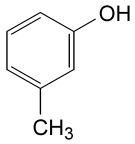
01/2008:2077

METACRESOL

Metacresolum



C_7H_8O M_r 108.1
[108-39-4]

DEFINITION

3-Methylphenol.

CHARACTERS

Appearance: colourless or yellowish liquid.

Solubility: sparingly soluble in water, miscible with ethanol (96 per cent) and with methylene chloride.

Relative density: about 1.03.

mp: about 11 °C.

bp: about 202 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of metacresol.*

TESTS

Solution S. Dissolve 1.5 g in *carbon dioxide-free water R* and dilute to 100 ml with the same solvent.

Appearance of solution. Freshly prepared solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Acidity. To 25 ml of solution S add 0.15 ml of *methyl red solution R*. The solution is red. Not more than 0.5 ml of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Dissolve 1.00 g of the substance to be examined in *methanol R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve 0.10 g of *cresol R*, 0.10 g of *p-cresol R* and 0.10 g of the substance to be examined in *methanol R* and dilute to 20.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with *methanol R*. Dilute 1.0 ml of this solution to 20.0 ml with *methanol R*.

Column:

– *material*: fused silica,
– *size*: *l* = 25 m, Ø = 0.25 mm,
– *stationary phase*: *poly[(cyanopropyl)(methyl)][(phenyl)(methyl)]siloxane R* (0.2 µm).

Carrier gas: *helium for chromatography R.*

Flow rate: 1.8 ml/min.

Split ratio: 1:30.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 35	100
	35 - 40	100 → 150
	40 - 50	150
Injection port		200
Detector		200

Detection: flame ionisation.

Injection: 1.0 µl.

Relative retention with reference to metacresol (retention time = about 28 min): impurity B = about 0.75; impurity C = about 0.98.

System suitability: reference solution (a):

– *resolution*: minimum 1.4 between the peaks due to impurity C and metacresol.

Limits:

– *impurities B, C*: for each impurity, not more than 0.5 per cent,
– *any other impurity*: for each impurity, not more than 0.1 per cent,
– *total*: not more than 1.0 per cent.
– *disregard limit*: the area of the peak due to metacresol in the chromatogram obtained with reference solution (b) (0.05 per cent).

Residue on evaporation: maximum 0.1 per cent.

Evaporate 2.0 g to dryness on a water-bath under a fume hood and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2 mg.

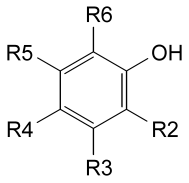
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities: *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, D, E, F, G, H, I, J, K, L, M.*



A. R2 = R3 = R4 = R5 = R6 = H: phenol,

B. R2 = CH_3, R3 = R4 = R5 = R6 = H: 2-methylphenol (*o*-cresol, cresol),

C. R2 = R3 = R5 = R6 = H, R4 = CH_3: 4-methylphenol (*p*-cresol),

D. R2 = R6 = CH_3, R3 = R4 = R5 = H: 2,6-dimethylphenol (2,6-xylenol),

E. R2 = C_2H_5, R3 = R4 = R5 = R6 = H: 2-ethylphenol (*o*-ethylphenol),

F. R2 = R4 = CH_3, R3 = R5 = R6 = H: 2,4-dimethylphenol (2,4-xylenol),

G. R2 = R5 = CH_3, R3 = R4 = R6 = H: 2,5-dimethylphenol (2,5-xylenol),

H. R2 = $CH(CH_3)_2$, R3 = R4 = R5 = R6 = H: 2-(1-methylethyl)phenol,

I. R2 = R3 = CH_3, R4 = R5 = R6 = H: 2,3-dimethylphenol (2,3-xylenol),

J. R2 = R4 = R6 = H, R3 = R5 = CH_3: 3,5-dimethylphenol (3,5-xylenol),

K. R2 = R3 = R5 = R6 = H, R4 = C_2H_5: 4-ethylphenol (*p*-ethylphenol),

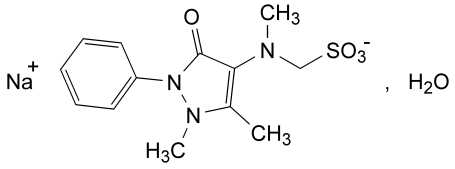
L. R2 = R5 = R6 = H, R3 = R4 = CH_3: 3,4-dimethylphenol (3,4-xylenol),

M. R2 = R3 = R5 = CH_3, R4 = R6 = H: 2,3,5-trimethylphenol.

01/2008:1346

METAMIZOLE SODIUM

Metamizolum natricum



$C_{13}H_{16}N_3NaO_4S,H_2O$ M_r 351.4
[5907-38-0]

DEFINITION

Sodium [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-methylamino]methanesulphonate monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *metamizole sodium CRS.*

B. Dissolve 50 mg in 1 ml of *strong hydrogen peroxide solution R*. A blue colour is produced which fades rapidly and turns to intense red in a few minutes.

C. Place 0.10 g in a test tube, add some glass beads and dissolve the substance in 1.5 ml of *water R*. Add 1.5 ml of *dilute hydrochloric acid R* and place a filter paper wetted with a solution of 20 mg of *potassium iodate R* in 2 ml of *starch solution R* at the open end of the test tube. Heat gently, the evolving vapour of sulphur dioxide colours the filter paper blue. After heating gently for 1 min take a glass rod with a drop of a 10 g/l solution of *chromotropic acid, sodium salt R* in *sulphuric acid R* and place in the opening of the tube. Within 10 min, a blue-violet colour develops in the drop of the reagent.

D. 0.5 ml of solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 40 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and immediately after preparation, not more intensely coloured than reference solution BY_6 (*2.2.2, Method I*).

Acidity or alkalinity. To 5 ml of solution S, add 0.1 ml of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.1 ml of *0.02 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 10.0 mg of *metamizole impurity A CRS* in *methanol R* and dilute to 20.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with *methanol R*.

Reference solution (c). Dissolve 40 mg of *metamizole sodium CRS* in *methanol R* and dilute to 20.0 ml with the same solvent.

Reference solution (d). In order to prepare impurity C *in situ*, boil 10 ml of reference solution (c) under reflux for 10 min. Allow to cool to room temperature and dilute to 20.0 ml with *methanol R*.

Reference solution (e). To 6 ml of reference solution (a) add 1 ml of reference solution (c).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 28 volumes of *methanol R* and 72 volumes of a buffer solution prepared as follows : mix 1000 volumes of a 6.0 g/l solution of *sodium dihydrogen phosphate R* and 1 volume of *triethylamine R*, then adjust to pH 7.0 with *strong sodium hydroxide solution R*.

Flow rate: 1.0 ml/min.