Synthesis and Antifungal Activities of a Series of (1,2-Disubstituted Vinyl)imidazoles

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A series of vinylimidazoles containing a hetero atom such as sulfur or oxygen at a β -position of the vinyl group was prepared and the antifungal activities were tested. It was found that sulfur-substituted derivatives such as (*E*)-1-[2-(methylthio)-1-[2-(pentyloxy)phenyl]ethenyl]-1*H*-imidazole (**5a-5**) and (*E*)-1-[1-[2-(hexyloxy)phenyl]-2-(methylthio)ethenyl]-1*H*-imidazole (**5a-6**) showed excellent antifungal activities against dermatophytes and yeast cells. The stereochemistry of the hydrochloride salt of **5a-5** was determined by X-ray crystallography. The structure-activity relationships were discussed.

Keywords antifungal activity; imidazole; X-ray crystallography; antifungal agent; structure-activity relationships

Imidazole derivatives have been widely investigated as antifungal agents for plant pathogenic fungi and dermatophytes since the late 1970's.¹⁾ Some imidazole-based antifungal agents are now clinically used, and these are classified into three general groups on the basis of chemical structures: the arylmethylimidazoles, the arylolethylimidazoles and the vinylimidazoles.²⁾ We have synthesized a new series of vinylimidazole derivatives containing a hetero atom such as sulfur or oxygen at a β -position of the vinyl group in order to obtain more potent and broad spectrum antifungal agents, and found that sulfur-substituted *E*-form derivatives were more active than the others against a variety of fungi including dermatophytes and yeast cells. In these compounds, **5a-5** and **5a-6** showed the most excellent antifungal activities. The minimum inhibitory concentrations (MICs) of both **5a-5** and **5a-6** were *Candida albicans* 12.5 μ g/ml, *Trichophyton mentagrophytes* 0.2 μ g/ml, *Trichophyton tonsurans* 0.2 μ g/ml, *Trichophyton rubrum* 0.2 μ g/ml and *Microsporum gypseum* 0.2 μ g/ml *in vitro*, respectively. The stereochemistry of the hydrochloride salt of **5a-5** was determined by X-ray crystallography. In this paper, we

wish to report the synthesis, characterization and antifungal activities of these synthetic compounds.

Synthesis The preparations of sulfur-substituted vinylimidazoles were carried out by the following method (Chart 1). Treatment of 2-bromo-2'-hydroxyacetophenone (**1a**) with methylmercaptan in base gave 2'-hydroxy-2-(methylthio)acetophenone (**2a**). The reaction of **2a** with 1,1'-diimidazolyl sulfoxide by the method of Ogata *et al.*³⁾ gave two geometric isomers, (*E*)-1-[1-(2-hydroxyphenyl)-2-(methylthio)ethenyl]-1*H*-imidazole (**3a**) and its *Z*-isomer (**4a**) in the ratio of about 5:1, which were separated by column chromatography. Ogata *et al.*⁴⁾ reported that the chemical shifts of the vinyl protons of *E*- and *Z*-1-[1-(2-hydroxyphenyl)-2-methylvinyl]-1*H*-imidazole were 6.01 and 6.28 ppm, respectively. Because the chemical shifts of the vinyl protons of **3a** and **4a** were 6.77 and 7.08, we presumed the configurations of the two isomers to be *E* and *Z*, respectively. In the same manner as above, **3b-f** (*E*-isomers) and **4b-f** (*Z*-isomers) were also prepared in the ratio of about 5:1. Equilibrium mixture of **3a** and **4a** was obtained by heating, and their ratio was about 2:3 by

a : R¹=H, R²=Me b : R¹=H, R²=Et c : R¹=H, R²=Pr d : R¹=H, R²=Bu e : R¹=H, R²=Ph f : R¹=Cl, R²=Me

Chart 1

TABLE I. Structures and Antifungal Activities of **5**

No.	R ¹	R ²	R ³	Formula	HRMS Calcd (Found)	MIC (μg/ml) ^{a)}				
						<i>C. albi</i>	<i>T. menta</i>	<i>T. tons</i>	<i>T. rub</i>	<i>M. gyp</i>
5a-1	H	Me	Me	C ₁₃ H ₁₄ N ₂ OS	246.0827 (246.0828)	>25	12.5	3.12	1.56	12.5
5a-2	H	Me	Et	C ₁₄ H ₁₆ N ₂ OS	260.0983 (260.1014)	>25	1.56	0.78	0.39	3.12
5a-3	H	Me	Pr	C ₁₅ H ₁₈ N ₂ OS	274.1139 (274.1158)	>25	0.78	0.39	0.39	1.56
5a-4	H	Me	Bu	C ₁₆ H ₂₀ N ₂ OS	288.1296 (288.1306)	>25	0.20	<0.20	<0.20	0.20
5a-5	H	Me	Pen	C ₁₇ H ₂₂ N ₂ OS	302.1453 (302.1501)	12.5	<0.20	<0.20	<0.20	<0.20
5a-6	H	Me	Hex	C ₁₈ H ₂₄ N ₂ OS	316.1609 (316.1568)	12.5	<0.20	<0.20	<0.20	<0.20
5a-7	H	Me	Heptyl	C ₁₉ H ₂₆ N ₂ OS	330.1766 (330.1730)	25	<0.20	<0.20	<0.20	<0.20
5a-8	H	Me	Octyl	C ₂₀ H ₂₈ N ₂ OS	344.1922 (344.1941)	>25	0.39	<0.20	<0.20	3.12
5a-9	H	Me	Bn	C ₁₉ H ₁₈ N ₂ OS	322.1141 (322.1122)	>25	1.56	0.78	1.56	3.12
5a-10	H	Me	Bn (2,4-diCl)	C ₁₉ H ₁₆ Cl ₂ N ₂ OS	390.0359 (390.0310)	>25	0.20	0.20	<0.20	0.78
5b-1	H	Et	Me	C ₁₄ H ₁₆ N ₂ OS	260.0983 (260.0953)	>25	12.5	6.25	6.25	25
5b-2	H	Et	Et	C ₁₅ H ₁₈ N ₂ OS	274.1139 (274.1138)	>25	3.12	0.78	0.78	6.25
5b-3	H	Et	Pr	C ₁₆ H ₂₀ N ₂ OS	288.1296 (288.1302)	>25	1.56	0.78	0.39	1.56
5b-4	H	Et	Bu	C ₁₇ H ₂₂ N ₂ OS	302.1453 (302.1513)	25	0.39	0.20	<0.20	0.78
5b-5	H	Et	Pen	C ₁₈ H ₂₄ N ₂ OS	316.1609 (316.1615)	25	<0.20	<0.20	<0.20	<0.20
5b-6	H	Et	Hex	C ₁₉ H ₂₆ N ₂ OS	330.1766 (330.1758)	25	0.39	<0.20	<0.20	0.78
5b-7	H	Et	Heptyl	C ₂₀ H ₂₈ N ₂ OS	344.1922 (344.1970)	>25	1.56	0.20	0.20	3.12
5c-1	H	Pr	Me	C ₁₅ H ₁₈ N ₂ OS	274.1140 (274.1092)	>25	6.25	3.12	3.12	6.25
5c-2	H	Pr	Et	C ₁₆ H ₂₀ N ₂ OS	288.1296 (288.1274)	>25	1.56	0.78	0.78	1.56
5c-3	H	Pr	Pr	C ₁₇ H ₂₂ N ₂ OS	302.1453 (302.1444)	12.5	0.20	0.20	<0.20	0.39
5c-4	H	Pr	Bu	C ₁₈ H ₂₄ N ₂ OS	316.1609 (316.1562)	12.5	<0.20	0.20	<0.20	<0.20
5c-5	H	Pr	Pen	C ₁₉ H ₂₆ N ₂ OS	330.1766 (330.1806)	12.5	<0.20	<0.20	0.20	0.20
5d-1	H	Bu	Me	C ₁₆ H ₂₀ N ₂ OS	288.1296 (288.1340)	25	3.12	0.78	1.56	6.25
5d-2	H	Bu	Et	C ₁₇ H ₂₂ N ₂ OS	302.1453 (302.1431)	25	0.20	<0.20	<0.20	0.20
5d-3	H	Bu	Pr	C ₁₈ H ₂₄ N ₂ OS	316.1610 (316.1600)	25	<0.20	<0.20	<0.20	<0.20
5d-4	H	Bu	Bu	C ₁₉ H ₂₆ N ₂ OS	330.1766 (330.1773)	25	<0.20	<0.20	<0.20	0.39
5d-5	H	Bu	Pen	C ₂₀ H ₂₈ N ₂ OS	344.1922 (344.1904)	>25	1.56	<0.20	0.20	1.56
5e-1	H	Ph	Et	C ₁₉ H ₁₈ N ₂ OS	322.1140 (322.1095)	25	0.78	0.78	0.39	3.12
5e-2	H	Ph	Pr	C ₂₀ H ₂₀ N ₂ OS	336.1296 (336.1282)	>25	0.78	1.56	<0.20	3.12
5e-3	H	Ph	Bu	C ₂₁ H ₂₂ N ₂ OS	350.1453 (350.1471)	>25	3.12	6.25	1.56	6.25
5f-1	Cl	Me	Pr	C ₁₅ H ₁₇ ClN ₂ OS	308.0750 (308.0773)	>25	0.78	0.39	0.39	1.56
5f-2	Cl	Me	Bu	C ₁₆ H ₁₉ ClN ₂ OS	322.0907 (322.0935)	>25	<0.20	<0.20	<0.20	0.39
5f-3	Cl	Me	Pen	C ₁₇ H ₂₁ ClN ₂ OS	336.1064 (336.1016)	>25	0.20	<0.20	<0.20	1.56

a) *C. albi*: *Candida albicans* NHL 4019, *T. menta*: *Trichophyton mentagrophytes* QM 248, *T. tons*: *Trichophyton tonsurans* IFO 5928, *T. rub*: *Trichophyton rubrum* NHL J, *M. gyp*: *Microsporum gypseum* IFO 8231.

high performance liquid chromatography (HPLC). To get both alkylated derivatives of **3a** and **4a**, the minor product **4a** was also prepared from **3a**. Heating of **3a** in diethylene glycol dimethyl ether at reflux temperature, followed by recrystallization, gave **4a** in 34% yield. Treatment of **3a** and **4a** with alkyl halides in the presence of alkali gave **5a-1-10** and **6a-1-3** in moderate yields, respectively. The stereochemistry of **5a** was confirmed by X-ray crystallography of its hydrochloride salt (Experimental section). Treatment of **3b-e** and **4e** with alkyl halides in the presence of alkali also gave **5b-e** (*E*-isomers) and **6e** (*Z*-isomers), respectively. The derivatives **5f-1-3**, which were substituted by the chloro group at the 5 position of the benzene ring, were also prepared.

Oxygen-substituted vinylimidazoles were obtained by the following method (Chart 2). Treatment of 2-(benzyloxy)-phenylmagnesium bromide with methoxyacetonitrile in tetrahydrofuran (THF) gave 2'-benzyloxy-2-methoxyace-

tophenone (**8**) in 57% yield. Reduction of **8** with Pd catalyst under hydrogen atmosphere gave 2'-hydroxy-2-methoxyacetophenone (**9**) in a quantitative yield. The reaction of **9** with 1,1'-diimidazolyl sulfoxide gave the single product **10** in 72% yield. Treatment of **10** with alkyl halides in the presence of alkali gave its *O*-alkyl derivatives (**11-1-4**).

Results and Discussion

The antifungal activities of the compounds in this study are summarized in Tables I (**5**-series), II (**6**-series), III (**11**-series). In the series of (*E*)-2-methylsulfides (**5a-1-10**), **5a-5** and **5a-6** were found to be most active against both dermatophytes and yeast cells. In this series, 2'-*O*-benzyl derivatives (**5a-9**, **5a-10**) were less active than corresponding 2'-*O*-pentyl (**5a-5**) or 2'-*O*-hexyl (**5a-6**) derivatives.

In the series of (*E*)-2-ethylsulfenyl (**5b-1-7**), (*E*)-2-propylsulfenyl (**5c-1-5**) and (*E*)-2-butylsulfenyl (**5d-1-5**) de-

TABLE II. Structures and Antifungal Activities of **6**

No.	R ¹	R ²	R ³	Formula	HRMS Calcd (Found)	<i>C. albi</i>	<i>T. menta</i>	MIC (μg/ml) ^{a)}		
								<i>T. tons</i>	<i>T. rub</i>	<i>M. gyp</i>
6a-1	H	Me	Bu	C ₁₆ H ₂₀ N ₂ OS	288.1297 (288.1347)	25	0.78	0.39	0.39	0.78
6a-2	H	Me	Pen	C ₁₇ H ₂₂ N ₂ OS	302.1453 (302.1497)	25	<0.20	<0.20	<0.20	0.39
6a-3	H	Me	Hex	C ₁₈ H ₂₄ N ₂ OS	316.1609 (316.1583)	25	<0.20	<0.20	<0.20	0.39
6e-1	H	Ph	Et	C ₁₉ H ₁₈ N ₂ OS	322.1139 (322.1170)	>25	6.25	>25	3.12	>25
6e-2	H	Ph	Pr	C ₂₀ H ₂₀ N ₂ OS	336.1297 (336.1301)	>25	6.25	6.25	6.12	12.5
6e-3	H	Ph	Bu	C ₂₁ H ₂₂ N ₂ OS	350.1453 (350.1457)	>25	>25	>25	>25	>25

a) *C. albi*: *Candida albicans* NHL 4019, *T. menta*: *Trichophyton mentagrophytes* QM 248, *T. tons*: *Trichophyton tonsurans* IFO 5928, *T. rub*: *Trichophyton rubrum* NHL J, *M. gyp*: *Microsporium gypseum* IFO 8231.

TABLE III. Structures and Antifungal Activities of **11**

No.	R ⁴	Formula	HRMS Calcd (Found)	<i>C. albi</i>	<i>T. menta</i>	MIC (μg/ml) ^{a)}		
						<i>T. tons</i>	<i>T. rub</i>	<i>M. gyp</i>
11-1	Pr	C ₁₅ H ₁₈ N ₂ O ₂	258.1368 (258.1394)	>25	12.5	12.5	3.12	12.5
11-2	Bu	C ₁₆ H ₂₀ N ₂ O ₂	272.1525 (272.1488)	>25	6.25	6.25	3.12	6.25
11-3	Pen	C ₁₇ H ₂₂ N ₂ O ₂	286.1682 (286.1662)	>25	3.12	3.12	0.78	3.12
11-4	Hex	C ₁₈ H ₂₄ N ₂ O ₂	300.1838	>25	1.56	1.56	0.78	3.12

a) *C. albi*: *Candida albicans* NHL 4019, *T. menta*: *Trichophyton mentagrophytes* QM 248, *T. tons*: *Trichophyton tonsurans* IFO 5928, *T. rub*: *Trichophyton rubrum* NHL J, *M. gyp*: *Microsporium gypseum* IFO 8231.

TABLE IV. Physical Properties and Spectral Data of **3** and **4**

No.	R ¹	R ²	Formula	HRMS Calcd (Found)	mp (°C) (Recry. solv. ^{a)})	IR (cm ⁻¹) (KBr)	NMR: δ ppm <i>J</i> (Hz) (solv. ^{b)})
3a	H	Me	C ₁₂ H ₁₂ N ₂ OS	232.0670 (232.0640)	201—203 (C, M)	1455 1245	(S) 2.30 (3H, s, SMe), 6.77 (1H, s, =CH), 6.85—7.40 (6H, m, ArH + imidaC4, C5-H), 7.74 (1H, br s, imidaC2-H), 9.70 (1H, br, OH)
3b	H	Et	C ₁₃ H ₁₄ N ₂ OS	246.0827 (246.0851)	154—156 (M)	1495 1230	(D) 1.30 (3H, t, <i>J</i> = 7, Me), 2.74 (2H, q, <i>J</i> = 7, SCH ₂), 6.42 (1H, s, =CH), 6.67—7.38 (6H, m, ArH + imidaC4, C5-H), 7.48 (1H, br s, imidaC2-H), 8.80 (1H, br, OH)
3c	H	Pr	C ₁₄ H ₁₆ N ₂ OS	260.0983 (260.1026)	127—128 (M)	1495 1230	(D) 0.98 (3H, t, <i>J</i> = 7, Me), 1.26—1.85 (2H, m, CH ₂), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 6.40 (1H, s, =CH), 6.65—7.40 (6H, m, ArH + imidaC4, C5-H), 7.46 (1H, br s, imidaC2-H), 8.50 (1H, br, OH)
3d	H	Bu	C ₁₅ H ₁₈ N ₂ OS	274.1140 (274.1137)	116—118 (EA, H)	1495 1230	(D) 0.88 (3H, t, <i>J</i> = 7, Me), 1.02—2.00 (4H, m, CH ₂ × 2), 2.69 (2H, t, <i>J</i> = 7, SCH ₂), 6.40 (1H, s, =CH), 6.61—7.30 (6H, m, ArH + imidaC4, C5-H), 7.42 (1H, br s, imidaC2-H), 8.38 (1H, br, OH)
3e	H	Ph	C ₁₇ H ₁₄ N ₂ OS	294.0827 (294.0843)	152—154 (M)	1450 1230	(A) 6.65 (1H, s, =CH), 6.63—7.40 (11H, m, ArH + imidaC4, C5-H), 7.47 (1H, br s, imidaC2-H)
3f	Cl	Me	C ₁₂ H ₁₁ ClN ₂ OS	266.0281 (266.0310)	193—195 (M)	1495 1240	(S) 2.33 (3H, s, S-Me), 6.82 (1H, s, =CH), 6.56—7.12 (5H, m, ArH + imidaC4, C5-H), 7.60 (1H, br s, imidaC2-H), 10.06 (1H, br, OH)
4a	H	Me	C ₁₂ H ₁₂ N ₂ OS	232.0670 (232.0623)	206—208 (M)	1450 1250	(S) 2.39 (3H, s, SMe), 7.08 (1H, s, =CH), 6.45—7.24 (6H, m, ArH + imidaC4, C5-H), 7.66 (1H, br s, imidaC2-H), 10.03 (1H, br, OH)
4b	H	Et	C ₁₃ H ₁₄ N ₂ OS	246.0827 (246.0851)	195—197 (M)	1495 1230	(D) 1.25 (3H, t, <i>J</i> = 7, Me), 2.77 (2H, q, <i>J</i> = 7, SCH ₂), 6.80 (1H, s, =CH), 6.75—7.40 (6H, m, ArH + imidaC4, C5-H), 7.68 (1H, br s, imidaC2-H), 9.08 (1H, br, OH)
4c	H	Pr	C ₁₄ H ₁₆ N ₂ OS	260.0984 (260.0936)	191—192 (M)	1495 1230	(D) 1.01 (3H, t, <i>J</i> = 7, Me), 1.20—1.82 (2H, m, CH ₂), 2.77 (2H, t, <i>J</i> = 7, SCH ₂), 6.80 (1H, s, =CH), 6.83—7.40 (6H, m, ArH + imidaC4, C5-H), 7.69 (1H, br s, imidaC2-H), 9.65 (1H, br, OH)
4d	H	Bu	C ₁₅ H ₁₈ N ₂ OS	274.1140 (274.1093)	166—167 (M)	1495 1230	(D) 0.88 (3H, t, <i>J</i> = 7, Me), 1.08—2.00 (4H, m, CH ₂ × 2), 2.76 (2H, t, <i>J</i> = 7, SCH ₂), 6.82 (1H, s, =CH), 6.86—7.37 (6H, m, ArH + imidaC4, C5-H), 7.65 (1H, br s, imidaC2-H), 8.96 (1H, br, OH)
4e	H	Ph	C ₁₇ H ₁₄ N ₂ OS	294.0827 (294.0757)	235—237 (M)	1440 1245	(D) 6.85 (1H, s, =CH), 7.00—7.53 (12H, m, ArH + imidaH), 9.26 (1H, br, OH)
4f	Cl	Me	C ₁₂ H ₁₁ ClN ₂ OS	266.0282 (266.0309)	250—252 (M)	1485 1245	(S) 2.41 (3H, s, S-Me), 7.10 (1H, s, =CH), 6.54—7.33 (5H, m, ArH + imidaC4, C5-H), 7.66 (1H, br s, imidaC2-H), 10.35 (1H, br, OH)

a) C = chloroform, M = methanol. b) S = *d*₆-DMSO, D = CDCl₃, A = CD₃OD.

TABLE V. Physical Properties and Spectral Data of **5**, **6** and **11**

No.	Yield (%)	mp (°C) (Recry. solv. ^a)	IR (cm ⁻¹) (KBr)	NMR: δ ppm (CDCl ₃) <i>J</i> (Hz)
5a-1	38	Oil	1490 1250	2.28 (3H, s, SMe), 3.68 (3H, s, OMe), 6.38 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-2	61	96—97 (IPE)	1485 1255	1.14 (3H, t, <i>J</i> = 7, Me), 2.28 (3H, s, SMe), 3.88 (2H, q, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-3	65	67—68 (IPE)	1485 1255	0.92 (3H, t, <i>J</i> = 7, Me), 1.12—1.93 (2H, m, CH ₂), 2.28 (3H, s, SMe), 3.85 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-4	67	63—65 (IPE)	1485 1255	0.86 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (4H, m, CH ₂ × 2), 2.28 (3H, s, SMe), 3.83 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-5	56	37—39 —	1485 1250	0.86 (3H, t, <i>J</i> = 7, Me), 1.00—1.72 (6H, m, CH ₂ × 3), 2.28 (3H, s, SMe), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-6	50	65—67 (IPE)	1485 1235	0.86 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (8H, m, CH ₂ × 4), 2.28 (3H, s, SMe), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-7	63	67—69 (IPE)	1485 1230	0.86 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (10H, m, CH ₂ × 5), 2.28 (3H, s, SMe), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.52 (7H, m, ArH + imidaH)
5a-8	68	37—38 (IPE)	1480 1230	0.86 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (12H, m, CH ₂ × 6), 2.28 (3H, s, SMe), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.34 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5a-9	46	85—87 (IPE)	1485 1240	2.27 (3H, s, SMe), 4.94 (2H, s, CH ₂), 6.36 (1H, s, =CH), 6.80—7.50 (12H, m, ArH + imidaH)
5a-10	59	106—107 (IPE)	1490 1245	2.28 (3H, s, SMe), 4.95 (2H, s, CH ₂), 6.36 (1H, s, =CH), 6.80—7.50 (10H, m, ArH + imidaH)
5b-1	32	Oil	1490 1250	1.31 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.72 (2H, q, <i>J</i> = 7, SCH ₂), 3.68 (3H, s, OMe), 6.43 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5b-2	63	79—80 (IPE)	1485 1245	1.14 (3H, t, <i>J</i> = 7, Me), 1.31 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.72 (2H, q, SCH ₂), 3.88 (2H, q, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5b-3	68	48—49 (IPE)	1490 1250	0.83 (3H, t, <i>J</i> = 7, Me), 1.32 (3H, t, <i>J</i> = 7, SCH ₂ Me), 1.20—1.70 (2H, m, CH ₂), 2.72 (2H, q, <i>J</i> = 7, SCH ₂), 3.82 (2H, t, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.65 (7H, m, ArH + imidaH)
5b-4	74	33—35 —	1480 1240	0.83 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (4H, m, CH ₂ × 2), 1.30 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.71 (2H, q, <i>J</i> = 7, SCH ₂), 3.82 (2H, t, <i>J</i> = 7, OCH ₂), 6.39 (1H, s, =CH), 6.70—7.65 (7H, m, ArH + imidaH)
5b-5	66	51—52 (IPE)	1480 1240	0.83 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (6H, m, CH ₂ × 3), 1.30 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.70 (2H, q, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.39 (1H, s, =CH), 6.70—7.65 (7H, m, ArH + imidaH)
5b-6	70	51—53 (IPE)	1485 1245	0.83 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (8H, m, CH ₂ × 4), 1.32 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.71 (2H, q, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.39 (1H, s, =CH), 6.70—7.65 (7H, m, ArH + imidaH)
5b-7	76	56—57 (IPE)	1490 1250	0.81 (3H, t, <i>J</i> = 7, Me), 1.00—1.70 (10H, m, CH ₂ × 5), 1.31 (3H, t, <i>J</i> = 7, SCH ₂ Me), 2.70 (2H, q, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.65 (7H, m, ArH + imidaH)
5c-1	35	71—72 (IPE)	1490 1250	0.96 (3H, t, <i>J</i> = 7, S(CH ₂) ₂ Me), 1.17—2.00 (2H, m, CH ₂), 2.64 (2H, t, <i>J</i> = 7, SCH ₂), 3.66 (3H, s, OMe), 6.38 (1H, s, =CH), 6.70—7.70 (7H, m, ArH + imidaH)
5c-2	63	68—69 (IPE)	1485 1245	0.99 (3H, t, <i>J</i> = 7, S(CH ₂) ₂ Me), 1.14 (3H, t, <i>J</i> = 7, OCH ₂ Me), 1.18—2.02 (2H, m, CH ₂), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.88 (2H, q, <i>J</i> = 7, OCH ₂), 6.38 (1H, s, =CH), 6.70—7.70 (7H, m, ArH + imidaH)
5c-3	58	Oil	1485 1245	0.70—1.90 (10H, m, Me × 2 + CH ₂ × 2), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.70 (7H, m, ArH + imidaH)
5c-4	58	Oil	1485 1245	0.70—2.00 (12H, m, Me × 2 + CH ₂ × 3), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.70 (7H, m, ArH + imidaH)
5c-5	65	Oil	1485 1250	0.70—2.00 (14H, m, Me × 2 + CH ₂ × 4), 2.67 (2H, t, <i>J</i> = 7, SCH ₂), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.40 (1H, s, =CH), 6.70—7.70 (7H, m, ArH + imidaH)
5d-1	39	72—74 (IPE)	1490 1245	0.90 (3H, t, <i>J</i> = 7, S(CH ₂) ₃ Me), 1.10—1.80 (4H, m, CH ₂ × 2), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.68 (3H, s, OMe), 6.41 (1H, s, =CH), 6.70—7.50 (7H, m, ArH + imidaH)
5d-2	51	Oil	1495 1250	0.70—1.80 (10H, m, Me × 2 + CH ₂ × 2), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.86 (2H, q, <i>J</i> = 7, OCH ₂), 6.39 (1H, s, =CH), 6.70—7.60 (7H, m, ArH + imidaH)
5d-3	48	Oil	1490 1250	0.70—1.80 (12H, m, Me × 2 + CH ₂ × 3), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.37 (1H, s, =CH), 6.70—7.60 (7H, m, ArH + imidaH)
5d-4	57	Oil	1485 1245	0.70—1.80 (14H, m, Me × 2 + CH ₂ × 4), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.37 (1H, s, =CH), 6.70—7.60 (7H, m, ArH + imidaH)
5d-5	62	Oil	1490 1250	0.70—1.80 (16H, m, Me × 2 + CH ₂ × 5), 2.68 (2H, t, <i>J</i> = 7, SCH ₂), 3.80 (2H, t, <i>J</i> = 7, OCH ₂), 6.38 (1H, s, =CH), 6.80—7.60 (7H, m, ArH + imidaH)
5e-1	65	Oil	1480 1230	1.12 (3H, t, <i>J</i> = 7, Me), 3.77 (2H, q, <i>J</i> = 7, OCH ₂), 6.42 (1H, s, =CH), 6.75—7.65 (12H, m, ArH + imidaH)
5e-2	68	Oil	1480 1230	0.88 (3H, t, <i>J</i> = 7, Me), 1.13—1.94 (2H, m, CH ₂), 3.73 (2H, t, <i>J</i> = 7, OCH ₂), 6.42 (1H, s, =CH), 6.79—7.58 (12H, m, ArH + imidaH)
5e-3	67	Oil	1480 1220	0.88 (3H, t, <i>J</i> = 7, Me), 1.02—1.90 (4H, m, CH ₂ × 2), 3.73 (2H, t, <i>J</i> = 7, OCH ₂), 6.44 (1H, s, =CH), 6.70—7.55 (12H, m, ArH + imidaH)
5f-1	51	91—93 (IPE)	1490 1245	0.88 (3H, t, <i>J</i> = 7, Me), 1.15—1.80 (2H, m, CH ₂), 2.25 (3H, s, SMe), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.39 (1H, s, =CH), 6.70—7.60 (6H, m, ArH + imidaH)
5f-2	58	46—47 (IPE)	1490 1245	0.87 (3H, t, <i>J</i> = 7, Me), 1.05—1.80 (4H, m, CH ₂ × 2), 2.25 (3H, s, SMe), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.38 (1H, s, =CH), 6.70—7.60 (6H, m, ArH + imidaH)
5f-3	63	Oil	1490 1250	0.87 (3H, t, <i>J</i> = 7, Me), 1.00—1.80 (6H, m, CH ₂ × 2), 2.25 (3H, s, SMe), 3.78 (2H, t, <i>J</i> = 7, OCH ₂), 6.36 (1H, s, =CH), 6.70—7.60 (6H, m, ArH + imidaH)

TABLE V. (continued)

No.	Yield (%)	mp (°C) (Recry. solv. ^a)	IR (cm ⁻¹) (KBr)	NMR: δ ppm (CDCl ₃) J (Hz)
6a-1	54	Oil	1490 1250	0.92 (3H, t, J = 7, Me), 1.10—1.80 (4H, m, CH ₂ × 2), 2.32 (3H, s, SMe), 3.88 (2H, t, J = 7, OCH ₂), 6.74 (1H, s, =CH), 6.76—7.40 (6H, m, ArH + imidaC4, C5-H), 7.56 (1H, br s, imidaC2-H)
6a-2	49	Oil	1490 1250	0.90 (3H, t, J = 7, Me), 1.10—1.80 (6H, m, CH ₂ × 3), 2.32 (3H, s, SMe), 3.86 (2H, t, J = 7, OCH ₂), 6.74 (1H, s, =CH), 6.76—7.40 (6H, m, ArH + imidaC4, C5-H), 7.54 (1H, br s, imidaC2-H)
6a-3	59	Oil	1490 1250	0.89 (3H, t, J = 7, Me), 1.10—1.80 (8H, m, CH ₂ × 4), 2.31 (3H, s, SMe), 3.86 (2H, t, J = 7, OCH ₂), 6.76 (1H, s, =CH), 6.75—7.40 (6H, m, ArH + imidaC4, C5-H), 7.55 (1H, br s, imidaC2-H)
6e-1	75	96—97 (IPE)	1480 1240	1.25 (3H, t, J = 7, Me), 3.87 (2H, q, J = 7, OCH ₂), 6.70—7.50 (12H, m, ArH + imidaC4, C5-H), 7.70 (1H, br s, imidaC2-H)
6e-2	61	75—76 (IPE)	1480 1230	0.88 (3H, t, J = 7, Me), 1.22—2.00 (2H, m, CH ₂), 3.86 (2H, t, J = 7, OCH ₂), 6.70—7.50 (12H, m, ArH + imidaC4, C5-H), 7.70 (1H, br s, imidaC2-H)
6e-3	66	97—98 (IPE)	1480 1240	0.88 (3H, t, J = 7, Me), 1.08—1.80 (4H, m, CH ₂ × 2), 3.87 (2H, t, J = 7, OCH ₂), 6.70—7.50 (12H, m, ArH + imidaC4, C5-H), 7.70 (1H, br s, imidaC2-H)
11-1	54	Oil	1450 1240	0.90 (3H, t, J = 7, Me), 1.20—1.70 (2H, m, CH ₂), 3.72 (3H, s, OMe), 3.80 (2H, t, J = 7, OCH ₂), 6.48 (1H, s, =CH), 6.70—7.50 (6H, m, ArH + imidaC4, C5-H), 7.56 (1H, br s, imidaC2-H)
11-2	60	Oil	1450 1240	0.90 (3H, t, J = 7, Me), 1.00—1.70 (4H, m, CH ₂ × 2), 3.74 (3H, s, OMe), 3.84 (2H, t, J = 7, OCH ₂), 6.50 (1H, s, =CH), 6.70—7.50 (6H, m, ArH + imidaC4, C5-H), 7.56 (1H, br s, imidaC2-H)
11-3	71	Oil	1450 1240	0.88 (3H, t, J = 7, Me), 1.00—1.70 (6H, m, CH ₂ × 3), 3.74 (3H, s, OMe), 3.84 (2H, t, J = 7, OCH ₂), 6.50 (1H, s, =CH), 6.70—7.50 (6H, m, ArH + imidaC4, C5-H), 7.56 (1H, br s, imidaC2-H)
11-4	68	Oil	1450 1240	0.88 (3H, t, J = 7, Me), 1.00—1.70 (8H, m, CH ₂ × 4), 3.74 (3H, s, OMe), 3.84 (2H, t, J = 7, OCH ₂), 6.48 (1H, s, =CH), 6.70—7.50 (6H, m, ArH + imidaC4, C5-H), 7.56 (1H, s, imidaC2-H)

a) IPE: isopropyl ether.

TABLE VI. Antifungal Activity of 5a-5, Clotrimazole and Miconazole (MIC: μ g/ml)

Organisms	Antifungals					
	5a-5		Clotrimazole ^{a)}		Miconazole ^{b)}	
	Without serum ^{c)}	With 10% serum	Without serum	With 10% serum	Without serum	With 10% serum
<i>Candida albicans</i> NHL 4019	12.5	50	25	50	25	100
<i>C. albicans</i> IFO 1060	0.39	3.12	1.56	12.5	0.39	25
<i>Trichophyton mentagrophytes</i> QM 248	0.05	0.39	0.20	3.12	1.56	50
<i>T. tonsurans</i> IFO 5928	0.025	0.39	0.20	3.12	0.20	50
<i>T. rubrum</i> NHL J	0.025	0.20	0.39	6.25	0.20	25
<i>Microsporum gypseum</i> IFO 8231	0.10	3.12	0.39	6.25	6.25	50
<i>M. audouinii</i> IFO 6074	0.05	0.39	0.20	3.12	1.56	50

a) 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole. b) 1-[2-(2,4-Dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole. c) Horse serum.

derivatives, the most active compound in each series was 5b-5, 5c-4 and 5d-3, respectively. These results showed that the compounds with 6 to 7 carbons, which were the sum of the carbons of *S*-alkyl and *O*-alkyl substituents, were most active in each series of 2-alkylsulfides.

The *Z*-isomers 6a-2 and 6a-3 were slightly less active than corresponding *E*-isomers 5a-5 and 5a-6.

In the series of (*E*)-2-phenylsulfides (5e-1-3), 5e-2 was most active. But it was less active than (*E*)-2-alkylsulfides (5a-5, 5a-6, 5b-4, 5c-4 or 5d-3), and in this case *Z*-isomers (6e-1-3) were also less active than *E*-isomers (5e-1-3). There was also a similarity observed in the case of 2-methylsulfides. Further, we compared the activities of 2-methylsulfides with chloro substituent at the 5 position of the benzene ring, (5f-1-3), with that of 5a-5. In this case, 5a-5 was also found to be most active.

Next, we compared the activities of 2-methylsulfides (5a) with those of 2-methoxy derivatives (11-1-4) and found that the 5a series was more active than the 11 series.

In conclusion, (2-sulfinylvinyl)imidazoles showed excellent antifungal activities against dermatophytes and yeast

cells, with the activities of 5a-5 and 5a-6 the best of all.

The antifungal activity of 5a-5 in comparison with some known synthetic antifungal agents is shown in Table VI.^{5a-e)} Against dermatophytes, 5a-5 was more active than the other antifungals, and when the agar was supplemented with 10% horse serum,⁶⁾ the activity of 5a-5 was also more active than the others. The antifungal activity of 5a-6 was equally as active as 5a-5, and further experiments are ongoing.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-102 IR spectrometer. Proton magnetic resonance (¹H-NMR) was taken on a Hitachi R-24B (60 MHz) or JEOL FX90Q spectrometer (90 MHz). Chemical shifts are expressed in ppm values relative to tetramethylsilane (TMS) as an internal standard: s=singlet, d=doublet, t=triplet, m=multiplet and br=broad. Positive mass spectra and high-resolution mass spectra (MS) were taken on a JEOL JMX-DX303 mass spectrometer by a direct inlet method. Column chromatography was carried out on silica gel (Wakogel C-200). HPLC was carried out on an apparatus consisting of a Hitachi L-600 pump with a Hitachi L-400 ultraviolet (UV) detector using a Lichrosorb SI 60

column (5 μ m, 4 i.d. $\times$ 250 mm) and the solvent system: chloroform-*n*-hexane-ethanol-acetic acid-triethylamine (1480:400:120:10:1 v/v) at a flow rate of 1.5 ml/min. The retention times of **3a** and **4a** were 5.4, 3.6 min, respectively.

Antifungal Test A susceptibility test for fungi was performed using the agar dilution test method on Sabouraud dextrose agar (SDA). Test samples, which were dissolved in 1% dimethyl sulfoxide (DMSO), were added to SDA at a final concentration range of 0.05 to 100 μ g/ml. Inocula suspension, 10^6 cells/ml, was spotted on the agar surface with a multipoint inoculator. The MIC was defined as the lowest concentration of the sample preventing macroscopically visible growth after incubation at 27 $^{\circ}$ C for 3 d (for yeasts) and for 7 d (for dermatophytic fungi). The effect of serum on MIC was determined using SDA containing 10% horse serum.

(E)-(3a) and (Z)-1-[1-(2-Hydroxyphenyl)-2-(methylthio)ethenyl]-1H-imidazole (4a) A solution of 15% sodium methylmercaptide (5.45 ml) was added to a stirred solution of 2-bromo-2'-hydroxyacetophenone (**1a**, 2.52 g) in methanol (190 ml) in an ice bath. The reaction mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure, and the residue was acidified with diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid and water, and dried over MgSO_4 . The solvent was evaporated under reduced pressure, and the residue was chromatographed (chloroform) to give 2'-hydroxy-2-(methylthio)acetophenone (**2a**, 2.10 g, 98%) as yellow liquid. MS m/z : 182 (M^+).

Thionyl chloride (2.06 g) was added to a stirred suspension of imidazole (4.71 g) in dichloromethane (25 ml) in an ice bath. The reaction mixture was stirred for 30 min at room temperature. Then a solution of **2a** (2.10 g) in dichloromethane (5 ml) was added to the above solution in an ice bath. The reaction mixture was stirred for 30 min at room temperature, washed with water and dried over MgSO_4 . After removal of the solvent under reduced pressure, the residue was chromatographed (chloroform: methanol=10:1). First, **4a** (0.32 g, 12%) was obtained as colorless needles, and secondly **3a** (1.50 g, 56%) was obtained as colorless prisms.

The series of **3b-f** and **4b-f** were prepared in the same manner. The yields were **3b**: 48%, **4b**: 10%; **3c**: 37%, **4c**: 7%; **3d**: 45%, **4d**: 8%; **3e**: 31%, **4e**: 7%; **3f**: 51%, **4f**: 12% (Table IV).

(Z)-1-[1-(2-Hydroxyphenyl)-2-(methylthio)ethenyl]-1H-imidazole (4a) **3a** (6.70 g) was suspended in diethylene glycol dimethyl ether (140 ml), and gently refluxed for about 1 h. Then the temperature was kept at 50 $^{\circ}$ C with stirring for 1 h. The precipitate was collected, washed with ether and recrystallized from methanol to give **4a** (2.27 g, 34%).

(E)-1-[2-(Methylthio)-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole (5a-5) A solution of **3a** (1.5 g), KOH (0.51 g) and pentyl bromide (1.15 g) in dimethylformamide (DMF) (10 ml) was stirred for 3 h at room temperature. Then the reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and dried over MgSO_4 . After removal of the solvent under reduced pressure, the residue was chromatographed (chloroform) to give **5a-5** (1.10 g, 56%) as colorless crystals. MS m/z : 302 (M^+).

The series of **5a-f**, **6a-e** and **11** were also prepared in the same manner (Table V).

X-Ray Crystallography The hydrochloride salt of **5a-5** was recrystallized from acetonitrile to give colorless columns. mp 145–147 $^{\circ}$ C. IR (KBr): 1595, 1445, 1250 cm^{-1} . $^1\text{H-NMR}$ (CD_3OD) δ : 0.89 (3H, t, $J=6$ Hz, C-Me), 1.01–1.72 (6H, m, $\text{CH}_2 \times 3$), 2.42 (3H, s, SMe), 3.88 (2H, t, $J=6$ Hz, OCH_2), 6.95–7.80 (6H, m, ArH+imida C4, C5-H), 7.22 (1H, s, =CH), 9.01 (1H, t, $J=1$ Hz, imida C2-H). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{OS} \cdot \text{HCl}$: C, 60.25; H, 6.84; Cl, 10.46; N, 8.27; S, 9.46. Found: C, 60.17; H, 6.78; Cl, 10.55; N, 8.25; S, 9.20.

Crystal data of this compound are listed in Table VII.

The lattice constants and intensity data were obtained on a Rigaku AFC-5 diffractometer using graphite-monochromated $\text{CuK}\alpha_1$ radiation by θ – 2θ scan method. A total of 3019 reflexions were measured within the 2θ of 120 $^{\circ}$. Intensity data were corrected for Lorentz and polarization factors, but no absorption correction was applied. The crystal structure was determined by the direct method using SAPI 85⁷⁾ and refined by the full-matrix least-squares method minimizing F^2 . Hydrogen atoms were located from difference Fourier map except pentyl hydrogens. The final R and R_w were 0.074 and 0.105, respectively, for 2634 reflexions with $F > F(\sigma)$, including anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. The ORTEP drawing is shown in Fig. 1.

(E)-1-[1-(2-Hydroxyphenyl)-2-methoxyethenyl]-1H-imidazole (10) A solution of Grignard reagent, prepared from 2-benzyloxy-bromobenzene

TABLE VII. Crystal Data of **5a-5**·HCl

Formula	$\text{C}_{17}\text{H}_{23}\text{ClN}_2\text{OS}$
Formula weight	338.90
Crystal size	$0.85 \times 0.35 \times 0.35$ mm
Space group	Triclinic $P\bar{1}$
Cell dimension	$a=9.729$ (2) $\text{\AA}$ $b=13.309$ (2) $\text{\AA}$ $c=8.703$ (4) $\text{\AA}$ $\alpha=95.71$ (2) $^{\circ}$ $\beta=109.05$ (3) $^{\circ}$ $\gamma=114.90$ (1) $^{\circ}$ $V=928.6$ (6) $\text{\AA}^3$
	$F(000)=360$
Calculated density	$D_c=1.212$ Mg m^{-3}
Number of formula units	$Z=2$
Radiation and wavelength	$\lambda(\text{CuK}\alpha_1)=1.5405$ $\text{\AA}$
Linear absorption coefficient	$\mu=2.839$ mm^{-1}

Fig. 1. ORTEP Drawing of **5a-5**·HCl

(7.90 g) and magnesium (0.73 g) in dry THF (4 ml), was added to a solution of methoxyacetonitrile (1.90 g) in dry THF (20 ml) in an ice bath. Following the addition, the solution was stirred for 2 h at room temperature and poured into 1 N hydrochloric acid. Then the mixture was washed with ether, made alkaline with diluted ammonium hydroxide and extracted with ether. After removal of the solvent, 1 N hydrochloric acid was added to the residue, and the reaction mixture was refluxed for 30 min, cooled to room temperature, and extracted with ether. The ether layer was dried over MgSO_4 , and evaporated under reduced pressure. The residue was distilled under reduced pressure to give 2'-benzyloxy-2-methoxyacetophenone (**8**, 4.07 g, 56%) as colorless oil. bp 192–194 (2 mmHg). MS m/z : 256 (M^+). IR (NaCl): 1680 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 3.45 (3H, s, OMe), 4.67 (2H, s, COCH_2), 5.24 (2H, s, OCH_2), 6.70–8.10 (9H, m, ArH).

The reaction mixture of **8** (0.40 g), Pd-black (0.1 g) in ethanol (30 ml) was stirred for 1 h at hydrogen atmosphere. Then the catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was chromatographed (chloroform), to give 2'-hydroxy-2-methoxyacetophenone (**9**, 0.25 g, 96%) as colorless oil. MS m/z : 166 (M^+). IR (NaCl): 1650 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 3.50 (3H, s, OMe), 4.68 (2H, s, COCH_2), 6.69–7.77 (4H, m, ArH), 11.96 (1H, s, OH).

Thionyl chloride (0.73 g) was added to a stirred suspension of imidazole (1.67 g) in dichloromethane (10 ml) in an ice bath; then reaction mixture was stirred for 30 min at room temperature. Then a solution of **9** (0.68 g) in dichloromethane (5 ml) was added to the above solution in an ice bath. The reaction mixture was stirred for 1 h at room temperature, washed with water and dried over MgSO_4 . After removal of the solvent under reduced pressure, the residue was recrystallized from MeOH to give **10** (0.63 g, 72%) as colorless needles. mp 200–203 $^{\circ}$ C (dec.). IR (KBr): 1450, 1225 cm^{-1} . $^1\text{H-NMR}$ (CD_3OD): 3.77 (3H, s, OMe), 6.59 (1H, s,

=CH), 6.68—7.35 (6H, m, ArH+imida C4, C5-H), 7.65 (1H, brs, C2-H). High resolution MS: Calcd for $C_{12}H_{12}N_2O_2$: 216.0899. Found: 216.0929.

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