Indian Journal of Chemistry
Vol. 48B, May 2009, pp. 741-745

Note

Synthesis of impurity A in Carvedilol: a β-adrenergic receptor

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Received 4 August 2008; accepted (revised) 29 January 2009

Carvedilol is prepared by different synthetic approaches. Almost in all the approaches the major impurities that are known in the literature **A**, **B, C, D** and **E** are listed in European pharmacopoeia. The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. In this publication, a description of these impurities and their origins in Carvedilol process are presented along with the preparation of impurity **A**.

Keywords: Carvedilol, impurities, β-adrenergic receptor

Carvedilol **1**, an adrenergic antagonist with non selective β and α_1 receptor blocking agent and a vasodilatation drug with antioxidant activity[1-3]. Carvedilol has demonstrated significant clinical benefits in the management of patients with heart failure and in the post-myocardial infarction setting. It also possesses unique ancillary properties that may account for positive results in a number of clinical trials. It appears to offer particular advantages in the treatment of co-morbid conditions, including coronary artery disease, stroke hypertension, renal failure, diabetes and arterial fibrillation[4-6] that can independently contribute to the progression of heart failure (**Figure 1**).

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (*i.e.* the identity as well as the quantity of impurity in the pharmaceuticals), is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) are slowly in-corporating limits to allowable levels of impurities present in the APIs or formulations.

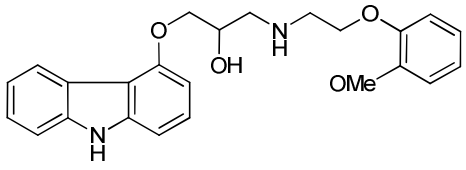

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Figure 1

The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances[7], products[8] and residual solvents[9]. There is a good significant demand for the impurity-reference standards along with the API reference standards for both regulatory authorities and pharmaceutical companies. A number of recent articles[10-12] have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using mass spectrometry, Nuclear Magnetic Resonance (NMR). High-performance liquid chromatography (HPLC), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), and tandem mass spectrometry for pharmaceutical substances.

The procedure of impurity profiling, begins with the detection of the impurities using the thin-layer chromatography, high-performance liquid chromatography or gas chromatography. Procurement of standard impurity samples from the synthetic organic chemists which include, last intermediate of the synthesis, products of predictable side reaction, degradation products if any, *etc*.

The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI/ESI facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

The important step in the impurity profiling is the synthesis of the material (*impurity standard*) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is useful for analytical method development and validation.

There are many synthetic methods known in the literature for the synthesis of Carvedilol. Innovator route for the preparation of Carvedilol[13] involves the formation of impurities **A**, **B**, **D** and **E**. The major drawback of this route is the formation of impurity **B** in excess.

Another route to avoid the formation of impurity **B** (Ref. 14) involves the formation of impurity **A**, **C** and **D**.

Sources of Impurities

Impurity A

In the reaction of 9*H*-carbazol-4-ol with epichlorohydrin, there is a slight formation of 4,9-bis(oxiran-2-ylmethyl)-9*H*-carbazole along with 4-(oxiran-2-ylmethyl)-9*H*-carbazole followed by reaction with 2-(2-methoxyphenoxy)ethanamine, 4-(oxiran-2-ylmethyl)-9*H*-carbazole converts to the Carvedilol and 4,9-bis(oxiran-2-ylmethyl)-9*H*-carbazole converts to the 1-(4-(2-hydroxy-3-(2-(2-methoxyphenoxy)ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethyl amino)propan-2-ol (impurity **A**).

Impurity B

While opening of 4-(oxiran-2-ylmethyl)-9*H*-carbazole with 2-(2-methoxyphenoxy)ethanamine there is a formation of impurity **B** in excess. Usually, when epoxides are opened with the primary amines, there is a chance of secondary amine formed attacking again to the epoxy molecule and forming a dimer impurity in the opening of the epoxide chemistry. This problem is generally solved by using excess of amino compound by mole ration or changing the addition pattern such that the availability of the amino compound is more for opening of the epoxide. This may not be possible in all cases in lieu of the cost and removal of the excess amine that is left unreacted.

Impurity C

To avoid the formation of impurity **B**, 4-(oxiran-2-ylmethoxy)-9*H*-carbazole is opened with *N*-benzyl-2-(2-methoxyphenoxy)ethanamine instead of 2-(2-methoxyphenoxy)ethanamine followed by catalytic *N*-debenzylation at the final stage. According to the literature knowledge, *N*-debenzylation reaction never goes 100% completion, leading the traces of *N*-benzyl Carvedilol (Impurity **C**) as major impurity in the final product. The European pharmacopoeia has covered the limit of impurity **C** not more than 0.02% due to its toxic nature and practically it is very difficult to achieve this level.

Impurity D and E

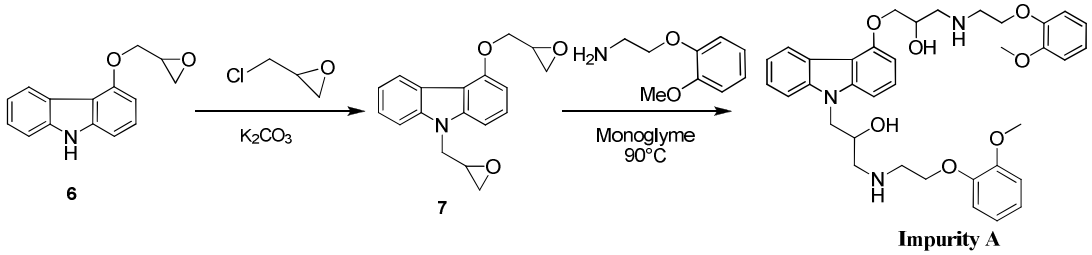
Impurity **D** (Ref. 15) is 4-(oxiran-2-ylmethoxy)-9*H*-carbazole and impurity **E** (Ref. 16) is 2-(2-methoxy phenoxy)ethanamine which are the starting materials for the preparation of Carvedilol in **Scheme I**.

Carvedilol impurities **B** and **C** are well documented in the literature[13,14]. However, there is no literature available for the synthetic approach of impurity **A** as on date. Out of five impurities, impurity **A** is critical to synthesis. This impurity standard is not well available with pharmaceutical companies. This made us to provide a feasible synthetic approach for the preparation of impurity **A** to cater the needs of the pharmaceutical industry as well as pharmacopoeias. Present paper describes the simple and facile synthesis for impurity **A**. This may serve as a standard for impurity profiling in drug development.

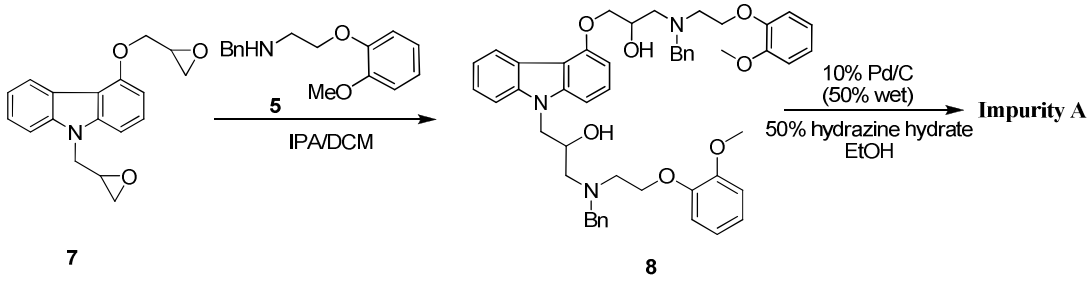
Results and Discussion

Condensation of 4-((oxiran-2-yl)methoxy)-9*H*-carbazole **6** with epichlorohydrin in the presence of a base afforded 4,9-bis(oxiran-2-ylmethyl)-9*H*-carbazole **7** which is reacted with 2-(2-methoxy phenoxy)ethanamine to give impurity **A** (**Scheme I**).

In another way it has been prepared by the coupling of 2-(2-methoxyphenoxy)-*N*-benzylethanamine **5** with disubtituted carbazole **7** affording the corresponding dibenzylated impurity **A 8**, which is subjected to reduction/debenzylation in presence of



Scheme I



Scheme II

10% palladium on carbon as a catalyst and hydrazine hydrate as hydrogen donor to give impurity **A** (**Scheme II**).

In the synthetic approach in **Scheme II**, the catalytic transfer hydrogenation (CTH), *i.e.* conversion of compound **8** to impurity **A** was attempted by using hydrogen donors like hydrazine hydrate, ammonium formate and sodium hypophosphite. Of the three hydrogen donors studied, ammonium formate and hydrazine hydrate are more effective. The conditions reported here are optimized as the reaction is highly dependent on the hydrogen donor and the solvent used.

4-((oxiran-2-yl)methoxy)-9*H*-carbazole **6** (Ref. 16), 2-(2-methoxyphenoxy)ethanamine[17a] and 2-(2-methoxy phenoxy)-*N*-benzylethanamine[17] **5** are prepared by the reported method.

Experimental Section

Melting points are determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra are recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra are recorded on Varian 400 MHz spectrometer using DMSO-d_6, $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra are recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts are dried over sodium sulfate after work-up. The dry reactions are carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used are of commercial grade. TLC is performed on precoated silica-gel plates.

Preparation of 1-(2-chloroethoxy)-2-methoxybenzene 4. To a solution of aqueous sodium hydroxide (145.5 g, 2.73 mole in water, 750 mL) and tetrabutylammoniumbormide (11.0 g; 0.0244 mole), 2-methoxyphenol (Guaiacol; 150.0 g, 0.906 mole) and ethylene dichloride (750 mL) were added slowly at RT. Reaction mixture was heated to reflux for 4 hr. After completion of the reaction, the two layers were separated and the organic layer was washed with 10% sodium hydroxide solution. The separated organic layer was distilled under vacuum and the obtained residual oil was purified by careful distillation at 110-120°C to give 1-(2-chloroethoxy)-2-methoxybenzene (189.9 g, 84.2%).

Preparation of *N*-benzyl-2-(2-methoxyphenolxy)ethanamine 5. To benzylamine (230 g, 2.149 mole), 1-(2-chloroethoxy)-2-methoxybenzene **4** (l00 g, 0.535 mole) was added at 130-145°C and the reaction mixture was heated to reflux for 2 hr. After completion of the reaction, the reaction mass quenched with ice cooled 10% hydrochloric acid solution. The reaction mixture was stirred at 15-20°C for 2 hr. The precipitated solid was filtered and washed with ice cold water. The solid obtained was taken into water and *p*H was adjusted to 10-12 with sodium hydroxide solution. The precipitated solid was filtered, washed with water and dried to give *N*-benzyl-2-(2-methoxy phenoxy)ethanamine dihydrate (55.4 g, 35.2%); ^{1}H NMR: 3.73 (s, 3H, OCH_3), 3.9 (t, 2H, CH_2), 4.8 (br, 1H, NH), 6.8-6.9 (d, 4H, Ar-H), 7.1-7.2 (dd, 4H, Ar); MS: *m/z* $[M]^+$ 257.

Preparation of 4-(oxiran-2-ylmethoxy)-9-(oxiran-2-ylmethyl)-9*H*-carbazole 7. A suspension of 4-(oxiran-2-ylmethoxy)-9*H*-carbazole **6** (50.0 g, 0.208 mole), potassium carbonate (100.0 g, 0.723 mole), and epichlorohydrin (300 mL, 3.84 mole) was heated to reflux for 20-25 hr. After completion of the reaction, the reaction mixture was cooled to 25-30°C. Reaction mass was filtered and the solids were washed with acetonitrile. The filtrate was concentrated under vacuum at 80°C. The obtained residue was dissolved in dichloromethane, washed with water, dried over sodium sulfate and the solvent was evaporated. The obtained residue was treated with methanol and the precipitated solid was filtered and dried to give 4-(oxiran-2-ylmethoxy)-9-(oxiran-2-

ylmethyl)-9*H*-carbazole **7** (23.2 g, 37.6%); m.p. 98-102°C; ^{1}H NMR ($CDCl_3$): δ 2.6-2.8 (dd, 2H, OCH_2), 3.3 (m, 1H, CH), 3.5 (s, 1H, CH), 4.4 (dd, 2H, N-CH_2), 4.6 (dd, 2H, O-CH_2), 6.8 (d, 1H, Ar-H), 7.2-7.6 (m, 5H, Ar-H), 8.2 (d, 1H, Ar-H), MS: *m/z* [M^+] 295.

Preparation of 1-(4-(2-hydroxy-3-(2-(2-methoxyphenoxy)ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino)propan-2-ol (impurity A). 2-(2-Methoxyphenoxy) ethanamine (14.1 g; 0.084 mole) was suspended in monoglyme (60 mL) and diepoxycarbazole **7** (5 g, 0.0169 mole) was added in portions for about 1 hr at 90°C. Reaction was maintained at the same temperature for 12 hr. After completion of the reaction, reaction mass was cooled to ambient temperature, and the solvent was removed under vacuum. The obtained residue was diluted with water and stirred at ambient temperature for about 30 min and the water layer was decanted. The same process was repeated for four times. Finally the title product was purified by flash column chromatography (3.5 g, 32.8%); ^{1}H NMR: δ 2.0 (s, 1H, NH), 2.8 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.0 (s, 1H, CH), 4.1 (m, 2H, CH_2), 4.2 (d, 2H, OCH_2), 5.2 (s, 1H, OH), 6.7-7.3 (m, 10H, Ar-H), 8.2 (s, 1H, Ar-H), 11.2 (s, 1H, NH); ^{13}C NMR: δ 48.4, 48.7, 51.9, 52.5, 55.8, 68.8, 68.9, 77.3, 102.4, 108.5, 114.0, 114.2, 111.8, 119.4, 120.8, 121.6, 122.1, 122.9, 124.8, 126.5, 140.1, 149.0, 142.3, 148.1, 149.0; MS: *m/z* 629 $[M]^+$

Alternative preparation of impurity A

Preparation of 1-(benzyl(2-(2-methoxyphenoxy)-ethyl)amino)-3-(4-(3-(benzyl(2-(2-methoxy phenolxy)ethyl)amino)-2-hydroxypropoxy)-9H-carbazol-9-yl)propan-2-ol 8. A mixture of 4-(oxiran-2-ylmethoxy)-9-(oxiran-2-ylmethyl)-9*H*-carbazole **7** (20 g; 0.067 mole), *N*-benzyl-2-(2-methoxyphenoxy)ethanamine dihydrate **5** (51.6 g 0.176 mole) and isopropyl alcohol (250 mL) was heated to reflux for 8 hr. After completion of the reaction, distill off the solvent from the reaction mass under vacuum at below 80°C. The crude compound was purified by column chromatography with 30-60% ethyl acetate and hexane as eluent to give **8** (17.0 g, 31.0%).

Preparation of 1-(4-(2-hydroxy-3-(2-(2-methoxyphenoxy)ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino)propan-2-ol (impurity A) from 8. To a solution of compound **8** (12 g; 0.067 mole) in ethanol (120 mL), 10% Pd-C (12 g) and 50% hydrazine hydrate (6 g) were added and the mixture was heated to reflux for 6 hr. After completion of the reaction, reaction mixture was cooled to RT. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The obtained residue was partitioned between ethyl acetate (3×50 mL) and water (50 mL). The combined organic layer was evaporated under vacuum and the residue was treated with diisopropylether (80 mL) to give the impurity **A** (3.2 g, 34.3%).

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