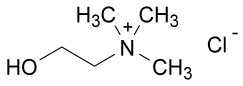
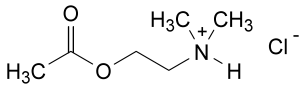
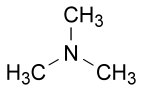
IMPURITIES



A. 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium chloride (choline chloride),



B. 2-(acetyloxy)-*N*,*N*-dimethylethanaminium chloride,

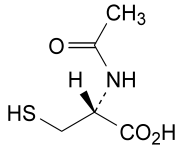


C. *N*,*N*-dimethylmethanamine.

01/2008:0967
corrected 6.0

ACETYLCYSTEINE

Acetylcysteinum



$C_5H_9NO_3S$ M_r 163.2
[616-91-1]

DEFINITION

(2*R*)-2-(Acetylamino)-3-sulfanylpropanoic acid.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

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

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Melting point (*2.2.14*): 104 °C to 110 °C.

C. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: discs of *potassium bromide R*.
Comparison: *acetylcysteine CRS*.

D. Examine the chromatograms obtained in the test for related substances.
Results: the principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

E. To 0.5 ml of solution S (see Tests) add 0.05 ml of a 50 g/l solution of *sodium nitroprusside R* and 0.05 ml of *concentrated ammonia R*. A dark violet colour develops.

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent.

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

pH (*2.2.3*): 2.0 to 2.8.

To 2 ml of solution S add 8 ml of *carbon dioxide-free water R* and mix.

Specific optical rotation (*2.2.7*): + 21.0 to + 27.0 (dried substance).

In a 25 ml volumetric flask, mix 1.25 g with 1 ml of a 10 g/l solution of *sodium edetate R*. Add 7.5 ml of a 40 g/l solution of *sodium hydroxide R*, mix and dissolve. Dilute to 25.0 ml with *phosphate buffer solution pH 7.0 R2*.

Related substances. Liquid chromatography (*2.2.29*). *Except where otherwise prescribed, prepare the solutions immediately before use.*

Test solution (a). Suspend 0.80 g of the substance to be examined in 1 ml of *1 M hydrochloric acid* and dilute to 100.0 ml with *water R*.

Test solution (b). Dilute 5.0 ml of test solution (a) to 100.0 ml with *water R*. Dilute 5.0 ml of this solution to 50.0 ml with *water R*.

Test solution (c). Use test solution (a) after storage for at least 1 h.

Reference solution (a). Suspend 4.0 mg of *acetylcysteine CRS*, 4.0 mg of *L-cystine R* (impurity A), 4.0 mg of *L-cysteine R* (impurity B), 4.0 mg of *acetylcysteine impurity C CRS* and 4.0 mg of *acetylcysteine impurity D CRS* in 1 ml of *1 M hydrochloric acid* and dilute to 100.0 ml with *water R*.

Reference solution (b). Suspend 4.0 mg of *acetylcysteine CRS* in 1 ml of *1 M hydrochloric acid* and dilute to 100.0 ml with *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: stir 3 volumes of *acetonitrile R* and 97 volumes of *water R* in a beaker; adjust to pH 3.0 with *phosphoric acid R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 220 nm.

Injection: 20 µl, 3 times; inject *0.01 M hydrochloric acid* as a blank.

Run time: 5 times the retention time of acetylcysteine (about 30 min).

Retention time: impurity A = about 2.2 min; impurity B = about 2.4 min; 2-methyl-2-thiazoline-4-carboxylic acid, originating in test solution (c) = about 3.3 min; acetylcysteine = about 6.4 min; impurity C = about 12 min; impurity D = about 14 min.

System suitability: reference solution (a):

– *resolution*: minimum 1.5 between the peaks due to impurities A and B and minimum 2.0 between the peaks due to impurities C and D.

From the chromatogram obtained with test solution (a), calculate the percentage content of the known impurities (T_1) and the unknown impurities (T_2) using the following equations:

$$T_1 = \frac{A_1 \times m_2 \times 100}{A_2 \times m_1}$$

$$T_2 = \frac{A_3 \times m_3 \times 100}{A_4 \times m_1}$$

A_1 = peak area of individual impurity (impurity A, impurity B, impurity C and impurity D) in the chromatogram obtained with test solution (a);

A_2 = peak area of the corresponding individual impurity (impurity A, impurity B, impurity C and impurity D) in the chromatogram obtained with reference solution (a);

A_3 = peak area of unknown impurity in the chromatogram obtained with test solution (a);

A_4 = peak area of acetylcysteine in the chromatogram obtained with reference solution (b);

m_1 = mass of the substance to be examined in test solution (a);

m_2 = mass of the individual impurity in reference solution (a);

m_3 = mass of acetylcysteine in reference solution (b).

Limits:

- *impurities A, B, C, D*: for each impurity, maximum 0.5 per cent;
- *any other impurity*: for each impurity, maximum 0.5 per cent;
- *total*: maximum 0.5 per cent;
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak with a retention time of about 3.3 min due to 2-methyl-2-thiazoline-4-carboxylic acid.

Heavy metals (*2.4.8*): maximum 10 ppm.

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

Zinc: maximum 10.0 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Dissolve 1.00 g in *0.001 M hydrochloric acid* and dilute to 50.0 ml with the same acid.

Reference solutions. Prepare the reference solutions using *zinc standard solution (5 mg/ml Zn) R*, diluting with *0.001 M hydrochloric acid*.

Source: zinc hollow-cathode lamp.

Wavelength: 213.8 nm.

Atomisation device: air-acetylene flame.

Use a correction procedure for non-specific absorption.

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 70 °C for 3 h.

Sulphated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.140 g in 60 ml of *water R* and add 10 ml of *dilute hydrochloric acid R*. After cooling in iced water, add 10 ml of *potassium iodide solution R* and titrate with *0.05 M iodine*, using 1 ml of *starch solution R* as indicator.

1 ml of *0.05 M iodine* is equivalent to 16.32 mg of $C_5H_9NO_3S$.

STORAGE

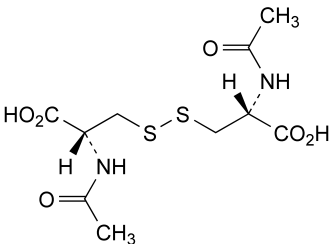
Protected from light.

IMPURITIES

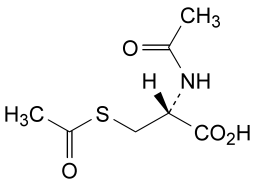
Specified impurities: *A, B, C, D.*

A. L-cystine,

B. L-cysteine,



C. *N,N'*-diacetyl-L-cystine,

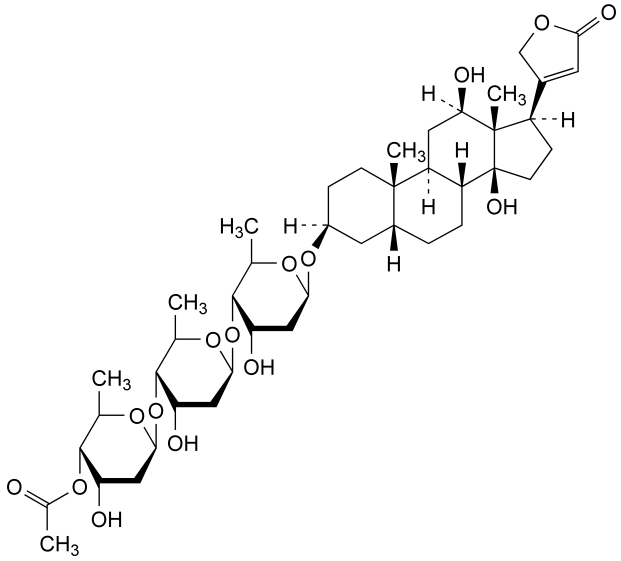


D. *N,S*-diacetyl-L-cysteine.

01/2008:2168
corrected 6.0

β-ACETYLDIGOXIN

β-Acetyldigoxinum



$C_{43}H_{66}O_{15}$ M_r 823
[5355-48-6]

DEFINITION

3β-[(4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide.

Content: 97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *β-acetyldigoxin CRS*.