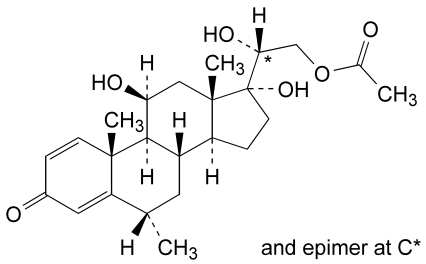
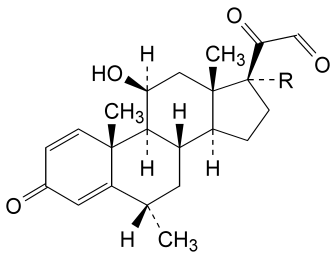
IMPURITIES



A. (20*RS*)-11β,17,20-trihydroxy-6α-methyl-3-oxopregna-1,4-dien-21-yl acetate,

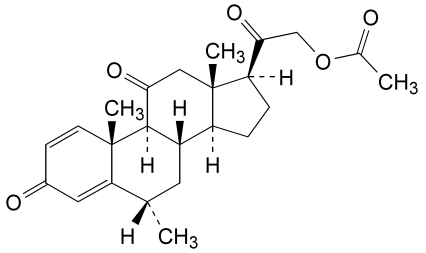
B. methylprednisolone,



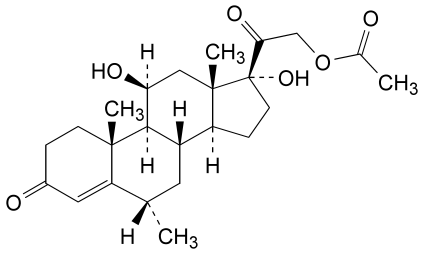
C. R = OH: 11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20,21-trione,

D. R = H: 11β-hydroxy-6α-methylpregna-1,4-diene-3,20,21-trione,

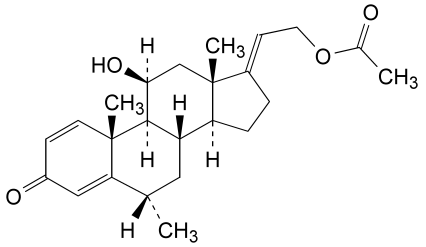
E. prednisolone acetate,



F. 6α-methyl-3,11,20-trioxopregna-1,4-dien-21-yl acetate,



G. 11β,17-dihydroxy-6α-methyl-3,20-dioxopregn-4-en-21-yl acetate,

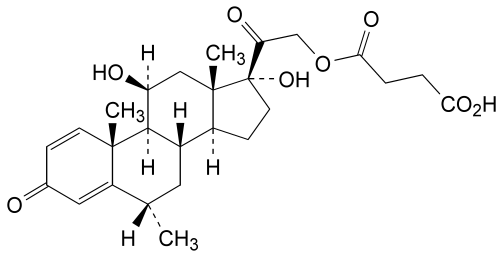


H. 11β-hydroxy-6α-methyl-3-oxopregna-1,4,17(20)-trien-21-yl acetate.

01/2008:1131
corrected 6.0

METHYLPREDNISOLONE HYDROGEN SUCCINATE

Methylprednisoloni hydrogenosuccinas



$C_{26}H_{34}O_8$ M_r 474.6
[2921-57-5]

DEFINITION

4-[(11β,17-Dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-21-yl)oxy]-4-oxobutanoic acid.

Content: 97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, hygroscopic powder.

Solubility: practically insoluble in water, slightly soluble in acetone and in anhydrous ethanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *methylprednisolone hydrogen succinate CRS.*

B. Thin layer chromatography (*2.2.27*).

Solvent mixture: *methanol R, methylene chloride R* (1:9 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 ml with the solvent mixture.

Reference solution (a). Dissolve 20 mg of *methylprednisolone hydrogen succinate CRS* in the solvent mixture and dilute to 20 ml with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *hydrocortisone hydrogen succinate CRS* in reference solution (a) and dilute to 10 ml with reference solution (a).

Plate: *TLC silica gel F_{254} plate R.*

Mobile phase: *anhydrous formic acid R, anhydrous ethanol R, methylene chloride R* (0.1:1:15 *V/V/V*).

Application: 10 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Monographs M

Detection B: spray with *alcoholic solution of sulphuric acid R*; heat at 120 °C for 10 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability: reference solution (b):

– the chromatogram shows 2 spots which may, however, not be completely separated.

C. Thin layer chromatography (*2.2.27*).

Test solution (a). Dissolve 25 mg of the substance to be examined in *methanol R* with gentle heating and dilute to 5 ml with the same solvent (solution A). Dilute 2 ml of this solution to 10 ml with *methylene chloride R*.

Test solution (b). Transfer 2 ml of solution A to a 15 ml glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 ml of a 0.8 g/l solution of *sodium hydroxide R* in *methanol R* and immediately pass a stream of *nitrogen R* through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C, protected from light, for 30 min. Allow to cool.

Reference solution (a). Dissolve 25 mg of *methylprednisolone hydrogen succinate CRS* in *methanol R* with gentle heating and dilute to 5 ml with the same solvent (solution B). Dilute 2 ml of this solution to 10 ml with *methylene chloride R*.

Reference solution (b). Transfer 2 ml of solution B to a 15 ml glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 ml of a 0.8 g/l solution of *sodium hydroxide R* in *methanol R* and immediately pass a stream of *nitrogen R* through the solution for 5 min. Stopper the tube. Heat in a water-bath at 45 °C, protected from light, for 30 min. Allow to cool.

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution.

Detection B: spray with *alcoholic solution of sulphuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B: the principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spot in each of the chromatograms obtained with test solution (b) and reference solution (b) has an R_F value distinctly higher than that of the principal spot in each of the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 ml of *sulphuric acid R* and shake to dissolve. Within 5 min a reddish-brown colour develops. Add this solution to 10 ml of *water R* and mix. The colour fades and a precipitate is formed.

TESTS

Appearance of solution. The solution is clear (*2.2.1*).

Dissolve 0.100 g in 5 ml of *sodium hydrogen carbonate solution R*.

Specific optical rotation (*2.2.7*): + 87 to + 95 (dried substance).

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). Dissolve 25 mg of *methylprednisolone hydrogen succinate for performance test CRS* in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R*, 3 per cent *V/V* solution of *glacial acetic acid R* (33:67 *V/V*).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Equilibration: with the mobile phase for about 30 min.

Injection: 20 µl.

Run time: twice the retention time of methylprednisolone hydrogen succinate.

Retention time: methylprednisolone hydrogen succinate = about 22 min; impurity D (eluting immediately after the main peak and appearing as a shoulder) = about 24 min.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 4, where H_p = height above the base line of the peak due to impurity D and H_v = height above the base line of the lowest point of the curve separating this peak from the peak due to methylprednisolone hydrogen succinate; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

– *impurities A, B, C, D*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of this solution to 50.0 ml with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 243 nm.

Calculate the content of $C_{26}H_{34}O_8$ taking the specific absorbance to be 316.

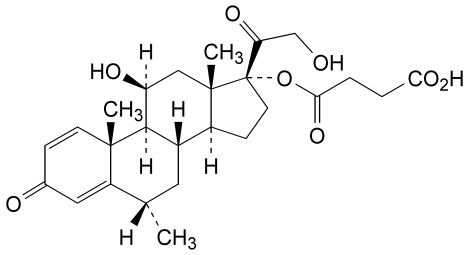
STORAGE

In an airtight container, protected from light.

IMPURITIES

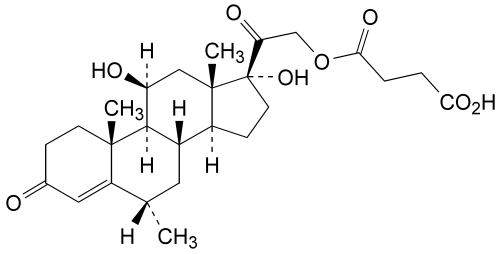
Specified impurities: A, B, C, D.

A. methylprednisolone,



B. 4-[(11β,21-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-17-yl)oxy]-4-oxobutanoic acid (methylprednisolone 17-(hydrogen succinate)),

C. methylprednisolone acetate,

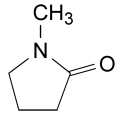


D. 4-[(11β,17-dihydroxy-6α-methyl-3,20-dioxopregn-4-en-21-yl)oxy]-4-oxobutanoic acid (methylhydrocortisone 21-(hydrogen succinate)).

01/2008:1675

N-METHYLPYRROLIDONE

N-Methylpyrrolidonum



C_5H_9NO M_r 99.1
[872-50-4]

DEFINITION

1-Methylpyrrolidin-2-one.

CHARACTERS

Appearance: clear, colourless liquid.

Solubility: miscible with water and with alcohol.

bp: about 204 °C.

Relative density: about 1.034.

Refractive index: about 1.469.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: films.

Comparison: *Ph. Eur. reference spectrum of N-methylpyrrolidone.*

TESTS

Appearance. The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Alkalinity. Dissolve 50 ml of the substance to be examined in 50 ml of *water R* previously adjusted with *0.02 M potassium hydroxide* or *0.02 M hydrochloric acid* until a yellow colour is obtained using 0.5 ml of *bromothymol blue solution R1* as indicator. Titrate with *0.02 M hydrochloric acid* to the initial coloration. Not more than 8.0 ml of *0.02 M hydrochloric acid* is required.

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

Test solution. The substance to be examined.

Reference solution. To 1 ml of the substance to be examined, add 1 ml of *2-pyrrolidone R* and dilute to 20 ml with *methylene chloride R.*

Column:

– *material*: fused silica,
– *size*: *l* = 30 m, Ø = 0.32 mm,
– *stationary phase*: *poly(dimethyl)siloxane R* (5 µm).

Carrier gas: *nitrogen for chromatography R.*

Linear velocity: 20 cm/s.

Split ratio: 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0	100
	0 - 23.3	100 → 170
	23.3 - 53	170
Injection port		280
Detector		280

Detection: flame ionisation.

Injection: 1 µl.

System suitability: reference solution:

– *resolution*: minimum 2.0 between the peaks due to *N*-methylpyrrolidone and impurity G.

Limits:

– *any impurity*: maximum 0.1 per cent,
– *total*: maximum 0.3 per cent,
– *disregard limit*: 0.02 per cent.

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

Dissolve 4.0 g in *water R* and dilute to 20.0 ml with the same solvent. 12 ml of the solution complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R.*

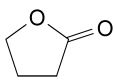
Water (*2.5.32*): maximum 0.1 per cent, determined on 1.000 g.

STORAGE

Protected from light.

IMPURITIES

A. $H_3C\text{-}NH_2$: methanamine (methylamine),



B. dihydrofuran-2(3*H*)-one (γ-butyrolactone),