Studies on the Synthesis and Anti-inflammatory Activity of 2,6-Di-tert-butylphenols with a Heterocyclic Group at the 4-Position. V. 1) Elimination Reaction of the Sulfanyl Group of 2,3-Dihydroimidazo[2,1-b]thiazole 1-Oxide

YASUO ISOMURA* and KAZUO KUBO

Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd.,
1-1-8, Azusawa, Itabashi-ku, Tokyo, Japan

(Received March 21, 1984)

Reaction of 6-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-b]thiazole 1-oxide (1) with superoxide anion gave 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazole (2). Compound 2 was also obtained by treatment of 1 with potassium tert-butoxide in dimethyl sulfoxide (DMSO) in the presence of oxygen, while 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (3) was obtained together with 2 in the absence of oxygen. When the same reaction was carried out in N, N-dimethyl formamide, 1 gave 2 and 3 in the absence of oxygen, and 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazole-2-sulfonic acid (4) in the presence of oxygen. A possible mechanistic explanation for the formation of these products is presented. Oxygenation of 2,6-di-hydroimidazo[2,1-b]thiazole 1-oxide (6) was also examined.

**Keywords**—2,6-di-tert-butylphenol; 2,3-dihydroimidazo[2,1-b]thiazole 1-oxide; sulfanyl group; elimination; superoxide; oxygenation

In the previous paper, we reported that 6-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-b]thiazole 1-oxide (1) has potent anti-inflammatory and analgesic activities. 2) 2,6-Di-tert-butylphenol derivatives are known to be antioxidants, and their oxygenation reactions have been extensively studied by several workers. 3) However, there is no report on the oxygenation of 2,6-di-tert-butylphenols with a heterocyclic group to our knowledge. We found that 1 has a radical scavenging activity through a pharmacological study of 1. Because of our interest in the chemical behavior of 1 in relation to its pharmacological activities, we studied the reaction of 1 with superoxide anion. The present paper describes an unexpected elimination reaction of the sulfanyl group of 1 encountered in these studies, as well as the base-catalyzed oxygenation of 1.

When compound 1 was treated with superoxide anion 4) under nitrogen at room temperature, the product isolated was 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazole (2). The structure of 2 was determined on the basis of mass and nuclear magnetic resonance (NMR) spectral data as well as elemental analysis. Mass spectral and microanalytical data indicated a molecular formula of C_{19}H_{26}N_{2}O. In the NMR spectra, vinyl group signals were newly observed at 4.84 ppm (d, J = 11 Hz), 5.32 ppm (d, J = 22 Hz) and 6.90 ppm (dd, J = 11, 22 Hz).

Superoxide anion is a mild multifunctional agent 5) which possesses both oxidizing and reducing abilities and also radical or anionic character, and in this reaction superoxide anion seemed to act as a base and oxidizing agent. Oae et al. 6) reported that the base-catalyzed oxygenation of organic sulfur compounds is closely similar to the oxidation with superoxide anion. Thus, 1 was next subjected to base-catalyzed oxygenation.

Treatment of 1 with potassium tert-butoxide in DMSO gave 2 in the presence of oxygen, and 2 and 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (3) in the
absence of oxygen. When \( N, N \)-dimethyl formamide (DMF) was used as a solvent, similar oxygenation of 1 gave 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazole-2-sulfonic acid (4), while in the absence of oxygen 1 gave 2 and 3. Formation of 2, 3 and 4 can be well rationalized in terms of involvement of the sulenate anion (5a), which is a proposed intermediate in the base-catalyzed oxygenation.\(^7\) Namely, 1 first reacts with base to form 5a. Then, in the presence of oxygen, 5a is oxidized with oxygen to give the sulfinate anion (5b) which undergoes elimination of \( \text{SO}_2 \) to give 2 or further oxidation to give 4. In the absence of oxygen, 5a disproportionates to 5b and 3. Such disproportionation of a sulenate anion has already been proposed.\(^7\) Thus, 2 most probably arises from \( \text{SO}_2 \) elimination of 5b. However, one cannot exclude 5a and the sulfonate anion as potential sources of 2 via \( \text{SO} \) and \( \text{SO}_3 \) elimination. It is reasonable to consider that the reaction of 1 with superoxide anion also proceeds via the above-mentioned mechanism.
For further mechanistic study, 6-phenyl-2,3-dihydropyrazole[2,1-b]thiazole 1-oxide (6) was utilized to avoid complications arising from the hydroxy function. Reaction of 6 with potassium tert-butoxide in DMSO gave 4-phenyl-1-vinylimidazole (7) in the presence of oxygen, and 7 and 4-phenyl-2-thioxo-1-vinyl-4-imidazoline (8) in the absence of oxygen. When DMF was used as a solvent, 6 gave 7 and 8 in the absence of oxygen. Evidence for the presence of the sulphenyl anion as a key intermediate was provided by the formation of methyl 4-phenyl-1-vinylimidazole-2-sulfenate (11). Compound 11 was isolated as a main product in addition to 2-methylthio-4-phenyl-1-vinylimidazole (9) and 2-methylsulfonyl-4-phenyl-1-vinylimidazole (10) when 6 was treated with potassium tert-butoxide in the absence of oxygen, followed by treatment with methyl iodide. In the presence of oxygen, 6 gave 10 and 11. The identity of 9 was confirmed by comparison with an authentic sample which was prepared from 8 and methyl iodide. The site of methylation in 10 and 11 was established by comparison with the isomers 12 and 13, which were obtained by oxidizing 9 and 11 with m-chloroperbenzoic acid, respectively. Namely, the sulfone 10 and sulfenate 11 markedly differed from the sulfoxide 12 and sulfinate ester 13, respectively, in the chemical shift of the methyl group in the NMR spectra.

![Chart 3](chart3.png)

Base-catalyzed elimination reaction of a sulfinyl group has been reported by Wallace et al., who proposed the sulphenyl anion as an intermediate. To our knowledge, however, base-catalyzed elimination of a sulfinyl group in a heterocyclic compound has not been reported. In order to rationalize the formation of 2, we propose a mechanism involving a sulphenyl anion intermediate. However, a detailed mechanistic interpretation must await further study.

**Experimental**

All melting points were determined by using a Yanagimoto micromelting point apparatus, and are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer. The NMR spectra were obtained with a JEOL-FX 90 or 100 spectrometer using (CH₃)₄Si as an internal standard. Mass spectra (MS) were obtained with an RMU-6MG spectrometer.

*4-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazole (2) — Method a: A solution of 6-(3,5-di-tert-butyl-4-
hydroxyphenyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide (1) (1.70 g, 5 mmol) in DMSO (10 ml) was added dropwise to a solution of 18-crown-6-ether (2.60 g, 10 mmol) and potassium superoxide (0.8 g, 10 mmol) in DMSO (25 ml) at room temperature under nitrogen. After being stirred for 4 h, the reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated in vacuo. The residue was subjected to silica gel column chromatography and eluted with CHCl₃ to give 2, 0.6 g (yield 40.3%). NMR (CDCl₃) δ: 1.24 (18H, s, C(CH₃)₃), 4.84 (1H, d, J = 11 Hz, C = CH₂), 5.26 (1H, s, OH), 5.32 (1H, d, J = 22 Hz, C = CH₂), 5.80 (1H, dd, J = 11, 22 Hz, CH = C), 7.36 (1H, s, imidazole-H), 7.60 (2H, s, aromatic-H), 7.65 (1H, s, imidazole-H). MS m/z: 298 (M⁺). IR (KBr): 3650 cm⁻¹ (OH). mp 151—152 °C (from iso-octane). Anal. Calcd for C₁₉H₁₈N₅O: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.24; H, 8.85; N, 9.14.

Method b): A solution of 1 (1.70 g, 5 mmol) and potassium tert-butoxide (1.12 g, 10 mmol) in DMSO (20 ml) was stirred under oxygen at below 25 °C. After being stirred for 15—30 min, the reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated in vacuo. The residue was subjected to silica gel column chromatography to give 2, 1.0 g (yield 67%). 6-Phenyl-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide (6) was treated in similar manner to give 4-phenyl-1-vinylimidazolide (7) (yield 58.8%). NMR (DMSO-d₆) δ: 5.34 (1H, d, J = 9 Hz, C = CH₂), 5.96 (1H, d, J = 16 Hz, C = CH₂), 7.28 (1H, dd, J = 9, 16 Hz, CH = C), 7.44 (3H, aromatic-H), 7.90 (2H, aromatic-H), 8.50 (1H, s, imidazole-H), 9.40 (1H, s, imidazole-H). MS m/z: 170 (M⁺). mp 48—49 °C (from C₆H₁₂). Anal. Calcd for C₁₁H₁₀N₂: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.62; H, 5.72; N, 16.39.

4-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-thioxo-1-vinyl-4-imidazoline (3) and 2 ——A solution of 1 (3.46 g, 10 mmol) and potassium tert-butoxide (2.24 g, 20 mmol) in DMSO (40 ml) was stirred for 0.5 h under argon at room temperature. The reaction mixture was poured into ice-cold dil. HCl solution. The whole was extracted with AcOEt and the extract was dried and concentrated in vacuo. The residue was subjected to silica gel column chromatography and eluted with CHCl₃ to give 2, 0.70 g (yield 23.5%) and 3, 1.53 g (yield 46.4%). NMR (CDCl₃) δ: 1.24 (18H, s, C(CH₃)₃), 4.96 (1H, d, J = 11 Hz, C = CH₂), 5.20 (1H, d, J = 22 Hz, C = CH₂), 5.40 (1H, s, OH), 7.02 (1H, s, imidazole-H), 7.24 (2H, s, aromatic-H), 7.58 (1H, dd J = 11, 22 Hz, C = CH₂), 11.0 (1H, br). MS m/z: 330 (M⁺). IR (KBr): 3500 cm⁻¹ (OH). mp 275—280 °C (dec.) (from CH₂Cl₂). Anal. Calcd for C₁₉H₁₇N₂O: C, 69.05; H, 7.93; N, 8.48. Found: C, 69.30; H, 8.06; N, 8.77. 6 was treated in a similar manner to give 7 (yield, 30.1%) and 4-phenyl-2-thioxo-1-vinyl-4-imidazoline (8) (yield 23.0%). NMR (CDCl₃) δ: 4.96 (1H, d, J = 10 Hz, C = CH₂), 5.20 (1H, d, J = 16 Hz, C = CH₂), 7.16 (1H, s, imidazole-H), 7.24—7.60 (6H, m), 11.70 (1H, br). MS m/z: 202 (M⁺). mp 194—196 °C (from C₆H₁₂). Anal. calcd for C₁₂H₁₀N₂S: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.48; H, 4.93; N, 13.80. When DMF was used as a solvent, 1 gave 2 (13.4%) and 3 (yield, 39.4%), and 6 gave 7 (yield, 39.2%) and 8 (yield, 25.7%).

4-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-vinylimidazolide-2-sulfonic Acid (4) —— A solution of 1 (3.40 g, 10 mmol) and potassium tert-butoxide (2.24 g, 20 mmol) in DMF (40 ml) was stirred for 1—2 h at room temperature under oxygen. The reaction mixture was poured into ice-cold dil. HCl and the whole was extracted with AcOEt. The extract was dried and concentrated in vacuo. The residue was subjected to silica gel column chromatography and eluted with CHCl₃-MeOH to give 4, 0.98 g (yield 25.9%). NMR (CDCl₃) δ: 1.28 (18H, s, C(CH₃)₃), 3.00 (1H, br), 5.40 (1H, d, J = 11 Hz, C = CH₂), 5.60 (1H, s, OH), 5.68 (1H, d, J = 22 Hz, C = CH₂), 7.20—7.44 (3H, aromatic-H), 7.52 (1H, s, imidazole-H), 7.76—7.90 (2H, aromatic-H). MS m/z: 216 (M⁺). mp 149—150 °C (from MeOH—Et₂O). Anal. Calcd for C₁₉H₁₈N₂O₂S·HCl·2H₂O: C, 49.91; H, 5.93; N, 9.69. Found: C, 49.98; H, 5.97; N, 9.69.

2-Methylsulfonyl-4-phenyl-1-vinylimidazolide (10): 0.31 g (yield, 12.4%). NMR (CDCl₃) δ: 3.44 (3H, s, CH₃), 5.14 (1H, d, J = 12 Hz), 5.44 (1H, d, J = 24 Hz), 7.24—7.52 (3H, aromatic-H), 7.58 (1H, dd, J = 12, 24 Hz), 7.60 (1H, s, imidazole-H), 7.76—7.88 (2H, aromatic-H). MS m/z: 248 (M⁺). mp 77—78 °C (from C₆H₁₂). Anal. Calcd for C₁₉H₁₈N₂O₂S·HCl·2H₂O: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.18; H, 4.73; N, 11.23.

Methyl 4-Phenyl-1-vinylimidazolide-2-sulfenate (11): 0.84 g (yield 36.2%). NMR (CDCl₃) δ: 3.88 (3H, s, CH₃), 6.08 (1H, d, J = 12 Hz), 6.28 (1H, d, J = 24 Hz), 6.92 (1H, dd, J = 12, 24 Hz), 7.20—7.74 (6H, m). MS m/z: 232 (M⁺). mp 74—75 °C (from toluene-n-C₆H₁₄). Anal. Calcd for C₁₃H₁₂N₂O·C₆H₆: C, 62.05; H, 5.21; N, 12.06. Found: C, 61.87; H, 5.10; N, 11.80. 6 was treated in similar manner under oxygen to give 10, 0.74 g (yield, 29.8%) and 11, 0.5 g (yield, 21.6%).

2-Methylthio-4-phenyl-1-vinylimidazolide (9) —— A solution of 8 (0.40 g, 2 mmol) and potassium tert-butoxide (0.23 g, 2 mmol) in MDF (5 ml) under nitrogen was stirred for 15 min, then methyl iodide (0.35 g, 2.5 mmol) in DMF (2 ml) was added. After being stirred for 1 h, the reaction mixture was poured into water and the whole was extracted
with AcOEt. The extract was dried and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 9, 0.38 g (yield 88%).

2-Methylsulfanyl-4-phenyl-1-vinylimidazole (12) —— Chloroperoxybenzoic acid (0.35 g, 2 mmol) was added portionwise to a solution of 9 (0.35 g, 1.6 mmol) in CHCl₃ (10 ml) below 10 °C. After being stirred for 1 h, the whole was washed with 1 N NaOH, dried and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 12, 0.26 g (yield 69.1%). NMR (CDCl₃) δ: 3.20 (3H, s, CH₃), 5.12 (1H, d, J = 11 Hz), 5.26 (1H, d, J = 24 Hz), 7.24—7.48 (3H, aromatic-H), 7.52 (1H, dd, J = 12, 24 Hz), 7.62 (1H, s, imidazole-H), 7.76—7.88 (2H, aromatic-H). MS m/z: 232 (M⁺). mp 80—81 °C (from C₆H₆-n-C₆H₄). Anal. Calcd for C₁₃H₁₂N₂O: C, 62.05; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.11; N, 12.16.

Methyl 4-Phenyl-1-vinylimidazole-2-sulfinate (13) —— Chloroperoxybenzoic acid (0.23 g, 1.3 mmol) was added to a solution of 11 (0.25 g, 1.1 mmol) in CHCl₃ (10 ml) below 10 °C. After being stirred overnight, the reaction mixture was washed with dil. NaHCO₃, dried and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 13, 0.2 g (yield 74.9%). NMR (CDCl₃) δ: 4.00 (3H, s, CH₃), 6.20 (1H, d, J = 12 Hz), 6.56 (1H, d, J = 24 Hz), 7.04 (1H, dd, J = 12, 24 Hz), 7.28—7.80 (6H). MS m/z: 248 (M⁺). mp 104—105 °C (from C₆H₆-n-C₆H₄). Anal. Calcd for C₁₃H₁₂N₂O₃S: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.19; H, 4.73; N, 11.14.

Acknowledgement The authors thank the staff of the physico-analysis center for measurement of spectral data and elemental analysis. Thanks are also due to Dr. Inukai and Dr. Yoshikawa for their advice.

References and Notes