Isoconazole nitrate

C_{18}H_{15}Cl_{4}N_{3}O_{4}  \quad M, 479.1

DEFINITION
1-[(2RS)-2-{(2,6-Dichlorobenzyl)oxy}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole nitrate.

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

CHARACTERS
Appearance: white or almost white powder.
Solubility: very slightly soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION
First identification: A, B, C, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 178 °C to 182 °C.

B. Infrared absorption spectrophotometry (2.2.24).
Preparation: discs.
Comparison: isoconazole nitrate CRS.

C. Thin-layer chromatography (2.2.27).
Test solution. Dissolve 30 mg of the substance to be examined in methanol R and dilute to 5 ml with the same solvent.
Reference solution (a). Dissolve 30 mg of isoconazole nitrate CRS in methanol R and dilute to 5 ml with the same solvent.
Reference solution (b). Dissolve 30 mg of isoconazole nitrate CRS and 30 mg of econazole nitrate CRS in methanol R, then dilute to 5 ml with the same solvent.
Plate: TLC octadeclsililicilica gel plate R.
Application: 5 µl.
Development: over a path of 15 cm.
Drying: in a current of warm air for 15 min.
Detection: expose to iodine vapour until the spots appear and examine in daylight.
System suitability: reference solution (b): the chromatogram shows 2 clearly separated spots.
Results: 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).

D. It gives the reaction of nitrates (2.3.1).

TESTS

Solution S. Dissolve 0.20 g in methanol R and dilute to 20.0 ml with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_{7} (2.2.2, Method II).

Optical rotation (2.2.7): −0.10° to +0.10°, determined on solution S.

Related substances. Liquid chromatography (2.2.29).
Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 10.0 ml with the same mobile phase.
Reference solution (a). Dissolve 2.5 mg of isoconazole nitrate CRS and 2.5 mg of econazole nitrate CRS in the mobile phase, then dilute to 100.0 ml with the same mobile phase.
Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the same mobile phase. Dilute 5.0 ml of this solution to 20.0 ml with the mobile phase.
Column:
– size: l = 0.1 m, 0 = 4.6 mm;
– stationary phase: octadeclsililicilica gel for chromatography R (3 µm).
Mobile phase: dissolve 6.0 g of ammonium acetate R in a mixture of 300 ml of acetonitrile R, 320 ml of methanol R and 380 ml of water R.
Flow rate: 2 ml/min.
Detection: spectrophotometer at 235 nm.
Equilibration: with the mobile phase for about 30 min.
Injection: 10 µl.
Run time: 1.5 times the retention time of isoconazole.
Retention time: econazole = about 10 min; isoconazole = about 14 min.

System suitability: reference solution (a):
- resolution: minimum 5.0 between the peaks due to econazole and isoconazole; if necessary, adjust the composition of the mobile phase.

Limits:
- impurities A, B, C: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);
- total: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- disregard limit: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to the nitrate ion.

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

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

ASSAY
Dissolve 0.350 g in 75 ml of a mixture of 1 volume of anhydrous acetic acid R and 7 volumes of methyl ethyl ketone R. 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 47.91 mg of C₁₈H₁₅Cl₄N₃O₄.

STORAGE
Protected from light.

IMPURITIES
Specified impurities: A, B, C.

A. (1RS)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol,

B. (2RS)-2-{[2,6-dichlorobenzyl]oxy}-2-(2,4-dichlorophenyl)ethanamine,