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Identification and synthesis of potential impurities of rabeprazole sodium*

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Received October 18, 2004, accepted December 31, 2004

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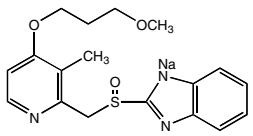
Pharmazie 60: 814–818 (2005)

Rabeprazole sodium (**1**, Achiphex®) is a gastric proton pump inhibitor. It causes dose-dependent inhibition of acid secretion and is useful as an anti-ulcer agent. In the process for the preparation of **1**, two potential unknown impurities were identified in HPLC at levels ranging from 0.05–0.8%. Based on mass spectral data *vide* LC-MS, the two impurities were characterized as 2-{[(4-chloro-3-methyl-2-pyridinyl) methyl] sulfinyl}-1*H*-bezimidazole (**2**, chloro analogue of rabeprazole) and 2-[{(4-methoxy-3-methyl-2-pyridinyl)methyl}sulfinyl]-1*H*-benzimidazole (**3**, methoxy analogue of rabeprazole). The structures were unambiguously established by independently synthesizing them and co-injecting in HPLC. To our knowledge, the compounds **2** and **3** have not been reported as process impurities elsewhere.

1. Introduction

Rabeprazole sodium (**1**) belongs to the class of 2-[[(2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazoles. In general, this class of compounds is used for the prevention and treatment of gastric acid related diseases (Kohl et al. 1998). Compound **1** is used in the treatment of gastro esophageal reflux disease (GERD) and of ulcers and it is chemically known as 2-[{[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl}sulfinyl]-1*H*-benzimidazole sodium (**1**).



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A literature survey revealed various synthetic methods of rabeprazole (Shigeru et al. 1991; Tagami et al. 1999; Cosme et al. 2001; Lim et al. 2000; Coppi et al. 2001). It was synthesized according to Scheme 1, with slight modifications to make it simpler and commercially viable. 4-Nitro-2,3-dimethylpyridine-1-oxide (**4**), on chlorination with $POCl_3$ gave 4-chloro-2,3-dimethylpyridine-1-oxide (**5**). This on condensation with methoxy propanol yielded 4-methoxy propoxy-2,3-dimethylpyridine-1-oxide (**6**), which on further reaction with acetic anhydride, gave 2-acetoxymethyl-4(methoxypropoxy)-3-methylpyridine (**7**). Hydrolysis of **7** with sodium hydroxide rendered 2-hydroxymethyl-4(methoxy propoxy)-3-methylpyridine (**8**), which on chlorination with $SOCl_2$, yielded 2-chloromethyl-4-(methoxy propoxy)-3-methylpyridine hydrochloride (**9**). Condensation of **9** with 2-mercapto-1*H*-benzimidazole (**10**) in the presence of aqueous sodium hydroxide yielded [{(4-methoxy propoxy-3-methyl pyridine-2-yl} methyl]-thio]-1*H*-benzimidazole (**11**), which on oxidation on sulfur with m-CPBA afforded the title compound 2-[[[4-methoxy propoxy-3-methyl-2-pyridinyl] methyl] sulfinyl]-1*H*-bezimidazole (**1**).

During the preparation of rabeprazole (**1**) in the laboratory, two unknown impurities were detected consistently in HPLC along with two known impurities (sulphone and N-oxide) in almost all the batches. A comprehensive study was undertaken to synthesize and characterize these impurities by spectroscopic techniques. An impurity profile study is necessary for any final product to identify and characterize all the unknown impurities that are present even at levels below 0.05%. This became essential in the wake of stringent purity requirements from regulatory authorities. The present study describes the synthesis and characterization of the potential impurities of **1**.

2. Investigations, results and discussion

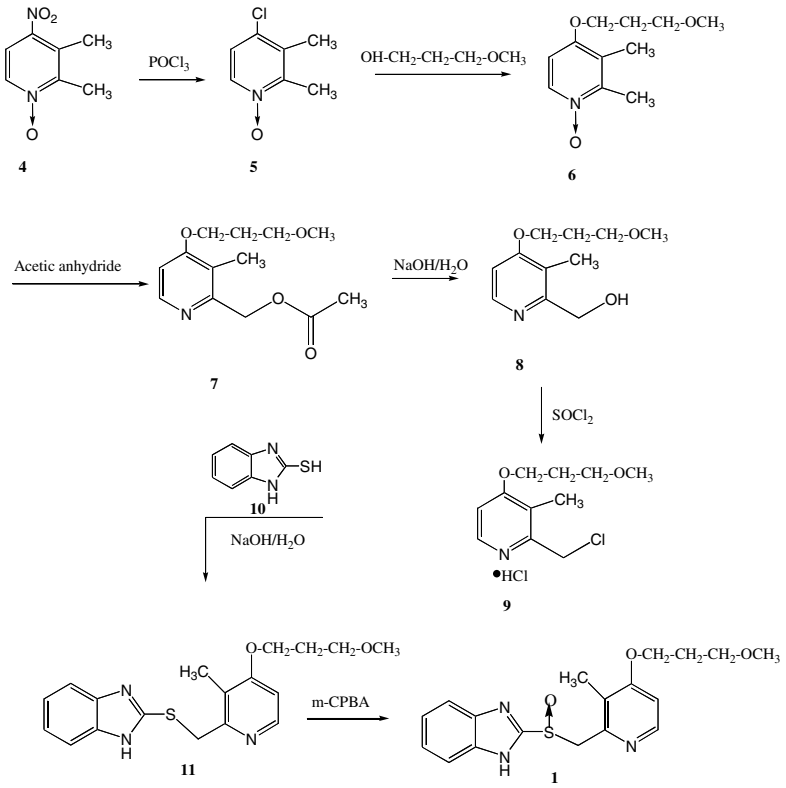
2.1. Detection and identification

The HPLC analysis of rabeprazole sodium showed relative retention times compared to rabeprazole at 0.470 (N-oxide), 0.738 (methoxy), 1.13 (chloro) and 1.36 (sulphone) (Fig. 1). The LC-MS showed two unknown peaks at M^+ ions 301 and 305, and after characterization of the corresponding compounds, they were synthesized independently and co-injected with the sample.

2.2. Formation of impurity **2** *(chloro impurity of rabeprazole)*

During the condensation of 4-chloro-2,3-dimethylpyridine-1-oxide (**5**) with methoxypropanol, trace amount of unreacted **5** was carried along the reaction pathway to yield chloro rabeprazole (0.05–0.8% *vide* HPLC). This impurity was synthesized independently (Scheme 2), and characterized as **2** (2-[[[4-Chloro-3-methyl-2-pyridinyl]methyl] sulfinyl]-1*H*-bezimidazole). It was further co-injected with com-

Scheme 1



pound **1**, to confirm its presence as an impurity. The retention time matched exactly that of impurity **2**.

2.3. Formation of impurity 3 *(methoxy impurity of rabeprazole)*

This impurity was formed during the condensation of 4-chloro-2,3-dimethylpyridine-1-oxide (**5**) with methoxy propanol in the presence of dimethyl sulfoxide and NaOH. Traces of methanol present in the methoxy propanol, also participate in the reaction. The side product is carried to the last stage and finally appears as an impurity, 2-[{(4-methoxy-3-methyl-2-pyridinyl) methyl}sulfinyl]-1*H*-benzimidazole (methoxy impurity of rabeprazole **3**). The preparation of methoxy impurity is shown in Scheme 3.

3. Experimental

3.1. Preparation of the chloro analogue

3.1.1. 4-Chloro-2,3-dimethylpyridine-1-oxide (**5**)

To a solution of 4-nitro-2,3-dimethyl pyridine-1-oxide (**4**, 25 g, 0.15 mol), dichloromethane (150 mL) and dimethyl formamide (5 mL), $POCl_3$ (27.4 g, 0.178 mol) were added slowly at 5 °C for 2 h. The temperature of the reaction was raised to 25 °C and maintained for 12 h. The reaction mass was quenched slowly with soda-ash water slowly at 25 °C, and basified with sodium hydroxide, and extracted with dichloromethane (3×50 mL). The organic layer was separated and concentrated under vacuum. The residue obtained was triturated with petroleum ether (100 mL), and the solid obtained was filtered and dried under vacuum: yield 18.7 g, 80%.

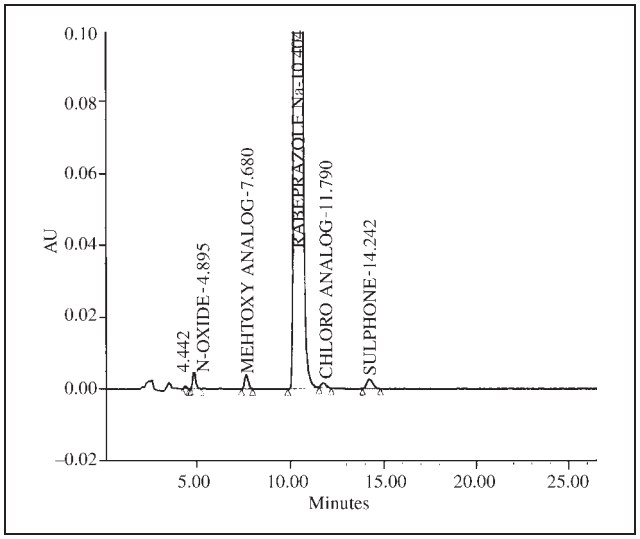


Fig. 1: HPLC chromatogram of rabeprazole sodium (1)

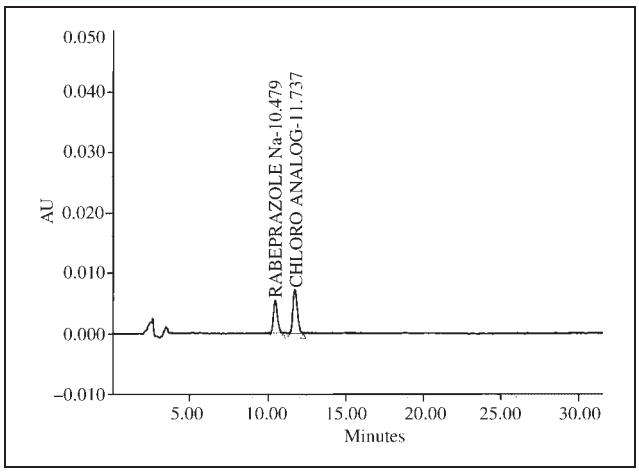
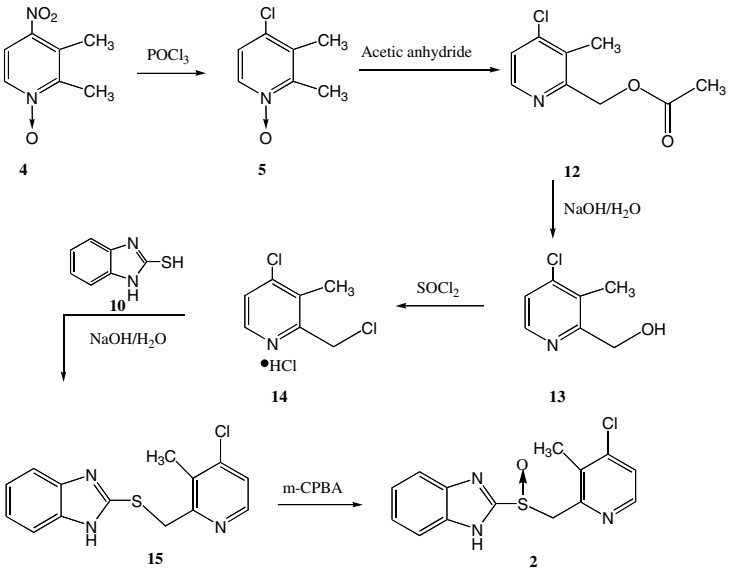


Fig. 2: HPLC chromatogram of chloro analogue of rabeprazole

Scheme 2



3.1.2. 2-Acetoxymethyl-4(chloro)-3-methylpyridine (**12**)

A mixture of 4-chloro-2,3-dimethylpyridine-1-oxide (**5**, 17 g, 0.11 mol), and acetic anhydride (33 g, 0.32 mol), was stirred at 120 °C for 5 h, and the excess acetic anhydride was distilled completely at the same temperature. Compound **12** was obtained as the residue. This residue was used without further purification.

3.1.3. 2-Hydroxymethyl-4(chloro)-3-methylpyridine (**13**)

A mixture of 2-acetoxymethyl-4-(chloro)-3-methylpyridine (**12**, 18 g, 0.09 mol), sodium hydroxide (15 g, 0.37 mol) and water (150 mL) was stirred at 25 °C for 1 h. The reaction mass was extracted with dichloromethane (2 × 50 mL) and the organic layer was distilled completely. A black residue was obtained, which was extracted with petroleum ether (3 × 50 mL), and excess solvent was distilled, resulting in a light brown crude product.

3.1.4. 2-Chloromethyl-4-(chloro)-3-methylpyridine hydrochloride (**14**)

To a mixture of 2-hydroxymethyl-4-(chloro)-3-methylpyridine (**13**, 14 g, 0.09 mol), and dichloromethane (100 mL), thionyl chloride (15.8 g, 0.13 mol) was added slowly at 25 °C for 1 h. After 1 h, excess thionyl chloride and dichloromethane were distilled under vacuum, and the isolated product on triturating with petroleum ether (50 mL) yielded **14** as a fine solid, 15 g, 80%.

3.1.5. [{(4-Chloro-3-methylpyridine-2-yl}methyl]-thio]-1H-benzimidazole (**15**)

To a mixture of 2-mercapto-1*H*-benzimidazole (**10**, 11.8 g, 0.08 mol), sodium hydroxide (14 g, 0.35 mol), and water (100 mL), was added a solu-

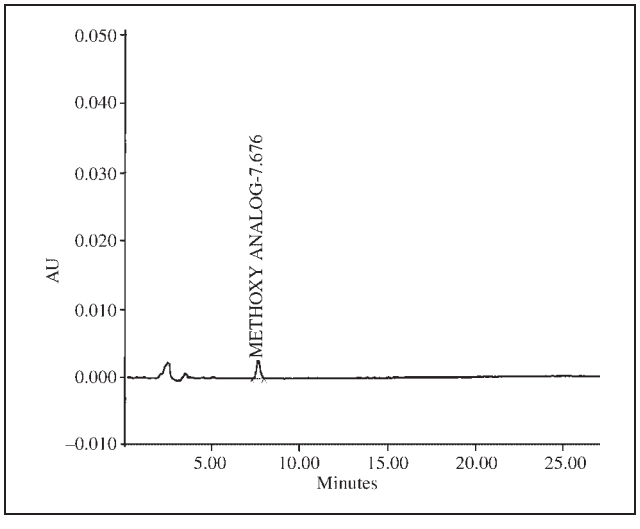


Fig. 3: HPLC chromatogram of methoxy analogue of rabeprazole

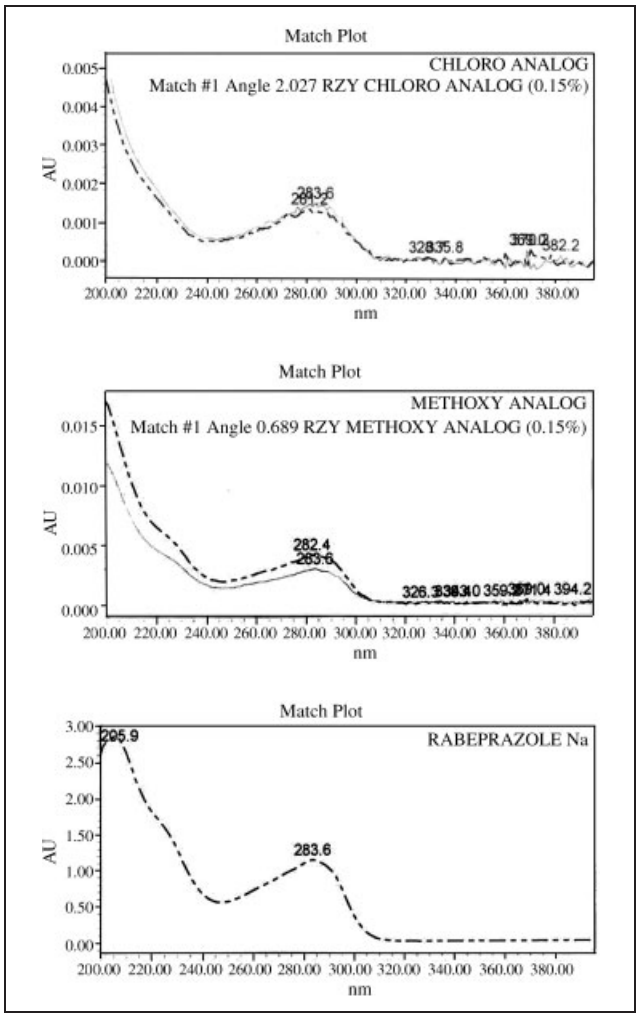
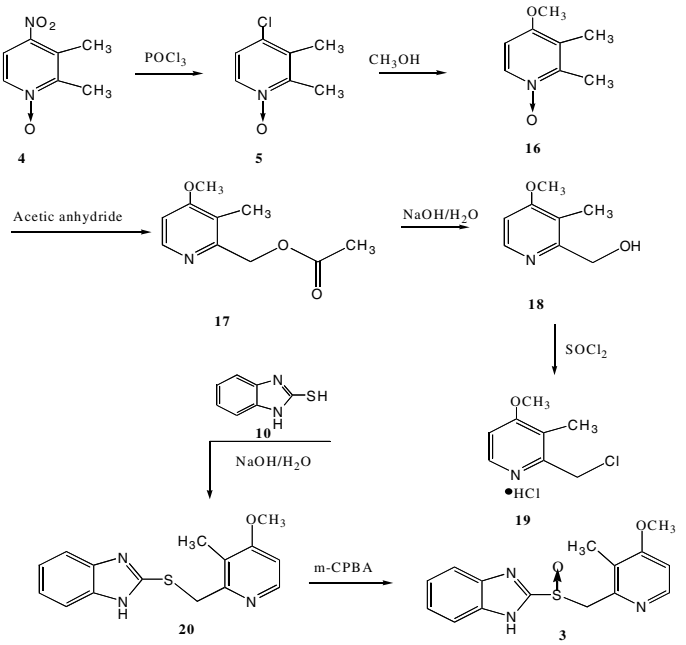


Fig. 4: UV spectrum of chloro and methoxy analogues of rabeprazole

Scheme 3



tion of 2-chloromethyl-4 (chloro)-3-methylpyridine hydrochloride (**14**, 14 g, 0.065 mol) in water (25 mL) at 25 °C for 3 h. After stirring for 1 h at the same temperature, a solid was separated which was filtered and dried under vacuum: yield 18 g, 94%.

3.1.6 2[[[4-Chloro-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-bezimidazole (**2**)

To a solution of [{(4-chloro-3-methyl pyridine-2-yl} methyl]-thio]-1*H*-benzimidazole (**15**, 16 g, 0.05 mol) and dichloromethane (160 mL) was added *m*-chloro per benzoic acid (10.8 g, 0.06 mol) in dichloromethane (100 mL) at −10 to −15 °C for 1 h. The reaction mass was quenched by adding sodium hydroxide (15 g), and water (25 ml). The pH of the reaction mass was adjusted to 8.0–8.5 with acetic acid and was extracted with dichloromethane (3 × 50 mL). The separated organic layer was distilled, and the obtained residue was triturated with petroleum ether at 10 °C until a solid separated. The solid was filtered and dried and characterized as compound **2**, yield: 10 g, 60%.
IR(KBr, cm^{-1}): 3420 (NH); 2972, 2872 (CH); 1560 (C=C). ^{1}H NMR ($CDCl_3$): 2.35 (s, 3 H, CH_3), 4.8 (dd, 2 H, CH_2), 7.29–7.32 (m, 5 H, Ar–H), 8.30 (d, 1 H, Ar–H). Mass (m/e): 305 (M^+). CHN Analysis: Calcd for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96; N, 13.74. Found: C, 54.96; H, 3.93; N, 13.71.

3.2. Preparation of the methoxy analogue

3.2.1. 4-Chloro-2,3-dimethylpyridine-1-oxide (**5**)

To a mixture of 4-nitro-2,3-dimethylpyridine-1-oxide (**4**, 25 g, 0.15 mol), dichloromethane (150 mL), dimethyl formamide (5 mL), $POCl_3$ (27.4 g, 0.18 mol) was added slowly at 5 °C for 2 h. The reaction temperature was raised to 25 °C and maintained for 12 h. The reaction mass was quenched by adding soda-ash water slowly at 25 °C, and then basified with sodium hydroxide. The reaction mass was extracted with dichloromethane (2 × 50 mL). The separated organic layer was distilled and the crude residue obtained was triturated with petroleum ether (100 mL). The solid separated was filtered and dried: yield 18.7 g, 80%.

3.2.2. 2,3-Dimethyl-4(methoxy)pyridine-1-oxide (**16**)

A mixture of sodium hydroxide (17 g, 0.42 mol), dimethyl sulfoxide (34 mL), and methanol (51 g, 1.59 mol) was stirred at 60 °C for 1 h, 4-chloro-2,3-dimethylpyridine-1-oxide (**5**, 17 g, 0.107 mol) was added slowly at same temperature for 1 h and maintained for 3 h. The reaction mass was quenched with water (100 mL) and extracted with dichloromethane (2 × 75 mL). Dichloromethane was evaporated resulting in 15 g of compound **16** as the residue.

3.2.3. 2-Acetoxymethyl-4(methoxy)-3-methylpyridine (**17**)

A mixture of 2,3-dimethyl-4(methoxy)pyridine-1-oxide (**16**, 14 g, 0.01 mol) and acetic anhydride (27.9 g, 0.28 mol) was stirred at 120 °C for 5 h. The excess acetic anhydride was distilled completely at same temperature resulting in 15 g of compound **17** as the residue.

3.2.4. 2-Hydroxymethyl-4(methoxy)-3-methylpyridine (**18**)

A mixture of 2-acetoxymethyl-4(methoxy)-3-methylpyridine (**17**, 14 g, 0.07 mol), sodium hydroxide (14 g, 0.35 mol) and water was stirred at 25 °C for 1 h. The reaction mass was extracted with dichloromethane and the organic layer was distilled completely to obtain the residue which was extracted with petroleum ether. The organic layer was distilled resulting in 10 g of compound **18**, as a light brown residue.

3.2.5. 2-Chloromethyl-4(methoxy)-3-methylpyridine hydrochloride (**19**)

To a mixture of 2-hydroxymethyl-4(methoxy)-3-methylpyridine (**18**, 9 g, 0.06 mol) and dichloromethane (70 mL), thionyl chloride (8.4 g, 0.07 mol) was added slowly at 25 °C for 1 h. The excess thionyl chloride and dichloromethane were distilled from the reaction mass and the product was isolated in petroleum ether (50 mL), 11 g, 90%, **19** as a fine solid.

3.2.6. [{(4-Methoxy-3-methyl pyridine-2-yl} methyl]-thio]-1H-benzimidazole (**20**)

To a mixture of 2-mercapto-1*H*-benzimidazole (**10**, 8.6 g, 0.06 mol), sodium hydroxide (10 g, 0.25 mol), and water (100 ml) was added a solution of 2-chloromethyl-4(methoxy)-3-methylpyridine hydrochloride (**19**, 10 g, 0.05 mol) in water (25 mL) at 25 °C for 3 h. The solid separated after 1 h was filtered to yield compound **20**, 12 g, 88%.

3.2.7. 2-[{(4-Methoxy-3-methyl-2-pyridinyl) methyl}-sulfinyl]-1H-benzimidazole (**3**)

To a solution of [{(4-methoxy-3-methyl pyridine-2-yl} methyl]-thio]-1*H*-benzimidazole (**20**, 10 g, 0.04 mol) and dichloromethane (100 mL) was added *m*-chloro per benzoic acid (8.5 g, 0.05 mol) in dichloromethane (85 mL) at −10 to −15 °C for 1 h. The reaction mass was quenched by adding sodium hydroxide (12 g), and water (25 mL). The pH of the reaction mass was adjusted to 8.0–8.5 with acetic acid and was extracted with dichloromethane (2 × 100 mL). The separated organic layer was distilled and the residue obtained was triturated with petroleum ether at 10 °C until the solid separated. The separated solid was filtered, dried and characterized as compound **3**, yield: 6 g, 57%.
IR(KBr, cm^{-1}): 3447 (NH); 2967, 2843 (CH); 1587 (C=C). ^{1}H NMR ($CDCl_3$): 2.20 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.90 (dd, 2 H, CH_2), 6.85 (d, 1 H, Ar–H), 7.29–7.32 (m, 4 H, Ar–H), 8.30 (d, 1 H, Ar–H). Mass (m/e): 301(M^+). CHN Analysis: Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.77; H, 4.99; N, 13.75.

3.3. Samples

The investigated samples of rabeprazole bulk material and crude samples were synthesized in Dr. Reddy's Laboratories Ltd., Bulk Actives-III, Hyderabad, India.

3.4. High performance liquid chromatography

A Waters Model Alliance 2695 with 2487 detector was used. An in-house LC method was developed for the analysis of rabeprazole, consisting of an Inertsil ODS-3V, 250×4.6 mm column (5 microns or equivalent) with a mobile phase mixture of buffer, acetonitrile in the ratio of 65 : 35, set at a flow rate of 1.0 ml/min for the separation of all impurities. Detection was done at $\lambda = 280$ nm.

3.5. Mass spectrometry

The MS was recorded on a QP-5080A mass spectrometer with ionization electron beam energy of 70 eV. The sample was introduced to the source with the help of a particle beam interface connected to GC by bypassing column. The source quadrupole temperature was maintained at 260 °C. Molecular ions of all the impurities were further confirmed by obtaining the mass spectra on a Perkin Elmer Sciex API 3000 ES/MS. The sample was introduced to the source through a turbo ion spray interface in positive ionization mode.

3.6. NMR spectroscopy

The ^{1}H NMR was carried out on Varian Gemini 200 MHz FT-NMR spectrometer at 25 °C in $CDCl_3$ and ^{1}H chemical shifts are reported on the δ scale in ppm, relative to TMS (δ 0.00).

3.7. FT-IR spectroscopy

FT-IR spectra for compounds **2** and **3** were recorded in the solid state as KBr dispersions using a Perkin-Elmer AD005 FT-IR spectrophotometer.

3.8. UV spectroscopy

UV spectra for compounds **2** and **3** were recorded on a Perkin Elmer lambda 45 UV/Visible spectrophotometer.

* DRL-IPDO-IPM communication No. 0004.

Acknowledgements: The authors wish to thank the management of Research and Development, Dr. Reddy's Laboratories Limited, Integrated Product Development, API, Unit-III, for providing facilities to carry out this work. Cooperation extended by all the colleagues of Analytical R&D division, is gratefully acknowledged.

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