System suitability: reference solution (e):

– *resolution*: minimum 6 between the peaks corresponding to benzoic acid and benzaldehyde.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.25 per cent),

– *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent),

– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.25 per cent),

– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Chlorides (*2.4.4*): maximum 0.4 per cent.

Dissolve a quantity of the substance to be examined containing the equivalent of 0.5 g of dibenzoyl peroxide in 15 ml of *acetone R*. Add, while stirring, 50 ml of *0.05 M nitric acid*. Allow to stand for 10 min and filter. Wash the residue with 2 quantities, each of 10 ml, of *0.05 M nitric acid*. Combine the filtrate and the washings and dilute to 100 ml with *0.05 M nitric acid*. 2.5 ml of the solution diluted to 15.0 ml with *water R* complies with the limit test for chlorides.

ASSAY

Solution (a). Dissolve 2.500 g immediately before use in 75 ml of *dimethylformamide R* and dilute to 100.0 ml with the same solvent.

Dibenzoyl peroxide. To 5.0 ml of solution (a) add 20 ml of *acetone R* and 3 ml of a 500 g/l solution of *potassium iodide R* and mix. Allow to stand for 1 min. Titrate with *0.1 M sodium thiosulphate* using 1 ml of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration.

1 ml of *0.1 M sodium thiosulphate* is equivalent to 12.11 mg of $C_{14}H_{10}O_4$.

Water (*2.5.12*). Carry out the semi-micro determination of water, using 5.0 ml of solution (a). Use as the solvent a mixture of 20.0 ml of *anhydrous methanol R* and 3.0 ml of a 100 g/l solution of *potassium iodide R* in *dimethylformamide R*. After adding solution (a), stir for 5 min before starting the titration. Carry out a blank determination.

Calculate the percentage content of water using the expression:

$$\frac{(n_1 - n_2) \times w \times 2}{m} + (p \times 0.0744)$$

n_1 = number of millilitres of *iodosulphurous reagent R* used in the sample determination,

n_2 = number of millilitres of *iodosulphurous reagent R* used in the blank determination,

w = water equivalent of *iodosulphurous reagent R* in milligrams of water per millilitre of reagent,

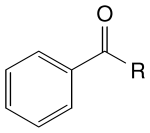
m = mass of the substance to be examined used for the preparation of solution (a) in grams,

p = percentage content of dibenzoyl peroxide.

STORAGE

In a container that has been treated to reduce static discharge and that has a device for release of excess pressure, at a temperature of 2 °C to 8 °C, protected from light.

IMPURITIES



A. R = H: benzaldehyde,

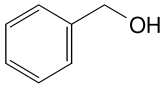
B. R = OH: benzoic acid,

C. R = O-CH_2-CH_3: ethyl benzoate.

01/2008:0256

BENZYL ALCOHOL

Alcohol benzylicus



C_7H_8O M_r 108.1

[100-51-6]

DEFINITION

Phenylmethanol.

Content: 98.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: clear, colourless, oily liquid.

Solubility: soluble in water, miscible with ethanol (96 per cent) and with fatty and essential oils.

Relative density: 1.043 to 1.049.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *benzyl alcohol CRS*.

TESTS

Appearance of solution. Shake 2.0 ml with 60 ml of *water R*. It dissolves completely. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity. To 10 ml add 10 ml of *ethanol (96 per cent) R* and 1 ml of *phenolphthalein solution R*. Not more than 1 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Refractive index (*2.2.6*): 1.538 to 1.541.

Peroxide value (*2.5.5*): maximum 5.

Related substances. Gas chromatography (*2.2.28*).

Test solution. The substance to be examined.

Standard solution (a). Dissolve 0.100 g of *ethylbenzene R* in the test solution and dilute to 10.0 ml with the same solution. Dilute 2.0 ml of this solution to 20.0 ml with the test solution.

Standard solution (b). Dissolve 2.000 g of *dicyclohexyl R* in the test solution and dilute to 10.0 ml with the same solution. Dilute 2.0 ml of this solution to 20.0 ml with the test solution.

Reference solution (a). Dissolve 0.750 g of *benzaldehyde R* and 0.500 g of *cyclohexylmethanol R* in the test solution and dilute to 25.0 ml with the test solution. Add 1.0 ml of

this solution to a mixture of 2.0 ml of standard solution (a) and 3.0 ml of standard solution (b) and dilute to 20.0 ml with the test solution.

Reference solution (b). Dissolve 0.250 g of *benzaldehyde R* and 0.500 g of *cyclohexylmethanol R* in the test solution and dilute to 25.0 ml with the test solution. Add 1.0 ml of this solution to a mixture of 2.0 ml of standard solution (a) and 2.0 ml of standard solution (b) and dilute to 20.0 ml with the test solution.

Column:

- *material*: fused silica;
- *size*: *l* = 30 m, Ø = 0.32 mm;
- *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas: *helium for chromatography R.*

Linear velocity: 25 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 34	50 → 220
	34 - 69	220
Injection port		200
Detector		310

Detection: flame ionisation.

Benzyl alcohol not intended for parenteral use

Injection: without air-plug, 0.1 µl of the test solution and reference solution (a).

Relative retention with reference to benzyl alcohol (retention time = about 26 min): ethylbenzene = about 0.28; dicyclohexyl = about 0.59; impurity A = about 0.68; impurity B = about 0.71.

System suitability: reference solution (a):

- *resolution*: minimum 3.0 between the peaks due to impurity A and impurity B.

In the chromatogram obtained with the test solution, verify that there are no peaks with the same retention time as ethylbenzene and dicyclohexyl.

Limits:

- *impurity A*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.15 per cent);
- *impurity B*: not more than the difference between the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) and the area of the peak due to impurity B in the chromatogram obtained with the test solution (0.10 per cent);
- *sum of other peaks with a relative retention less than that of benzyl alcohol*: not more than 4 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (a) (0.04 per cent);
- *sum of peaks with a relative retention greater than that of benzyl alcohol*: not more than the area of the peak due to dicyclohexyl in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *disregard limit*: 0.01 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (a) (0.0001 per cent).

Benzyl alcohol intended for parenteral use

Injection: without air-plug, 0.1 µl of the test solution and reference solution (b).

Relative retention with reference to benzyl alcohol (retention time = about 26 min): ethylbenzene = about 0.28; dicyclohexyl = about 0.59; impurity A = about 0.68; impurity B = about 0.71.

System suitability: reference solution (b):

- *resolution*: minimum 3.0 between the peaks due to impurity A and impurity B.

In the chromatogram obtained with the test solution, verify that there are no peaks with the same retention time as the standards.

Limits:

- *impurity A*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.05 per cent);
- *impurity B*: not more than the difference between the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity B in the chromatogram obtained with the test solution (0.10 per cent);
- *sum of other peaks with a relative retention less than that of benzyl alcohol*: not more than twice the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (b) (0.02 per cent);
- *sum of peaks with a relative retention greater than that of benzyl alcohol*: not more than the area of the peak due to dicyclohexyl in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *disregard limit*: 0.01 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (b) (0.0001 per cent).

Residue on evaporation: maximum 0.05 per cent.

After ensuring that the substance to be examined complies with the test for peroxide value, evaporate 10.0 g to dryness in a tared quartz or porcelain crucible or platinum dish on a hot plate at a temperature not exceeding 200 °C. Ensure that the substance to be examined does not boil during evaporation. Dry the residue on the hot plate for 1 h and allow to cool in a desiccator. The residue weighs a maximum of 5 mg.

ASSAY

To 0.900 g (*m* g) add 15.0 ml of a freshly prepared mixture of 1 volume of *acetic anhydride R* and 7 volumes of *pyridine R* and boil under a reflux condenser on a water-bath for 30 min. Cool and add 25 ml of *water R*. Using 0.25 ml of *phenolphthalein solution R* as indicator, titrate with *1 M sodium hydroxide* (n_1 ml). Carry out a blank titration (n_2 ml).

Calculate the percentage content of C_7H_8O using the following expression:

$$\frac{10.81\left(n_2 - n_1\right)}{m}$$

STORAGE

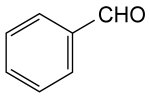
In an airtight container, under nitrogen, protected from light and at a temperature between 2 °C and 8 °C.

LABELLING

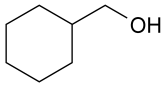
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.

IMPURITIES

Specified impurities: A, B.



A. benzaldehyde,

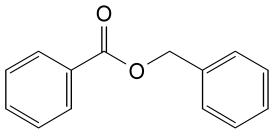


B. cyclohexylmethanol.

01/2008:0705

BENZYL BENZOATE

Benzylis benzoas



$C_{14}H_{12}O_2$ M_r 212.2
[120-51-4]

DEFINITION

Phenylmethyl benzoate.

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: colourless or almost colourless crystals or colourless or almost colourless, oily liquid.

Solubility: practically insoluble in water, miscible with ethanol (96 per cent), with methylene chloride and with fatty and essential oils.

Eb: about 320 °C.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of benzyl benzoate.*

B. To 2 g add 25 ml of *alcoholic potassium hydroxide solution R* and boil under a reflux condenser for 2 h. Remove the ethanol on a water-bath, add 50 ml of *water R* and distill. Collect about 25 ml of distillate and use it for identification test C. Acidify the liquid remaining in the distillation flask with *dilute hydrochloric acid R*. A white precipitate is formed that, when washed with *water R* and dried *in vacuo* melts (*2.2.14*) at 121 °C to 124 °C.

C. To the distillate obtained in identification test B add 2.5 g of *potassium permanganate R* and 5 ml of *dilute sodium hydroxide solution R*. Boil under a reflux condenser for 15 min, cool and filter. Acidify the filtrate with *dilute hydrochloric acid R*. A white precipitate is formed that, when washed with *water R* and dried *in vacuo*, melts (*2.2.14*) at 121 °C to 124 °C.

TESTS

Acidity. Dissolve 2.0 g in *ethanol (96 per cent) R* and dilute to 10 ml with the same solvent. Titrate with *0.1 M sodium hydroxide* using *phenolphthalein solution R* as indicator. Not more than 0.2 ml is required to change the colour of the indicator to pink.

Relative density (*2.2.5*): 1.118 to 1.122.

Refractive index (*2.2.6*): 1.568 to 1.570.

Freezing point (*2.2.18*): minimum 17.0 °C.

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

ASSAY

To 2.000 g add 50.0 ml of *0.5 M alcoholic potassium hydroxide* and boil gently under a reflux condenser for 1 h. Titrate the hot solution with *0.5 M hydrochloric acid* using 1 ml of *phenolphthalein solution R* as indicator. Carry out a blank determination.

1 ml of *0.5 M alcoholic potassium hydroxide* is equivalent to 106.1 mg of $C_{14}H_{12}O_2$.

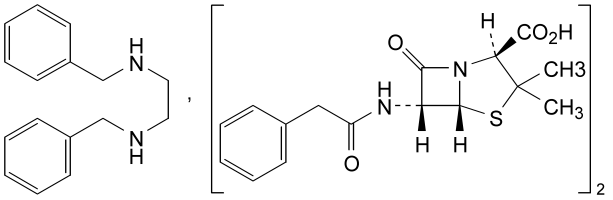
STORAGE

In an airtight, well-filled container, protected from light.

01/2008:0373
corrected 6.0

BENZYLPENICILLIN, BENZATHINE

Benzylpenicillinum benzathinum



$C_{48}H_{56}N_6O_8S_2$ M_r 909
[1538-09-6]

DEFINITION

N,N'-Dibenzylethane-1,2-diamine compound (1:2) with (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Substance produced by the growth of certain strains of *Penicillium notatum* or related organisms, or obtained by any other means.

Content:

– *benzathine benzylpenicillin*: 96.0 per cent to 102.0 per cent (anhydrous substance);
– *N,N'-dibenzylethylenediamine* (benzathine $C_{16}H_{20}N_2$; M_r 240.3): 24.0 per cent to 27.0 per cent (anhydrous substance).

It contains a variable quantity of water. Dispersing or suspending agents may be added.

CHARACTERS

Appearance: white or almost white powder.

Solubility: very slightly soluble in water, freely soluble in dimethylformamide and in formamide, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *benzathine benzylpenicillin CRS.*

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 25 mg of the substance to be examined in 5 ml of *methanol R.*
Reference solution. Dissolve 25 mg of *benzathine benzylpenicillin CRS* in 5 ml of *methanol R.*