB2005-104914, 2004) p III-104.

USE: Manuf dyes; also as very sensitive reagent for gold (1:10 million detectable), and for free chlorine in water.

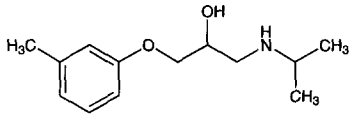
9515. Tolindate. [27877-51-6] Methyl (3-methylphenyl)-carbamothioic acid *O*-(2,3-dihydro-1*H*-inden-5-yl) ester; *m,N*-dimethylthiocarbanilic acid *O*-5-indanyl ester; *O*-(5-indanyl) *m,N*-dimethylthiocarbanilate; Dalnate. $C_{18}H_{19}NOS$; mol wt 297.41. C 72.69%, H 6.44%, N 4.71%, O 5.38%, S 10.78%. Prepared by treating 5-indanyl thionochloroformate with *N*-methyl-*m*-toluidine: Elpern, Youlus, **US 3509200** (1970 to USV).



Crystals, mp 94-95°.

THERAP CAT: Antifungal.

9516. Toliprolol. [2933-94-0] 1-[(1-Methylethyl)amino]-3-(3-methylphenoxy)-2-propanol; 1-(isopropylamino)-3-(*m*-tolyloxy)-2-propanol; 1-(3-methylphenoxy)-3-(isopropylamino)-2-propanol; 1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropane; MHIP. $C_{13}H_{21}NO_2$; mol wt 223.31. C 69.92%, H 9.48%, N 6.27%, O 14.33%. β-Adrenergic blocker. Prepn: **NL 6409883;** H. Koppe *et al.,* **US 3459782** (1965, 1969 both to Boehringer, Ing.); **NL 6410522;** R. Howe, **US 3432545** (1965, 1969 both to I.C.I.). The (−)-isomer is the more potent adrenergic β-receptor antagonist. Resolution of isomers: Howe, Rao, *J. Med. Chem.* **11,** 1118 (1968). Structure-activity studies: Crowther *et al., ibid.* **12,** 638 (1969); Somani, Laddu, *Eur. J. Pharmacol.* **14,** 209 (1971). Metabolism: Stock, Westermann, *Biochem. Pharmacol.* **14,** 227 (1965). Review of pharmacology and clinical data: Marmo *et al., Clin. Ter.* **62,** 11-51, 117-163 (1972).



Crystals from ethyl acetate-petr ether, mp 75-76°. Also reported as mp 79°.

Hydrochloride. [306-11-6] ICI-45763; Ko-592; Doberol; Sinorytmal. $C_{13}H_{22}NO_2.HCl$; mol wt 260.78. Crystals from ethanol-ether, mp 120-121°. uv max (water): 270 nm ($E^{1\%}_{1cm}$ 49.8).

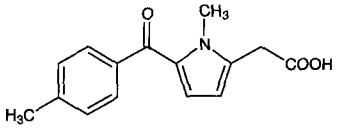
THERAP CAT: Antianginal, antihypertensive.

9517. Tollens Reagent. A solution prepd from equal amounts of 10% silver nitrate and 10% sodium hydroxide solutions to which enough dilute ammonia solution has been added to dissolve the precipitated silver oxide. Tollens reagent oxidizes aldehydes to the corresponding acids; during the reaction the silver, bound in form of a complex, is reduced to metallic silver and forms a characteristic silver mirror. *Refs:* B. Tollens, *Ber.* **15,** 1635 (1882); W. Ponndorf, *ibid.* **64B,** 1913 (1937); S. Siggia, E. Segel, *Anal. Chem.* **25,** 640 (1953); J. M. Kolthoff, P. J. Elving, *Treatise on Analytical Chemistry* **vol. 13** (New York, 1966) p 183.

Caution: Tollens reagent should always be prepared freshly; old, opaque or "dried out" solutions are explosive, H. Waldmann, *Chimia* **13,** 297 (1959).

USE: Reagent in characterization of sugars, aldehydes, hydrazides. As oxidizing agent.

9518. Tolmetin. [26171-23-3] 1-Methyl-5-(4-methylbenzoyl)-1*H*-pyrrole-2-acetic acid; 1-methyl-5-*p*-toluoylpyrrole-2-acetic acid; 5-(*p*-toluoyl)-1-methylpyrrole-2-acetic acid; McN-2559. $C_{15}H_{15}NO_3$; mol wt 257.28. C 70.03%, H 5.88%, N 5.44%, O 18.66%. Prepn: Carson, **FR 1574570** (1969 to McNeil Labs.), *C.A.* **72,** 100498y (1969). Pharmacology: Carson *et al., J. Med. Chem.* **14,** 646 (1971); S. Wong *et al., J. Pharmacol. Exp. Ther.* **185,** 127 (1973). *Review:* S. Wong in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 1,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1977) pp 233-255. Review of pharmacology and therapeutic efficacy: R. N. Brogden *et al., Drugs* **15,** 429-450 (1978).

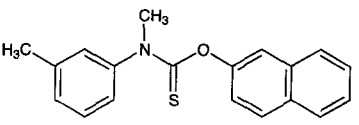


Crystals from acetonitrile, mp 155-157° (dec).

Sodium salt dihydrate. [64490-92-2] McN-2559-21-98; Reutol; Tolectin; Tolmene. $C_{15}H_{14}NNaO_3.2H_2O$; mol wt 315.30.

THERAP CAT: Anti-inflammatory.

9519. Tolnaftate. [2398-96-1] Methyl(3-methylphenyl)-carbamothioic acid *O*-2-naphthalenyl ester; *m,N*-dimethylthiocarbanilic acid *O*-2-naphthyl ester; *O*-2-naphthyl *m,N*-dimethylthiocarbanilate; 2-naphthyl *N*-methyl-*N*-(3-tolyl)thionocarbamate; Sch-10144; Aftate; Chinofungin; Fungistop; Hi-Alarzin; Sporiline; Timoped; Tinactin; Tinaderm; Tonoftal. $C_{19}H_{17}NOS$; mol wt 307.41. C 74.23%, H 5.57%, N 4.56%, O 5.20%, S 10.43%. Prepn: **FR 1337797**; Miyazaki *et al.,* **US 3334126** (1963, 1967 to Japan Soda); Noguchi *et al., J. Pharm. Soc. Jpn.* **88,** 335 (1968). Pharmacology and toxicology: Noguchi *et al., Antimicrob. Agents Chemother.* **1962,** 259; Hashimoto *et al., Toxicol. Appl. Pharmacol.* **8,** 380 (1966); Noguchi *et al., ibid.* 368. Clinical comparison with undecylenic acid: J. F. Fuerst *et al., Cutis* **25,** 544 (1980); F. Battistini *et al., Int. J. Dermatol.* **22,** 388 (1983). Mode of action study: M. P. Gupta *et al., J. Vet. Med. Mycol.* **29,** 45 (1991). LC determn in pharmaceuticals: A. K. Dash, *J. Pharm. Biomed. Anal.* **11,** 847 (1993). Comprehensive description: *idem, Anal. Profiles Drug Subs. Excip.* **23,** 543-570 (1994).

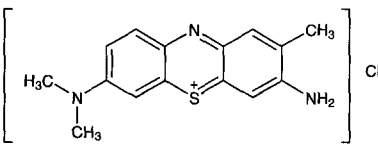


Crystals from alcohol, mp 110.5-111.5°. Practically insol in water. Sparingly sol in methanol, ethanol. Sol in chloroform (1:1.5), acetone (1:7), CCl_4 (1:9). uv max (methanol): 258, 222 nm. LD_{50} in mice, rats (g/kg): >10, >6 orally; >6, >4 s.c. (Hashimoto).

THERAP CAT: Antifungal.

THERAP CAT (VET): Antifungal.

9520. Tolonium Chloride. [92-31-9] 3-Amino-7-(dimethylamino)-2-methylphenothiazin-5-ium chloride; 3-amino-7-dimethylamino-2-methylphenazathionium chloride; toluidine blue O; dimethyltoluthionine chloride; C.I. Basic Blue 17; C.I. 52040; Blutene; Klot; Tolazul. $C_{15}H_{16}ClN_3S$; mol wt 305.83. C 58.91%, H 5.27%, Cl 11.59%, N 13.74%, S 10.48%. Prepd from dimethyl-*p*-phenylenediamine, sodium thiosulfate, and *o*-toluidine: Dändliker, Bernthsen, **US 416055** (1888 to BASF). Prepn of hemostatic compositions contg tolonium chloride: D. A. Hoff, **US 2809913** (1957 to Warren-Teed). Prepn of clear, colorless, stable, isotonic solns of purified leucotoluidine blue O by reducing toluidine blue O with sodium hydrosulfite at pH 2.5-3.5: B. March, E. E. Moore, **US 2571593** (1951 to Abbott). Clinical studies in bleeding disorders: J. Allen *et al., Surg. Gynecol. Obstet.* **89,** 692 (1949). Clinical use for parathyroid identification during thyroidectomy: R. M. Yeager, E. T. Krementz, *Ann. Surg.* **169,** 829 (1969). Acute and chronic toxicity study: T. J. Haley, F. Stolarsky, *Stanford Med. Bull.* **9,** 96 (1951). Review of therapeutic and diagnostic use: A. Mashberg, *J. Am. Dent. Assoc.* **106,** 319-323 (1983). *See also Colour Index* **vol. 4** (3rd ed., 1971) p 4471; *H. J. Conn's Biological Stains,* R. D. Lillie, Ed. (Williams & Wilkins, Baltimore, 9th ed., 1977) p 428.

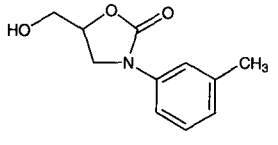


Dark green powder. Sol in water (3.82 g/100 ml), giving a blue to violet soln; sol in alc (0.57 g/100 ml), giving a blue soln. Absorption max (water): 640.4 nm. LD_{50} in mice, rats, rabbits (mg/kg): 27.56, 28.93, 13.44 i.v. (Haley, Storlarsky).

USE: Direct dyeing, printing of wool, silk. Biological stain.

THERAP CAT: Hemostatic. Diagnostic aid (oral carcinoma).

9521. Toloxatone. [29218-27-7] 5-(Hydroxymethyl)-3-(3-methylphenyl)-2-oxazolidinone; 5-(hydroxymethyl)-3-*m*-tolyl-2-oxazolidinone; MD-69276; Humoryl; Perenum. $C_{11}H_{13}NO_3$; mol wt 207.23. C 63.75%, H 6.32%, N 6.76%, O 23.16%. Reversible monoamine oxidase type A inhibitor. Prepn: C. Fauran *et al.,* **DE 2012120**; *eidem,* **US 3655687** (1970, 1972 both to Delalande); *eidem, Chim. Ther.* **8,** 324 (1973). Pharmacology: G. Raynaud *et al., ibid.* 328. Psychopharmacological profile: J.-P. Kan *et al., Eur. J. Med. Chem.* **12,** 13 (1977); H. Giono-Barber *et al., Arzneim.-Forsch.* **27,** 1188 (1977). Pharmacokinetics: M. S. Benedetti *et al., ibid.* **32,** 276 (1982). Metabolism: A. Malnoe, M. S. Benedetti, *Xenobiotica* **9,** 281 (1979). GLC determn in plasma: S. Vajta *et al., J. Chromatogr.* **274,** 139 (1983). Clinical evaluation in panic disorder: G. Perna *et al., J. Clin. Psychopharmacol.* **14,** 414 (1994).

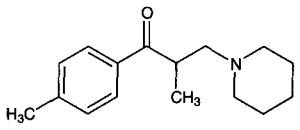


Crystals from isopropyl alcohol, mp 76°. LD_{50} orally in mice (mg/kg): 1850 (Fauran); also reported as 1500 (Raynaud).

THERAP CAT: Antidepressant.

9522. Tolperisone. [728-88-1] 2-Methyl-1-(4-methylphenyl)-3-(1-piperidinyl)-1-propanone; 2,4′-dimethyl-3-piperidinopropiophenone; 1-piperidino-2-methyl-3-(*p*-tolyl)-3-propanone; 2-methyl-3-piperidino-1-*p*-tolylpropan-1-one; mydetone. $C_{16}H_{23}NO$; mol wt 245.36. C 78.32%, H 9.45%, N 5.71%, O 6.52%. Prepn: Nádor *et al.,* **HU 144997** (1956); Yokoyama *et al.,* **JP 65**

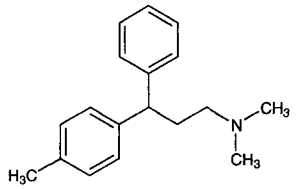
20390 (1965 to Eisai). Pharmacology and toxicity: J. Porszasz *et al., Acta Physiol. Acad. Sci. Hung.* **18,** 149 (1960); *eidem, Arzneim.-Forsch.* **11,** 257 (1961).



Hydrochloride. [3644-61-9] N-553; Abbsa; Atmosgen; Arantoick; Besnoline; Isocalm; Kineorl; Menopatol; Metosomin; Minacalm; Muscalm; Mydocalm; Naismeritin; Tolisartine. $C_{16}H_{23}NO.HCl$; mol wt 281.82. Crystals from methyl ethyl ketone, mp 176-177°. LD_{50} s.c. in mice: 620 mg/kg (Porszasz, 1961).

THERAP CAT: Muscle relaxant (skeletal).

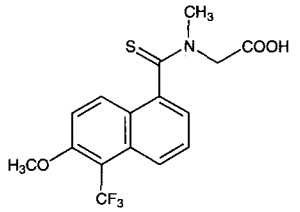
9523. Tolpropamine. [5632-44-0] *N,N,*4-Trimethyl-γ-phenylbenzenepropanamine; *N,N*-dimethyl-3-phenyl-3-*p*-tolylpropylamine; 3-dimethylamino-1-phenyl-1-*p*-tolylpropane. $C_{18}H_{23}N$; mol wt 253.38. C 85.32%, H 9.15%, N 5.53%. Prepn: Bockmühl, Stein, **DE 925468** (1955 to Hoechst); Klosa, *J. Prakt. Chem.* **34,** 312 (1966). Pharmacology: Sendrail, Gleizes, *Therapie* **15,** 119 (1960).



Hydrochloride. Pragman Gelee. $C_{18}H_{23}N.HCl$; mol wt 289.84. mp 182-184°.

THERAP CAT: Topical antihistaminic, antipruritic.

9524. Tolrestat. [82964-04-3] *N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-methylglycine; tolrestatin; AY-27773; Alredase; Lorestat. $C_{16}H_{14}F_3NO_3S$; mol wt 357.35. C 53.78%, H 3.95%, F 15.95%, N 3.92%, O 13.43%, S 8.97%. Orally active aldose reductase inhibitor. Prepn and pharmacology: K. Sestanj *et al.,* **EP 59596** (1982 to Ayerst); *eidem, J. Med. Chem.* **27,** 255 (1984). Prevention of cataracts in galactosemic rats: N. Simard-Duquesne *et al., Proc. Soc. Exp. Biol. Med.* **178,** 599 (1985). Kinetics and metabolism in man: D. R. Hicks *et al., Clin. Pharmacol. Ther.* **36,** 493 (1984). Ultraviolet and HPLC determn in serum: D. R. Hicks, M. Kraml, *Ther. Drug Monit.* **6,** 328 (1984). Effect on erythrocyte sorbitol levels in diabetic patients: P. Raskin *et al., Clin. Pharmacol. Ther.* **38,** 625 (1985).

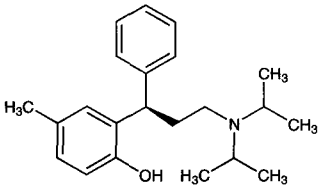


mp 164-165°.

Methyl ester. $C_{17}H_{16}F_3NO_3S$. mp 109-110°.

THERAP CAT: Treatment of diabetic neuropathy.

9525. Tolterodine. [124937-51-5] 2-[(1*R*)-3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol; (+)-(*R*)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-*p*-cresol; (+)-*N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine; Kabi 2234. $C_{22}H_{31}NO$; mol wt 325.49. C 81.18%, H 9.60%, N 4.30%, O 4.92%. Muscarinic receptor antagonist. Prepn: N. A. Jönsson *et al.,* **EP 325571** (1989 to KabiVitrum); *eidem,* **US 5382600** (1995 to Pharmacia). Asymmetric total synthesis: C. Hedberg, P. G. Andersson, *Adv. Synth. Catal.* **347,** 662 (2005). Pharmacology: L. Nilvebrant *et al., Life Sci.* **60,** 1129 (1997). Receptor binding study: *idem et al., Eur. J. Pharmacol.* **327,** 195 (1997). GC-MS determn in biological fluids: L. Palmér *et al., J. Pharm. Biomed. Anal.* **16,** 155 (1997). Clinical pharmacokinetics: N. Brynne *et al., Int. J. Clin. Pharmacol. Ther.* **35,** 287 (1997). Review of clinical trials: R. A. Appell, *Urology* **50,** Suppl. 6A, 90-96 (1997); of use in overactive bladder: E. S. Rovner, *Expert Opin. Pharmacother.* **6,** 653-666 (2005).

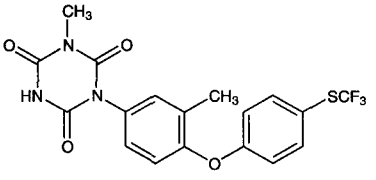


$[\alpha]_D^{25}$ +72° (c = 1.0 in CH_2Cl_2).

Tartrate. [124937-52-6] PNU-200583E; Detrol; Detrusitol. $C_{22}H_{31}NO.C_4H_6O_6$; mol wt 475.57. Crystals from ethanol. $[\alpha]_{546}^{25}$ +36.0°. pKa 9.87. Soly in water: 12 mg/ml. Sol in methanol; slightly sol in ethanol. Practically insol in toluene. Partition coefficient (*n*-octanol/water): 1.83 (pH 7.3). LD_{50} i.v. in male mice: 10-20 mg/kg (Jönsson).

THERAP CAT: In treatment of urinary incontinence.

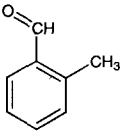
9526. Toltrazuril. [69004-03-1] 1-Methyl-3-[3-methyl-4-[4-[(trifluoromethyl)thio]phenoxy]phenyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione; 1-methyl-3-[4-[*p*-[(trifluoromethyl)thio]phenoxy]-*m*-tolyl]-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione; Bay Vi 9142; Baycox. $C_{18}H_{14}F_3N_3O_4S$; mol wt 425.38. C 50.82%, H 3.32%, F 13.40%, N 9.88%, O 15.04%, S 7.54%. Triazinetrione anticoccidial. General prepn: **BE 826900**; J. H. Reisdorff *et al.,* **US 3966725** (1975, 1976 both to Bayer). Prepn and use as animal growth promotant: **BE 866389**; A. Haberkorn *et al.,* **US 4219552** (1978, 1980 both to Bayer). Series of articles on efficacy vs coccidia in chickens: E. Kutzer *et al., Wien. Tieraerztl. Monatssch.* **72,** 321-340 (1985). Field trial in sheep: B. Gjerde, O. Helle, *Acta Vet. Scand.* **27,** 124 (1986); in chickens: H. D. Chapman, *J. Comp. Pathol.* **97,** 21 (1987).



mp 194°.

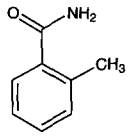
THERAP CAT (VET): Coccidiostat.

9527. *o*-Tolualdehyde. [529-20-4] 2-Methylbenzaldehyde; *o*-toluylaldehyde. C_8H_8O; mol wt 120.15. C 79.97%, H 6.71%, O 13.32%. Prepd by reacting nitropropane with *o*-xylyl bromide in the presence of sodium ethanoate: Hass, Bender, *Org. Synth.* **30,** 99 (1950).



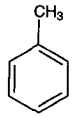
Liquid. d_4^{19} 1.0386. bp_{760} 200-202°; bp_{15} 94-96°; bp_6 68-72°. n_D^{25} 1.5430; n_D^{19} 1.549; n_α^{19} 1.5423; n_β^{19} 1.5650; n_γ^{19} 1.5798.

9528. *o*-Toluamide. [527-85-5] 2-Methylbenzamide. C_8H_9NO; mol wt 135.16. C 71.09%, H 6.71%, N 10.36%, O 11.84%. Prepd by reacting *o*-tolunitrile, hydrogen peroxide, 95% alcohol, and sodium hydroxide at 40-50°: Noller, *Org. Synth.* **coll. vol. II,** 586 (1943). Also prepared by reacting the nitrile with boron fluoride in dil acetic acid: Hauser, Hoffenberg, *J. Org. Chem.* **20,** 1448 (1955).



Crystals from water, mp 144-145°. Very sol in alcohol, hot water, concd HCl, less sol in ether. Sparingly sol in benzene. Practically insol in cold water. *Explosive. Keep away from open flame.*

9529. Toluene. [108-88-3] Methylbenzene; toluol; phenylmethane; Methacide. C_7H_8; mol wt 92.14. C 91.25%, H 8.75%. Obtained mainly from tar oil. Review of mfg processes: *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 822-830. Solubility: F. P. Schwarz, *Anal. Chem.* **52,** 10 (1980). Myelotoxic potential: L. Greenburg *et al., J. Am. Med. Assoc.* **118,** 573 (1942). Comparison with benzene of effects on hematopoiesis and bone marrow metabolism: H. W. Gerarde, *AMA Arch. Ind. Health* **13,** 468 (1956). Acute toxicity: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30,** 470 (1969). Evaluation of chronic occupational exposure: H. Tahti *et al., Int. Arch. Occup. Environ. Health* **48,** 61 (1981). *Review:* M. C. Hoff in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 23** (Wiley-Interscience, New York, 3rd ed., 1983) pp 246-273. Review of reproductive toxicity: J. M. Donald *et al., Environ. Health Perspect.* **94,** 237-244 (1991); of toxicology and human exposure: *Toxicological Profile for Toluene* (PB2000-108028, 2000) 357 pp.

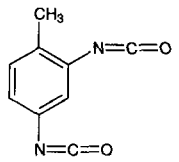


Flammable, refractive liq; benzene-like odor. d_4^{20} 0.866. mp −95°. bp 110.6°. n_D^{20} 1.4967. Flash pt, closed cup: 40°F (4.4°C). Soly in water at 23.5°C (w/w): 0.067%. Very slightly sol in water; misc with alc, chloroform, ether, acetone, glacial acetic acid, carbon disulfide. LD_{50} orally in rats: 7.53 g/kg (Smyth).

Caution: Readily absorbed by inhalation, ingestion and somewhat by skin contact. Direct contact may cause severe dermatitis due to drying and defatting action. May present lung aspiration hazard if ingested. Potential symptoms of acute overexposure by inhalation may include local irritation; CNS excitation and depression. Low concentrations may result in transitory mild upper respiratory tract irritation, mild eye irritation, lacrimation, metallic taste, slight nausea, hilarity, lassitude, drowsiness and impaired balance. High concentrations may cause paresthesia, vision disturbances, dizziness, nausea, headache, narcosis and collapse; death from respiratory failure or sudden ventricular fibrillation. Chronic overexposure by inhalation has been associated with hepatotoxicity and nephrotoxicity. Syndromes following chronic inhallation involve severe muscle weakness, cardiac arrhythmias, gastrointestinal and neuropsychiatric complaints. *See Patty's Industrial Hygiene and Toxicology* **vol. 2B,** G. D. Clayton, F. E. Clayton, Eds. (Wiley-Interscience, New York, 4th ed., 1994) pp 1326-1332; *Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section II, p 153, Section III, p 397-404.

USE: In manuf benzoic acid, benzaldehyde, explosives, dyes, and many other organic compds; as a solvent for paints, lacquers, gums, resins; thinner for inks, perfumes, dyes; in the extraction of various principles from plants; as gasoline additive.

9530. Toluene 2,4-Diisocyanate. [584-84-9] 2,4-Diisocyanato-1-methylbenzene; 2,4-diisocyanatotoluene; 2,4-tolylene diisocyanate; TDI; Nacconate 100. $C_9H_6N_2O_2$; mol wt 174.16. C 62.07%, H 3.47%, N 16.08%, O 18.37%. Usually prepd from toluene-2,4-diamine and phosgene. *Review:* Astle, *Industrial Organic Nitrogen Compounds* (New York, 1961) pp 284-313; *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 831-835.

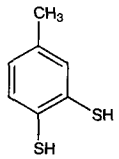


Liquid at room temperature. Sharp, pungent odor. mp 19.5-21.5°. d_4^{20} liq 1.2244. bp_{760} 251°; bp_{11} 126°. Darkens on exposure to sunlight. Reacts with water with evolution of carbon dioxide. Flash pt, open cup: 132°C (270°F). Misc with alcohol (decompn), diglycol monomethyl ether, ether, acetone, carbon tetrachloride, benzene, chlorobenzene, kerosene, olive oil. Concd alkaline compds such as NaOH or *tert*-amines may cause run-away polymerization.

Caution: Potential symptoms of overexposure are irritation of eyes, skin, nose and throat; choking, paroxysmal cough; chest pain, retrosternal soreness; nausea, vomiting and abdominal pain; bronchitis, bronchospasm, pulmonary edema; dyspnea, asthma; conjunctivitis, lacrimation; dermatitis, skin sensitization. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 312. *See also Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section II, p 414. This substance is reasonably anticipated to be a human carcinogen: *Report on Carcinogens, Eleventh Edition* (PB2005-104914, 2004) p III-256.

USE: In the manuf of polyurethane foams and other elastomers.

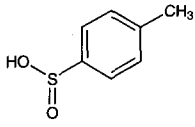
9531. Toluene-3,4-dithiol. [496-74-2] 1,2-Dimercapto-4-methylbenzene; "dithiol". $C_7H_8S_2$; mol wt 156.27. C 53.80%, H 5.16%, S 41.04%. Prepd from toluene-3,4-disulfonyl chloride with tin and hydrochloric acid: Mills, Clark, *J. Chem. Soc.* **1936,** 178.



Crystals, mp 31°. bp_{84} 185-187°. Sol in benzene, in aq alkali hydroxide solns.

USE: For the detection of bismuth, molybdenum, rhenium, tin, tungsten, *see* Bickford *et al., J. Am. Pharm. Assoc. Sci. Ed.* **37,** 255 (1948).

9532. *p*-Toluenesulfinic Acid. [536-57-2] $C_7H_8O_2S$; mol wt 156.20. C 53.83%, H 5.16%, O 20.49%, S 20.53%. Prepd by reduction of *p*-toluenesulfonyl chloride with zinc dust: Whitmore, Hamilton, *Org. Synth.* **2,** 89 (1922). Because the sulfinic acid is difficult to dry without partial conversion to the sulfonic acid, the sodium salt, $CH_3C_6H_4SO_2Na.2H_2O$, is usually prepd. The free sulfinic acid is then obtained as needed by dissolving the sodium salt in cold water and carefully acidifying the soln with the exact amt of HCl needed.



Long, rhombic plates or needles from water. mp 85°. Freely sol in alc, ether; sparingly sol in water, hot benzene.

9533. *p*-Toluenesulfonic Acid. [104-15-4] 4-Methylbenzenesulfonic acid; tosic acid. $C_7H_8O_3S$; mol wt 172.20. C 48.82%, H 4.68%, O 27.87%, S 18.62%. $CH_3C_6H_4SO_3H$. Prepd by sulfonation of toluene with 96-100% H_2SO_4; when carried out at 75° the compn of the reaction product is 75% *para*-, 19% *ortho*- and 6% *meta*-toluenesulfonic acid. Convenient lab prepn: L. F. Fieser, *Experiments in Organic Chemistry* (Boston, 3rd ed., 1955) p 144. The separation of toluene from petroleum fractions can be accomplished by sulfonation with H_2SO_4 at 60°.

Monoclinic leaflets or prisms. Also reported as crystallizing with $1H_2O$ or $4H_2O$. When anhydrous, mp 106-107°. Metastable form, mp 38°. bp_{20} 140°. $bp_{0.1}$ 185-187°. Freely sol in water, about 67 g/100 ml. Sol in alc and ether.

Sodium salt. $C_7H_7NaO_3S$. Orthorhombic plates, very sol in water.

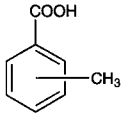
Caution: Highly irritating to skin, mucous membranes.

USE: In dye chemistry; in manuf of oral antidiabetic drugs.

9534. *p*-Toluenesulfonyl Chloride. [98-59-9] Tosyl chloride. $C_7H_7ClO_2S$; mol wt 190.65. C 44.10%, H 3.70%, Cl 18.60%, O 16.78%, S 16.82%. $CH_3C_6H_4SO_2Cl$. Made by treating toluene with chlorosulfonic acid.

Crystals, mp 69-71°. bp_{15} 146°. Insol in water; freely sol in alcohol, benzene, ether.

9535. Toluic Acid. Methylbenzoic acid. $C_8H_8O_2$; mol wt 136.15. C 70.57%, H 5.92%, O 23.50%. Prepn of *m*- and *o*-forms by oxidation of corresponding xylene: Toland, **US 2903480** (1959 to California Res. Corp.); Hay *et al., J. Org. Chem.* **25,** 616 (1960). Prepn of *p*-form by reaction of *p*-tolyldiazonium tetrafluoroborate with nickel carbonyl and acetic acid: Clark, Cookson, *J. Chem. Soc.* **1962,** 686; by oxidation of *p*-xylene: Taves, **US 3030413** (1962 to Hercules Powder). Manuf of *p*-form from toluene: Braunworth, **US 3046305** (1962 to Pure Oil).

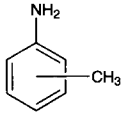


***m*-Toluic acid.** Prisms from water, mp 111-113°, bp 263°. Sublimes. Sol in 1170 parts water at 15°, 60 parts boiling water; very sol in alcohol, ether.

***o*-Toluic acid.** Crystals, mp 107-108°; bp 258-260°; volatile with steam. Slightly sol in cold water; sol in 35 parts boiling water; very sol in alcohol.

***p*-Toluic acid.** Crystals, mp 180-181°; bp 274-275°. Sparingly sol in hot water; very sol in alcohol, ether, methanol.

9536. Toluidine. C_7H_9N; mol wt 107.15. C 78.46%, H 8.47%, N 13.07%. Prepn: J. S. Muspratt, A. W. Hofmann, *Ann.* **54,** 1 (1845); of each isomer: F. Beilstein, A. Kuhlberg, *ibid.* **156,** 66 (1870); P. Kovacic, J. L. Foote, *J. Am. Chem. Soc.* **83,** 743 (1961); P. Kovacic *et al., ibid.* **84,** 759 (1962). Toxicity data: H. F. Smyth, *Am. Ind. Hyg. Assoc. J.* **23,** 95 (1962). GC determn in urine: K. El-Bayoumy *et al., Cancer Res.* **46,** 6064 (1986).



***m*-Toluidine.** [108-44-1] 3-Methylbenzamine; 3-aminotoluene; 3-methylaniline. Liquid, mp ~−50°. bp 203-204°. d_{25}^{25} 0.990. n_D^{22} 1.5711. Slightly sol in water; sol in alcohol, ether, dil acids.

***o*-Toluidine.** [95-53-4] 2-Methylbenzamine; 2-aminotoluene; 2-methylaniline. Light yellow liquid becoming reddish brown on exposure to air and light. bp 200-202°. d_{20}^{20} 1.008. n_D^{20} 1.5688. Flash pt, closed cup: 185°F (85°C). Slightly sol in water; sol in alcohol, ether, dil acids. Keep well closed and protected from light. LD_{50} orally in rats: 0.94 g/kg (Smyth).

***p*-Toluidine.** [106-49-0] 4-Methylbenzamine; 4-aminotoluene; 4-methylaniline. Lustrous plates or leaflets, mp 44-45°. bp 200-201°. d_{20}^{4} 1.046. n_D^{59} 1.5532. Flash pt, closed cup: 188°F (86°C). Sol in about 135 parts water; freely sol in alcohol, ether, acetone, methanol, carbon disulfide, oils, dil acids.

Caution: Potential symptoms of overexposure to *o*-toluidine are eye irritation; anoxia, headache, cyanosis; weakness, dizziness, drowsiness; microhematuria; eye burns; dermatitis. Potential symptoms of overexposure to *m*- or *p*- toluidine are eye, skin irritation; hematuria, methemoglobinemia; cyanosis, nausea, vomiting, low blood pressure, convulsions; anemia, weakness. *p*-Toluidine is a potential occupational carcinogen. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 312. *o*-Toluidine and its hydrochloride are reasonably anticipated to be human carcinogens: *Report on Carcinogens, Eleventh Edition* (PB2005-104914, 2004) p III-258.

USE: Manufacture of various dyes and other organic chemicals. *o*-Isomer also in printing textiles blue black; making colors fast to acids. *p*-Isomer also as a reagent for lignin, nitrite, phloroglucinol.

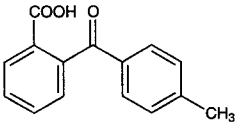
9537. *o*-Tolunitrile. [529-19-1] 2-Methylbenzonitrile; 2-methylbenzenecarbonitrile; *o*-cyanotoluene; *o*-methylbenzonitrile. C_8H_7N; mol wt 117.15. C 82.02%, H 6.02%, N 11.96%. $CH_3C_6H_4CN$. Prepd from *o*-toluidine by diazotization in HCl soln and treatment of the diazonium chloride with potassium cuprocyanide: Herb, *Ann.* **258,** 9 (1890); Clarke, Read, *Org. Synth.* **coll. vol. I** (2nd ed., 1941) p 514.

Liquid; d_4^{20} 0.9955; d_4^{45} 0.9737; d_4^{75} 0.9481; mp −13°; bp_{760} 205.2°; bp_{100} 135°; bp_{40} 110°; bp_{20} 93°; bp_{10} 77.9°; bp_5 64°; $bp_{1.0}$ 36.7°; n_D^{23} 1.52720. Absorption spectrum: Baly, Ewbank, *J. Chem. Soc.* **87,** 1357 (1905); Purvis, *ibid.* **107,** 503 (1915). Insol in water. Miscible with alc, ether.

9538. *p*-Tolunitrile. [104-85-8] Prepd from *p*-toluidine in the manner described for *o*-tolunitrile.

Needles from alc. d_4^{30} 0.9785; d_4^{45} 0.9640; d_4^{60} 0.9512; d_4^{75} 0.9390; mp 29.5°; bp_{760} 217.6°; bp_{100} 145.2°; bp_{60} 130°; bp_{40} 109.5°; bp_{20} 101.7°; bp_{10} 85.8°; bp_5 71.3°; $bp_{1.0}$ 42.5°. Absorption spectrum: Baly, Ewbank, *J. Chem. Soc.* **87,** 1357 (1905); Purvis, *ibid.* **107,** 503 (1915). Insol in water. Very sol in alcohol, ether.

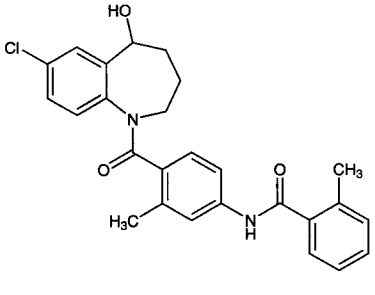
9539. 2-(*p*-Toluyl)benzoic Acid. [85-55-2] *p*-Toluyl-*o*-benzoic acid; 4′-methylbenzophenone-2-carboxylic acid. $C_{15}H_{12}O_3$; mol wt 240.25. C 74.99%, H 5.03%, O 19.98%. Prepd from phthalic anhydride and toluene in the presence of aluminum chloride: Friedel, Crafts, *Ann. Chim. Phys.* [6] **14,** 447 (1888); Fieser, *Org. Synth.* **4,** 73 (1925).



Monohydrate. Triclinic pinacoidal crystals from alcohol. Sweet taste. Becomes anhydr at 100°, then melts at 146°. Slightly sol in boiling water; freely sol in alcohol, benzene, ether, acetone, boiling toluene.

Methyl ester. $C_{16}H_{14}O_3$. Plates from methanol, mp 53°. Soluble in alcohol, benzene.

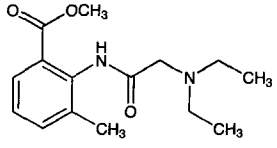
9540. Tolvaptan. [150683-30-0] *N*-[4-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-3-methylphenyl]-2-methylbenzamide; 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine; OPC-41061. $C_{26}H_{25}ClN_2O_3$; mol wt 448.94. C 69.56%, H 5.61%, Cl 7.90%, N 6.24%, O 10.69%. Nonpeptide arginine vasopressin V_2 receptor antagonist. Prepn: H. Ogawa *et al.*, **WO 9105549**; *eidem*, **US 5258510** (1991, 1993 both to Otsuka); K. Kondo *et al., Bioorg. Med. Chem.* **7,** 1743 (1999). Pharmacology: Y. Yamamura *et al., J. Pharmacol. Exp. Ther.* **287,** 860 (1998). Clinical trial in heart failure: M. Gheorghiade *et al., J. Am. Med. Assoc.* **291,** 1963 (2004).



Colorless prisms, mp 225.9°.

THERAP CAT: In treatment of congestive heart failure.

9541. Tolycaine. [3686-58-6] 2-(2-Diethylaminoacetamido)-*m*-toluic acid methyl ester; 2-methyl-6-carbomethoxy-*N*-diethylaminoacetanilide; methyl 2-diethylaminoacetamido-*m*-toluate; 3-methyl-2-diethylaminoacetylaminobenzoic acid methyl ester. $C_{15}H_{22}N_2O_3$; mol wt 278.35. C 64.72%, H 7.97%, N 10.06%, O 17.24%. Prepn: Hiltmann *et al.*, **DE 1018070** (1957 to Bayer); **US 2921077** (1960 to Schenley).

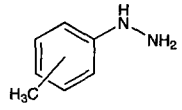


Oil, bp_5 190-192°.

Hydrochloride. [7210-92-6] Baycain. $C_{15}H_{22}N_2O_3.HCl$; mol wt 314.81. Crystals, mp 139-140.5°.

THERAPCAT: Anesthetic (local).

9542. Tolylhydrazine. $C_7H_{10}N_2$; mol wt 122.17. C 68.82%, H 8.25%, N 22.93%. Prepd by stannous chloride reduction of the diazonium salt of the corresponding toluidine: Hunsberger *et al.*, *J. Org. Chem.* **21,** 394 (1956).



***m*-Tolylhydrazine.** Oily liquid. bp_{760} 243°, bp_{16} 132-134°. d_{15}^{15} 1.061-1.062, d_4^{20} 1.057-1.058. Insol in water; sol in alc, chloroform, ether.

Nitrate. $C_7H_{10}N_2.HNO_3$. Needles, mp 145-147°.

***o*-Tolylhydrazine.** Needles, mp 56-59°. Sparingly sol in water; sol in alcohol, chloroform, ether, slightly in cold petr ether.

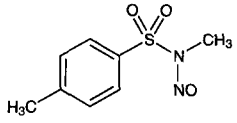
Nitrate. Leaflets, mp 98-100°. Very sol in water, alcohol; insol in ether.

***p*-Tolylhydrazine.** Rhombic bipyramids, mp 61° or 65-66°. bp 240-244° with slight decompn. Sparingly sol in water; sol in alcohol, benzene, ether.

Nitrate. Leaflets, mp 152-153°.

USE: *o*-Tolylhydrazine as reagent for galactose.

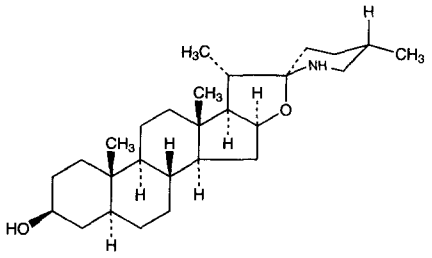
9543. *p*-Tolylsulfonylmethylnitrosamide. [80-11-5] *N*,4-Dimethyl-*N*-nitrosobenzenesulfonamide; *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; Diazald. $C_8H_{10}N_2O_3S$; mol wt 214.24. C 44.85%, H 4.70%, N 13.08%, O 22.40%, S 14.97%. Prepd by the action of nitrous acid on *p*-tolylsulfonylmethylamide: **DE 224388** (1910 to Bayer); *Frdl.* **10,** 1216; *Chem. Zentralbl.* **1910, II,** 609; Takizawa, *J. Pharm. Soc. Jpn.* **70,** 490 (1950); de Boer, Backer, *Rec. Trav. Chim.* **73,** 229 (1954); *Org. Synth.* **34,** 96 (1954).



Yellow crystals from benzene + petr ether, mp 62°. Stable in an ordinary brown bottle for several years. A white coating (formed of *p*-tolylsulfonylmethylamide) does no harm. Insol in water. Sol in ether, petr ether, benzene, chloroform, carbon tetrachloride. Yields diazomethane on treatment with alkali.

USE: In the laboratory prepn of diazomethane. Directions for use: de Boer, Backer, *Rec. Trav. Chim.* **73,** 232 (1954).

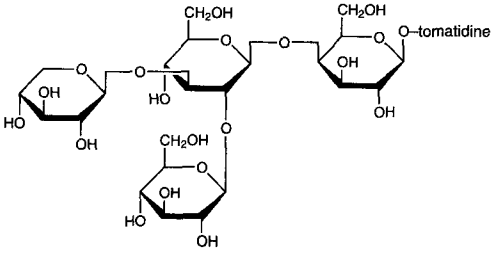
9544. Tomatidine. [77-59-8] (3β,5α,22β,25*S*)-Spirosolan-3-ol; 5α-tomatidan-3β-ol; 5α,20β_F,22α_F,25β_F,27-azaspirostan-3β-ol. $C_{27}H_{45}NO_2$; mol wt 415.65. C 78.02%, H 10.91%, N 3.37%, O 7.70%. By hydrolysis of tomatine: Kuhn *et al.*, *Ber.* **83,** 448 (1950). Isoln from the roots of Rutgers tomato plant [*Lycopersicon esculentum* Mill., cultivar. "Rutgers"]: Brink, Folkers, *J. Am. Chem. Soc.* **73,** 4018 (1951); Fontaine *et al.*, *ibid.* 878; Sato *et al.*, *ibid.* 880; Kuhn, Low, **US 2770618** (1956 to Amer. Home Prod.). Structure: Sato *et al.*, *J. Org. Chem.* **25,** 783 (1960); Schreiber, Adams, *Experientia* **17,** 13 (1961). Synthesis: Uhle, Moore, *J. Am. Chem. Soc.* **76,** 6412 (1954); Uhle, *ibid.* **83,** 1460 (1961); Kessar *et al.*, *Tetrahedron* **27,** 2869 (1971).



Plates from ethyl acetate, mp 202-206°. $[\alpha]_D^{25}$ +8° (chloroform).

Hydrochloride. $C_{27}H_{45}NO_2.HCl$. Crystals from abs ethanol, mp 265-270°. $[\alpha]_D^{25}$ −5° (methanol).

9545. Tomatine. [17406-45-0] (3β,5α,22β,25*S*)-Spirosolan-3-yl *O*-β-D-glucopyranosyl-(1 → 2)-*O*-[β-D-xylopyranosyl-(1 → 3)]-*O*-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside; lycopersicin. $C_{50}H_{83}NO_{21}$; mol wt 1034.19. C 58.07%, H 8.09%, N 1.35%, O 32.49%. Occurs in the extract of leaves of wild tomato plants: Fontaine *et al.*, *Arch. Biochem.* **18,** 467 (1948); Kuhn, Low, *Ber.* **81,** 552 (1948); Kuhn *et al.*, *ibid.* **83,** 448 (1950); Bognar, Makleit, *Pharmazie* **11,** 376 (1956). Yields on partial hydrolysis, besides α-tomatine, the main constituent, β_1-, β_2-, γ- and δ-tomatine: Kuhn *et al.*, *Ber.* **90,** 203 (1957). α-Tomatine consists of one mol tomatidine linked to a tetrasaccharide composed of 2 mols D-glucose, 1 mol D-xylose and 1 mol D-galactose: Kuhn *et al.*, *Angew. Chem.* **68,** 212 (1956). Proposed as an alternate precipitant to digitonin: Schultz, Sander, *Z. Physiol. Chem.* **308,** 122 (1957). Structure: Reichstein, *ibid.* **74,** 887 (1962). Toxicity study: Wilson *et al.*, *Toxicol. Appl. Pharmacol.* **3,** 39 (1961).



Needles from methanol, mp 263-268°. $[\alpha]_D^{20}$ −18° (c = 0.55 in pyridine). Sol in ethanol, methanol, dioxane, propylene glycol. Practically insol in water, ether, petr ether. Stable to strong alkali but hydrolyzed by acids to produce cryst tomatidine and a soln rich in reducing sugars. Has been found to inhibit the growth of various fungi and bacteria. LD orally in rats: 900-1000 mg/kg (Wilson).

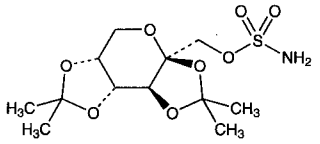
USE: Precipitating agent for steroids.

9546. Tonin. [53414-68-9] β-Angiotensin I converting enzyme (formerly). A converting enzyme that differs from renin, *q.v.*, in its ability to form angiotensin II directly from angiotensinogen by cleaving the Phe-His bond; it can also convert angiotensin I to angiotensin II. Its presence was discovered in rat submaxillary glands: R. Boucher *et al.*, *Hypertension 72,* J. Genest, E. Koiw, Eds. (Springer-Verlag, New York, 1972) p 512; *eidem, Circ. Res.* **Suppl. I,** 203 (1974). Purification and characterization: S. Demassieux *et al.*, *Can. J. Biochem.* **54,** 788 (1976). Crystal data: K. Hayakawa *et al.*, *J. Mol. Biol.* **123,** 107 (1978). Radioimmunoassay: J. Gutkowska *et al.*, *Can. J. Biochem.* **56,** 769 (1978).

Purification by affinity chromatography: M. Ikeda *et al., Hypertension* **3,** 81 (1981); by gel permeation and HPLC: C. Lazure *et al., Anal. Biochem.* **125,** 406 (1982). Isoln using chromatofocusing: E. S. P. Cheng, B. J. Morris, *ibid.* **126,** 295 (1982). *N*-Terminal amino acid sequence of rat tonin: N. G. Seidah *et al., Can. J. Biochem.* **56,** 920 (1978). Substrate specificity studies: *eidem, Proc. Am. Peptide Symp. 6th,* E. Gross, J. Meienhofer, Eds. (Pierce Chem. Co., Rockford, Ill., 1979) p 921; M. Chretien *et al., FEBS Lett.* **113,** 173 (1980). Formation of angiotensin II by tonin from partially purified human angiotensinogen: C. Grise *et al., Can. J. Biochem.* **59,** 250 (1981). Pressor effect in anephric animals: E. L. Schiffrin *et al., Can. J. Physiol. Pharmacol.* **59,** 864 (1981). Sequence homologies between tonin and other peptides: C. Lazure *et al., Nature* **292,** 383 (1981). Immunohistochemical study: T. B. Oerstavik *et al., J. Histochem. Cytochem.* **30,** 1123 (1982). Role as renin activator: J. Gutkowska *et al., Can. J. Biochem.* **60,** 843 (1982). Role in exptl hypertension: R. Garcia *et al., Hypertension, Int. Symp., 3rd,* H. Villarreal, Ed. (Wiley, New York, 1981) p 79. *Reviews:* R. Boucher *et al., Circ. Res.* **Suppl. II,** 26-29 (1977); R. Boucher, J. Genest, *Endocrine Functions of the Brain,* M. Motta, Ed. (Raven Press, New York, 1980) pp 373-384; J. Genest, *Heterogeneity of Renin and Renin Substrate,* M. P. Sambhi, Ed. (Elsevier, New York, 1981) pp 11-24.

Mol wt determn is 31,400 by gel filtration and 28,700 by sedimentation equilibrium. Activity is not affected by pepstatin. Can be incubated at 20° for 150 min, between pH 3.4-8 without significant loss of enzymatic activity; loses 15% of its original activity at pH 2.8. After 5 min of incubation at 100°, 60-65% activity remains.

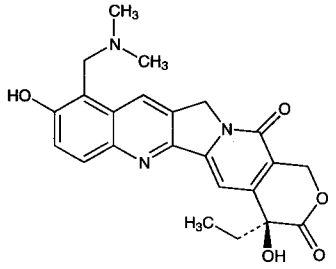
9547. Topiramate. [97240-79-4] 2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate; 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose sulfamate; McN-4853; RWJ-17021-000; Topamax. $C_{12}H_{21}NO_8S$; mol wt 339.36. C 42.47%, H 6.24%, N 4.13%, O 37.72%, S 9.45%. Sulfamate substituted monosaccharide; structurally distinct antiepileptic agent. Prepn: B. E. Maryanoff, J. F. Gardocki, **US 4513006** (1985 to McNeil); and anticonvulsant activity: B. E. Maryanoff *et al., J. Med. Chem.* **30,** 880 (1987). GC determn in plasma: M. L. Holland *et al., J. Chromatogr.* **433,** 276 (1988). Comparative pharmacokinetics: M. Bialer, *Clin. Pharmacokinet.* **24,** 441 (1993). Series of articles on pharmacology and clinical experience in epilepsy: *Epilepsia* **38,** Suppl. 1, 1-62 (1997). Review of clinical trials in migraine prevention: G. Bussone *et al., Int. J. Clin. Pract.* **59,** 961-968 (2005); of pharmacology and clinical experience: S. D. Silberstein *et al., Clin. Ther.* **27,** 154-165 (2005).



Crystals from ethyl acetate + hexane, mp 125-126°. $[\alpha]_D^{23}$ −34.0° (c = 0.4 in methanol).

THERAP CAT: Anticonvulsant; antimigraine.

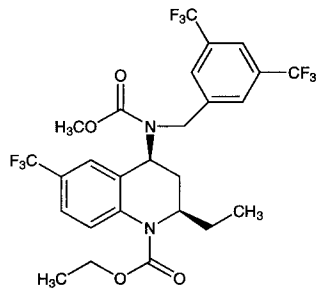
9548. Topotecan. [123948-87-8] (4*S*)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino-[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione; 9-[(dimethylamino)methyl]-10-hydroxy-(20*S*)-camptothecin; hycamptamine; SKF-104864. $C_{23}H_{23}N_3O_5$; mol wt 421.45. C 65.55%, H 5.50%, N 9.97%, O 18.98%. DNA topoisomerase I inhibitor; semisynthetic analog of camptothecin, *q.v.* Prepn: J. C. Boehm *et al.,* **EP 321122;** *eidem,* **US 5004758** (1989, 1991 both to SmithKline Beecham); W. D. Kingsbury *et al., J. Med. Chem.* **34,** 98 (1991). HPLC determn in plasma: J. H. Beijnen *et al., J. Pharm. Biomed. Anal.* **8,** 789 (1990). Clinical pharmacology: E. K. Rowinsky *et al., J. Clin. Oncol.* **10,** 647 (1992); and pharmacokinetics: L. J. C. van Warmerdam *et al., Cancer Chemother. Pharmacol.* **38,** 254 (1996). Clinical evaluation in ovarian cancer: A. P. Kudelka *et al., J. Clin. Oncol.* **14,** 1552 (1996); in small cell lung cancer: J. H. Schiller *et al., ibid.* 2345. Review of clinical toxicity: K. Seiter, *Expert Opin. Drug Safety* **4,** 45-53 (2005).



Hydrochloride. [119413-54-6] NSC-609669; SKF-104864A; Hycamtin. $C_{23}H_{23}N_3O_5.HCl$; mol wt 457.91. Light yellow to greenish powder, mp 213-218° (dec). Soluble in water up to 1 mg/ml.

THERAP CAT: Antineoplastic.

9549. Torcetrapib. [262352-17-0] (2*R*,4*S*)-4-[[[3,5-Bis(trifluoromethyl)phenyl]methyl](methoxycarbonyl)amino]-2-ethyl-3,4-dihydro-6-(trifluoromethyl)-1(2*H*)-quinolinecarboxylic acid ethyl ester; (2*R*,4*S*)-4-[(3,5-bis-trifluoromethylbenzyl)methoxycarbonylamino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; CP-529414. $C_{26}H_{25}F_9N_2O_4$; mol wt 600.47. C 52.01%, H 4.20%, F 28.48%, N 4.67%, O 10.66%. Cholesteryl ester transfer protein (CETP) inhibitor. Prepn: M. P. DeNinno *et al.,* **WO 0017164;** *eidem,* **US 6197786** (2000, 2001 both to Pfizer); of crystalline forms: D. J. M. Allen *et al.,* **WO 0140190** (2001 to Pfizer). Mechanism of action study: R. W. Clark *et al., J. Lipid Res.* **47,** 537 (2006). Clinical evaluation of effects on HDL cholesterol levels: R. W. Clark *et al., Arterioscler. Thromb. Vasc. Biol.* **24,** 490 (2004); M. E. Brousseau *et al., N. Engl. J. Med.* **350,** 1505 (2004). Review of clinical development in combination with atorvastatin: J. R. Burnett, *Curr. Opin. Invest. Drugs* **6,** 944-950 (2005).

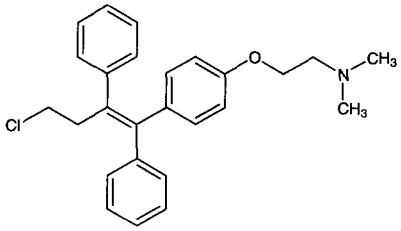


Anhydrous, non-hygroscopic crystals, mp 89-90°. d 1.406.

Ethanolate. [343798-00-5] $C_{26}H_{25}F_9N_2O_4.C_2H_6O$; mol wt 646.54. White crystalline powder, mp 54-58°. $[\alpha]_D$ −93.3° (c = 1.08 in methanol). d 1.402. Non-hygroscopic. Higher aqueous soly than anhydrous form.

THERAP CAT: Antilipemic; antiatherosclerotic.

9550. Toremifene. [89778-26-7] 2-[4-[(1*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]-*N*,*N*-dimethylethanamine; (*Z*)-4-chloro-1,2-diphenyl-1-[4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl]-1-butene. $C_{26}H_{28}ClNO$; mol wt 405.96. C 76.92%, H 6.95%, Cl 8.73%, N 3.45%, O 3.94%. Nonsteroidal antiestrogen structurally similar to tamoxifen, *q.v.* Prepn: R. J. Toivola *et al.,* **EP 95875;** *eidem,* **US 4696949** (1983, 1987 both to Farmos). Pharmacology: S. Kallio *et al., Cancer Chemother. Pharmacol.* **17,** 103 (1986). Antitumor effects *in vitro* and *in vivo:* L. Kangas *et al., ibid.* 109. HPLC determn in plasma: W. M. Holleran *et al., Anal. Lett.* **20,** 871 (1987). Clinical evaluation in high-grade prostatic intraepithelial neoplasia: M. S. Steiner, C. R. Pound, *Clin. Prostate Cancer* **2,** 24 (2003). Review of pharmacology and clinical efficacy in advanced breast cancer: L. R. Wiseman, K. L. Goa, *Drugs* **54,** 141-160 (1997); in postmenopausal breast cancer: J. U. Mäenpää, S.-L. Ala-Fossi, *Drugs Aging* **11,** 261-270 (1997).



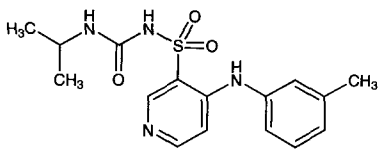
mp 108-110°.

Citrate. [89778-27-8] FC-1157a; Acapodene; Fareston. $C_{26}H_{28}ClNO.C_6H_8O_7$; mol wt 598.08. mp 160-162°.

THERAP CAT: Antineoplastic.

9551. Toril Oil. From the fruit of *Torilis anthriscus* (L.) Gmel., *Umbelliferae*. A Japanese folk remedy for ascaris. It is relatively non-toxic for higher animals and very toxic for Lumbricus, leech and ascaris.

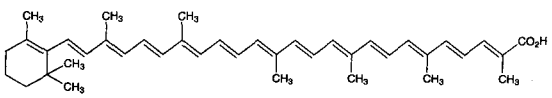
9552. Torsemide. [56211-40-6] *N*-[[(1-Methylethyl)amino]carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide; 1-isopropyl-3-[(4-*m*-toluidino-3-pyridyl)sulfonyl]urea; 3-isopropylcarbamylsulfonamido-4-(3′-methylphenyl)aminopyridine; torasemide; AC-4464; BM-02015; JDL-464; Demadex; Toradiur; Torem; Unat. $C_{16}H_{20}N_4O_3S$; mol wt 348.42. C 55.16%, H 5.79%, N 16.08%, O 13.78%, S 9.20%. Sulfonylurea loop diuretic. Prepn: J. E. DeLarge *et al.*, **DE 2516025**; *eidem*, **US 4018929** (1975, 1977 both to A. Christiaens, S.A.); J. DeLarge, C. L. Lapiere, *Ann. Pharm. Fr.* **36,** 369 (1978). Pharmacokinetics in humans: M. Lesne *et al.*, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **20,** 382 (1982). Preliminary evaluation in acute heart failure: R. Stroobandt *et al.*, *Arch. Int. Pharmacodyn.* **260,** 151 (1982). Clinical pharmacology: D. C. Brater *et al.*, *Clin. Pharmacol. Ther.* **42,** 187 (1987). Series of articles on pharmacology, mode of action and renal effects in animals: *Arzneim.-Forsch.* **35,** 1520-1541 (1985); on pharmacology, pharmacokinetics and clinical studies: *Eur. J. Clin. Pharmacol.* **31,** Suppl., 1-55 (1986); *Arzneim.-Forsch.* **38,** 143-214 (1988). Clinical comparison with furosemide, *q.v.*, in congestive heart failure: J. Cosin *et al.*, *Eur. J. Heart Fail.* **4,** 507 (2002).



mp 163-164°. pKa 6.44.

THERAP CAT: Diuretic.

9553. Torularhodin. [514-92-1] 3′,4′-Didehydro-β,ψ-caroten-16′-oic acid. $C_{40}H_{52}O_2$; mol wt 564.84. C 85.06%, H 9.28%, O 5.67%. Carotenoid pigment found in *Torula rubra* and *Rhodotorula mucilaginosa* yeasts. Isoln: Karrer, Rutschmann, *Helv. Chim. Acta* **26,** 2109 (1943). Structure and synthesis: Isler *et al.*, *ibid.* **42,** 864 (1959).



Fine dark purple needles from methanol + ether or toluene, mp 210-212° (vac, some decompn). Absorption max in CS_2: 582, 541, 502 nm; in methanol: 529, 493, 460 nm. Freely sol in carbon disulfide, chloroform, pyridine; less sol in ether, benzene, hot ethanol; sparingly sol in methanol. Practically insol in petr ether.

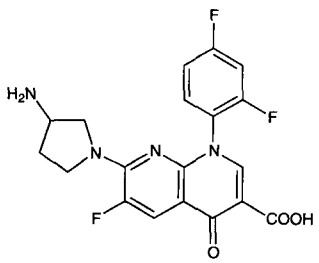
Methyl ester. $C_{41}H_{54}O_2$. Dark red needles from benzene + methanol, mp 172-173°.

9554. Tositumomab. [208921-02-2] Anti-(human CD20 antigen) immunoglobulin G2a (mouse monoclonal clone B1R1 γ_{2a}-chain) disulfide with mouse monoclonal clone B1R1 λ_x-chain, dimer; anti-B1 antibody. Murine monoclonal antibody targeted against CD-20 antigen located on mature B lymphocytes but not on normal stem cells or progenitor cells. ^{131}Iodine radioimmunoconjugate designed for tumor-targeted treatment of non-Hodgkin's lymphoma (NHL). Prepn: M. S. Kaminski *et al.*, **US 5595721** (1997 to Coulter); and clinical evaluation: *idem et al.*, *N. Engl. J. Med.* **329,** 459 (1993). Clinical study of radioimmunotherapy in NHL: *eidem, Blood* **96,** 1259 (2000). Review of mechanism of action and clinical application: A. K. Gopal, O. W. Press, *J. Lab. Clin. Med.* **134,** 445 (1999); of use in follicular lymphoma: A. J. Davies, *Expert Opin. Biol. Ther.* **5,** 577-588 (2005).

^{131}I-Labeled form. [192391-48-3] SB-393229; Bexxar.

THERAP CAT: Antineoplastic.

9555. Tosufloxacin. [100490-36-6] 7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid; A-61827. $C_{19}H_{15}F_3N_4O_3$; mol wt 404.34. C 56.44%, H 3.74%, F 14.10%, N 13.86%, O 11.87%. Trifluorinated quinolone antibacterial. Prepn: H. Narita *et al.*, **DE 3514076** (1985 to Toyama), *C.A.* **104,** 129888r (1986); D. T. W. Chu, **EP 153580**; *idem*, **US 4616019** (1985, 1986 both to Abbott); and activity: *idem et al.*, *J. Med. Chem.* **29,** 2363 (1986); H. Narita *et al.*, *Yakugaku Zasshi* **106,** 802 (1986), *C.A.* **106,** 196291v (1987). *In vitro* activity studies of the base: P. B. Fernandes *et al.*, *Antimicrob. Agents Chemother.* **32,** 27 (1988); and *in vivo* animal studies of the toluenesulfonate: M. Takahata *et al.*, *J. Antimicrob. Chemother.* **22,** 143 (1988). Series of articles on antibacterial activity and clinical evaluation: *Chemotherapy (Tokyo)* **36,** Suppl. 9, 1-1538 (1988).

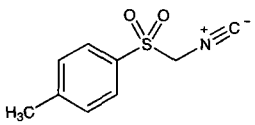


Hydrochloride. [104051-69-6] A-60969. $C_{19}H_{15}F_3N_4O_3.HCl$; mol wt 440.80. Crystals from conc HCl-ethanol (1:3), mp 247-250° (dec).

Toluenesulfonate. [115964-29-9] Tosufloxacin tosylate; A-64730; T-3262; Ozex; Tosuxacin. $C_{19}H_{15}F_3N_4O_3.C_7H_8O_3S$; mol wt 576.54. Prepd as the monohydrate, mp 258-260°.

THERAP CAT: Antibacterial.

9556. Tosylmethyl Isocyanide. [36635-61-7] 1-[(Isocyanomethyl)sulfonyl]-4-methylbenzene; (4-methylphenylsulfonyl)-methyl isocyanide; *p*-toluenesulfonylmethyl isocyanide; TosMIC. $C_9H_9NO_2S$; mol wt 195.24. C 55.37%, H 4.65%, N 7.17%, O 16.39%, S 16.42%. Isonitrile reagent with reversed polarity; serves as a carbonyl anion equivalent in organic synthesis. Prepn: U. Schöllkopf *et al.*, *Ann.* **766,** 130 (1972); A. M. van Leusen *et al.*, *Tetrahedron Lett.* **13,** 2367 (1972); B. E. Hoogenboom *et al.*, *Org. Synth.* **57,** 102 (1977). Review of applications in organic synthesis: C. Lamberth, *J. Prakt. Chem. Chem.-Ztg.* **340,** 483-485 (1998); V. K. Tandon, S. Rai, *Sulfur Rep.* **24,** 307-385 (2003).



Crystals from methanol, mp 116-117° (dec).

USE: Versatile synthon in organic chemistry, esp in the synthesis of heterocyclic compds.

9557. Toxaphene. [8001-35-2] Chlorinated camphene; camphechlor; polychlorocamphene; Hercules 3956; Alltox; Geniphene; Motox; Phenacide; Phenatox; Strobane-T; Toxakil. A very

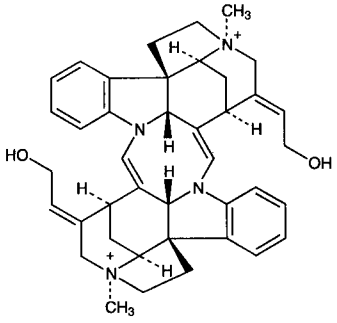
complex, but reproducible mixture of at least 177 C_{10} polychloro derivs, having an approx overall empirical formula of $C_{10}H_{10}Cl_8$. Produced by the chlorination of camphene to 67-69% chlorine by weight and made up of compds of $C_{10}H_8Cl_{10}$, $C_{10}H_{18-n}Cl_n$ (mostly polychlorobornanes) and $C_{10}H_{16-n}Cl_n$ (polychlorobornenes and/or polychlorotricyclenes) with n = 6 to 9. Prepn: Buntin, **US 2565471** (1951 to Hercules Powder). Isoln of components in crystalline form: Casida *et al., Science* **183,** 520 (1974); *eidem, J. Agric. Food Chem.* **22,** 939 (1974). Acute toxicity data: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969). Mutagenicity studies: N. K. Hooper *et al., Science* **205,** 591 (1979). Livestock toxicity and tissue residues: L. Penumarthy *et al., Vet. Toxicol.* **18,** 60 (1976). *Reviews:* Liebmann *et al., Arch. Pflanzenschutz* **7,** 131-150 (1971); F. Korte *et al., Pure Appl. Chem.* **51,** 1583-1601 (1979); M. A. Saleh, *Rev. Environ. Contam. Toxicol.* **118,** 1-85 (1990). Review of toxicology and human exposure: *Toxicological Profile for Toxaphene* (PB97-121057, 1996) 252 pp.

Yellow waxy solid, mp 65-90°. Pleasant piney odor. Vapor pressure at 20°: 3×10^{-7}mm Hg. d^{25} 1.630. Log P (octanol/water): 6.44. Dehydrochlorinates in the presence of alkali, prolonged exposure to sunlight, and at temps about 155°. Soly in water: 3 mg/l. Freely sol in aromatic hydrocarbons. Corrosive to iron. LD_{50} in male, female rats (mg/kg): 90, 80 orally; 1075, 780 dermally (Gaines).

Caution: Potential symptoms of overexposure are nausea, confusion, agitation, tremors, convulsions and unconsciousness; dry, red skin. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 58. *See also Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section III, pp 386-387. This substance is reasonably anticipated to be a human carcinogen: *Report on Carcinogens, Eleventh Edition* (PB2005-104914, 2004) p III-259

USE: Insecticide. Not recommended for use in dairy barns or on milking animals (Penumarthy).

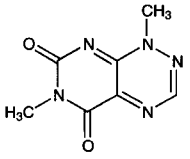
9558. Toxiferine I. [6888-23-9] *C*-Toxiferine I. $[C_{40}H_{46}N_4O_2]^{2+}$. Naturally occurring neuromuscular blocker. From calabash curare: Schmid, Karrer, *Helv. Chim. Acta* **30,** 1162 (1947); from *Strychnos toxifera* Schomb., *Loganiaceae:* Wieland *et al., Ann.* **547,** 156 (1941); King, *J. Chem. Soc.* **1949,** 3263. Identity with ***toxiferine V*** and ***toxiferine XI***: Battersby *et al., ibid.* **1960,** 1848. Structure: Arnold *et al., Helv. Chim. Acta* **44,** 620 (1961). Synthesis: Berlage *et al., ibid.* **42,** 394 (1959); Grdinic *et al., J. Am. Chem. Soc.* **86,** 3357 (1964). Pharmacokinetics: P. G. Waser, J. Reller, *Agents Actions* **2,** 170 (1972). ^{13}C-NMR study: E. Wenkert *et al., J. Org. Chem.* **43,** 1099 (1978).



Dichloride. $C_{40}H_{46}Cl_2N_4O_2$. Crystals. $[\alpha]_D^{22}$ −546° (c = 0.30). uv max (ethanol): 292 nm (log ε 4.62). Sol in water.

***C*-Toxiferine II.** [7257-29-6] *C*-Calebassine; *C*-strychnotoxine. $[C_{40}H_{48}N_4O_2]^{2+}$. From calabash-curare: Karrer, Schmidt, *Helv. Chim. Acta* **29,** 1853 (1946); Zürcher *et al., J. Am. Chem. Soc.* **80,** 1500 (1958). Identity as *C*-toxiferine II and *C*-strychnotoxine: Wieland, Merz, *Ber.* **85,** 731 (1952). Structure: Hesse *et al., Helv. Chim. Acta* **44,** 2211 (1961); Fehlmann *et al., ibid.* **48,** 303 (1965).

9559. Toxoflavin. [84-82-2] 1,6-Dimethylpyrimido[5,4-*e*]-1,2,4-triazine-5,7(1*H*,6*H*)-dione; 1,6-dimethyl-5,7-dioxo-1,5,6,7-tetrahydropyrimido[5,4-*e*]-*as*-triazine; xanthothricin. $C_7H_7N_5O_2$; mol wt 193.16. C 43.53%, H 3.65%, N 36.26%, O 16.57%. Highly toxic antibiotic from cultures of *Pseudomonas cocovenenans* which also produces bongkrekic acid, *q.v.* Isoln: van Veen, Mertens, *Rec. Trav. Chim.* **53,** 257, 398 (1934); R. A. Machlowitz *et al., Antibiot. Chemother.* **4,** 259 (1954). Structure: Van Damm *et al., Rec. Trav. Chim.* **79,** 255 (1960). Synthesis: Daves *et al., J. Am. Chem. Soc.* **83,** 3904 (1961); **84,** 1724 (1962); Yoneda *et al., Tetrahedron Lett.* **1971,** 851. Mode of action: Latuasan, Berends, *Biochim. Biophys. Acta* **52,** 502 (1961). Biosynthesis: Levenberg, Linton, *J. Biol. Chem.* **241,** 846 (1966). Production by *Burkholderia glumae* and pathogenicity to rice seedlings: K. Yoneyama *et al., Ann. Phytopathol. Soc. Jpn.* **64,** 91 (1998).

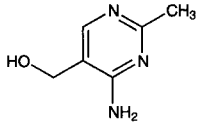


Bright yellow platelets from propanol, dec 172-173°. uv max: 257.5, 394 nm (ε 16400, 2500). Acts as a pH indicator with a sharp loss of color at pH 10.5, but is destroyed by alkali. Sol in water, chloroform, ethyl acetate, ethanol. LD_{50} in mice (mg/kg): 1.7 i.v.; 8.4 orally (Machlowitz).

9560. Toxohormone. [9014-44-2] Name given in 1948 by Nakahara and Fukuoka to a factor produced by living cancer cells and released into the circulation to produce decreases in liver catalase activity, tryptophan pyrrolase activity, liver ferritin and plasma iron. *See* Nakahara, Fukuoka, *Jpn. J. Cancer Res.* **40,** 45 (1949). This tumor-specific concept has been questioned: Greenfield, Meister, *J. Natl. Cancer Inst.* **11,** 997 (1951); Olivares *et al., Science* **157,** 327 (1967); Kampschmidt, Upchurch, *Proc. Soc. Exp. Med. Biol.* **127,** 632 (1968). Described as a polypeptide of low mol wt having 30-40 amino acid residues of which 12-13 are different, and with a high content of glycine, glutamic acid, aspartic acid, alanine and leucine. Amino acid and lipid composition of a highly purified toxohormone prepd from human malignant tissue: Yunoki, Griffin, *Cancer Res.* **21,** 537 (1961); from cell-free fluid of ascites sarcoma 180: H. Masuno *et al., ibid.* **41,** 284 (1981). *Reviews:* W. Nakahara, F. Fukuoka, *Chemistry of Cancer Toxin Toxohormone* (C. C. Thomas, Springfield, Illinois, 1961) 75 pp; Nakahara, *Methods Cancer Res.* **2,** 203-237 (1967); Olivares, Kampschmidt in *Oncology, Proc. Int. Cancer Congr., 10th, Houston 1970* **3,** 158-170 (1971); S. Fujii, *Gann Monogr. Cancer Res.* **24,** 215-222 (1979).

Thermostable, non-heat-coagulable, water-sol and alcohol precipitable.

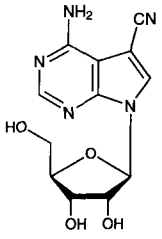
9561. Toxopyrimidine. [73-67-6] 4-Amino-2-methyl-5-pyrimidinemethanol; 6-amino-5-hydroxymethyl-2-methylpyrimidine; 4-amino-5-hydroxymethyl-2-methylpyrimidine; pyramin; pyramine. $C_6H_9N_3O$; mol wt 139.16. C 51.79%, H 6.52%, N 30.20%, O 11.50%. A metabolite of thiamine. Prepd from 4-amino-5-aminomethyl-2-methylpyrimidine dihydrochloride or ethyl 4-amino-2-methyl-5-pyrimidinecarboxylate: Dornow, Petsch, *Ber.* **86,** 1404 (1953); DiBella, Hennessy, *J. Org. Chem.* **26,** 2017 (1961).



Needles from water, mp 193-198°; crystals from methanol + ether, mp 198-200°. Sublimes at 0.01 mm between 155-170°.

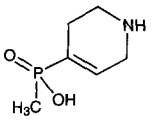
9562. Toyocamycin. [606-58-6] 4-Amino-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-5-cyano-7-(D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; uramycin B; vengicide; antibiotic 1037; E-212. $C_{12}H_{13}N_5O_4$; mol wt 291.26. C 49.48%, H 4.50%, N 24.05%, O 21.97%. Antibiotic substance extracted from the culture filtrate and mycelium of *Streptomyces toyocaensis*. Isoln: Nishimura *et al., J. Antibiot.* **9A,** 60 (1956). Structure: Ohkuma, *ibid.* **14A,** 343 (1961). Synthesis of

aglycone: Taylor, Hendess, *J. Am. Chem. Soc.* **86,** 951 (1964). Total synthesis: Tolman *et al., ibid.* **90,** 524 (1968); **91,** 2102 (1969). Biosynthesis: Uematsu, Suhadolnik, *Biochemistry* **9,** 1260 (1970); *eidem, J. Biol. Chem.* **245,** 4365 (1970). Crystal and molecular structure: P. Prusiner, M. Sundaralingam, *Acta Crystallogr.* **B34,** 517 (1978).



Fine needles from methanol or acetone, mp 243°. Recrystallization from water yields the hydrate, $C_{12}H_{13}N_5O_4.H_2O$, mp 239-243°. $[\alpha]_D^{16}$ −45.7° (c = 1.05 in 0.1*N* HCl). uv max (H_2O): 230, 277 nm ($E_{1cm}^{1\%}$ 400, 548). Soluble in acetic acid, acidic solns. Moderately sol in methanol, ethanol, acetone, dioxane, butanol, water, ether. Practically insol in chloroform, ethyl acetate, petr ether. LD_{100} s.c. in mice: 10-20 mg/kg (Nishimura).

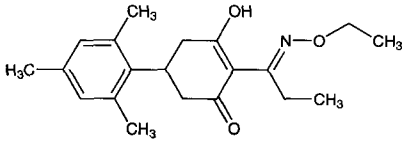
9563. TPMPA. [182485-36-5] Methyl (1,2,3,6-tetrahydro-4-pyridinyl)phosphinic acid; (1,2,5,6-tetrahydropyridine-4-yl)methylphosphinic acid. $C_6H_{12}NO_2P$; mol wt 161.14. C 44.72%, H 7.51%, N 8.69%, O 19.86%, P 19.22%. Selective antagonist for $GABA_C$ receptors. Prepn: Y. Murata *et al., Bioorg. Med. Chem. Lett.* **6,** 2073 (1996); R. Miledi *et al.,* **US 5627169** (1997 to Univ. California). Design and *in vitro* pharmacology: D. Ragozzino *et al., Mol. Pharmacol.* **50,** 1024 (1996). Specificity vs human receptors and alternate synthesis: M. Chebib *et al., Eur. J. Pharmacol.* **357,** 227 (1998). Use as antagonist: A. Rozzo *et al., Neuroscience* **90,** 1085 (1999).



Off-white solid from ethanol, mp 252-254°. Soly in water 16 mg/ml. Insol in DMSO.

USE: Neurochemical tool.

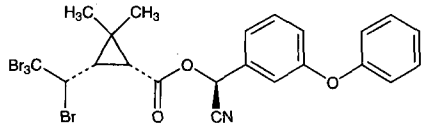
9564. Tralkoxydim. [87820-88-0] 2-[1-(Ethoxyimino)propyl]-3-hydroxy-5-(2,4,6-trimethylphenyl)-2-cyclohexen-1-one; 2-[1-(ethoxyimino)propyl]-3-hydroxy-5-mesitylcyclohex-2-en-1-one; PP-604; Achieve; Grasp. $C_{20}H_{27}NO_3$; mol wt 329.43. C 72.92%, H 8.26%, N 4.25%, O 14.57%. Cereal selective post-emergent herbicide. Prepn: R. B. Warner *et al.,* **EP 80301**; *eidem,* **US 4717418** (1983, 1988 both to ICI). Physical properties and herbicidal activity: R. B. Warner *et al., Proc. Br. Crop Prot. Conf. - Weeds* **1987,** 19. Field trials on grass weeds: J. Rola, *ibid.* 363; P. B. Sutton *et al., ibid.* 389. Mechanism of action study: J. Secor, C. Cseke, *Plant Physiol.* **86,** 10 (1988).



White crystalline solid, mp 106°. Vapor pressure at 20°: 4×10^{-10} kPa. Soly at 20° (mg/l): water 6 at pH 6.5, 5 at pH 5.0; at 24° (g/l): hexane 18; toluene 213; dichloromethane >500; methanol 25; acetone 89; ethyl acetate 110. LD_{50} orally in male and female rats, male and female mice, male rabbit (mg/kg): 1324, 934, 1231, 1100, 519; dermally in male and female rats: >2000, >2000 mg/kg (Warner 1987).

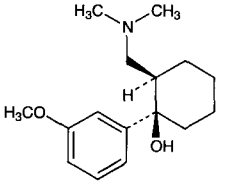
USE: Post-emergent herbicide.

9565. Tralomethrin. [66841-25-6] 2,2-Dimethyl-3-(1,2,2,-2-tetrabromoethyl)cyclopropanecarboxylic acid cyano(3-phenoxyphenyl)methyl ester; (*S*)-α-cyano-3-phenoxybenzyl (1*R*)-*cis*-2,2-dimethyl-3-[(*RS*)-1,2,2,2-tetrabromoethyl]cyclopropanecarboxylate; RU-25474; OMS-3048; Saga; Scout; Tracker; Tralate; Tralox. $C_{22}H_{19}Br_4NO_3$; mol wt 665.01. C 39.73%, H 2.88%, Br 48.06%, N 2.11%, O 7.22%. Synthetic pyrethroid consisting of two active diastereomers whose absolute configurations differ at the monobrominated carbon atom. Prepn: **BE 873201**; J. Martel *et al.,* **US 4279835** (1979, 1981 both to Roussel-Uclaf). Insecticidal activity: M. Benoit *et al., Pestic. Biochem. Physiol.* **26,** 284 (1986). Mechanism of action study: M. Roche *et al., ibid.* **24,** 306 (1985). HPLC determn in water, sediment and fish tissue: J. Mao *et al., J. Agric. Food Chem.* **41,** 596 (1993). Field trials: D. D. Amalraj *et al., Indian J. Malariol.* **28,** 141 (1991); W. R. Halliday *et al., J. Agric. Entomol.* **9,** 145 (1992). Review of toxicology and human exposure: *Toxicological Profile for Pyrethrins and Pyrethroids* (PB2004-100004, 2003) 332 pp.



USE: Insecticide.

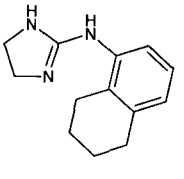
9566. Tramadol. [27203-92-5] (1*R*,2*R*)-*rel*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol; E-265; CG-315E; U-26225A. $C_{16}H_{25}NO_2$; mol wt 263.38. C 72.96%, H 9.57%, N 5.32%, O 12.15%. Prepn: **GB 997399**; K. Flick, E. Frankus, **US 3652589** (1965, 1972 both to Grünenthal); K. Flick *et al., Arzneim.-Forsch.* **28,** 107 (1978). Series of articles on pharmacology and clinical studies: *ibid.* 114-219. Toxicology: F. Lagler *et al., ibid.* 164. Mechanism of action study: R. B. Raffa *et al., J. Pharmacol. Exp. Ther.* **267,** 331 (1993). HPLC determn in urine: B. Elsing, G. Blaschke, *J. Chromatogr.* **612,** 223 (1993). HPLC determn in plasma and pharmacokinetics: A. Küçük *et al., J. Chromatogr. B* **816,** 203 (2005). Symposium on pharmacology and clinical experience: *Drugs* **47,** Suppl. 1, 1-46 (1994).



Hydrochloride. [22204-88-2] Amadol; Contramal; Crispin; Tradonal; Tramal; Ultram; Zamadol; Zydol. $C_{16}H_{25}NO_2.HCl$; mol wt 299.84. White crystals, mp 180-181°. Sol in water. LD_{50} in mice, rats (mg/kg): 350, 228 orally; 200, 286 s.c. (Lagler).

THERAP CAT: Analgesic.

9567. Tramazoline. [1082-57-1] 4,5-Dihydro-*N*-(5,6,7,8-tetrahydro-1-naphthalenyl)-1*H*-imidazol-2-amine; 2-[(5,6,7,8-tetrahydro-1-naphthyl)amino]-2-imidazoline. $C_{13}H_{17}N_3$; mol wt 215.29. C 72.53%, H 7.96%, N 19.52%. α-Adrenergic agonist. Prepn: Berg, **DE 1191381**; **DE 1195323** (both 1965 to Thomae), *C.A.* **63,** 8373c; 13274d (1965). Pharmacology and toxicity data: R. Engelhorn, H. Klupp, *Arzneim.-Forsch.* **12,** 971 (1962). Activity studies: Sachsenröder *et al., ibid.* **22,** 392 (1972).



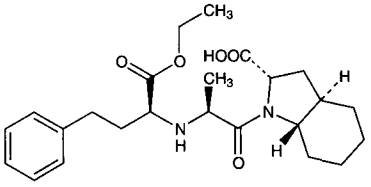
Crystals from isopropanol, mp 142-143°.

Hydrochloride monohydrate. [3715-90-0] KB-227; Biciron; Ellatun; Rhinaspray; Rhinogutt; Rhinospray; Rinogutt; Towk. C_{13}-

$H_{17}N_3$.HCl.H_2O; mol wt 269.77. Crystals from alc + ether or acetone + ether, mp 172-174°. Sol in water. LD_{50} orally in mice: 195 mg/kg (Engelhorn, Klupp).

THERAP CAT: Decongestant.

9568. Trandolapril. [87679-37-6] (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydro-1*H*-indole-2-carboxylic acid; (3a*R*,7a*S*)-1-[*N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-(*S*)-alanyl]octahydroindole-2(*S*)-carboxylic acid; (2*S*,3a*R*,7a*S*)-1-[(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl]hexahydro-2-indolinecarboxylic acid 1-ethyl ester; RU-44570; Mavik; Odrik; Gopten. $C_{24}H_{34}N_2O_5$; mol wt 430.54. C 66.95%, H 7.96%, N 6.51%, O 18.58%. Angiotensin converting enzyme (ACE) inhibitor. Prepn: H. Urbach *et al.*, **EP 84164**; *eidem*, **US 4933361** (1983, 1990 both to Hoechst). Enzyme inhibition and pharmacology: N. L. Brown *et al.*, *Eur. J. Pharmacol.* **148,** 79 (1988). Clinical pharmacology: F. De Ponti *et al.*, *Eur. J. Clin. Pharmacol.* **40,** 149 (1991). Clinical trial in prevention of death after myocardial infarction: L. Kober *et al.*, *N. Engl. J. Med.* **333,** 1670 (1995). Series of articles on pharmacology and clinical trials: *Am. J. Hypertens.* **8,** 63S-74S (1995). Clinical trial in diabetic neuropathy: R. A Malik *et al.*, *Lancet* **352,** 1978 (1998).

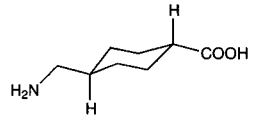


Colorless, crystalline solid, mp 125°. Sol in chloroform, dichloromethane, methanol.

Diacid. [87679-71-8] Trandolaprilat; RU-44403. $C_{22}H_{30}N_2O_5$; mol wt 402.48.

THERAP CAT: Antihypertensive.

9569. Tranexamic Acid. [1197-18-8] *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid; AMCHA; RP-18429; Anvitoff; Cyklokapron; Exacyl; Spiramin; Spotof; Tranex; Transamin; Ugurol. $C_8H_{15}NO_2$; mol wt 157.21. C 61.12%, H 9.62%, N 8.91%, O 20.35%. Antifibrinolytic agent; blocks lysine binding sites of plasminogen. Prepn: A. Einhorn, C. Ladisch, *Ann.* **310,** 194 (1900); M. Levine, R. Sedlecky, *J. Org. Chem.* **24,** 115 (1959); **NL 6503605**; T. Naito *et al.*, **US 3499925** (1965, 1970 to both Daiichi Seiyaku and Mitsubishi Chem.). Pharmacology: Andersson *et al.*, *Scand. J. Haematol.* **2,** 230 (1965). Resoln of isomers and antiplasmin activity: M. Shimizu *et al.*, *Chem. Pharm. Bull.* **16,** 357 (1968), T. Naito *et al.*, *ibid.*, 728. Toxicity data: B. Melander *et al.*, *Acta Pharmacol. Toxicol.* **22,** 340 (1965). Clinical study in treatment of acute upper gastrointestinal tract bleeding: D. Barer *et al.*, *N. Engl. J. Med.* **308,** 1571 (1983); in menorrhagia: J. Bonnar, B. L. Sheppard, *Br. Med. J.* **313,** 579 (1996). Review of pharmacology and therapeutic use: C. J. Dunn, K. L. Goa, *Drugs* **57,** 1005-1032 (1999).

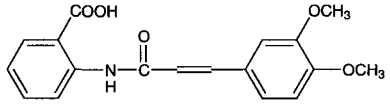


mp 386-392° (dec). Soly in water: about 1 g/6 ml. Very slightly sol in alcohol, ether. Practically insol in most other organic solvents. Chemically stable; not hygroscopic. LD_{50} in mice, rats (mg/kg): 1500, 1200 i.v. (Melander).

***cis*-form.** [1197-17-7] mp 236-238° (dec).

THERAP CAT: Hemostatic.

9570. Tranilast. [53902-12-8] 2-[[3-(3,4-Dimethoxyphenyl)-1-oxo-2-propenyl]amino]benzoic acid; *N*-(3′,4′-dimethoxycinnamoyl)anthranilic acid; N-5′; Rizaben. $C_{18}H_{17}NO_5$; mol wt 327.33. C 66.05%, H 5.23%, N 4.28%, O 24.44%. Orally active anti-allergic agent. Prepn: K. Harita *et al.*, **DE 2402398**; *idem*, **US 3940422** (1974, 1976 both to Kissei). Pharmacological properties: H. Azuma *et al.*, *Br. J. Pharmacol.* **58,** 483 (1976). Mechanism of action study: Y. Iijima *et al.*, *Biochem. Biophys. Res. Commun.* **93,** 912 (1980). Clinical study in pediatric bronchial asthma: H. Shioda, *Allergy* **34,** 213 (1979). Toxicity studies: M. Nakazawa *et al.*, *Oyo Yakuri* **12,** 385, 407 (1976), *C.A.* **88,** 115327-8 (1978). Series of articles on teratogenicity tests: *Iyakuhin Kenkyu* **9,** 148-193 (1978), *C.A.* **88,** 130930f, 146300m-303q (1978).



Crystals from chloroform, mp 211-213°. LD_{50} in male, female mice, male, female rats (mg/kg): 780, 680, 1600, 1100 orally; 410, 385, 405, 395 i.p.; 2630, 2820, 3630, 3060 s.c. (Nakazawa, p 385).

THERAP CAT: Antiallergic.

9571. Transferrins. A group of homologous non-heme, iron-binding glycoproteins of approx mol wts of 76,000-81,000. They are widely distributed in a variety of physiological fluids and cells, esp in the sera of most vertebrates, in egg whites and in mammalian milk, tears and leukocytes. They are involved in iron transport to developing red cells for hemoglobin synthesis. Each protein molecule specifically binds with two Fe^{3+} ions to form salmon-pink complexes; bicarbonate or carbonate ions are involved in the formation of these colored complexes. Reviews of isoln, properties and biological functions: Feeney, Komatsu, *Struct. Bonding* **1,** 149-206 (1966); Aisen, "The Transferrins" in *Inorganic Biochemistry* **vol. 1,** G. L. Eichhorn, Ed. (Elsevier, New York, 1973) pp 280-305; Bezkorovainy, Zschocke, *Arzneim.-Forsch.* **24,** 476-485, 726-737 (1974); P. Aisen, A. Leibman, *Bioinorg. Chem.* **II,** K. N. Raymond, Ed. (A.C.S., Washington, 1977) pp 104-126; P. Aisen, I. Listowsky, *Annu. Rev. Biochem.* **49,** 357-393 (1980). Review of transferrin receptors: R. Newman *et al.*, *Trends Biochem. Sci.* **7,** 397-399 (1982).

Serum transferrin. β_1-Metal-combining protein; siderophilin. Commonly called transferrin. Structure of carbohydrate moiety: Jamieson *et al.*, *J. Biol. Chem.* **246,** 3686 (1971). Composed of two homologous domains, each containing a binding site for metal ions. The sites are similar, but not identical, in their metal-binding properties. X-ray studies: L. J. DeLucas *et al.*, *J. Mol. Biol.* **123,** 285 (1978). Resolution of the two sites by Eu(III) excitation spectroscopy: P. B. O'Hara, R. Bersohn, *Biochemistry* **21,** 5269 (1982). N-Terminal amino acid sequence of human serum transferrin: M.-H. Metz-Boutigue *et al.*, *Biochim. Biophys. Acta* **670,** 243 (1981). Absorption max of human serum Fe^{3+}-transferrin: about 465 nm ($E^{1\%}_{1cm}$ 0.57); uv max: 280 nm ($E^{1\%}_{1cm}$ 14.3).

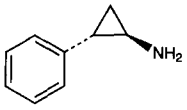
Conalbumin. Ovotransferrin; Diarconal. Isolated from egg white; distinguished from ovalbumin by its lower thermal coagulation point: Osborne, Campbell, *J. Am. Chem. Soc.* **22,** 422 (1900). Sepn from other egg-white proteins: Longworth *et al.*, *ibid.* **62,** 2580 (1940). Primary structure of hen ovotransferrin: J. Williams *et al.*, *Eur. J. Biochem.* **122,** 297 (1982). Purification, characterization and function of the iron-binding fragments: W.-M. Keung *et al.*, *J. Biol. Chem.* **257,** 1177, 1184 (1982). Antibacterial activity: P. Valenti *et al.*, *Antimicrob. Agents Chemother.* **21,** 840 (1982). Absorption max of Fe^{3+}-complex: 470 nm ($E^{1\%}_{1cm}$ 0.62).

Lactoferrin. Lactotransferrin. Important component of the human milk bacteriostatic system; also found in human and bovine tear proteins. Isoln from human whey by a single chromatographic step: L. Bläckberg, O. Hernell, *FEBS Lett.* **109,** 180 (1980). Sequential purification of lactoferrin, lysozyme, and secretory IgA from human milk: M. Boesman-Finkelstein, R. A. Finkelstein, *ibid.* **144,** 1 (1982). Partial C-terminal amino acid sequence of human lactoferrin: M.-H. Metz-Boutigue *et al.*, *ibid.* **142,** 107 (1982).

9572. Transforming Growth Factor-β. TGF-β. Family of multifunctional cytokines that regulate cellular differentiation, motility and growth. Also regulate the synthesis and deposition of the extracellular matrix. Involved in various physiological processes including embryogenesis, immunoregulation, bone remodeling and wound healing. Secreted by virtually all cell types as a biologically inactive (latent) form which is stored at the cell surface and in the extracellular matrix. The mature, active cytokine is a homodimer; mol wt 25 kDa. At least 5 isoforms have been identified. The three

mammalian isoforms (TGF-β_1, β_2, and β_3) exhibit 70-80% sequence homology, bind to the same receptors and exert similar biological effects. TGF-β_1 is the most abundant. Biological effects are mediated by binding to membrane receptors that exist on virtually all cells. Released from degranulating platelets at the site of a wound, TGF-β initiates angiogenesis and collagen synthesis. Acts as a chemoattractant and activator of macrophages and fibroblasts. Dysregulation is implicated in the pathogenesis of fibrotic diseases. Inhibits the growth of most epithelial and lymphoid cells. Escape from this normal control mechanism is implicated in carcinogenic transformation. Initial description: J. E. DeLarco, G. J. Todaro, *Proc. Natl. Acad. Sci. USA* **75,** 4001 (1978). Crystal structure of TGF-β_2: S. Daopin *et al., Science* **257,** 369 (1992). Review of physiological actions: A. B. Roberts, M. B. Sporn, *Growth Factors* **8,** 1-9 (1993); of latent forms, binding proteins and receptors: K. Miyazono *et al., ibid.,* 11-22. Proposed mechanisms for tumor cell transformation: M. J. Newman, *Cancer Metastasis Rev.* **12,** 239-254 (1993). Role in embryogenesis: N. L. McCartney-Francis, S. M. Wahl, *J. Leukocyte Biol.* **55,** 401-409 (1994); in tissue fibrosis: W. A. Border, N. A. Noble, *N. Engl. J. Med.* **331,** 1286-1292 (1994); in kidney disease: K. Sharma, F. N. Ziyadeh, *Am. J. Physiol.* **266,** F829-F842 (1994). Review of potential clinical applications in oncology: J. Kekow, G. J. Wiedemann, *Int. J. Oncol.* **7,** 177-182 (1995).

9573. Tranylcypromine. [155-09-9] (1*R*,2*S*)-*rel*-2-Phenylcyclopropanamine; SKF-385. $C_9H_{11}N$; mol wt 133.19. C 81.16%, H 8.32%, N 10.52%. Monoamine oxidase inhibitor. Prepn: Burger, Yost, *J. Am. Chem. Soc.* **70,** 2198 (1948); R. E. Tedeschi, **US 2997422** (1961 to SK & F).



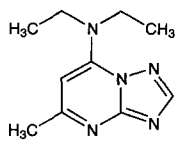
Liquid, $bp_{1.5-1.6}$ 79-80°.

Hydrochloride. $C_9H_{11}N.HCl$. Crystals from ethyl acetate + ether, mp 164-166°.

Sulfate. [13492-01-8] Parnate; Tylciprine. $(C_9H_{11}N)_2.H_2SO_4$; mol wt 364.46. Crystals, sol in water; very slightly sol in alcohol, ether. Practically insol in chloroform.

THERAP CAT: Antidepressant.

9574. Trapidil. [15421-84-8] *N,N*-Diethyl-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine; 7-diethylamino-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine; trapymin; AR-12008; Avantrin; Rocornal. $C_{10}H_{15}N_5$; mol wt 205.26. C 58.51%, H 7.37%, N 34.12%. First triazolopyrimidine registered as a drug. Prepn: E. Tenor *et al.,* **DD 55956** (1967), *C.A.* **67,** 90830f (1967); E. Tenor, R. Ludwig, *Pharmazie* **26,** 534 (1971). Physical and chemical properties: S. Pfeifer *et al., ibid.* 539. Pharmacology and toxicology: H. Fuller *et al., ibid.* 554. Metabolic studies: S. Pfeifer *et al., ibid.* 549; *ibid.* **27,** 752 (1972); I. Bornschein *et al., ibid.* **33,** 51 (1978). Mechanism of action: K. Satoh *et al., Arzneim.-Forsch.* **30,** 1264 (1980). Antiarrhythmic activities in rabbits: M. Sakanashi *et al., ibid.* **33,** 215 (1983). Clinical hemodynamic effects: M. Di Donato *et al., ibid.* **35,** 1295 (1985). GC determn in biological fluids: A. Marzo *et al., ibid.* **37,** 947 (1987).



White to yellowish, odorless and bitter crystalline powder, mp 98-99.4° (Pfeifer); 102-104° from heptane (Tenor). Eutectic temp of mixture with azobenzene: 48°. Very sol in water, 1*N* sulfuric acid, 10% ammonium hydroxide; easily sol in methanol, isopropanol, *n*-butanol, chloroform and benzene; sol in ether. Practically insol in hexane, heptane. $pK_a = 2.79$. uv max (methanol): 222, 270, 307 nm (log ε 4.28, 3.83, 4.28). Very stable except under extremely alk conditions. LD_{50} in mice, rats (mg/kg): 115, 76 i.v.; 380, 235 orally; 155, 100 i.p.; 132, 100 s.c. (Fuller).

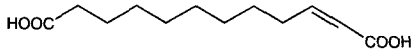
Hydrochloride. $C_{10}H_{15}N_5.HCl$. mp 212°.

THERAP CAT: Vasodilator (coronary).

9575. Trastuzumab. [180288-69-1] Anti-(human p185*neu* receptor) immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ_1-chain) disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer; rhuMab HER2; Herceptin. Humanized monoclonal antibody directed against the protein product of the HER2/*neu* oncogene which is homologous to the human epidermal growth factor receptor and is overexpressed by certain tumor cells. Constructed by inserting the antigen binding regions of murine monoclonal antibody 4D5 into the framework of a consensus human immunoglobulin G_1. Prepn: R. M. Hudziak *et al.,* **WO 8906692**; *eidem,* **US 5677171** (1989, 1997 both to Genentech); P. Carter *et al., Proc. Natl. Acad. Sci. USA* **89,** 4285 (1992). Analysis by capillary electrophoresis: G. Hunt *et al., J. Chromatogr. A* **744,** 295 (1996). Clinical evaluation in combination with cisplatin in breast cancer: M. D. Pegram *et al., J. Clin. Oncol.* **16,** 2659 (1998). Review of clinical efficacy: G. N. Hortobagyi, *Semin. Oncol.* **28,** Suppl. 18, 43-47 (2001); of clinical safety and tolerability in breast cancer: S. Rueckert *et al., Expert Opin. Biol. Ther.* **5,** 853-866 (2005).

THERAP CAT: Antineoplastic.

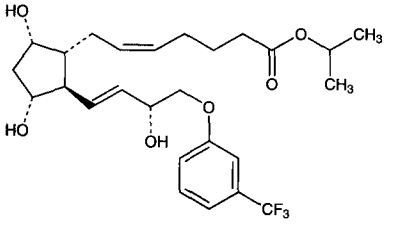
9576. Traumatic Acid. [6402-36-4] 2-Dodecenedioic acid; 1-decene-1,10-dicarboxylic acid. $C_{12}H_{20}O_4$; mol wt 228.28. C 63.14%, H 8.83%, O 28.03%. A wound hormone of plants. Isoln from pods of green beans: English *et al., Proc. Natl. Acad. Sci. USA* **25,** 323 (1939). The naturally occurring traumatic acid is the *trans*-form. Synthesis of the *trans*-form: *eidem, J. Am. Chem. Soc.* **61,** 3434 (1939); **US 2339259** (1944); **US 2391824** (1945); Truscheit, Eiter, *Ann.* **658,** 86 (1962); Dolezal, *Collect. Czech. Chem. Commun.* **35,** 1932 (1970); Schreurs *et al., Recl. Trav. Chim. Pays-Bas Belg.* **90,** 1331 (1971); Prakasa Rao, Nayak, *Synthesis* **1975,** 608; J. H. Babler, R. K. Moy, *Synth. Commun.* **9,** 669 (1979). Synthesis of the *cis*-form: Lauer, Gensler, *J. Am. Chem. Soc.* **67,** 1171 (1945).



***trans*-Form.** Crystals from alc, acetone, or 1,2-dimethoxyethane, mp 166-167°. $bp_{0.001}$ 150-160°. Very sparingly sol in water; sol in alc, ether, benzene, chloroform.

***cis*-Form.** Crystals from ethyl acetate and petr ether, mp 67-68°.

9577. Travoprost. [157283-68-6] (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester; (+)-16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester; (+)-9α,11α,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-*cis*-13-*trans*-prostadienoic acid isopropyl ester; AL-6221; Travatan. $C_{26}H_{35}F_3O_6$; mol wt 500.55. C 62.39%, H 7.05%, F 11.39%, O 19.18%. Selective FP prostaglandin receptor agonist. Isopropyl ester of (+)-fluprostenol, *q.v.* General prepn (not claimed): J. W. Stjernschantz, **EP 364417** (1989 to Pharmacia). Large scale synthesis: L. T. Boulton *et al., Org. Process Res. Dev.* **6,** 138 (2002). Pharmacology: M. R. Hellberg *et al., J. Ocul. Pharmacol. Ther.* **17,** 421 (2001). LC/MS/MS determn in plasma: B. A. McCue *et al., J. Pharm. Biomed. Anal.* **28,** 199 (2002). Ocular hypotensive effects in dogs: A. B. Carvalho *et al., Vet. Ophthalmol.* **9,** 121 (2006). Clinical trial in glaucoma or ocular hypertension: R. L. Fellman *et al., Ophthalmology* **109,** 998 (2002); in combination with timolol: J. S. Schuman *et al., Am. J. Ophthalmol.* **140,** 242-250 (2005).

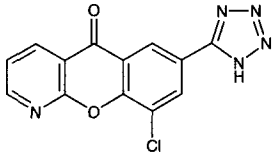


Colorless oil. $[\alpha]_D^{20}$ +14.6° (c = 1.0 in methylene chloride). Very sol in acetonitrile, methanol, octanol, chloroform. Practically insol in water.

THERAP CAT: Antiglaucoma.

THERAP CAT (VET): Antiglaucoma.

9578. Traxanox. [58712-69-9] 9-Chloro-7-(1*H*-tetrazol-5-yl)-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one; 9-chloro-7-(5-1*H*-tetrazolyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine. $C_{13}H_6ClN_5O_2$; mol wt 299.67. C 52.10%, H 2.02%, Cl 11.83%, N 23.37%, O 10.68%. Antiallergic agent which selectively inhibits release of allergic mediators from mast cells. Prepn: T. Oe, M. Tsuruda, **DE 2521980**; *eidem*, **US 4085111** (1975, 1978 both to Yoshitomi). Antianaphylactic activity in animals: K. Goto *et al.*, *Jpn. J. Pharmacol.* **30,** 537 (1980). Mechanism of action study: K. Goto *et al.*, *Int. Arch. Allergy Appl. Immunol.* **68,** 332 (1982). Clinical pharmacology and pharmacokinetics: A. Ebihara *et al.*, *Arzneim.-Forsch.* **37,** 1388 (1987). Metabolism in humans: M. Tateno *et al.*, *Yakuri to Chiryo* **16,** 3251 (1988), *C.A.* **110,** 18040n (1989).

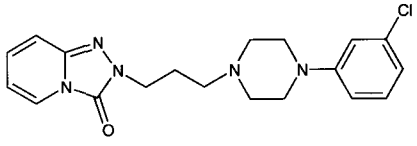


mp >300°.

Sodium salt pentahydrate. Y-12141; Clearnal. $C_{13}H_5ClN_5NaO_2.5H_2O$; mol wt 411.73.

THERAP CAT: Antiallergic; antiasthmatic.

9579. Trazodone. [19794-93-5] 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one. $C_{19}H_{22}ClN_5O$; mol wt 371.86. C 61.37%, H 5.96%, Cl 9.53%, N 18.83%, O 4.30%. Prepn: Palazzo, Silvestrini, **US 3381009** (1968 to Angelini Francesco). Pharmacology: Catanese, Lisciani, *Boll. Chim. Farm.* **109,** 369 (1970); B. Silvestrini, E. Quadri, *Eur. J. Pharmacol.* **12,** 231 (1970). Analytical data: Baiocchi *et al.*, *Arzneim.-Forsch.* **23,** 400 (1973). Crystal structure: J. P. Fillers, S. W. Hawkinson, *Acta Crystallogr.* **B35,** 498 (1979). Review of pharmacological properties and therapeutic use: R. N. Brogden *et al.*, *Drugs* **21,** 401-429 (1981); B. Silvestrini *et al.*, in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 3,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1981) pp 94-119. Comprehensive description: D. Gorecki, R. Verbeeck, *Anal. Profiles Drug Subs.* **16,** 693-729 (1986). Symposium on clinical efficacy: *Psychopharmacology* **95,** Suppl., 1-56 (1988).

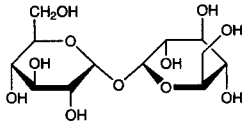


Crystals, mp 86-87°. Also reported as mp 96° (Baiocchi). pKa (50% ethanol): 6.14.

Hydrochloride. [25332-39-2] AF-1161; Bimaran; Desyrel; Molipaxin; Pragmazone; Thombran; Tombran; Trazolan; Trittico. $C_{19}H_{22}ClN_5O.HCl$; mol wt 408.32. White, odorless plates from ethanol, mp 223°. Soluble in chloroform; sparingly sol in water, ethanol, methanol. Practically insol in common organic solvents. uv max (water): 211, 246, 274, 312 nm (ε 50100, 11730, 3840, 3840). LD_{50} *i.v. in mice:* 96 mg/kg (Silvestrini, Quadri).

THERAP CAT: Antidepressant.

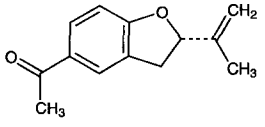
9580. Trehalose. [99-20-7] α-D-Glucopyranosyl-α-D-glucopyranoside; mushroom sugar; mycose; α,α-trehalose. $C_{12}H_{22}O_{11}$; mol wt 342.30. C 42.11%, H 6.48%, O 51.41%. Non-reducing disaccharide found in fungi, bacteria, yeasts, and insects; 45% as sweet as sucrose. Provides the energy source for flight in many insects. Incorporated into mycobacterial structural glycolipids such as cord factors, *q.v.* Isoln from the ergot of rye: H. A. L. Wiggers, *Ann.* **1** 129 (1832). Prepn and review of early history: T. S. Harding, *Sugar* **25,** 476-478 (1923). Isoln from yeast: E. M. Koch, F. C. Koch, *Science* **61,** 570 (1925); L. C. Stewart *et al.*, *J. Am. Chem. Soc.* **72,** 2059 (1950). Synthesis: Lemieux, Bauer, *Can. J. Chem.* **32,** 340 (1954). Crystal structure: G. A. Jeffrey, R. Nanni, *Carbohydr. Res.* **137,** 21 (1985). Review of metabolism: A. D. Elbein, *Adv. Carbohydr. Chem. Biochem.* **30,** 227-256 (1974). *In vitro* evaluation in cryopreservation of human oocytes: A. Eroglu *et al.*, *Fertil. Steril.* **77,** 152 (2002). Use in freeze-drying human platelets: W. F. Wolkers *et al.*, *Cryobiology* **42,** 79 (2001); *eidem, Cell Preservation Technol.* **1,** 175 (2003). Review of properties, toxicity and safety studies: A. B. Richards *et al.*, *Food Chem. Toxicol.* **40,** 871-898 (2002); of stabilizing functions and applications: T. Higashiyama, *Pure Appl. Chem.* **74,** 1263-1269 (2002).



Dihydrate. [6138-23-4] Orthorhombic, bisphenoidal crystals from dil alcohol. Sweet taste. mp 96.5-97.5°. The water of crystn escapes around 130°. Anhydrous trehalose melts at 203°. $[\alpha]_D^{20}$ +178° (c = 7 of the dihydrate). Sol in water, hot alcohol. Insol in ether. Does not reduce Fehling's soln. Is fermented by yeast. Is not split by α-glucosidase. Acid hydrolysis gives 2 mols D-glucose.

USE: Stabilizes cells during freezing, freeze-drying and air-drying. Sweetener and stabilizer in foods; cryoprotectant for freeze-dried foods. Additive in cosmetics and personal care products.

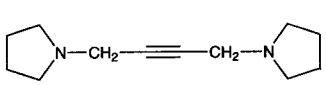
9581. Tremetone. [4976-25-4] 1-[2,3-Dihydro-2-(1-methylethenyl)-5-benzofuranyl]ethanone; 2,3-dihydro-2-isopropenyl-5-benzofuranyl methyl ketone; 2-isopropenyl-2,3-dihydro-5-acetylbenzofuran. $C_{13}H_{14}O_2$; mol wt 202.25. C 77.20%, H 6.98%, O 15.82%. Principal ketone suspected of being the active toxin of *Eupatorium urticaefolium* Reichard, *Compositae* (white snakeroot). Isoln and structure: Bonner, DeGraw, *Tetrahedron* **18,** 1295 (1962). Synthesis of dihydrotremetone: DeGraw, Bonner, *ibid.* 1311. Synthesis of racemic tremetone: DeGraw *et al.*, *ibid.* **19,** 19 (1963); Bohlmann, Buehmann, *Ber.* **105,** 863 (1972). Abs config: Bonner *et al.*, *Tetrahedron* **20,** 1419 (1964). *Review:* Christensen, *Econ. Bot.* **19,** 293-300 (1965).



Liquid. $[\alpha]_D^{28}$ −59.6° (c = 5.52 in absolute ethanol). n_D^{25} 1.5658. d_4^{28} 1.080. uv max (ethanol): 227, 280, 285 nm (ε 11,950, 12,600, 12,300).

Dihydrotremetone. (*R*)-1-[2,3-Dihydro-2-(1-methylethyl)-5-benzofuranyl]ethanone. $C_{13}H_{16}O_2$. Liquid. bp 216-221°. $[\alpha]_D^{25}$ −47.0° (c = 1.78 in abs ethanol). uv max (ethanol): 231, 279 nm (ε 39,500; 18,800).

9582. Tremorine. [51-73-0] 1,1′-(2-Butyne-1,4-diyl)bispyrrolidine; 1,1′-(2-butynylene)dipyrrolidine; 1,4-dipyrrolidino-2-butyne. $C_{12}H_{20}N_2$; mol wt 192.30. C 74.95%, H 10.48%, N 14.57%. Prepn from pyrrolidine + 1,4-dichloro-2-butyne: Maier, **DE 896810** (1953 to BASF); Reppe *et al.*, *Ann.* **596,** 79 (1955); Biel, DiPierro, *J. Am. Chem. Soc.* **80,** 4609 (1958). Review of chemical and biological studies: Karlen, *Acta Pharm. Suec.* **1970,** 169-200; *see also* Kolla, Obvintseva, *Farmakol. Toksikol.* **36,** 736-745 (1973).

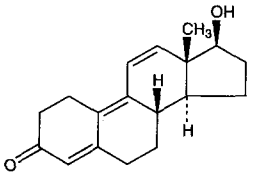


Liquid. $bp_{2.5}$ 116-116.5°; $bp_{0.1}$ 93-95°.

Methiodide. $C_{12}H_{20}N_2.2CH_3I$. Crystals, mp 239-240°.

USE: To produce exptl parkinsonism: Everett *et al.*, *Science* **124,** 79 (1956).

9583. Trenbolone. [10161-33-8] (17β)-17-Hydroxyestra-4,9,11-trien-3-one; 4,9,11-estratrien-17β-ol-3-one; 17β-hydroxy-19-norandrosta-4,9,11-trien-3-one; 19-norandrosta-4,9,11-trien-17β-ol-3-one; trienbolone; trienolone. $C_{18}H_{22}O_2$; mol wt 270.37. C 79.96%, H 8.20%, O 11.84%. Prepn of base: Velluz *et al., C.R. Hebd. Seances Acad. Sci.* **257,** 569 (1963); Heller *et al., Steroids* **10,** 211 (1967). Base and 17-acetate: **FR M1958** and **GB 1035683** (1963 and 1966 to Roussel-UCLAF), *C.A.* **60,** 3039h (1964); **65,** 17027c (1966). 17-Cyclohexylmethylcarbonate: Nedelec, Costerousse, **FR M5979** (1968 to Roussel-UCLAF), *C.A.* **71,** 50356g (1969). Pharmacology of the acetate: Krüskemper *et al., Arzneim.-Forsch.* **17,** 449 (1967). Animal studies: Beranger, Malterre, *C.R. Seances Soc. Biol. Ses Fil.* **162,** 1157 (1968); Best, *Vet. Rec.* **91,** 624 (1972). Environmental degradation study: B. Schiffer *et al., Environ. Health Perspect.* **109,** 1145 (2001).



Crystals, mp 186°. $[\alpha]_D^{20}$ +19° (c = 0.45 in ethanol). Also reported as mp 183-186° from acetone-water. uv max: 239, 340.5 nm (ε 5260, 28000) (Heller).

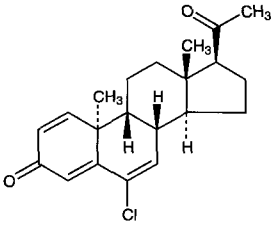
Acetate. [10161-34-9] (17β)-17-Acetyloxyestra-4,9,11-trien-3-one; 17β-acetoxy-3-oxoestra-4,9,11-triene; 17β-acetoxyestra-4,9,11-trien-3-one; Finaplix; Parabolan. $C_{20}H_{24}O_3$; mol wt 312.40. Crystals, mp 96-97°. $[\alpha]_D^{20}$ +36.8° (c = 0.37 in methanol).

Cyclohexylmethylcarbonate. [23454-33-3] (17β)-17-[(cyclohexylmethoxy)carbonyl]oxyestra-4,9,11-trien-3-one; trenbolone hexahydrobenzylcarbonate. $C_{26}H_{34}O_4$; mol wt 410.55. Crystals from cyclohexane-petr ether, mp 90-95°. $[\alpha]_D^{20}$ +41.6° (c = 0.5 in ethanol).

Note: This is a controlled substance (anabolic steroid): **21 CFR,** 1308.13, as defined in 1300.01.

THERAP CAT (VET): Anabolic.

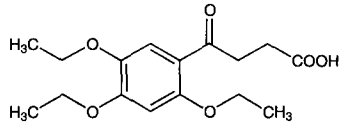
9584. Trengestone. [5192-84-7] (9β,10α)-6-Chloropregna-1,4,6-triene-3,20-dione; 6-chloro-1,6-didehydroretroprogesterone; 6-chloro-1,6-bisdehydroretroprogesterone; Ro-4-8347; Retroid. $C_{21}H_{25}ClO_2$; mol wt 344.88. C 73.13%, H 7.31%, Cl 10.28%, O 9.28%. A member of a class of hormonally active steroids termed "retrosteroids", which are characterized by a (9β, 10α)-configuration in contrast to the usual (9α,10β)-configuration of steroids. Prepn: Threadgold, **BE 652597** corresp to Reerink *et al.,* **US 3422122** (1965, 1969 to Phillips). Activity studies: Sadovsky *et al., Gynecol. Invest.* **1,** 319 (1970); Kalra *et al., J. Endocrinol.* **51,** 675 (1971). Metabolism: Breuer *et al., Acta Endocrinol.* **74,** 127 (1973); Dixon *et al., Steroids* **22,** 35 (1973).



Crystals from acetone, mp 208-209° (dec). uv max: 229, 253, 302 nm (ε 11500, 10520, 10650).

THERAP CAT: Progestogen.

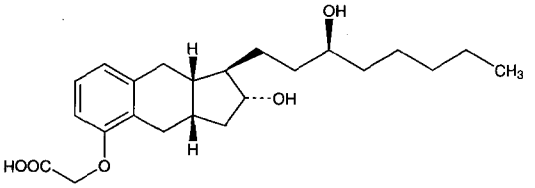
9585. Trepibutone. [41826-92-0] 2,4,5-Triethoxy-γ-oxobenzenebutanoic acid; 3-(2,4,5-triethoxybenzoyl)propionic acid; AA-149; Supacal. $C_{16}H_{22}O_6$; mol wt 310.34. C 61.92%, H 7.15%, O 30.93%. Prepn: T. Murata *et al.,* **DE 2244324** corresp to **US 3943169** (1973, 1976 both to Takeda). Properties and stabilities: M. Mitani *et al., Takeda Kenkyushoho* **36,** 206 (1977), *C.A.* **88,** 126284f (1978). Pharmacokinetics: *eidem, ibid.* 215, *C.A.* **88,** 115067m (1978). Biotransformation: T. Kobayashi *et al., Xenobiotica* **8,** 535 (1978). Metabolism studies: S. Tanayama *et al., ibid.* 365, 377. Spasmolytic action in dogs: H. Satoh *et al., Eur. J. Pharmacol.* **48,** 309 (1978). Mechanism of choleretic action: *eidem, ibid.* 125. Toxicity studies: S. Sato *et al., Takeda Kenkyushoho* **36,** 263 (1977), *C.A.* **88,** 11535x (1978).



Colorless needles from aq ethanol or plates from aq acetone, mp 150-151°. Stable to heat, humidity, indoor diffused sunlight. Aq solns heated to 100° for 10 hr showed no degradation.

THERAP CAT: Choleretic; antispasmodic.

9586. Treprostinil. [81846-19-7] [[(1*R*,2*R*,3a*S*,9a*S*)-2,3,-3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz-[*f*]inden-5-yl]oxy]acetic acid; 9-deoxy-2′,9α-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-interphenylene)-13,14-dihydroprostaglandin F_1. $C_{23}H_{34}O_5$; mol wt 390.51. C 70.74%, H 8.78%, O 20.49%. Synthetic analog of prostacyclin, *q.v.* Prepn: P. A. Aristoff *et al.,* **GB 2070596**; *idem,* **US 4306075** (both 1981 to Upjohn). Pharmacology: R. P. Steffen, M. de la Mata, *Prostaglandins Leukotrienes Essen. Fatty Acids* **43,** 277 (1991). Pharmacokinetics: M. J. McNulty *et al., ibid.* 159; of intravenous and subcutaneous administration: K. Laliberte *et al., J. Cardiovasc. Pharmacol.* **44,** 209 (2004). RIA determn in plasma: J. W. A. Findlay *et al., ibid.* 167. Clinical study in pulmonary arterial hypertension: G. Simonneau *et al., Am. J. Respir. Crit. Care Med.* **165,** 800 (2002); by s. c. infusion: R. J. Oudiz *et al., Chest* **126,** 420 (2004); by continuous i.v.: V. F. Tapson *et al., ibid.* **129,** 683 (2006).

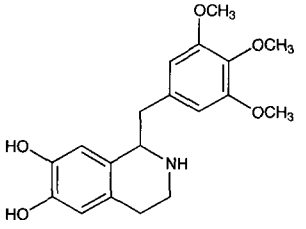


Crystals from ethyl acetate in hexane, mp 121-123°.

Sodium salt. [289480-64-4] 15AU81; BW15AU; U-62840; UT-15; Remodulin. $C_{23}H_{33}NaO_5$; mol wt 412.49.

THERAP CAT: Antihypertensive.

9587. Tretoquinol. [21650-42-0] 1,2,3,4-Tetrahydro-1-[(3,4,5-trimethoxyphenyl)methyl]-6,7-isoquinolinediol; 1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; trimethoquinol. $C_{19}H_{23}NO_5$; mol wt 345.39. C 66.07%, H 6.71%, N 4.06%, O 23.16%. Synthesis of *dl*-form: Yamato *et al., Tetrahedron Suppl.* **8,** 129 (1966). Pharmacology: Fogelman, Grundy, *Br. J. Pharmacol.* **38,** 416 (1970). Metabolic studies: Meshi *et al., Biochem. Pharmacol.* **19,** 2937 (1970); Satoh *et al., Chem. Pharm. Bull.* **19,** 667 (1971).



***dl*-Form hydrochloride.** [18559-63-2] Pale yellow crystals from methanol + ether, decomp 224.5-226°.

***l*-Form hydrochloride.** [18559-59-6] AQ-110; Inolin; Vems. $C_{19}H_{23}NO_5$.HCl; mol wt 381.85. Pale yellow crystals, freely sol in water; sol in alcohol.

THERAP CAT: Bronchodilator.