Synthesis and ^{13}C NMR Spectra of *endo*-5-(4-Imidazolyl)bicyclo-[2.2.2]oct-*endo*- and *exo*-2-yl *trans*-Cinnamates

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(Received February 4, 1977)

The Synthesis of *endo*-5-(4-imidazolyl)bicyclo[2.2.2]oct-*endo*- and *exo*-2-yl *trans*-cinnamates was carried out starting from 2-butyn-1,4-diol. The key intermediate, *endo*-5-(4-imidazolyl)bicyclo[2.2.2]octan-2-one, was obtained by oxidation of *endo*-5-(4-imidazolyl)bicyclo[2.2.2]oct-2-ene with palladium chloride, the oxidation being stereo- and regiospecific. The mode of 2,5 disubstitution and endo, exo stereochemistry were determined by means of ^{13}C chemical shifts of the bicyclo[2.2.2]octane framework.

In a previous paper[1] a report was given on the synthesis and separation of *endo*- and *exo*-5-(4-imidazolyl)bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamates *via* 5-(1-oxo-2-hydroxyethyl)bicyclo[2.2.2]hept-2-enes. These cinnamates were synthesized as a model for acyl-α-chymotrypsin since the bicyclo[2.2.1]heptane ring system possesses a rigid framework which can bear the imidazolyl and acyloxy groups with correct spatial alignment as in the acyl enzyme.

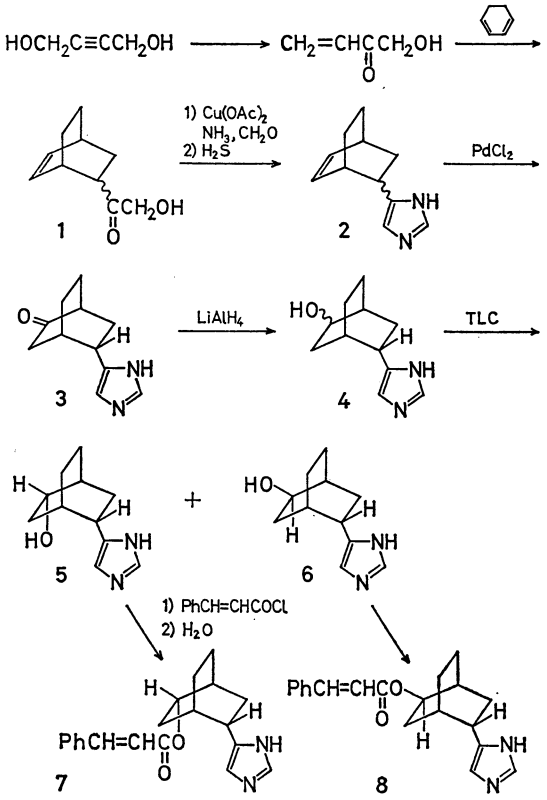
In this report we describe the synthesis of the title compounds which also simulate the acyl enzyme and have a less rigid framework of bicyclo[2.2.2]octane as compared to that of bicyclo[2.2.1]heptane. It seems of interest to investigate the difference in reactivity caused by the less rigid framework.[2,3] The endo, endo compound has a correct stereochemistry, but not the endo, exo compound. Properties of the former can be compared with those of the latter.

The synthesis was carried out following the scheme for the bicyclo[2.2.1]heptane derivatives, several key steps being found to be quite different. For elucidation of the structures of the title compounds ^{13}C NMR spectroscopy was indispensable, although ^1H NMR spectra were used effectively for the corresponding bicyclo-[2.2.1]heptane derivatives.

Results and Discussion

Synthesis. The synthetic route is shown in Scheme 1. The starting ketone **1** was obtained in 12% yield from 2-butyn-1,4-diol. The yield is lower than the 20% yield for the corresponding bicyclo[2.2.1]-heptenyl ketone which can be attributed to the low reactivity of 1,3-cyclohexadiene as a Diels-Alder diene. The endo: exo ratio of the ketone **1** was determined to be 9: 1 referring to the relative intensity of the ^1H NMR signals of the alcoholic methylene protons at δ 4.30 (exo) and 4.26 (endo). The signals of the olefinic protons were useless for the determination unlike the case of the corresponding bicyclo[2.2.1]heptenyl ketone.

Formation of the imidazolyl derivative **2** was achieved in a similar way to that for the corresponding bicyclo-[2.2.1]heptane derivative. The yield was 60—70%, comparable to that of the latter. The endo: exo ratio was 3: 1 as determined by the ^1H NMR signals of the imidazolyl C-4 proton at δ 6.87 (exo) and 6.65 (endo).



Scheme 1.

These values are similar to those (6.83 and 6.63) for 5-(4-imidazolyl)bicyclo[2.2.1]hept-2-enes.

Introduction of an oxo group to the olefinic bond of **2** was attained effectively using palladium chloride in dilute hydrochloric acid. The crude oxidation product obtained from the endo, exo mixture of **2** was chromatographed over basic alumina to give the endo ketone **3** in 30% yield (40% based on the *endo*-imidazolyl derivative of **2**). Neither exo ketone nor the isomeric 2,6-disubstituted product was detected. The reaction conditions such as temperature, time, speed of addition of the substrate, acidity of the solution, and mole ratios of the substrate to the oxidant were varied without any appreciable increase in the yield. The *exo*-imidazolyl derivative of **2** was recovered only in part by chromatography, being lost mostly as unidentified products.

The oxidation was stereo- and regiospecific. It seems to proceed *via* a palladium complex intermediate which requires both the ethylenic double bond and the *endo*-

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imidazolyl ring as a bidentate ligand. So far, no such palladium complex seems to have been reported.[4,5]

The mode of 2,5 disubstitution and the endo stereochemistry of **3** were determined by the ^{13}C chemical shift.

In order to obtain the desired compounds **7** and **8**, the endo ketone **3** was reduced to the hydroxy derivative **4** followed by acylation and partial hydrolysis after separation of the endo, endo derivative **5** and the endo, exo derivative **6**. The procedure is similar to that for the corresponding bicyclo[2.2.1]heptane derivatives.

An alternative method of introducing an oxo group to the olefinic double bond was the use of 98—100% formic acid which was utilized for the corresponding bicyclo[2.2.1]heptene. An addition reaction of formic acid to the olefinic double bond of **2** proceeded slowly at 160 °C over a period of 50 h to give the expected formate and its corresponding alcohol in a combined yield of 50—60% and these reaction products afforded the oxo derivative by oxidation with chromium trioxide. However, the total yield from **2** was not improved. The presence of both the *endo*- and *exo*-imidazolyl derivatives in the oxidation product complicated the isolation of the isomers. The situation became more serious when the oxo derivative were reduced to the hydroxy derivatives since almost equimolecular amounts of the *endo*- and *exo*-hydroxy derivatives were produced. Thus the use of formic acid was abandoned.

Hydrogenation of **2** with 10% Pd–C gave a hygroscopic glassy solid of 2-(4-imidazolyl)bicyclo[2.2.2]-octane (**9**), which could be distilled but not crystallized. The ^{13}C chemical shifts are indispensable for elucidation of the stereochemistry of **3**, **7**, and **8** as shown in Tables 1 and 2.

^{13}C Chemical Shifts. The ^{13}C chemical shifts for a number of bicyclo[2.2.2]octanes substituted in the 2 and 2,5 positions have been reported by Garratt and Riguera.[3] They derived substitution parameters from the 2-substituted compounds and utilized them for the determination of the relative stereochemistry of substituents at C-2 and C-5. Their parameters for the hydroxyl and oxo groups are given in Table 1. The down field shifts for the α-, β-, and γ-carbon atoms were obtained by comparing the chemical shifts in the 2-substituted bicyclo[2.2.2]octanes with those in the parent hydrocarbon, where the α-carbon atom is C-2 and the γ-carbon atom is C-6 or C-7. The parameters for the 4-imidazolyl and *trans*-cinnamoyloxy groups (Table 1) were derived from the present work.

Table 1. Substituent effects on ^{13}C chemical shifts for 2-substituted bicyclo[2.2.2]octanes[a]

Substituent	α	β(C-1)	β(C-3)	γ-syn	γ-anti
4-Imidazolyl	8.3	5.7	5.8	−5.2	−0.9
trans-Cinnamoyloxy	46.5	6.3	8.8	−7.0	−3.0
Hydroxy[b]	43.3	7.5	11.3	−7.5	−2.3
Oxo[b]	190.7	18.3	18.6	−2.7	−2.7

a) The values show downfield shifts in ppm. Values for the 4-imidazolyl group were derived from the chemical shifts of 5-(4-imidazolyl) bicyclo[2.2.2]-octane (Table 2) by comparison with the shifts (24.14 for C-1 and 26.16 for C-2) for bicyclo[2.2.2]-octane. For the *trans*-cinnamoyloxy group an average value has been taken from the endo and exo cinnamates (Table 2). b) Values taken from Ref. 3.

The ^{13}C chemical shifts for various 2-substituted 5-(4-imidazolyl)bicyclo[2.2.2]octanes are given in Table 2. The agreement between the observed and the calculated values is good within $\pm$0.6 ppm. Deviations as large as 0.8—1.2 ppm are seen for C-2 and C-3 of the oxo derivative and C-4 and C-5 of the *exo*-cinnamoyloxy derivative, but no ambiguity in their assignment results from these deviations.

In order to obtain the substitution parameters for the 4-imidazolyl group, the ^{13}C NMR spectrum of 5-(4-imidazolyl)bicyclo[2.2.2]octane (**9**)[6] was assigned as follows. The tertiary carbons C-1, C-4, and C-5 were shown to be doublets by an off-resonance experiment and the chemical shift of 24.44 ppm was attributed to C-1 since it shifts least from the value of 24.14 ppm[3] for the C-1 of the parent hydrocarbon. The largest and the moderate downfield shifts from the value of 26.16 ppm[3] for the C-2 of the parent hydrocarbon are ascribed to the carbons C-5 and C-4, respectively. The

Table 2. ^{13}C Chemical shifts for 2-substituted *endo*-5-(4-imidazolyl)bicyclo[2.2.2]octanes[a]

2-Substituent (Compound)	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Imidazolyl carbons
Unsubstituted (**9**)	24.44	26.55*	20.95	29.80	34.43	31.91	25.82*	25.25	140.83
									134.57
									117.92
Oxo (**3**)	42.98	218.11	40.40	33.74	33.91	29.35	22.92	25.61	142.85
	(42.4)	(216.9)	(39.6)	(29.8)	(34.5)	(29.1)	(23.5)	(25.3)	135.25
				(33.8)[b]					114.38
endo-trans-Cinnamoyloxy (**7**)	30.40	72.90	29.49	29.49	34.30	25.46	22.87	25.46	140.99
	(30.4)	(72.7)	(29.8)	(29.8)	(34.5)	(25.0)	(23.2)	(25.3)	134.49
									117.21
exo-trans-Cinnamoyloxy (**8**)	30.37	72.45	30.07	28.71	33.54	29.39	18.79	25.97	142.42
	(30.4)	(72.7)	(29.8)	(29.8)	(34.5)	(29.0)	(19.2)	(25.3)	134.90
									115.62

a) The chemical shifts are in ppm downfield from internal tetramethylsilane in chloroform-*d*. The values in parentheses are those calculated with use of parameters in Table 1. The chemical shifts for the *trans*-cinnamoyloxy group were found to be essentially the same as those for ethyl *trans*-cinnamate. The asterisks designate a reversible pair of shifts. b) Corrected for the downfield shift (4.0 ppm) of C-4 in bicyclo[2.2.2]octan-2-one (Ref. 3).

remaining five carbons showed triplets by an off-resonance experiment. The carbons C-2 and C-7 are expected to show chemical shifts nearest to 26.16 ppm The largest downfield shift of 31.91 ppm was assigned to C-6 and the largest upfield shift of 20.95 ppm to C-3 which is γ-syn to C-5. The remaining shift of 25.25 ppm corresponds to the carbon C-8 which is γ-anti to C-5.

The parameters for the *trans*-cinnamoyloxy group were calculated from the *endo*- and *exo-trans*-cinnamoyloxy derivatives **7** and **8** by subtracting the shifts due to the imidazolyl group. An average was taken from the values for **7** and **8**. As expected, the parameters for the imidazolyl and *trans*-cinnamoyloxy groups show a similar trend in their magnitudes as compared with that for the hydroxyl group.

Physical Properties and endo, exo Stereochemistry. Using ^{13}C chemical shifts as described above, we determined the mode of 2,5 disubstitution and the endo, exo stereochemistry of the oxo, hydroxy, and cinnamoyloxy derivatives. In conformity with the determination, the *exo*-hydroxy-*endo*-imidazolyl derivative **6** and the hydrochloride of the *exo*-cinnamoyloxy-*endo*-imidazolyl derivative **8** were observed to have higher melting points than their corresponding *endo*-hydroxy-*endo*-imidazolyl derivative **5** and hydrochloride of the *endo*-cinnamoyloxy-*endo*-imidazolyl derivative **7**, respectively. The exo, endo derivative **6** was also found to have a smaller R_f value than the corresponding endo, endo derivative **5**. These observations are understandable on the basis of the relative spatial alignment of the two functional groups, the same situation being observed for the bicyclo[2.2.1]heptane system previously.[1)]

Another means for differentiating the endo or exo stereochemistry is the ^1H chemical shift for the proton attached to the C-4 carbon of the imidazolyl group. The chemical shifts for the endo, endo derivatives **5** and **7** were found to be 0.08 ppm downfield from those of the corresponding exo, endo derivatives **6** and **8**. Although it cannot be explained clearly, a similar downfield shift of 0.06—0.15 ppm is also observed for the bicyclo-[2.2.1]heptane system.[1)]

Thus the physical properties so far observed are consistent with the endo, exo stereochemistry determined by the ^{13}C chemical shift.

Experimental

All melting points and boiling points are uncorrected. ^1H NMR spectra were obtained on a Hitachi Model R-24 spectrometer at 60 MHz. Tetramethylsilane was used as an internal standard unless otherwise noted. ^{13}C NMR spectra were recorded with a JEOL JNM FX-100 spectrometer at 25.05 MHz equipped with Fourier transform facilities. Mass spectra were obtained with a Hitachi Model RMS-4 mass spectrometer at 70 eV. Elemental analyses were carried out by Mr. E. Amano of our laboratory.

endo- *and* exo-*5-(1-Oxo-2-hydroxyethyl)bicyclo[2.2.2]oct-2-enes (1).* In order to obtain a Diels-Alder dienophile, 26.8 g (0.313 mol) of 2-butyn-1,4-diol was isomerized to hydroxymethyl vinyl ketone.[1)] The crude ketone was heated with 5.0 g (0.063 mol) of 1,3-cyclohexadiene at 100—120 °C for 13 h. The resulting viscous reddish oil was distilled to give 6.1 g (0.037 mol) of crude **1**: bp 110—125 °C (12 Torr); IR (neat) 3650—3200 (OH), 3030 (=C–H), 1710 (C=O), 1615 (C=C), and 1065 cm^{-1} (C–O); ^1H NMR ($CDCl_3$) δ 6.4—5.9 (m, 2, CH=CH), 4.30 (s, *ca.* 0.2, *exo*-CH_2–O), 4.26 (s, *ca.* 1.8, *endo*-CH_2–O), 3.3 (s, 1, OH), 3.0—2.3 (m, 3), and 2.0—1.0 ppm (m, 6).

endo- *and* exo-*5-(4-Imidazolyl)bicyclo[2.2.2]oct-2-enes (2).* The hydroxymethyl ketone **1** was treated with 28% aq ammonia, copper(II) acetate, and 37% aq formaldehyde,[1)] giving a very viscous, transparent, and reddish oil of crude **2** in 60—70% yield: IR (neat) 3500—2200 (NH), 1615 (CH=CH), and 1580—1560 cm^{-1} (imidazole ring); ^1H NMR ($CDCl_3$) δ 9.1 (s, 1, NH), 7.58, 7.48 (two s, 1, N=CH–N), 6.87 (s, 0.25, N–CH=C), 6.65 (s, 0.75, N–CH=C), 6.5—5.95 (m, 2, CH=CH), 3.0 (m, 1, H_5), 2.85—2.4 (m, 2, H_1 and H_4), and 2.3—1.0 ppm (m, 6).

In order to obtain the picrate of **2**, an equimolar amount of picric acid in chloroform was added to a solution of **2** in chloroform. The picrate precipitated by cooling was collected and recrystallized: mp 151—152 °C; ^1H NMR (DMSO-d_6) δ (solvent peak, δ 2.50 as internal standard) 8.98 (d, 0.15, N–CH=N), 8.88 (d, 0.85, N–CH=N), 8.55 (s, 2, picrate anion), 7.57 (d, 0.15, N–CH=C), 7.18 (d, 0.85, N–CH=C), 6.5—5.85 (m, 2, CH=CH), 3.04 (m, 1, H_5), 2.9—2.4 (m, 2, H_1 and H_4), and 2.3—1.0 ppm (m, 6). Found: C, 50.99; H, 4.18; N, 17.19%. Calcd for $C_{17}H_{16}N_5O_7$: C, 50.75; H, 4.01; N, 17.46%.

endo-*5-(4-Imidazolyl)bicyclo[2.2.2]octan-2-one (3).* In a solution of 2.85 ml of 1 M hydrochloric acid and 25 ml of water, 560 mg (3.16 mmol) of palladium chloride was dissolved by heating at 80 °C for 30 min. To this solution was added dropwise 500 mg (2.87 mmol) of **2** in 2.85 ml of 1 M hydrochloric acid and 8 ml of water over a period of 10 min with stirring. The mixture was then heated at 95 °C for 30 min and filtered. The filtrate was concentrated to half the original volume and extracted with chloroform after the pH of solution had been adjusted to 9 with 28% aq ammonia. After being dried over magnesium sulfate, the solvent was removed to give 320 mg of a viscous yellow oil. This oil was developed three times over basic alumina (Merck, HF_{254} Type E) using dichloromethane–methanol (50/1 vol/vol), to give 170 mg (31%) of the ketone **3** (R_f value 0.1—0.4). This was recrystallized from chloroform–carbon tetrachloride: mp 147—148 °C; IR (KBr) 3500—2200 (NH), 1720 (C=O), and 1580—1560 cm^{-1} (imidazole ring); ^1H NMR ($CDCl_3$) δ 9.15 (s, 1, NH), 7.55 (s, 1, N–CH=N), 6.75 (s, 1, N–CH=C), 3.18 (m, 1, H_5), and 2.6—1.5 ppm (m, 10); MS *m/e* 190 (M^+). Found: C, 69.60; H, 7.42; N, 14.68%. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72%.

Twenty mg of **2** was recovered (R_f value 0.5).

endo-*5-(4-Imidazolyl)bicyclo[2.2.2]octan*-endo- *and* exo-*2-ols (4).* With lithium aluminum hydride in THF 1.48 g of the crude oil of **3** was reduced to give 1.23 g of a crude solid of **4**.[1)]

endo-*5-(4-Imidazolyl)bicyclo[2.2.2]octan*-endo-*2-ol (5).* Isolation of **5** from **4** was achieved by preparative TLC. About 240 g of basic alumina (Merck, HF_{254} Type E) was coated on ten glass plates (20×20 cm) and activated. After application of 1.23 g of the crude **4** in methanol, the plates were developed four times with use of dichloromethane–methanol (15/1 vol/vol). The endo alcohol **5** obtained (R_f value 0.4—0.65) amounted to 450 mg. This gave white crystals from methanol by adding carbon tetrachloride: mp 144—146 °C; IR (KBr) 3550 (OH), 3400—2200 (NH), and 1580—1560 cm^{-1} (imidazole ring); ^1H NMR ($CDCl_3$) δ 7.48 (s, 1, N–CH=N), 6.82 (s, 1, N–CH=C), 3.82 (m, 1, H_2), 2.89 (m, 1, H_5), and 2.3—1.2 ppm (m, 10).

endo-5-(4-Imidazolyl)bicyclo[2.2.2]octan-exo-*2-ol* (**6**). The exo alcohol **6** obtained (R_f value 0.1—0.4) amounted to 420 mg. This gave white crystals from methanol-carbon tetrachloride: mp 219—220 °C; IR (KBr) 3550 (OH), 3400 2200 (NH), and 1580—1560 cm^{-1} (imidazole ring); ^1H NMR ($CDCl_3$) δ 7.51 (s, 1, N-CH=N), 6.74 (s, 1, N-CH=C), 3.88 (m, 1, H_2), 2.90 (m, 1, H_5), and 2.4—1.0 ppm (m, 10). Found: C, 68.59; H, 8.11; N, 14.28%. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57%.

endo-*5-(4-Imidazolyl)bicyclo[2.2.2]octan*-endo-*2-yl* trans-*Cinnamate* (**7**). In 5 ml of freshly distilled ethanol-free chloroform 230 mg (1.2 mmol) of **5** was heated with 720 mg (4.3 mmol) of *trans*-cinnamoyl chloride at 85 °C for 2 h. The clear, light yellow solution was evaporated to dryness and the residual solid was dissolved in THF-methanol-water. The pH of the solution was then adjusted to 9 with aqueous sodium carbonate and allowed to stand for 6 h at room temperature. Removal of the organic solvents by a rotary evaporator gave a heterogeneous aqueous solution, which was extracted with chloroform twice. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave 390 mg (100%) of crude **7**. This was passed through a column of basic alumina using dichloromethane-methanol to give 220 mg of a colorless brittle solid of **7**: IR (KBr) 3400—2200 (NH), 1700 (C=O), 1635 (C=C), 1575 (imidazole ring), and 1170 cm^{-1} (C-O); ^1H NMR ($CDCl_3$) δ 8.3 (s, 1, NH), 7.59 (d, 1, J=16 Hz, C*H*=CH), 7.53 (s, 1, N-CH=N), 7.65—7.15 (m, 5, phenyl), 6.87 (s, 1, N-CH=C), 6.33 (d, 1, J=16 Hz, CH=C*H*), 4.98 (m, 1, H_2), 2.94 (m, 1, H_5), and 2.4—1.2 ppm (m, 10).

To crystallize **7** as hydrochloride, 93 mg of **7** was dissolved in 0.1 M hydrochloric acid and the solution was evaporated to dryness. The residual solid was crystallized from a minimum quantity of chloroform by dilution with warm carbon tetrachloride and cooling in a refrigerator, giving 91 mg of the colorless hydrochloride of **7**: mp 167.5—170 °C (dec). Found: C, 66.61; H, 6.49; N, 8.17%. Calcd for $C_{20}H_{23}N_2O_2Cl$: 66.93; H, 6.46; N, 7.81%.

endo-*5-(4-Imidazolyl)bicyclo[2.2.2]octan*-exo-*2-yl* trans-*Cinnamate* (**8**). In a similar way to that for **5**, 200 mg of **6** was converted into 109 mg of a colorless brittle solid of **8**: IR (KBr) 3400—2200 (NH), 1700 (C=O), 1635 (CH=CH), 1575 (imidazole ring), and 1170 cm^{-1} (C-O); ^1H NMR ($CDCl_3$) δ 9.4 (s, 1, NH), 7.63 (d, 1, J=16 Hz, C*H*=CH), 7.55 (s, 1, N-CH=N), 7.6—7.15 (m, 5, phenyl), 6.79 (s, 1, N-CH=C), 6.37 (d, 1, J=16 Hz, CH=C*H*), 5.00 (m, 1, H_2), 3.00 (m, 1, H_5), and 2.4—1.1 ppm (m, 10).

In a similar way to that for **7**, 47 mg of **8** gave 44 mg of the hydrochloride: mp 208 °C (dec). Found: C, 66.72; H, 6.56; N, 8.09%. Calcd for $C_{20}H_{23}N_2O_2Cl$: C, 66.93; H, 6.46; N, 7.81%.

2-(4-Imidazolyl)bicyclo[2.2.2]octane (**9**). To 200 mg of crude **2** in 10 ml of methanol was added 50 mg of 10% Pd-C[7] and the mixture was shaken under a hydrogen atmosphere (1 atm) for 3 h until the theoretical volume of hydrogen was absorbed. The mixture was filtered and the catalyst was washed with methanol. The combined filtrate and washings were evaporated to give 173 mg (87%) of a slightly yellow, brittle solid. This was distilled in a glass tube at 160 °C (0.15 mmHg) to give a colorless viscous oil, which solidified on cooling. The hygroscopic solid obtained could not be crystallized: IR (neat) 3400—2200 (NH) and 1590—1560 cm^{-1} (imidazole ring); ^1H NMR ($CDCl_3$) δ 9.3 (s, 1, NH), 7.56 (s, 1, N-CH=N), 6.83 (s, 1, N-CH=C), 2.97 (m, 1, H_2), and 2.3—1.1 ppm (m, 12); MS *m/e* (rel intensity), 176 (M^+, 50), 175 (14), 147 (16), 146 (10), 145 (13), 119 (10), 110 (8), 109 (8), 96 (25), 95 (100), 94 (25), 82 (18), 81 (25), 80 (13), and 79 (10).

The present work was supported partially by a Grant-in-Aid for Scientific Research from the Ministry of Education.

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