THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

FOURTEENTH EDITION

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(Springer, New York, 1967) 164 pp; Hulet, Bode, "Separation Chemistry of the Lanthanides and Transplutonium Actinides" in *MTP Int. Rev. Sci.: Inorg. Chem., Ser. One* **vol. 7,** K. W. Bagnall, Ed. (University Park Press, Baltimore, 1972) pp 1-45; Moeller, "The Lanthanides" in *Comprehensive Inorganic Chemistry* **vol. 4,** J. C. Bailar, Jr. *et al.,* Eds. (Pergamon Press, Oxford, 1973) pp 1-101; F. H. Spedding in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 19** (John Wiley & Sons, New York, 3rd ed., 1982) pp 833-854; *Chemistry of the Elements*, N. N. Greenwood, A. Earnshaw, Eds. (Pergamon Press, New York, 1984) pp 1423-1449. Brief review of properties: G. T. Seaborg, *Radiochim. Acta* **61,** 115-122 (1993).

Body-centered cubic crystal lattice; d 5.244; mp 826°. bp 1429°. Heat of fusion: 9.221 kJ/mol. Heat of sublimation (25°): 144.7 kJ/mol. Sol in liq ammonia. Shows two reduction potentials −0.710 and −2.510 v. (referred to a normal calomel electrode): Noddack, Brukl, *Angew. Chem.* **50,** 362 (1937); gives two definite series of salts, in one the metal is divalent, and in the other it is trivalent.

Sesquioxide. Europia. Eu_2O_3. Pink powder, d 7.42, prepd by heating the hydroxide, nitrate, oxalate or sulfate at 1600°. The oxide of the divalent metal is prepd by reduction of the sesquioxide at elevated temp.

Hydroxide. $Eu(OH)_3$. Prepd by adding ammonia or an alkali hydroxide to a soln of an europic salt.

Europic chloride. $EuCl_3$. Greenish-yellow needles; mp 623° in nitrogen (in a closed tube), d^{35} 4.471, prepd by passing sulfur chloride over the heated oxide at 200-500°. LD_{50} of trichloride in mice: 550 mg/kg i.p.; 5 g/kg orally (Haley).

Europous chloride. $EuCl_2$. Prepd by reduction of $EuCl_3$ with hydrogen at 600°. White amorphous powder, sol in water.

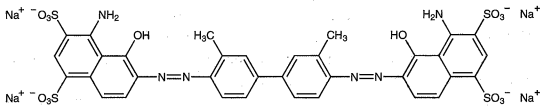
Europic sulfate. $Eu_2(SO_4)_3$. Octahydrate, a pinkish cryst solid, prepd by dissolving the oxide in sulfuric acid. Soly in water: 2.56 parts per 100 parts at 20°, 1.93 parts per 100 parts at 40°. On heating at 375° yields the anhydr sulfate.

Europic nitrate. $Eu(NO_3)_3$. Hexahydrate, mp 85° in its water of crystallization (sealed tube). LD_{50} in rats (mg/kg): 210 i.p.; >5000 orally (Haley).

Europous sulfate. $EuSO_4$. Colorless crystals. Insol in water and in dil acids. Prepd by electrolytic reduction of europic salts.

USE: The salts in cathode ray tube coatings for color television receivers. Eu has a very high cross-section for the capture of thermal neutrons which is of value in the construction of electric atomic power stations. Organic derivs as shift reagents in NMR spectroscopy: C. C. Hinckley, *J. Am. Chem. Soc.* **91,** 5160 (1969); R. E. Sievers, *Nuclear Magnetic Resonance Shift Reagents* (Academic Press, New York, 1973).

3905. Evan's Blue. [314-13-6] 6,6′-[(3,3′-Dimethyl[1,1′-biphenyl]-4,4′-diyl)bis(azo)]bis[4-amino-5-hydroxy-1,3-naphthalenedisulfonic acid] tetrasodium salt; C.I. Direct Blue 53; 4,4′-bis[7-(1-amino-8-hydroxy-2,4-disulfo)naphthylazo]-3,3′-bitolyl tetrasodium salt; C.I. 23860; T-1824; Azovan Blue. $C_{34}H_{24}N_6Na_4O_{14}S_4$; mol wt 960.81. C 42.50%, H 2.52%, N 8.75%, Na 9.57%, O 23.31%, S 13.35%. Prepd by coupling 1 mol of diazotized *o*-tolidine with 2 mols of Chicago acid (1-amino-8-naphthol-2,4-disulfonic acid): **DE 35341**; **DE 38802** *Frdl.* **1,** 469, 488 (1877-1887); **DE 3949**; **DE 57327**; **DE 75469** *Frdl.* **3,** 685, 687, 690 (1890-1894); Hartwell, Fieser, *Org. Synth.* **coll. vol. II,** 145 (1943). Diagnostic use: M. H. Nielsen, N. C. Nielsen, *Scand. J. Clin. Lab. Invest.* **14,** 605 (1962); O. Linderkamp *et al., Eur. J. Pediatr.* **125,** 135 (1977).



Blue crystals with bronze to green luster. Sol in water, alcohol, acids, alkalies. Indicator changing color near pH 10. Destroyed by strong oxidizing and reducing agents and precipitated from soln by strong concns of neutral salts. Rather stable in aq soln, and may be autoclaved at 15 lbs pressure for 30 min. Dye made up in physiological saline should not be autoclaved.

THERAP CAT: Diagnostic aid (blood volume determination).

3906. Evening Primrose Oil. EPO. Seed oil of the evening primrose, *Oenothera biennis* L., *Onagraceae,* which contains approx 72% linoleic acid and approx 9% γ-linolenic acid, *q.q.v.*, as the two main constituents. Unique among vegetable oils because of its high content of γ-linolenic acid. Effect on prostaglandin biosynthesis in rats: B. A. Schölkens *et al., Prostaglandins Leukotrienes Med.* **8,** 273 (1982). Clinical studies in atopic eczema: C. R. Lovell *et al., Lancet* **1,** 278 (1981); S. Wright, J. L. Burton, *ibid.* **2,** 1120 (1982); P. L. Biagi *et al., Drugs Exp. Clin. Res.* **14,** 285 (1988). Ingredient in cosmetics for aging skin: J. P. Marty, **DE 3447618** (1985 to Roussel-UCLAF), *C.A.* **103,** 146984r (1985). Brief review including discussion of uses: A. J. Barber, *Pharm. J.* **240,** 723-725 (1988).

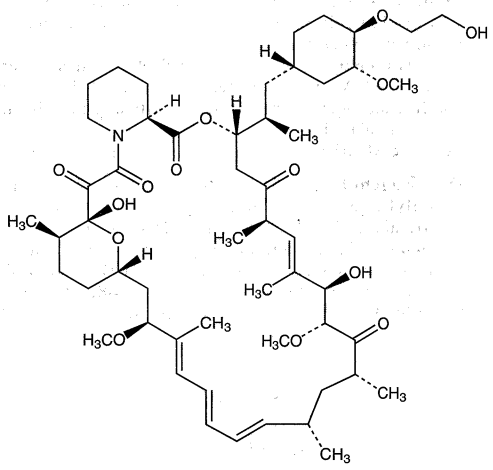
Clear, golden yellow oil. d_{15} 0.9283. n_D^{25} 1.4782. Sapon. no. 287.8. Iodine no. 154.8.

Note: Evening primrose oil products include ***Efamol***, ***Efamast***, ***Epogam***.

USE: Dietary supplement.

THERAP CAT: In treatment of atopic eczema and mastaglia.

3907. Everolimus. [159351-69-6] 42-*O*-(2-Hydroxyethyl)-rapamycin; 40-*O*-(2-hydroxyethyl)rapamycin; RAD-001; SDZ RAD; Certican. $C_{53}H_{83}NO_{14}$; mol wt 958.22. C 66.43%, H 8.73%, N 1.46%, O 23.38%. Macrolide immunosuppressant; derivative of rapamycin, *q.v.* Inhibits cytokine-mediated lymphocyte proliferation. Prepn: S. Cottens, R. Sedrani, **WO 9409010**; *eidem,* **US 5665772** (1994, 1997 both to Sandoz). Pharmacology: W. Schuler *et al., Transplantation* **64,** 36 (1997). Whole blood determn by LC/MS: N. Brignol *et al., Rapid Commun. Mass Spectrom.* **15,** 898 (2001); by HPLC: S. Baldelli *et al., J. Chromatogr. B* **816,** 99 (2005). Clinical pharmacokinetics in combination with cyclosporine: J. M. Kovarik *et al., Clin. Pharmacol. Ther.* **69,** 48 (2001). Clinical study in prevention of cardiac-allograft vasculopathy: H. J. Eisen *et al., N. Engl. J. Med.* **349,** 847 (2003). *Review:* F. J. Dumont *et al., Curr. Opin. Invest. Drugs* **2,** 1220-1234 (2001); B. Nashan, *Ther. Drug Monit.* **24,** 53-58 (2002).



THERAP CAT: Immunosuppressant.

3908. Evodiamine. [518-17-2] 8,13,13b,14-Tetrahydro-14-methylindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one. $C_{19}H_{17}N_3O$; mol wt 303.36. C 75.23%, H 5.65%, N 13.85%, O 5.27%. From *Evodia rutaecarpa* Hook. & Thoms and bark of *Zanthoxylum rhetsa* DC., *Rutaceae:* Y. Asahina, K. Kashiwaki, *J. Pharm. Soc. Jpn.* **1915,** 1293, *C.A.* **10,** 607 (1916); Gopinath *et al., Tetrahedron* **8,** 293 (1960). Structure: Y. Asahina *J. Pharm. Soc. Jpn.* **1924,** 1; Ohta, *J. Pharm. Soc. Jpn.* **65,** 15 (1945), *C.A.* **45,** 5697 (1951). Synthesis: Asahina, Ohta, *Ber.* **61B,** 319 (1928); T. Kametani *et al., J. Am. Chem. Soc.* **98,** 6186 (1976); *eidem, Heterocycles* **4,** 23 (1976). Biosynthesis: M. Yamazaki *et al., Tetrahedron Lett.* **1966,** 3221; **1967,** 3317. Mass spec.: J. Tamas *et al., Acta Chim. Acad. Sci. Hung.* **89,** 85 (1976).

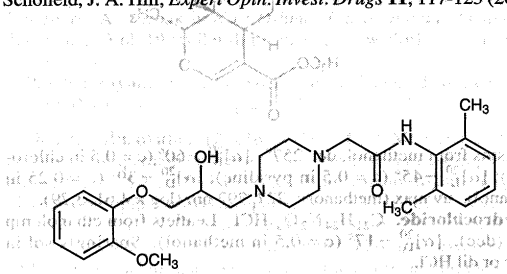
Solid, mp 69-70°.

Hydrochloride. [66357-59-3] AH-19065; Azantac; Melfax; Noctone; Raniben; Ranidil; Raniplex; Sostril; Taural; Terposen; Trigger; Ulcex; Ultidine; Zantac; Zantic. $C_{13}H_{22}N_4O_3S.HCl$; mol wt 350.86. Off-white solid, mp 133-134°. Freely sol in acetic acid and water, sol in methanol, sparingly sol in ethanol. Practically insol in chloroform.

Bismuth citrate. [128345-62-0] Ranitidine bismutrex; GR-122311X; Pylorid; Tritec. $C_{13}H_{22}N_4O_3S.C_6H_5BiO_7$; mol wt 712.48. Pharmacology and activity vs *Helicobacter* sp: R. Stables *et al., Aliment. Pharmacol. Ther.* **7,** 237 (1993).

THERAP CAT: Antiulcerative.

8111. Ranolazine. [95635-55-5] *N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide; (±)-4-[2-hydroxy-3-(*o*-methoxyphenoxy)propyl]-1-piperazineaceto-2′,6′-xylidide; (±)-1-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-4-[*N*-(2,6-dimethylphenyl)carbamoylmethyl]piperazine; Ranexa. $C_{24}H_{33}N_3O_4$; mol wt 427.54. C 67.42%, H 7.78%, N 9.83%, O 14.97%. Anti-ischemic agent which modulates myocardial metabolism. Prepn: A. F. Kluge *et al.*, **EP 126449**; *eidem*, US **4567264** (1984, 1986 both to Syntex). HPLC resolution of enantiomers: E. Delée *et al.*, *Chromatographia* **24,** 357 (1987). Clinical trial in angina: B. R. Chaitman *et al.*, *J. Am. Coll. Cardiol.* **43,** 1375 (2004). Review of pharmacology and clinical development: J. G. McCormack *et al.*, *Gen. Pharmacol.* **30,** 639-645 (1998); R. S. Schofield, J. A. Hill, *Expert Opin. Invest. Drugs* **11,** 117-123 (2002).



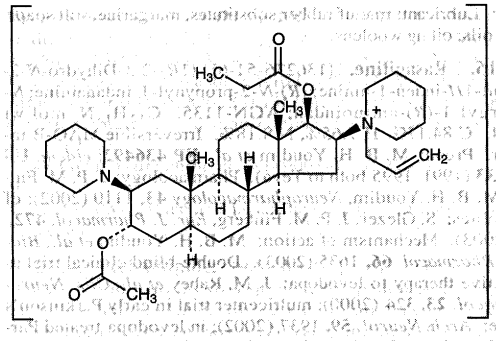
Dihydrochloride. [95635-56-6] RS-43285. $C_{24}H_{33}N_3O_4.2HCl$; mol wt 500.46. White crystalline powder from methanol/ether, mp 164-166°. Readily sol in water.

THERAP CAT: Antianginal.

8112. Ranpirnase. [133737-96-9] Ribonuclease (*Rana pipiens* reduced); P-30 protein; Onconase. Antitumor ribonuclease isolated from oocytes and early embryos of *Rana pipiens*. Single chain protein containing 104 amino acid residues; mol wt ~12 kDa. Description of cytotoxic activity: Z. Darzynkiewicz *et al.*, *Cell Tissue Kinet.* **21,** 169 (1988). Amino acid sequence and identification as a ribonuclease: W. Ardelt *et al.*, *J. Biol. Chem.* **266,** 245 (1991). Crystallization: S. C. Mosimann *et al.*, *Proteins: Struct. Funct. Genet.* **14,** 392 (1992). Mechanism of action: Y. Wu *et al.*, *J. Biol. Chem.* **268,** 10686 (1993). Prepn by recombinant technology: E. Notomista *et al.*, *FEBS Lett.* **463,** 211 (1999). Clinical trial in malignant mesothelioma: S. M. Mikulski *et al.*, *J. Clin. Oncol.* **20,** 274 (2002).

THERAP CAT: Antineoplastic.

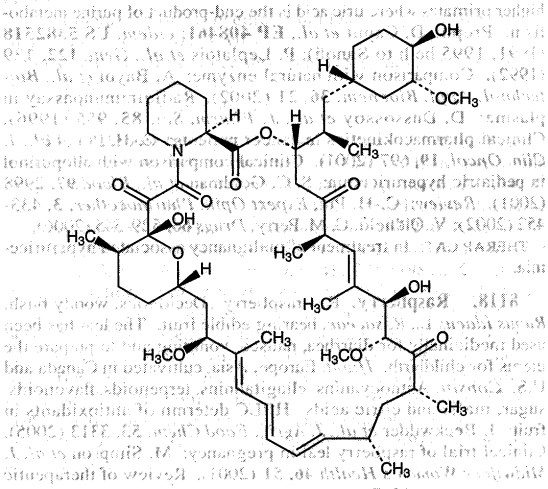
8113. Rapacuronium Bromide. [156137-99-4] 1-[(2β,3α,5α,16β,17β)-3-(Acetyloxy)-17-(1-oxopropoxy)-2-(1-piperidinyl)-androstan-16-yl]-1-(2-propenyl)piperidinium bromide; 1-allyl-2-(3α,17β-dihydroxy-2β-piperidino-5α-androstan-16β-yl)piperidinium bromide 3-acetate 17-propionate; Org-9487; Raplon. $C_{37}H_{61}N_2O_4.Br$; mol wt 677.80. C 65.56%, H 9.07%, N 4.13%, O 9.44%, Br 11.79%. Aminosteroid, competitive neuromuscular blocker. Prepn: T. Sleigh *et al.*, **CA 2094457**; *eidem*, **US 5418226** (both to Akzo). Clinical pharmacodynamics: P. M. C. Wright *et al.*, *Anesthesiology* **90,** 16 (1999). Clinical trial in pediatric patients: R. F. Kaplan *et al.*, *Anesth. Analg.* **89,** 1172 (1999). Review of pharmacology and use in endotracheal intubation: S. V. Onrust, R. H. Foster, *Drugs* **58,** 887-918 (1999).



Crystals from diethyl ether-acetone, mp 184°. $[\alpha]_D^{20}$ −12.7° (c = 1.01 in $CHCl_3$).

THERAP CAT: Neuromuscular blocking agent.

8114. Rapamycin. [53123-88-9] Sirolimus; RAPA; RPM; AY-22989; NSC-226080; Rapamune. $C_{51}H_{79}NO_{13}$; mol wt 914.17. C 67.01%, H 8.71%, N 1.53%, O 22.75%. Triene macrolide antibiotic isolated from *Streptomyces hygroscopicus*. Name derived from the native word for Easter Island, Rapa Nui. Isoln: S. N. Sehgal *et al.*, **DE 2347682**; *eidem*, **US 3929992** (1974, 1975 both to Ayerst McKenna Harrison); purification and characterization: C. Vézina *et al.*, *J. Antibiot.* **28,** 721 (1975); S. N. Sehgal *et al.*, *ibid.* 727. Inhibition of immune response: R. R. Martel *et al.*, *Can. J. Physiol. Pharmacol.* **55,** 48 (1977); of graft rejection in mice: C. P. Eng *et al.*, *Transplant. Proc.* **23,** 868 (1991). Total synthesis: K. C. Nicolaou *et al.*, *J. Am. Chem. Soc.* **115,** 4419 (1993); D. Romo *et al.*, *ibid.* 7906. Series of articles on therapeutic monitoring and pharmacokinetics: *Clin. Ther.* **22,** Suppl. 2, B1-B132 (2000); on pharmacology and clinical experience in transplantation: *Transplant. Proc.* **35,** Suppl. 1, S1-S233 (2003). Clinical trial in prevention of coronary restenosis: D. R. Holmes, Jr. *et al.*, *Circulation* **109,** 634 (2004).



Colorless crystalline solid from ether, mp 183-185°. uv max (95% ethanol): 267, 277, 288 nm ($E_{1cm}^{1\%}$ 417, 541, 416). $[\alpha]_D^{25}$ −58.2° (methanol). Sol in ether, chloroform, acetone, methanol and DMF; very sparingly sol in hexane and petr ether. Substantially insol in water. LD_{50} in mice (mg/kg): =600 i.p.; >2,500 orally (Vézina).

USE: Tool for immunochemistry.

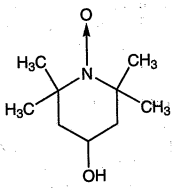
THERAP CAT: Immunosuppressant; antirestenotic.

8115. Rapeseed Oil. Colza oil. Oil expressed from seeds of *Brassica campestris* L., *Cruciferae*.

Pale yellow, rather viscid liq. d 0.913-0.917; n_D^{20} 1.4720-1.4752. Solidif −2° to −10°. Sapon no. 170-177. Iodine no. 97-105. Sol in chloroform, ether, CS_2.

USE: In organic chemistry as a radical trap, a catalyst and in polymerization mediation.

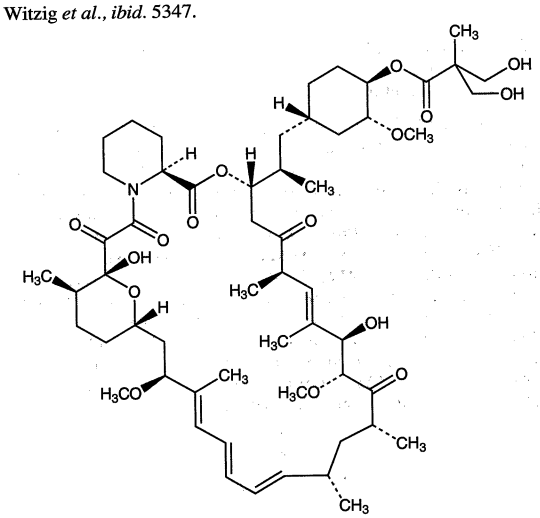
9141. TEMPOL. [2226-96-2] 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy; 4-hydroxy-TEMPO; 4-hydroxy-2,2,6,6-tetramethyl piperidine *N*-oxide; 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy. $C_9H_{18}NO_2$; mol wt 172.24. C 62.76%, H 10.53%, N 8.13%, O 18.58%. Stable nitroxyl radical; water-soluble analogue of TEMPO, *q.v.* Functions as a membrane-permeable radical scavenger. Prepn: E. G. Rozantsev, *Bull. Acad. Sci. USSR Div. Chem. Sci.* **12**, 2085 (1964). Energy transfer studies: N. N. Quan, A. V. Guzzo, *J. Phys. Chem.* **85**, 140 (1981). IR conformation study: W. A. Bueno, L. Degrève, *J. Mol. Struct.* **74**, 291 (1981). Solid state NMR spectra: C. J. Groombridge, M. J. Perkins, *J. Chem. Soc. Chem. Commun.* **1991**, 1164. LC/MS/MS determn: I. D. Podmore, *J. Chem. Res. Synop.* **2002**, 574. Use as a phase transfer catalyst: X.-Y. Wang *et al., Synth. Commun.* **29**, 157 (1999). Review of effects in animal models for shock, ischemia-reperfusion injury, and inflammation: C. Thiemermann, *Crit. Care Med.* **31**, S76-S84 (2003).



Crystals from ether + hexane, mp 71.5°. uv max (hexane): 240, 450-500 (ε ~1800, ~5). uv max (ethanol): 242, 435-455 (ε ~3800, ~10). Sol in water.

USE: Spin label for EPR studies; phase transfer dehydration catalyst; antioxidant; inhibitor of olefin free radical polymerization.

9142. Temsirolimus. [162635-04-3] Rapamycin 42-[3-Hydroxy-2-(hydroxymethyl)-2-methylpropanoate]; rapamycin 42-ester with 2,2-bis-(hydroxymethyl)propionic acid; CCI-779. $C_{56}H_{87}NO_{16}$; mol wt 1030.29. C 65.28%, H 8.51%, N 1.36%, O 24.85%. Ester analog of rapamycin, *q.v.*; selectively inhibits mammalian target of rapamycin (mTOR). Prepn: J. S. Skotnicki *et al.*, **US 5362718** (1994 to Am. Home Prod.). Lipase-catalyzed synthesis from rapamycin: J. Gu *et al., Org. Lett.* **7**, 3945 (2005). Clinical pharmacology: E. Raymond *et al., J. Clin. Oncol.* **22**, 2336 (2004). Clinical study in advanced refractory renal cell carcinoma: M. B. Atkins *et al., ibid.* 909. Clinical evaluation in glioblastoma multiforme: E. Galanis *et al., J. Clin. Oncol.* **23**, 5294 (2005); in breast cancer: S. Chan *et al., ibid.* 5314; in mantle cell lymphoma: T. E. Witzig *et al., ibid.* 5347.



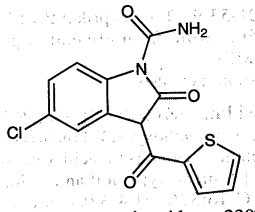
White solid. Sol in water. Lipophilic.

THERAP CAT: Antineoplastic.

9143. Tenecteplase. [191588-94-0] 103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanineplasminogen activator (human tissue-type); TNK-tPA; Metalyse. Genetically engineered variant of human tissue plasminogen activator (t-PA), *q.v.*; expressed in Chinese hamster ovary cells. mol wt ~65 kDa. Constructed by oligonucleotide-directed mutagenesis at 3 specific sites. Prepn: W. F. Bennett *et al.*, **WO 9324635** (1993 to Genentech); B. A. Keyt *et al., Proc. Natl. Acad. Sci. USA* **91**, 3670 (1994). Pharmacology: C. R. Benedict *et al., Circulation* **92**, 3032 (1995). Clinical pharmacokinetics: N. B. Modi *et al., Thromb. Haemostasis* **79**, 134 (1998). Clinical trial in acute myocardial infarction: ASSENT-2 Investigators, *Lancet* **354**, 716 (1999).

THERAP CAT: Thrombolytic.

9144. Tenidap. [120210-48-2] (Z)-5-Chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1*H*-indole-1-carboxamide; 5-chloro-2,3-dihydro-2-oxo-3-(2-thienylcarbonyl)-1*H*-indole-1-carboxamide; 5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide; CP-66248. $C_{14}H_9ClN_2O_3S$; mol wt 320.75. C 52.42%, H 2.83%, Cl 11.05%, N 8.73%, O 14.96%, S 10.00%. Inhibitor of 5-lipoxygenase and interleukin-1 (IL-1) activity. Prepn: S. B. Kadin, **EP 156603**; *idem*, **US 4556672** (both 1985 to Pfizer). Effect on 5-lipoxygenase activity *in vitro*: K. Fogh *et al., Arch. Dermatol. Res.* **280**, 430 (1988). Effect on IL-1 activity in patients with rheumatoid arthritis: B. McDonald *et al., Arthritis Rheum.* **31**, Suppl., S52 (1988). Clinical evaluation: P. Katz *et al., ibid.* S52.



Fluffy, yellow crystals from acetic acid, mp 230° (dec).

Sodium salt. [119784-94-0] CP-66248-2. $C_{14}H_8ClN_2NaO_3S$; mol wt 342.73. Crystals from methanol-isopropanol, mp 237-238°.

THERAP CAT: Anti-inflammatory.

9145. Teniposide. [29767-20-2] (5*R*,5a*R*,8a*R*,9*S*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-*O*-[(*R*)-2-thienylmethylene]-β-D-glucopyranosyl]oxy]furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-demethylepipodophyllotoxin 9-(4,6-*O*-2-thenylidene-β-D-glucopyranoside); 4′-demethylepipodophyllotoxin-β-D-thenylidine glucoside; ETP; NSC-122819; VM-26; Vehem-Sandoz; Vumon. $C_{32}H_{32}O_{13}S$; mol wt 656.65. C 58.53%, H 4.91%, O 31.67%, S 4.88%. Semi-synthetic derivative of podophyllotoxin, *q.v.* Prepn: A. Von Wartburg, **ZA 6607585**; C. Keeler-Juslen *et al.*, **US 3524844** (1968, 1970 both to Sandoz). Mechanism of action: H. Stähln, *Eur. J. Cancer* **6**, 303 (1970). Pharmacology: M. Hacker, D. Roberts, *Cancer Res.* **37**, 3287 (1977); S. M. Sieber *et al., Teratology* **18**, 31 (1978); T. J. Vietti *et al., Cancer Treat. Rep.* **62**, 1313 (1978). Metabolism: L. Allen, *Drug Metab. Rev.* **8**, 119 (1978); *Cancer Res.* **38**, 2549 (1978). Clinical studies: N. M. Gadel-Mawla *et al., Cancer Treat. Rep.* **62**, 993 (1978); R. E. Bellet *et al., ibid.* 445. Studies on delayed toxicity in mice after i.p. injections: M. Hacker, D. Roberts, *Cancer Res.* **35**, 1756 (1975); H. Stähln, *Eur. J. Cancer* **12**, 925 (1976). Review of pharmacology, pharmacokinetics and assay methods: P. I. Clark, M. L. Slevin, *Clin. Pharmacokinet.* **12**, 223-252 (1987). Comprehensive description: J. J. Kettenes-van den Bosch *et al., Anal. Profiles Drug Subs.* **19**, 575-600 (1990).