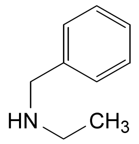

F. *N*-benzylethanamine (benzylethylamine).

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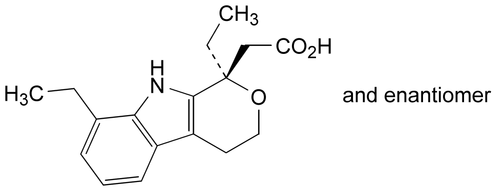
ETODOLAC

Etodolacum



$C_{17}H_{21}NO_3$ M_r 287.4
[41340-25-4]

DEFINITION

2-[(1*RS*)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 144 °C to 150 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *etodolac CRS*.

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

Test solution. Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 10 mg of *etodolac CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel GF_{254} plate R* previously activated by heating at 105 °C for 1 h.

Place the plate in an unsaturated chamber containing a mixture of 20 volumes of a 25 g/l solution of *ascorbic acid R* and 80 volumes of *methanol R*. Allow the solution to ascend 1 cm above the line of application on the plate, remove the plate and allow it to dry for at least 30 min.

Mobile phase: *glacial acetic acid R, anhydrous ethanol R, toluene R* (0.5:30:70 *V/V/V*).

Application: 10 µl.

Development: 2/3 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: 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 the reference solution.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20.0 mg of the substance to be examined in *acetonitrile R1* and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with *acetonitrile R1*. Dilute 1.0 ml of this solution to 20.0 ml with *acetonitrile R1*.

Reference solution (b). Dissolve 4 mg of *etodolac impurity H CRS* in the test solution and dilute to 10 ml with the same solution. Dilute 0.5 ml of this solution to 50 ml with *acetonitrile R1*.

Reference solution (c). Dissolve 4 mg of *etodolac for peak identification CRS* (containing impurities A, B, C, D, E, F, G, H, I and K) in 10 ml of *acetonitrile R1*.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (3.5 µm);
- *temperature*: 35 °C.

Mobile phase:

- *mobile phase A*: 0.77 g/l solution of *ammonium acetate R*;
- *mobile phase B*: mobile phase A, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	80 → 50	20 → 50
25 - 42	50	50
42 - 48	50 → 80	50 → 20

Flow rate: 1 ml/min.

Detection: spectrophotometer at 225 nm.

Injection: 5 µl.

Identification of impurities: use the chromatogram supplied with *etodolac for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E, F, G, H, I and K.

Relative retention with reference to etodolac (retention time = about 16.7 min): impurity A = about 0.68; impurity B = about 0.83; impurity C = about 0.85; impurity H = about 1.09; impurity D = about 1.17; impurity G = about 1.19; impurity E = about 1.20; impurity F = about 1.22; impurity I = about 1.50; impurity K = about 2.37.

System suitability: reference solution (b):

- *resolution*: minimum 5.0 between the peaks due to etodolac and impurity H.

Limits:

- *impurity C*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *impurities A, B, D, E, F, G, H, I, K*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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: maximum 300 ppm.

Dissolve 1.0 g of the substance to be examined in 60 ml of *methanol R*, add 10 ml of *water R* and 20 ml of *dilute nitric acid R*. Titrate with *0.01 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.01 M silver nitrate* is equivalent to 0.3545 mg of Cl.

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

2.0 g complies with test C. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R.*

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

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

ASSAY

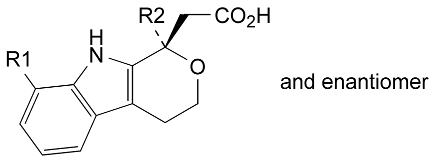
Dissolve 0.250 g in 60 ml of *methanol R*. Titrate with *0.1 M tetrabutylammonium hydroxide* determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 28.74 mg of $C_{17}H_{21}NO_3$.

IMPURITIES

Specified impurities: A, B, C, D, E, F, G, H, I, K.

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*): *J, L.*



A. R1 = H, R2 = CH_2-CH_3: 2-[(1*RS*)-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (8-desethyl etodolac),

B. R1 = CH_3, R2 = CH_2-CH_3: 2-[(1*RS*)-1-ethyl-8-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (8-methyl etodolac),

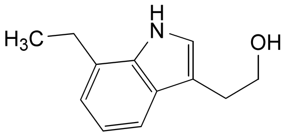
C. R1 = CH_2-CH_3, R2 = CH_3: 2-[(1*RS*)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (1-methyl etodolac),

D. R1 = $CH(CH_3)_2$, R2 = CH_2-CH_3: 2-[(1*RS*)-1-ethyl-8-(1-methylethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (8-isopropyl etodolac),

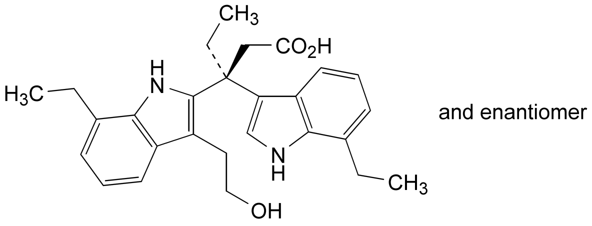
E. R1 = CH_2-CH_2-CH_3, R2 = CH_2-CH_3: 2-[(1*RS*)-1-ethyl-8-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (8-propyl etodolac),

F. R1 = CH_2-CH_3, R2 = $CH(CH_3)_2$: 2-[(1*RS*)-8-ethyl-1-(1-methylethyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (1-isopropyl etodolac),

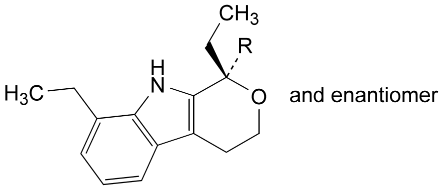
G. R1 = CH_2-CH_3, R2 = CH_2-CH_2-CH_3: 2-[(1*RS*)-8-ethyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetic acid (1-propyl etodolac),



H. 2-(7-ethyl-1*H*-indol-3-yl)ethanol,

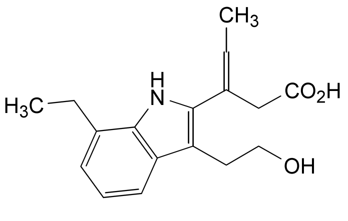


I. (3*RS*)-3-[7-ethyl-3-(2-hydroxyethyl)-1*H*-indol-2-yl]-3-(7-ethyl-1*H*-indol-3-yl)pentanoic acid (etodolac dimer),



J. R = CH_3: (1*RS*)-1,8-diethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (decarboxy etodolac),

K. R = CH_2-CO-O-CH_3: methyl 2-[(1*RS*)-1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl]acetate (etodolac methyl ester),



L. (*EZ*)-3-[7-ethyl-3-(2-hydroxyethyl)-1*H*-indol-2-yl]pent-3-enoic acid.