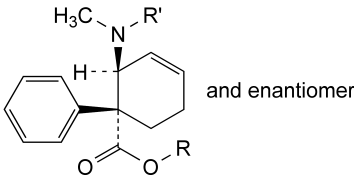
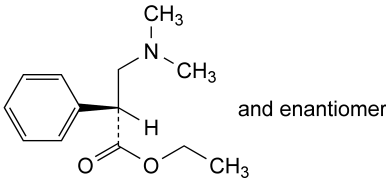


and enantiomer

B. R = R′ = CH_3: methyl (1*RS*,2*SR*)-2-(dimethylamino)-1-phenylcyclohex-3-enecarboxylate,

C. R = C_2H_5, R′ = H: ethyl (1*RS*,2*SR*)-2-(methylamino)-1-phenylcyclohex-3-enecarboxylate,



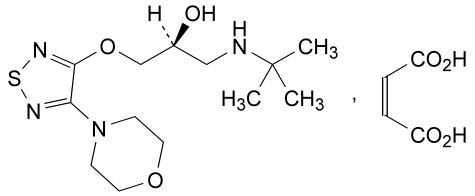
and enantiomer

D. ethyl (2*RS*)-3-dimethylamino-2-phenylpropanoate.

01/2008:0572
corrected 6.0

TIMOLOL MALEATE

Timololi maleas



$C_{17}H_{28}N_4O_7S$ M_r 432.5
[26921-17-5]

DEFINITION

Timolol maleate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, soluble in water and in ethanol (96 per cent).

It melts at about 199 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Dissolve 1.000 g in *1 M hydrochloric acid* and dilute to 10.0 ml with the same acid. The specific optical rotation (*2.2.7*) is −5.7 to −6.2.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *timolol maleate CRS*.

C. Examine the chromatograms obtained in the test for related substances after exposure to iodine vapour. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Triturate 0.1 g with a mixture of 1 ml of *dilute sodium hydroxide solution R* and 3 ml of *water R*. Shake with 3 quantities, each of 5 ml, of *ether R*. To 0.1 ml of the aqueous layer add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min. No violet-red colour develops. Neutralise the remainder of the aqueous layer with *dilute sulphuric acid R* and add 1 ml of *bromine water R*. Heat on a water-bath for 15 min, then heat to boiling and cool. To 0.2 ml of this solution add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min; a violet-red colour develops. Add 0.2 ml of a 100 g/l solution of *potassium bromide R* and heat for 5 min on a water-bath; the colour becomes violet-blue.

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_8 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 3.8 to 4.3.

Enantiomeric purity. Examine by liquid chromatography (*2.2.29*). *Carry out the test protected from actinic light.*

Test solution. Dissolve 30.0 mg of the substance to be examined in a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R* and dilute to 10.0 ml with the same mixture of solvents.

Reference solution (a). Dissolve 30 mg of *timolol maleate CRS* in a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R* and dilute to 10 ml with the same mixture of solvents.

Reference solution (b). Dissolve 15.0 mg of *(R)-timolol CRS* in a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R* and dilute to 10.0 ml with the same mixture of solvents. Dilute 1.0 ml of the solution to 50.0 ml with a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R*.

Reference solution (c). Dilute 1 ml of reference solution (a) to 100 ml with a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R*. Mix 1 ml of this solution with 1 ml of reference solution (b).

Reference solution (d). Dilute 1.0 ml of the test solution to 100.0 ml with a mixture of 1 volume of *methylene chloride R* and 3 volumes of *2-propanol R*.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *silica gel OD for chiral separations R* (5 µm);

– as mobile phase at a flow rate of 1 ml/min a mixture of 2 ml of *diethylamine R*, 40 ml of *2-propanol R* and 960 ml of *hexane R*;

– as detector a spectrophotometer set at 297 nm.

Under these conditions the peak corresponding to the (*R*)-isomer appears first.

Inject 5 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is at least 50 per cent of the full scale of the recorder. Inject 5 µl of each solution. The test is not valid unless: in the chromatogram obtained with reference solution (c), the resolution between the peaks corresponding to the (*R*)-enantiomer and to the (*S*)-enantiomer is at least 4.0; the retention times of the principal peaks (corresponding to the (*S*)-enantiomer) in the chromatograms obtained with the test solution and reference solution (a) are identical. In the chromatogram obtained with the test solution, the area of any peak corresponding

to the (*R*)-enantiomer is not greater than the area of the principal peak in the chromatogram obtained with reference solution (d) (1 per cent).

Related substances. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel plate GF_{254} R*.

Test solution (a). Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Test solution (b). Dilute 1 ml of test solution (a) to 50 ml with *methanol R*.

Reference solution (a). Dissolve 10 mg of *timolol maleate CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dilute 10 ml of test solution (b) to 50 ml with *methanol R*.

Apply to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 20 volumes of *methanol R* and 80 volumes of *methylene chloride R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.4 per cent). Disregard the spot remaining at the starting point. Expose the plate to iodine vapour for 2 h. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.4 per cent). Disregard the spot remaining at the starting point.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

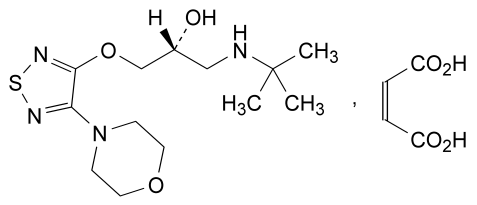
Dissolve 0.350 g in 60 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 43.25 mg of $C_{17}H_{28}N_4O_7S$.

STORAGE

Store protected from light.

IMPURITIES

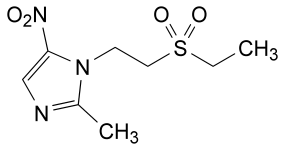


A. (2*R*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate.

01/2008:1051
corrected 6.0

TINIDAZOLE

Tinidazolum



$C_8H_{13}N_3O_4S$ M_r 247.3
[19387-91-8]

DEFINITION

Tinidazole contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 1-[2-(ethylsulphonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole, calculated with reference to the dried substance.

CHARACTERS

An almost white or pale yellow, crystalline powder, practically insoluble in water, soluble in acetone and in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (*2.2.14*): 125 °C to 128 °C.

B. Dissolve 10.0 mg in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 10.0 ml with *methanol R*. Examined between 220 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 310 nm. The specific absorbance at the maximum is 340 to 360.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *tinidazole CRS*. Examine the substances prepared as discs.

D. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

E. To about 10 mg add about 10 mg of *zinc powder R*, 0.3 ml of *hydrochloric acid R* and 1 ml of *water R*. Heat in a water-bath for 5 min and cool. The solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Appearance of solution. Dissolve 1.0 g in *acetone R* and dilute to 20 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a). Dissolve 0.20 g of the substance to be examined in *methanol R* with the aid of ultrasound and dilute to 10 ml with the same solvent.

Test solution (b). Dilute 1.0 ml of test solution (a) to 10 ml with *methanol R*.

Reference solution (a). Dissolve 20 mg of *tinidazole CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of test solution (b) to 20 ml with *methanol R*.