Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm),

– *temperature*: 60 °C.

Mobile phase: weigh 60.0 g of *2-methyl-2-propanol R* and transfer into a 1000 ml volumetric flask with the aid of 200 ml of *water R*; add 400 ml of *buffer solution pH 8.0 R*, 50 ml of a 10 g/l solution of *tetrabutylammonium hydrogen sulphate R* adjusted to pH 8.0 with *dilute sodium hydroxide solution R* and 10 ml of a 40 g/l solution of *sodium edetate R* adjusted to pH 8.0 with *dilute sodium hydroxide solution R*; dilute to 1000.0 ml with *water R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µl; inject the test solution and reference solutions (d) and (e).

Relative retention with reference to doxycycline: impurity E = about 0.2; impurity D = about 0.3; impurity C = about 0.5; impurity F = about 1.2.

System suitability: reference solution (d):

– *resolution*: minimum 1.25 between the peaks due to impurity B (1st peak) and impurity A (2nd peak) and minimum 2.0 between the peaks due to impurity A and doxycycline (3rd peak); if necessary, adjust the 2-methyl-2-propanol content in the mobile phase,

– *symmetry factor*: maximum 1.25 for the peak due to doxycycline.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (2.0 per cent),

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (2.0 per cent),

– *any other impurity*: not more than 0.25 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (e) (0.5 per cent),

– *disregard limit*: 0.05 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (e) (0.1 per cent).

Heavy metals (*2.4.8*): maximum 50 ppm.

0.5 g complies with limit test C. Prepare the standard using 2.5 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): 3.6 per cent to 4.6 per cent, determined on 0.200 g.

Sulphated ash (*2.4.14*): maximum 0.4 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

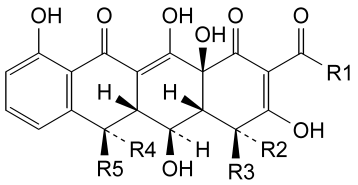
Injection: test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{24}N_2O_8$.

STORAGE

Protected from light.

IMPURITIES



A. R1 = NH_2, R2 = R5 = H, R3 = $N(CH_3)_2$, R4 = CH_3: (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (6-epidoxycycline),

B. R1 = NH_2, R2 = H, R3 = $N(CH_3)_2$, R4 + R5 = CH_2: (4*S*,4a*R*,5*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (metacycline),

C. R1 = NH_2, R2 = $N(CH_3)_2$, R3 = R4 = H, R5 = CH_3: (4*R*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidoxycycline),

D. R1 = NH_2, R2 = $N(CH_3)_2$, R3 = R5 = H, R4 = CH_3: (4*R*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epi-6-epidoxycycline),

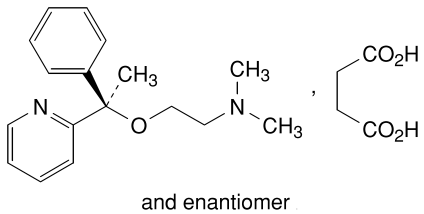
E. R1 = NH_2, R2 = H, R3 = $N(CH_3)_2$, R4 = OH, R5 = CH_3: oxytetracycline,

F. R1 = CH_3, R2 = R4 = H, R3 = $N(CH_3)_2$, R5 = CH_3: (4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyldoxycycline).

01/2008:1589

DOXYLAMINE HYDROGEN SUCCINATE

Doxylamini hydrogenosuccinas



and enantiomer

$C_{21}H_{28}N_2O_5$ M_r 388.5
[562-10-7]

DEFINITION

N,N-dimethyl-2-[(1*RS*)-1-phenyl-1-(pyridin-2-yl)ethoxy(ethanamine hydrogen butanedioate.

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

CHARACTERS

Appearance: a white or almost white powder.

Solubility: very soluble in water, freely soluble in alcohol.

IDENTIFICATION

First identification: C.

Second identification: A, B.

A. Melting point (*2.2.14*): 103 °C to 108 °C.

B. Dissolve 0.200 g in *0.1 M hydrochloric acid* and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with *0.1 M hydrochloric acid*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 262 nm. The specific absorbance at the maximum is 229 to 243 (anhydrous substance).

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of doxylamine hydrogen succinate.*

TESTS

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

Dissolve 0.4 g of the substance to be examined in *water R* and dilute to 20 ml with the same solvent.

Optical rotation (*2.2.7*): - 0.10° to + 0.10°.

Dissolve 2.50 g of the substance to be examined in *water R* and dilute to 25.0 ml with the same solvent.

Related substances. Gas chromatography (*2.2.28*).

Test solution. Dissolve 0.650 g of the substance to be examined in 20 ml of *0.1 M hydrochloric acid*. Add 3 ml of a 100 g/l solution of *sodium hydroxide R* and extract 3 times with 25 ml of *methylene chloride R*. Combine the methylene chloride extracts and filter using hydrophobic phase-separation filter paper. Rinse the filter with 10 ml of *methylene chloride R* and combine the rinsings with the methylene chloride extracts. Evaporate the solvent under reduced pressure at a temperature not exceeding 40 °C. Dissolve the residue in 20.0 ml of *ethanol R*.

Reference solution (a). Dilute 1.0 ml of the test solution to 200.0 ml with *ethanol R*.

Reference solution (b). Dissolve 40 mg of *doxylamine impurity A CRS* and 40 mg of *2-benzoylpyridine R* in *ethanol R* and dilute to 20 ml with the same solvent. Dilute 1 ml of this solution to 20 ml with *ethanol R*.

Column:

– *material*: fused silica,

– *size*: *l* = 30 m, Ø = 0.53 mm,

– *stationary phase*: *poly(dimethyl)(diphenyl)siloxane R* (film thickness 1.5 µm).

Carrier gas: *helium for chromatography R*.

Flow rate: 7 ml/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	160 → 220
	12 - 27	220
Injection port		250
Detector		250

Detection: flame ionisation.

Injection: 1 µl.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity A and impurity D.

Limits:

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent),

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 0.5 per cent, determined on 2.00 g.

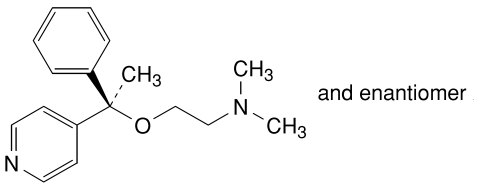
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

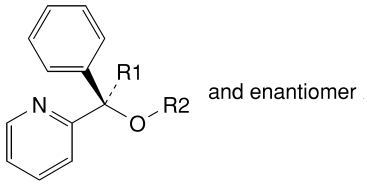
Dissolve 0.150 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 19.43 mg of $C_{21}H_{28}N_2O_5$.

IMPURITIES

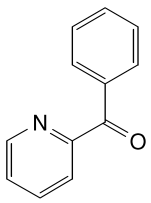


A. *N,N*-dimethyl-2-[1(*RS*)-1-phenyl-1-(pyridin-4-yl)ethoxy]ethanamine,



B. R1 = CH_3, R2 = H: (1*RS*)-1-phenyl-1-(pyridin-2-yl)ethanol,

C. R1 = H, R2 = CH_2-CH_2-$N(CH_3)_2$: *N,N*-dimethyl-2-[(*RS*)-1-phenyl(pyridin-2-yl)methoxy]ethanamine,



D. phenyl(pyridin-2-yl)methanone (2-benzoylpyridine).