Mobile phase:

– *mobile phase A*: 2 g/L solution of *sodium heptanesulfonate monohydrate R*;

– *mobile phase B*: mix 25 volumes of a 2 g/L solution of *sodium heptanesulfonate R* and 75 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	63	37
4 - 15	63 → 12	37 → 88

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 242 nm.

Injection: 5 µL.

Relative retention with reference to brotizolam (retention time = about 7.4 min): impurity A = about 0.5; impurity B = about 0.9.

System suitability: reference solution (b):

– *resolution*: minimum 5.0 between the peaks due to impurity B and brotizolam.

Limits:

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

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*): maximum 100 ppm.

Dissolve 0.67 g in 20.0 mL of *methanol R*, mix and filter.

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

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

ASSAY

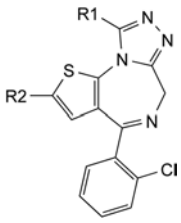
Dissolve 0.150 g in a mixture of 25 mL of *glacial acetic acid R* and 50 mL of *acetic anhydride R*. Titrate to the second point of inflexion with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 19.68 mg of $C_{15}H_{10}BrClN_4S$.

IMPURITIES

Specified impurities: B.

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.*



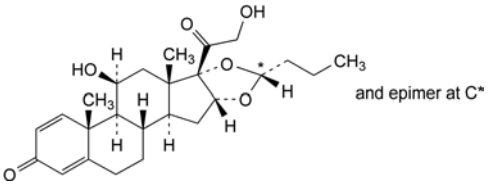
A. R1 = CH_3, R2 = H: 4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (desbromobrotizolam),

B. R1 = H, R2 = Br: 2-bromo-4-(2-chlorophenyl)-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (desmethylbrotizolam).

01/2010:1075

BUDESONIDE

Budesonidum



$C_{25}H_{34}O_6$ M_r 430.5

[51333-22-3]

DEFINITION

Mixture of the C-22*S* (epimer A) and the C-22*R* (epimer B) epimers of 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

Content: 97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *budesonide CRS.*

B. Thin-layer chromatography (*2.2.27*).

Solvent mixture: *methanol R, methylene chloride R* (10:90 *V/V*).

Test solution. Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a). Dissolve 25 mg of *budesonide CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b). Dissolve 12.5 mg of *triamcinolone acetonide CRS* in reference solution (a) and dilute to 5 mL with reference solution (a).

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 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).

Detection B: spray with *alcoholic solution of sulfuric acid R*; heat at 120 °C for 10 min or until the spots appear and allow to cool; examine the chromatograms 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 clearly separated spots.

C. Dissolve about 2 mg in 2 mL of *sulfuric acid R*. Within 5 min a yellow colour develops. Within 30 min the colour changes to brown or reddish-brown. Cautiously add the solution to 10 mL of *water R* and mix. The colour fades and a clear solution remains.

D. Dissolve about 1 mg in 2 mL of a solution containing 2 g of *phosphomolybdic acid R* dissolved in a mixture of 10 mL of *dilute sodium hydroxide solution R*, 15 mL of *water R* and 25 mL of *glacial acetic acid R*. Heat for 5 min on a water-bath. Cool in iced water for 10 min and add 3 mL of *dilute sodium hydroxide solution R*. The solution is blue.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture: *acetonitrile R, phosphate buffer solution pH 3.2 R* (32:68 *V/V*).

Test solution (a). Dissolve 50 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50 mL with *phosphate buffer solution pH 3.2 R*.

Test solution (b). Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *phosphate buffer solution pH 3.2 R*.

Reference solution (a). Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dissolve 5 mg of *budesonide for system suitability CRS* (containing impurities A, D, G, K and L) in 1.5 mL of *acetonitrile R* and dilute to 5 mL with *phosphate buffer solution pH 3.2 R*.

Reference solution (c). Dissolve 25.0 mg of *budesonide CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *phosphate buffer solution pH 3.2 R*.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

– *temperature*: 50 °C.

Mobile phase:

– *mobile phase A*: *anhydrous ethanol R, acetonitrile R, phosphate buffer solution pH 3.2 R* (2:32:68 *V/V/V*);

– *mobile phase B*: *acetonitrile R, phosphate buffer solution pH 3.2 R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 38	100	0
38 - 50	100 → 0	0 → 100
50 - 60	0	100

Flow rate: 1 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities: use the chromatogram supplied with *budesonide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, D, G, K and L.

Relative retention with reference to budesonide epimer B (retention time = about 17 min): impurity A = about 0.1; epimers of impurity D = about 0.63 and 0.67; impurity L = about 0.95; epimers of impurity G = about 1.2 and 1.3; epimers of impurity K = about 2.9 and 3.0.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the 1st of the 2 peaks due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer A (the 2nd of the 2 principal peaks); and minimum 3, where H_p = height above the baseline of the peak due to impurity L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer B (the 1st of the 2 principal peaks).

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.8; impurity K = 1.3;

– *impurities A, L*: for each impurity, not more than twice the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *impurities D, K*: for each impurity, for the sum of the areas of the 2 epimer peaks, not more than twice the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *unspecified impurities*: for each individual peak, not more than the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than 5 times the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.5 per cent);

– *disregard limit*: 0.5 times the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.05 per cent).

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

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 21	100	0
21 - 22	100 → 0	0 → 100
22 - 31	0	100

Injection: 20 µL of test solution (b) and reference solutions (b) and (c).

Retention time: budesonide epimer B = about 17 min; budesonide epimer A = about 19 min.

System suitability:

– *resolution*: minimum 1.5 between the 2 principal peaks (budesonide epimers A and B) in the chromatogram obtained with reference solution (c);

– *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer B (the 1st of the 2 principal peaks) in the chromatogram obtained with reference solution (b).

Limit:

– *epimer A*: 40.0 per cent to 51.0 per cent of the sum of the areas of the 2 peaks due to the budesonide epimers.

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

ASSAY

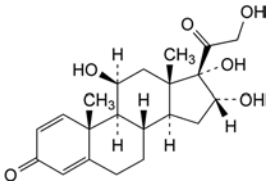
Liquid chromatography (*2.2.29*). Examine the chromatograms obtained in the test for epimer A.

Calculate the percentage content of $C_{25}H_{34}O_6$ from the sum of the areas of the 2 peaks due to the budesonide epimers and the declared content of *budesonide CRS*.

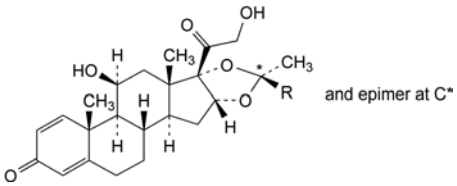
IMPURITIES

Specified impurities: A, D, K, L.

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*): *B, C, E, F, G, H, I, J.*

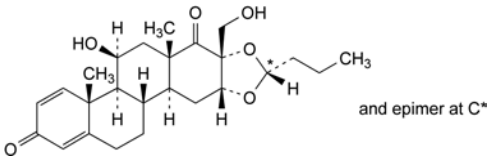


A. 11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione,

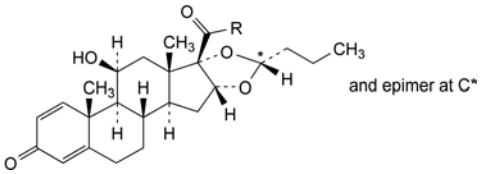


B. R = H: 16α,17-[(1*RS*)-ethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione,

F. R = CH_3: 16α,17-[1-methylethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione,

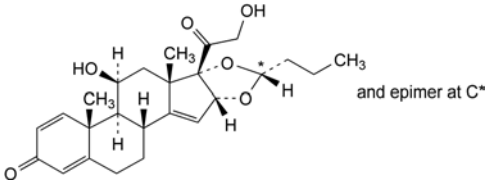


C. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-*D*-homoandrosta-1,4-diene-3,17a-dione,

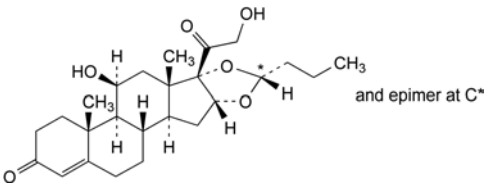


D. R = CHO: 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al,

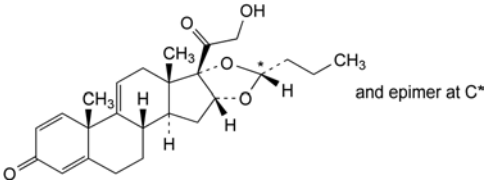
K. R = CH_2-O-CO-CH_3: 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione-21-acetate,



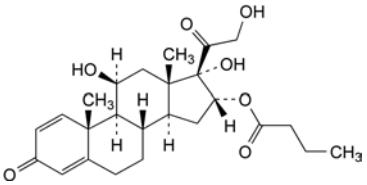
E. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4,14-triene-3,20-dione,



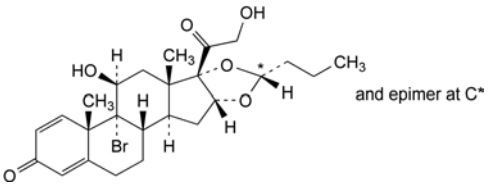
G. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregn-4-ene-3,20-dione.



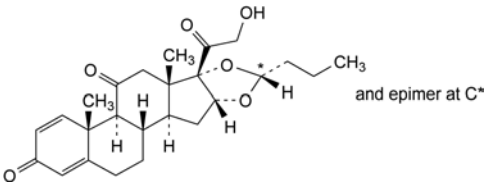
H. 16α,17-[(1*RS*)-butylidenebis(oxy)]-21-hydroxypregna-1,4,9(11)-triene-3,20-dione,



I. 11β,17,21-trihydroxy-3,20-dioxopregna-1,4-dien-16α-yl butanoate,



J. 16α,17-[(1*RS*)-butylidenebis(oxy)]-9α-bromo-11β,21-dihydroxypregna-1,4-diene-3,20-dione,



L. 16α,17-[(1*RS*)-butylidenebis(oxy)]-21-hydroxypregna-1,4-diene-3,11,20-trione.

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BUFEXAMAC

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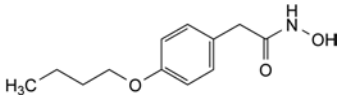

$C_{12}H_{17}NO_3$ M_r 223.3

[2438-72-4]

DEFINITION

2-(4-Butoxyphenyl)-*N*-hydroxyacetamide.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, soluble in dimethylformamide, slightly soluble in ethyl acetate and in methanol.