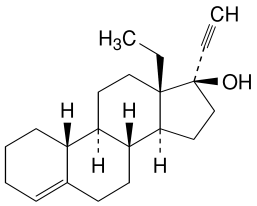
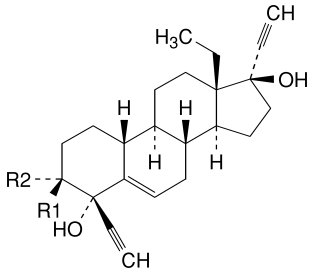


D. 13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-17-ol,



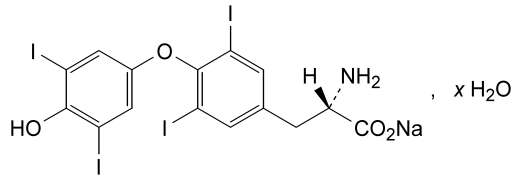
E. R1 = OH, R2 = C≡CH: 13-ethyl-3,4-diethynyl-18,19-dinor-17α-pregn-5-en-20-yn-3β,4α,17-triol,

F. R1 = C≡CH, R2 = OH: 13-ethyl-3,4-diethynyl-18,19-dinor-17α-pregn-5-en-20-yn-3α,4α,17-triol.

01/2008:0401
corrected 6.0

LEVOTHYROXINE SODIUM

Levothyroxinum natricum



$C_{15}H_{10}I_4NNaO_4,xH_2O$ M_r 799 (anhydrous substance)
[55-03-8]

DEFINITION

Levothyroxine sodium contains not less than 97.0 per cent and not more than the equivalent of 102.0 per cent of sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate, calculated with reference to the dried substance. It contains a variable amount of water.

CHARACTERS

An almost white or slightly brownish-yellow powder, or a fine, crystalline powder, very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. It complies with the test for specific optical rotation (see Tests).

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

C. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 5 mg of the substance to be examined in a mixture of 5 volumes of *concentrated ammonia R* and 70 volumes of *methanol R* and dilute to 5 ml with the same mixture of solvents.

Reference solution (a). Dissolve 5 mg of *levothyroxine sodium CRS* in a mixture of 5 volumes of *concentrated ammonia R* and 70 volumes of *methanol R* and dilute to 5 ml with the same mixture of solvents.

Reference solution (b). Dissolve 5 mg of *liothyronine sodium CRS* in a mixture of 5 volumes of *concentrated ammonia R* and 70 volumes of *methanol R* and dilute to 5 ml with the same mixture of solvents. Mix 1 ml of this solution and 1 ml of the test solution.

Apply separately to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of 20 volumes of *concentrated ammonia R*, 35 volumes of *2-propanol R* and 55 volumes of *ethyl acetate R*. Allow the plate to dry in air and spray with *ninhydrin solution R*. Heat at 100-105 °C until the spots appear. Examine in daylight. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

D. To about 50 mg in a porcelain dish add a few drops of *sulphuric acid R* and heat. Violet vapour is evolved.

E. To 200 mg add 2 ml of *dilute sulphuric acid R*. Heat on a water-bath and then carefully over a naked flame, increasing the temperature gradually up to about 600 ± 50 °C. Continue the ignition until most of the black particles have disappeared. Dissolve the residue in 2 ml of *water R*. The solution gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 0.500 g in 23 ml of a gently boiling mixture of 1 volume of *1 M hydrochloric acid* and 4 volumes of *ethanol (96 per cent) R*. Cool and dilute to 25.0 ml with the same mixture of solvents.

Appearance of solution. Freshly prepared solution S is not more intensely coloured than reference solution BY_3 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*): + 16 to + 20, determined on solution S and calculated with reference to the dried substance.

Liothyronine and other related substances. Examine the chromatograms obtained in the assay. In the chromatogram obtained with test solution (a), the area of any peak due to liothyronine is not greater than that of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent) and the sum of the areas of all the peaks apart from the principal peak and any peak due to liothyronine is not greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Disregard any peak with an area less than that of the peak in the chromatogram obtained with reference solution (d).

Loss on drying (*2.2.32*): 6.0 per cent to 12.0 per cent, determined on 0.100 g by drying in an oven at 105 °C.

ASSAY

Examine by liquid chromatography (*2.2.29*). *Protect the solutions from light throughout the assay.*

Test solution (a). Dissolve 20.0 mg of the substance to be examined in *methanolic sodium hydroxide solution R* and dilute to 100.0 ml with the same solvent.

Test solution (b). Dilute 2.0 ml of test solution (a) to 200 ml with *methanolic sodium hydroxide solution R*.

Reference solution (a). Dissolve 20.0 mg of *levothyroxine sodium CRS* in *methanolic sodium hydroxide solution R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of this solution to 200 ml with *methanolic sodium hydroxide solution R*.

Reference solution (b). Dissolve 5 mg of *liothyronine sodium CRS* in *methanolic sodium hydroxide solution R* and dilute to 50.0 ml with the same solvent. Dilute 10.0 ml of the solution to 50 ml with *methanolic sodium hydroxide solution R*. Dilute 10.0 ml of this solution to 100 ml with *methanolic sodium hydroxide solution R*.

Reference solution (c). Mix equal volumes of reference solution (a) and reference solution (b).

Reference solution (d). Dilute 1 ml of reference solution (a) to 10 ml with *methanolic sodium hydroxide solution R*.

The chromatographic procedure may be carried out using:

– a column 0.25 m long and 4 mm in internal diameter packed with *nitrile silica gel for chromatography R* (5-10 µm);

– as mobile phase at a flow rate of 1 ml/min a mixture of 1 volume of *phosphoric acid R*, 300 volumes of *acetonitrile R* and 700 volumes of *water R*;

– as detector a spectrophotometer set at 225 nm;

– a loop injector.

Inject separately 50 µl of each solution. Continue the chromatography for 3.5 times the retention time of the principal peak. The assay is not valid unless the resolution between the peaks due to levothyroxine and liothyronine in the chromatogram obtained with reference solution (c) is at least 4 and the principal peak in the chromatogram obtained with reference solution (d) has a signal-to-noise ratio of at least 5.

Calculate the percentage content of $C_{15}H_{10}I_4NNaO_4$ from the declared content of *levothyroxine sodium CRS*.

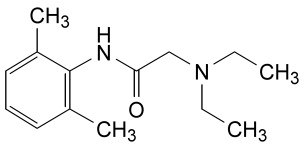
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

01/2008:0727

LIDOCAINE

Lidocainum



$C_{14}H_{22}N_2O$ M_r 234.3
[137-58-6]

DEFINITION

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 66 °C to 70 °C, determined without previous drying.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *lidocaine CRS*.

C. Dissolve 0.20 g in a mixture of 0.5 ml of *dilute hydrochloric acid R* and 10 ml of *water R* with warming and add 10 ml of *picric acid solution R*. The precipitate, washed with *water R* and dried, melts (*2.2.14*) at about 230 °C, with decomposition.

D. To about 5 mg add 0.5 ml of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool and dissolve the residue in 5 ml of *acetone R*. Add 0.2 ml of *alcoholic potassium hydroxide solution R*. A green colour is produced.

E. Dissolve about 0.1 g in 1 ml of *ethanol (96 per cent) R* and add 0.5 ml of a 100 g/l solution of *cobalt nitrate R*. A bluish-green precipitate is formed.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 1.0 g in 3 ml of *dilute hydrochloric acid R* and dilute to 10 ml with *water R*.

2,6-Dimethylaniline: maximum 100 ppm.

Dissolve 0.25 g in *methanol R* and dilute to 10 ml with the same solvent. To 2 ml of the solution add 1 ml of a freshly prepared 10 g/l solution of *dimethylaminobenzaldehyde R* in *methanol R* and 2 ml of *glacial acetic acid R* and allow to stand for 10 min. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 2 ml of a 2.5 mg/l solution of *2,6-dimethylaniline R* in *methanol R*.

Chlorides (*2.4.4*): maximum 35 ppm.

Dissolve 1.4 g in a mixture of 3 ml of *dilute nitric acid R* and 12 ml of *water R*.

Sulphates (*2.4.13*): maximum 0.1 per cent.

Dissolve 0.2 g in 5 ml of *ethanol (96 per cent) R* and dilute to 20 ml with *distilled water R*.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 1.0 per cent, determined on 1.000 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.200 g add 50 ml of *anhydrous acetic acid R* and stir until dissolution is complete. 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 23.43 mg of $C_{14}H_{22}N_2O$.