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Neighboring Group Participation of the *N*-Oxide Group in the Reaction of Methyl 1-Oxido-2-pyridyl Ketone Oxime with Tosyl Chloride

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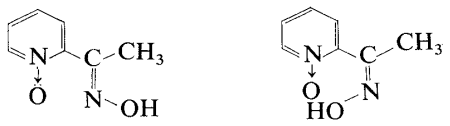
The reactions of methyl 1-oxido-2-pyridyl ketone oximes, *E*- (I_E) and *Z*-forms (I_Z), with tosyl chloride in the presence of NaOH were investigated to compare the reactivity of the *N*-oxide with that of the oxime group in the same molecule. In the reaction of I_E, neighboring group participation of the *N*-oxide group apparently occurred, and 3-methyl-2-tosyloxy-2*H*-[1,2,5]-oxadiazolo[2,3-*a*]pyridine (III) was obtained. The mechanism of the formation of III is discussed. The hydrogenation of III with H_2/Pd-C afforded two 1,2,5-oxadiazole derivatives (IV and V); the hydrogenation conditions were examined in detail.

Keywords——methyl 1-oxido-2-pyridyl ketone oxime; Schotten–Baumann reaction; tosylation; neighboring group participation; 1,2,5-oxadiazole; hydrogenolysis; NMR

It is well known that both the *N*-oxide group and the oxime group readily react with acylating agents to give various types of products depending upon the reaction conditions. A previous report from our group showed that the reaction of 2-ethylpyridine 1-oxide with amyl nitrite and potassium amide in liquid ammonia gave *E*- (I_E) and *Z*-oximes (I_Z) of methyl 1-oxido-2-pyridyl ketone.[1] In the present work, in order to compare the reactivity of the *N*-oxide with that of the oxime group in I_E and I_Z toward acylating agents, we investigated the reaction of I with tosyl chloride in the presence of NaOH and found that neighboring group participation of the *N*-oxide group occurred in the reaction of I_E. There are few reports on neighboring group participation of the *N*-oxide group[2] or the nitrogen atom of the heterocyclic nucleus[3] (Chart 1).



I_E (*E*-form) I_Z (*Z*-form)

Chart 1

Compound I_Z reacted easily with tosyl chloride in the presence of NaOH to give only the tosylate (II) of the oxime group of I_Z in good yield, and no tosylation of the *N*-oxide was noticed. On the other hand, in the reaction of I_E with tosyl chloride under the same conditions, neighboring group participation of the *N*-oxide group was observed. Addition of tosyl chloride in tetrahydrofuran (THF) to an alkaline solution of I_E under ice-cooling followed by stirring of the mixture at room temperature for 2 h gave a colorless crystalline

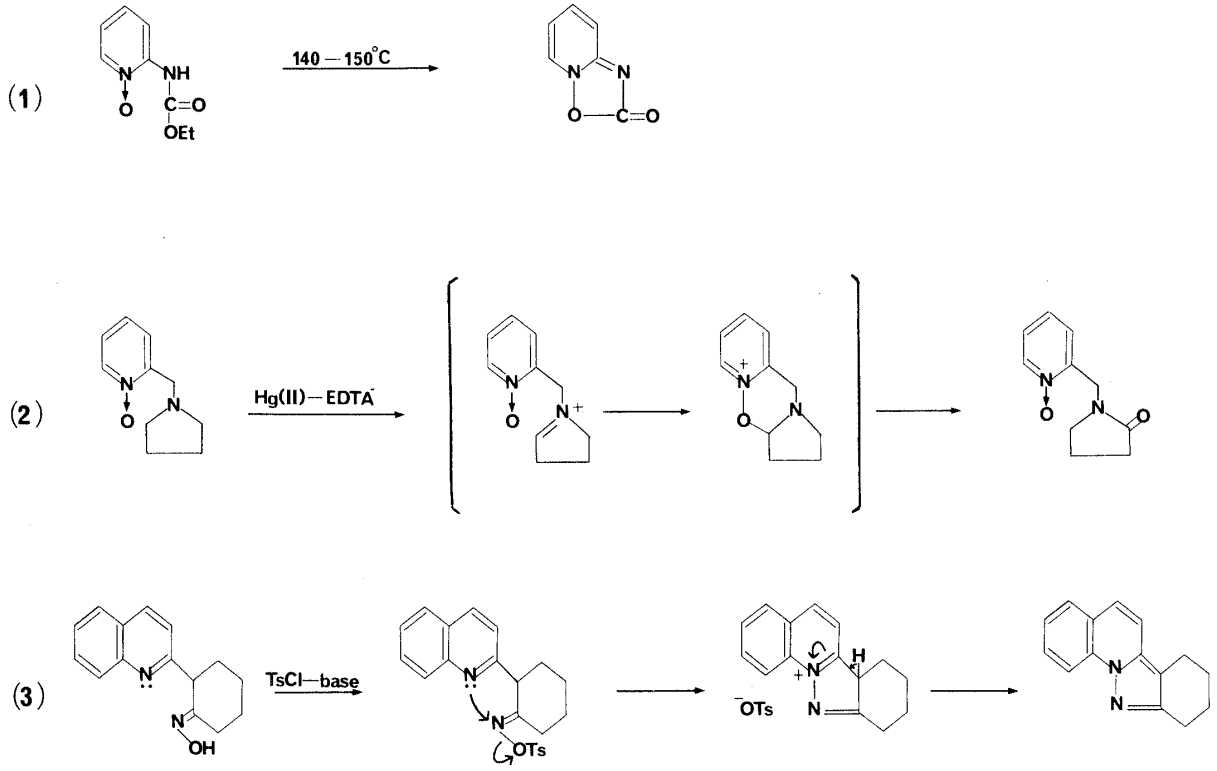


Chart 2

substance, $C_{14}H_{14}N_2O_4S$ (III), in 67% yield. Compound III is thermodynamically very stable and insensitive to acids. In the ultraviolet (UV) spectrum of III the absorption maximum appeared at 283 nm, and in the infrared (IR) spectrum no absorption bands of *N*-oxide, secondary amino group or carbonyl group could be seen.

The mass spectrum (MS) of III is shown in Fig. 1. The main fragment ions of III are as follows: *m/z* 306 (M^+), 155, 135 and 91. The symbol "*" in Fig. 1 represents metastable ions detected by the linked scan method. The *m/z* 155 ion is formed by the loss of $C_7H_7N_2O_2$ from the molecular ion, and undergoes subsequent loss of SO_2 to give the tropylium ion (*m/z* 91). The peak at *m/z* 135 is formed by loss of the tosyloxy group from the molecular ion.

In the ^1H NMR spectrum of III (Fig. 2-A), A_2B_2 type proton signals due to the *p*-substituted benzene ring (δ 7.31 and 7.78) and signals between δ 5.9 and 7.2 due to the adjacent four protons of the 1,2-dihydropyridine ring are observed. The signals due to the protons of two methyl groups (δ 2.33 and 2.44) are also observed, but these are not shown in Fig. 2-A. Assignment of the protons H_a, H_b, H_c, and H_d on the 1,2-dihydropyridine ring (shown in Fig. 2-A) was made by comparison with the spectra of similar compounds, and by the spin decoupling method. The spectrum in Fig. 2-B was obtained by irradiation at the frequency indicated by the arrow. The signals at δ 5.97 and 6.45 were assigned to the protons H_a and H_b, respectively, by the method of double resonance. In general, when the ratio of the chemical shift difference and the spin coupling constant ($\Delta\nu/J$) is smaller than about 6, the spectrum exhibits complicated splitting patterns, *i.e.* the chemical shift difference no longer corresponds to the distance between the midpoints of the signals, and moreover, the *J*-value is no longer constant. The spectrum of III is still rather complicated at 100 MHz. Therefore, the signals of H_c and H_d could not be separately assigned. The ^{13}C nuclear magnetic resonance (NMR) spectrum of III shows the signals arising from carbon atoms of two methyl groups and four quaternary carbon atoms.

The hydrogenation of III over Pd-C in THF at atmospheric pressure was carried out in

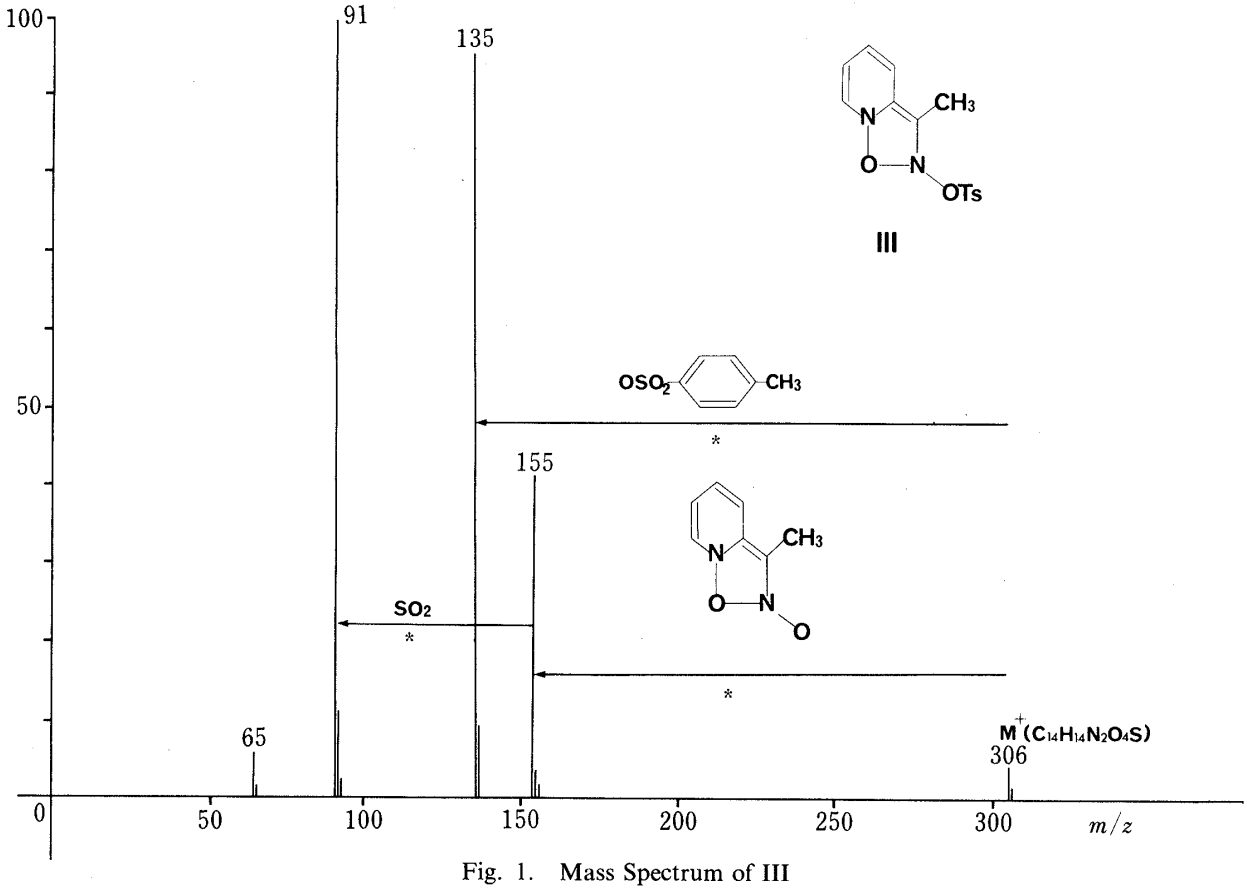


Fig. 1. Mass Spectrum of III

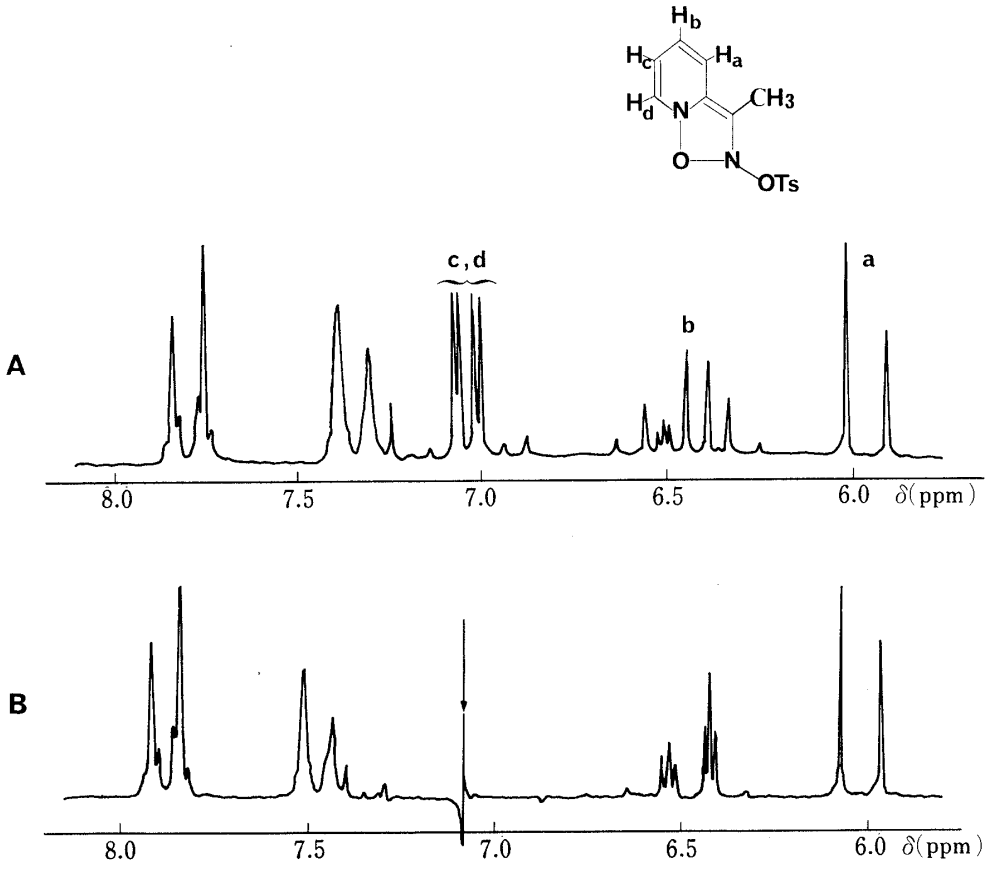


Fig. 2. NMR Spectra of III in $CDCl_3$ at 100 MHz

order to elucidate chemically the structure of III. Less than 3 mol of hydrogen was absorbed, and compounds IV ($C_{14}H_{18}N_2O_4S$) and V ($C_7H_{12}N_2O$) were obtained. The former is insoluble and the latter is soluble in petroleum ether. The structure of IV was determined from the spectral data, *i.e.*, IR, UV, mass, ^1H and ^{13}C NMR spectra. The IR spectrum of V was identical with that of an authentic sample prepared by a method similar to that of Behr and Brent,[4] and the structure of V is also supported by the other spectral data.

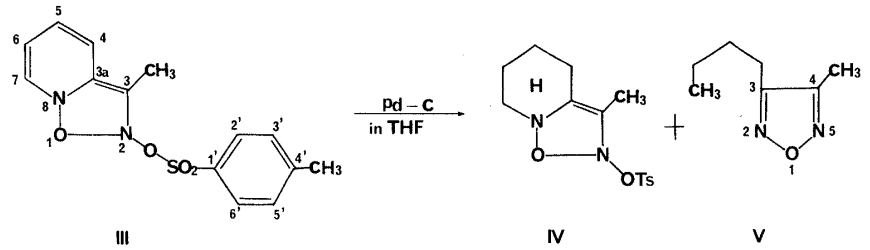


Chart 3

The reduction conditions were investigated in detail in order to confirm whether compound V is formed *via* IV or directly from III. The experimental results are listed in Table I. On hydrogenation of III over Pd-C under neutral (A) or acidic (B) conditions at atmospheric pressure, no significant differences were observed in the ratio of IV to V, as

TABLE I. Hydrogenation of III and IV

Compound	Conditions					
	(A) Pd-C (neutral)		(B) Pd-C (acidic)		(C) PtO_2, AcOH	
	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
III	IV	22	IV	25		
	V	52	V	55		
IV	Recovery	77	Recovery	90	V	89
	V	Trace[a]	V	Trace[a]		

a) Detected by thin layer chromatography.

shown in Table I. On the other hand, when IV was treated under the same conditions A and B, most of the starting material was recovered, together with a trace of V. Under more drastic reduction conditions, C (PtO_2 in acetic acid), compound V was obtained from IV in 89% yield. On the basis of the present results, it is concluded that V is formed not from IV, but directly from III under conditions A and B.

From the chemical and spectral data described above, all the reactions reported in this paper are considered to proceed according to the scheme in Chart 4. First, tosylation of the hydroxyl group of I_E by tosyl chloride occurs, and subsequently the oxygen atom of the *N*-oxide group attacks the nitrogen atom of the oxime group to give III. Clearly, neighboring group participation of the *N*-oxide group is involved in this reaction. The formation of V on hydrogenation over Pd-C is illustrated by path A in Chart 4.

Based on the results described above, it is concluded that the oxime group reacts with tosyl chloride more easily than the *N*-oxide group in the reaction of I with tosyl chloride.

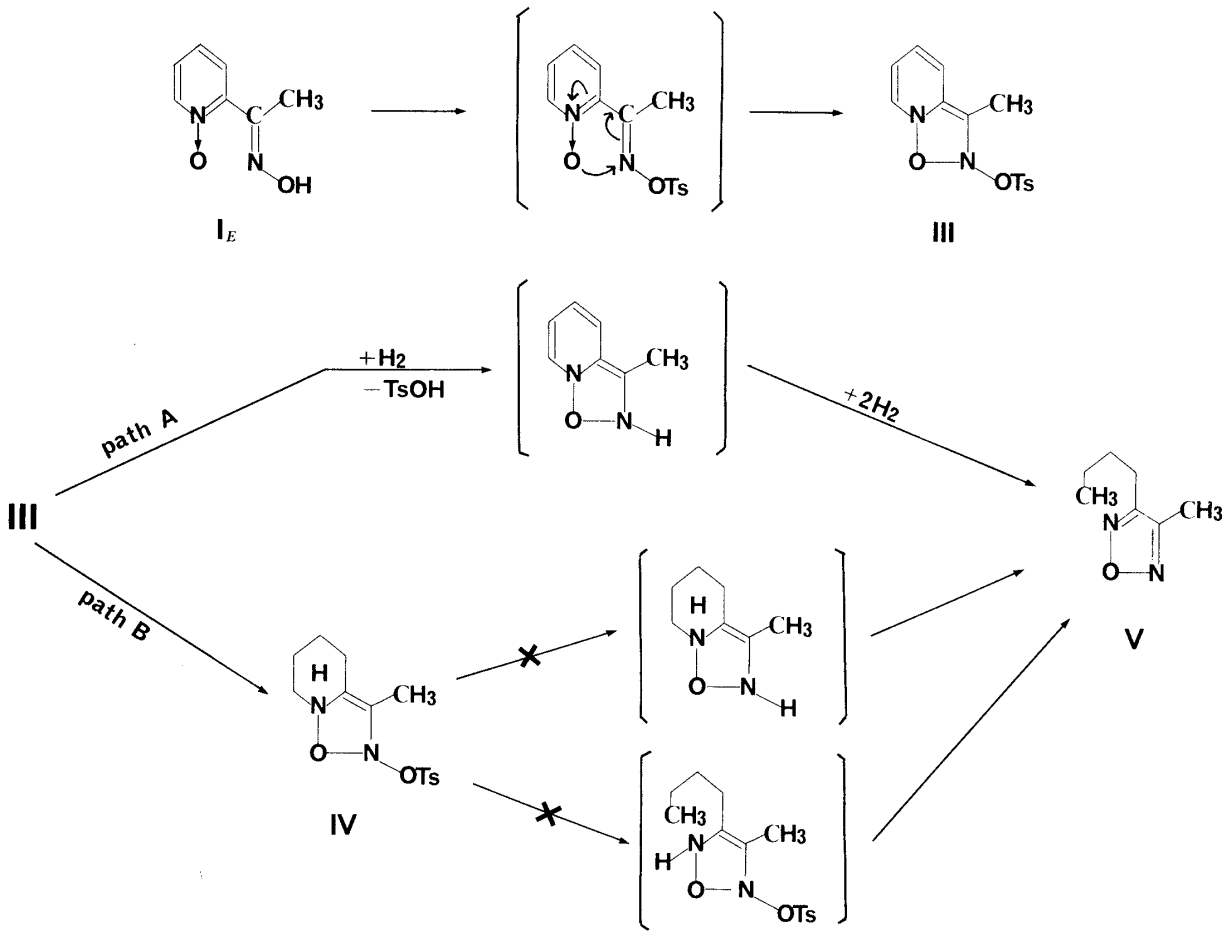


Chart 4

Experimental

Melting points were determined on a micro melting point apparatus (Yanaco) and are uncorrected. Spectral data were recorded on the following spectrometers: UV spectra, Hitachi 556; IR spectra, Hitachi 295; ^{1}H NMR spectra, JNM C-60-H (60 MHz), Hitachi R-22 (90 MHz) and JEOL FX-100 (100 MHz); ^{13}C NMR spectra, JEOL FX-100 (25.1 MHz); mass spectra, JEOL JMS-DX300.

Reaction of I_Z with Tosyl Chloride——Tosyl chloride (1.90 g) in dioxane (10 ml) was added drowpwise to a mixture of I_Z (1.0 g) and aqueous NaOH solution (NaOH 1.08 g and H_2O 5 ml) with shaking under ice-cooling. A crystalline substance separated out within a few min. The resulting mixture was further shaken for 2 h at room temperature. The crystalline substance was filtered off, and recrystallized from benzene to give colorless needles (II), mp 186 °C (dec.), 1.78 g (89% yield). *Anal.* Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.18; H, 4.72; N, 9.07. UV λ_{max}^{EtOH} nm (log ε): 269.5 (4.09), λ_{max}^{THF} nm: 282.5. IR ν_{max}^{KBr} cm^{-1}: 1634 (C=N), 1366 (SO_2), 1238 (N→O), 1185, 1172 (SO_2). ^{1}H NMR $\delta_{ppm}^{CDCl_3}$ (60 MHz): 2.32 (3H, s, CH_3), 2.43 (3H, s, tolyl-CH_3), 7.17—7.50 (5H, m, arom-H), 7.85 (2H, d, J=8 Hz, arom-H), 8.22 (1H, m, arom-H).

Reaction of I_E with Tosyl Chloride——Tosyl chloride (1.90 g) in THF (10 ml) was added dropwise to a solution of I_E (1.0 g) in aqueous NaOH solution (NaOH 1.08 g and H_2O 5 ml) with shaking under ice-cooling. The resulting solution was further shaken for 2 h at room temperaure. The solution was concentrated *in vacuo* to a half of its original volume. The precipitated crystals were filtered off and recrystallized from acetone–petr. ether to give colorless prisms (III), mp 96 °C, 1.33 g (67% yield). *Anal.* Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.75; H, 4.58; N, 9.07. UV λ_{max}^{EtOH} nm (log ε): 283 (4.05). IR ν_{max}^{KBr} cm^{-1}: 1393, 1196, 1182 (SO_2), no $\nu_{N\to O}$, ν_{NH}, $\nu_{C=O}$. ^{1}H NMR $\delta_{ppm}^{CDCl_3}$ (90 MHz): 2.33 (3H, s, 3-CH_3), 2.44 (3H, s, 4′-CH_3), 5.97 (1H, d, J=11 Hz, 4-H), 6.3—6.7 (1H, m, 5-H), 7.0—7.1 (2H, m, 6, 7-H), 7.36, 7.80 (4H, AB q, J=8 Hz, arom-H). Decoupling $\delta_{ppm}^{CDCl_3}$ (100 MHz): 7.08 (6, 7-H)→ 6.55 (m→dt, J=11 Hz, 5-H). ^{13}C NMR $\delta_{ppm}^{CDCl_3}$ (25.1 MHz): 150.4 (s, C-3), 145.8 (s, C-3a and C-4′), 132.2 (s, C-1′), 21.7 (s, 4′-$\underline{C}H_3$), 8.0 (s, 3-$\underline{C}H_3$). MS Calcd for $C_{14}H_{14}N_2O_4S$: M, 306.067. Found *m/z*: M^+, 306.067.

Hydrogenation of III over Pd-C (Neutral Conditions)——A solution of III (0.5 g (0.0016 mol)) in THF (15 ml) was

shaken with Pd-C (prepared from 1.7% $PdCl_2$ soln. (3.5 ml) and active charcoal (0.25 g); acid-free) in an H_2 stream at atmospheric pressure. Reduction was complete when *ca.* 110 ml of H_2 had been absorbed. The catalyst was removed by filtration. The solvent was evaporated off *in vacuo* and the residue was taken up in ether. The ether layer was washed with 10% NaOH aq. solution, then dried over Na_2SO_4, and the solvent was removed. The residue was divided into petr. ether-insoluble (IV) and -soluble (V) fractions. Compound IV was recrystallized from ether–petr. ether to give colorless prisms, mp 59—60 °C, 0.11 g (22% yield). *Anal.* Calcd for $C_{14}H_{18}N_2O_4S$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.05; H, 5.83; N, 8.92. UV λ_{max}^{EtOH} nm (log ε): 263.2 (2.72). IR ν_{max}^{KBr} cm^{-1}: 1355, 1193 (SO_2). ^1H NMR $\delta_{ppm}^{CDCl_3}$ (90 MHz): 1.64—1.94 (4H, m, 5- and 6-CH_2), 2.32 (3H, s, 3-CH_3), 2.44 (3H, s, 4′-CH_3), 2.52—2.80 (2H, m, 4-CH_2), 3.98—4.22 (2H, m, 7-CH_2), 7.32, 7.77 (4H, AB q, J=9 Hz, arom-H). ^{13}C NMR $\delta_{ppm}^{CDCl_3}$ (25.1 MHz): 153.7 (s, C-3a), 150.4 (s, C-3), 144.9 (s, C-4′), 132.9 (s, C-1′), 21.6 (s, 4′-CH_3), 8.1 (s, 3-CH_3). MS Calcd for $C_{14}H_{18}N_2O_4S$: M, 310.098. Found *m/z*: M^+, 310.098. Compound V was distilled under reduced pressure to give a colorless liquid, bp 100—103 °C (28 mmHg), 0.12 g (52% yield). *Anal.* Calcd for $C_7H_{12}N_2O$: C, 59.97; H, 8.63; N, 19.99. Found: C, 59.89; H, 8.66; N, 19.84. UV λ_{max}^{EtOH} nm (log ε): 218 (4.02). ^1H NMR $\delta_{ppm}^{CDCl_3}$ (90 MHz): 0.82—1.10 (3H, m, CH_3–$(CH_2)_3$–), 1.20—1.94 (4H, m, CH_3–$(CH_2)_2$–CH_2–), 2.33 (3H, s, 4-CH_3), 2.55—2.82 (2H, m, CH_3–$(CH_2)_2$–CH_2–). ^{13}C NMR $\delta_{ppm}^{CDCl_3}$ (25.1 MHz): 154.6 (s, C-4), 150.6 (s, C-3), 13.6 (s, 3-CH_3), 8.0 (s, 4-CH_3). MS Calcd for $C_7H_{12}N_2O$: M, 140.094. Found *m/z*: M^+, 140.095.

Hydrogenation of III over Pd-C (Acidic Conditions)——A mixture of 1.7% $PdCl_2$ soln. (3.5 ml) and active charcoal (0.25 g) was shaken in an H_2 stream at atmospheric pressure. After the absorption of H_2 had stopped, a solution of III (0.5 g) in THF (15 ml) was added to the solution, and the resulting mixture was further shaken in an H_2 stream at atmospheric pressure. The reaction mixture was treated in a manner similar to that described above. Compound IV, 0.12 g (25% yield). Compound V, 0.12 g (55% yield).

Hydrogenation of IV over Pd-C (Neutral Conditions)——Compound IV (0.08 g) was treated under the same conditions as described for the hydrogenation of III (neutral conditions). IV was recovered in 77% yield (0.06 g). A trace of V was detected by thin layer chromatography (TLC).

Hydrogenation of IV over Pd-C (Acidic Conditions)——Compound IV (0.1 g) was treated under the same conditions as described for the hydrogenation of III (acidic conditions). IV was recovered in 90% yield (0.09 g). A trace of V was detected by TLC.

Hydrogenation of IV over PtO_2 in Acetic Acid——A solution of IV (0.5 g) in acetic acid (10 ml) was shaken with PtO_2 (0.1 g) in an H_2 stream at atmospheric pressure. Compound V was obtained in 89% yield (0.2 g).

Treatment of III with HCl——A solution of III in conc. HCl (or conc. HCl–dioxane or conc. HCl–MeOH) was refluxed for 7—10 h. III was recovered in *ca.* 80% yield.

Synthesis of 3-Butyl-4-methylfurazan[4]——A mixture of succinic anhydride 6.33 g (0.063 mol) and methyl butyl glyoxime[5] 10 g (0.063 mol) was placed into a three-necked flask equipped with a stirrer, a thermometer, and an outlet tube connected to an air-cooled condenser, arranged for distillation. The mixture was heated slowly on an oil bath with stirring, and the mixture liquefied at about 120 °C. Distillation of the product began at about 160 °C and continued until the temperature reached 200 °C; this temperature was maintained for 10 min. The reaction mixture was then steam-distilled, and the distillate was extracted with ether. The extracts were combined with the product obtained by direct distillation. The ether solution was dried over anhydrous $MgSO_4$, and the solvent was removed. The residue was distilled at 100—103 °C (28 mmHg) as a colorless liquid. The yield was 4.0 g (45%).

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