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IDENTIFICATION OF THE HYDROLYTIC DEGRADATION PRODUCT OF IRBESARTAN IN AQUEOUS SOLUTION

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Abstract

The hydrolytic degradation of irbesartan in borate buffer (pH 9.80) at 70 ± 1° C was studied. The degradation was hydroxide ion catalyzed. The separation of irbesartan from the degraded product was achieved by high performance liquid chromatography. The isolated degraded product was confirmed by its retention time. The characterization was done by elemental and infrared spectroscopic analyses. The characterized degraded product is methyl-biphenyltetrazole.

Keywords: hydrolysis, degradation, irbesartan, aqueous solution, buffer

INTRODUCTION

Irbesartan (Fig. 1), 2-n –butyl-4-spirocyclopentane-1-[{(2'-tetrazol-5-yl)biphenyl-4-yl}methyl]-2-imidazol-5-one is a potent, long-acting nonpeptide A II receptor antagonist with a high specificity for the angiotensin type 1 subtype (Waber, 2001; Gillis 1997). Clinically, it is used in the treatment of hypertension, diabetic neuropathy and heart failure (Cazaubon *et al*., 1993). As drug purity is synonymous with drug safety, this investigation was undertaken to isolate, identify and characterize the degradation product (s) of irbesartan. Previous study (Mbah, 2004) has reported the kinetics of degradation of irbesartan in basic aqueous solutions. Since high performance liquid chromatography is a stability indicating technique used to determine the purity of both bulk and formulated pharmaceutical substances (Arii *et al*., 1999), it was therefore considered the method of choice in this investigation. The objective of this present study was to isolate and identify the degradation product(s) of irbesartan using a stability indicating high performance liquid chromatography.

EXPERIMENTAL

Materials and Apparatus

Irbesartan (Bristol-Meyers, USA), benzoic acid (Fisher Scientific, USA). All the other organic solvents used were of HPLC grade (Fisher Scientific). All separations were carried out on Hitachi LC 6200 pump and AS 2000 autosampler, Kratos Spectroflow 783 detector. A Vydac preparative column C_{18}, 150 mm x 22 mm, 3.5 μm was used. Infrared spectra were obtained on a Perkin-Elmer Grating IR-983G spectrophotometer using KBr pellets.

Chromatographic procedure

The mobile phase consisted of 1 % aqueous acetic acid in methanol (30 : 70). The flow rate was 5 ml/min at room temperature. The injection volume was 20 µl and detection was effected at 254 nm.

Standard solution

The stock solution of irbesartan (100 µg/ml) was prepared in methanol. Aliquots (10-50 µg/ml) of the standard stock solution and 1-ml aliquot of the internal standard solution (400 µg/ml) were pipetted into a 10 ml volumetric flask and diluted to volume with methanol. The solutions were used to determine the system suitability.

Kinetic measurement

The kinetic study was performed in borate buffer solution (pH 9.80) at 70 ± 1° C. The total buffer concentration was 0.1 mol/L and a constant ionic strength (µ) of 0.5 was maintained by adding a calculated amount of potassium chloride. The buffer solution containing irbesartan (250 mg/ml) was kept in a water bath at 70 ± 1° C. Aliquots were withdrawn at intervals and injected into the chromatograph after the addition of internal standard (benzoic acid). Eluate was collected after the injection of the solution containing only the degraded product at the retention time of the degraded product.

RESULTS AND DISCUSSION

The kinetics of hydrolysis of irbesartan was studied at pH 9.80 and temperature of 70 ± 1° C. Irbesartan and the degraded product (Fig. 2) were successively resolved as shown in the chromatogram (Fig. 3). The base-catalyzed hydrolytic degradation of irbesartan yielded a single major degraded product that could absorb within the UV wavelength region. The reaction was found to be represented as first-order with respect to irbesartan. The degradation was followed till irbesartan was completely degraded. The degraded product was isolated and characterized by elemental and spectroscopic analyses. The elemental analysis gave the following percent content. Irbersartan : Cal. for $C_{25}N_6OH_{28}$:C, 70.06; N, 19.60; H, 6.53. Found: C, 70.22; N, 19.71; H, 6.58. Degraded product: Cal. for $C_{14}H_{11}N_4$: C, 71.49; N, 23.83; H, 4.68. Found : C, 71.46; N, 23.88; H, 4.71.The IR spectra of irbesartan and the degraded product gave the following vibrational frequencies. Irbesartan : 2980 (C-H, triplets, Ar), 1730 (C=O), 1620 (C=N), 1550 (C=C, Ar), 1430 (N=N) and 1400 (α-CH_2). Degraded product : 2990 (C-H, triplets, Ar), 1640 (C=N), 1580 (C=C, Ar) and 1445 (N=N). The carbonyl functional group of the lactam ring and the α-methylene group both present in irbesartan were found to be absent in the degraded product. On the basis of

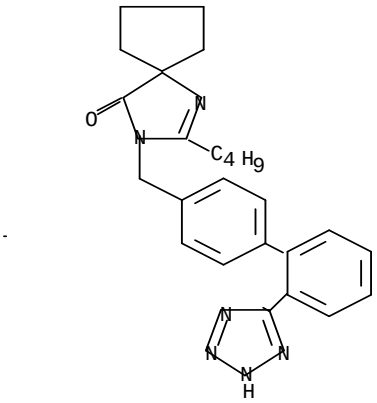

Figure 1 Irbesartan

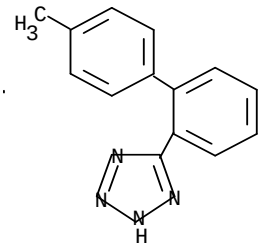

Figure 2 Degraded Product

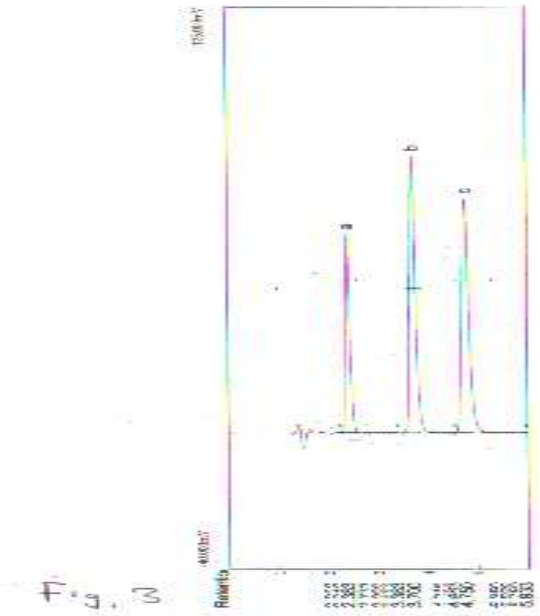

Figure 3: Chromatogram of irbesartan, benzoic acid (internal standard) and degraded product. Peak a = internal standard, Peak b = degraded product, Peak c = irbesartan.

the infrared spectra of irbesartan and the degraded product, a plausible reaction mechanism of the hydrolysis is the cleavage of n-butyl-spirocyclopentane-imidazolinone side chain to give methyl-biphenyltetrazole as the major degraded product.

CONCLUSION

The hydrolytic degradation of irbesartan at 70 ± 1° C gave a single major degraded product absorbable within the UV wavelength region. The elemental and spectroscopic analyses confirmed the
degraded compound to be methyl-biphenyl tetrazole. The other degraded product that could not be detected is n-butylspiropentanyl-imidazolinone.

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