Syntheses and Properties of 5-Substituted [n](2,4)Pyridinophanes, Model Compounds of NAD(P)

Tadayoshi Oikawa, Nobuhiro Kanomata, and Masaru Tada*

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku, Tokyo 169, Japan

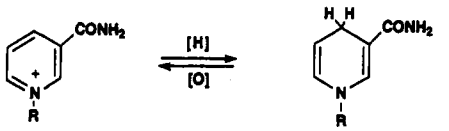
Received September 14, 1992

[n](2,4)Pyridinophane derivatives **5–8** having an ester or an amide group at the 5-position were synthesized by aza-Wittig reactions between β-substituted vinyliminophosphoranes and cyclic α,β-unsaturated ketones. [β-(Methoxycarbonyl)vinyl]- (**1**), [β-(*N*,*N*-tetramethylenecarbamoyl)vinyl]- (**2**), [β-(*N*-benzylcarbamoyl)vinyl]- (**3**), and (β-carbamoylvinyl)iminophosphorane (**4**) were synthesized from the corresponding vinyl azides and triphenylphosphine. The heptamethylene chains of 5-(methoxycarbonyl)[7](2,4)pyridinophane (**5**), 5-(*N*,*N*-tetramethylenecarbamoyl)[7](2,4)pyridinophane (**6**), and 5-(*N*-benzylcarbamoyl)[7](2,4)pyridinophane (**7**) flipped with $\Delta G^{\ddagger} = 11.2$ (T_c = 10.3 °C), 10.8 (T_c = 0.2 °C), and 10.5 kcal/mol (T_c = −5.2 °C), respectively. At lower temperatures, the three conformations of the heptamethylene bridge were frozen. Methylpyridinium iodides **10** (*n* = 7, 6, and 5) derived from **6** were reduced more easily [$E_{1/2}$* (half height potential) = −1.65 V (*n* = 7); −1.63 V (*n* = 6); −1.29 V vs Ag/AgCl (*n* = 5)] than the reference compound, 2,4-diethyl-5-(*N*,*N*-tetramethylenecarbamoyl)pyridinium ion (**11**) [$E_{1/2}$* = −1.82 V vs Ag/AgCl]. The reduced species dimerized quickly.

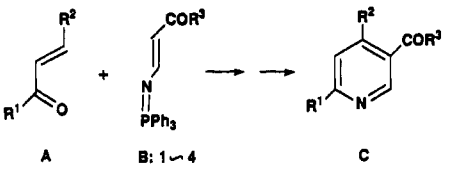
Coenzyme NAD(P) is one of the most important and abundant redox coenzymes and acts as both reductant and oxidant in biological systems (Scheme I).[1,2] Apoenzymes mediate the biological reactions of this conflicting dual nature. Much attention has been directed to studies on NAD(P) models, and our understanding of the reaction mechanism has been broadened through a variety of model compounds.[3-5] In these model studies, however, essentially all the reactions involve reduction of carbonyl functions by 1,4-dihydronicotinamide derivatives, NAD(P)H models, and only a few studies involve oxidation by pyridinium ions, NAD(P) models.[6,7] The 1,4-dihydropyridine systems in these models lack aromaticity and assume nonplanar conformations,[8] whereas the oxidized forms, 1-alkylpyridiniums, have aromaticity and planar geometry (Scheme I).

Because a cyclophane brings ring strain into an aromatic ring, the ring becomes puckered and its aromaticity is reduced.[9-12] In a similar way, the oligomethylene bridge in [n](2,4)pyridinophanes may alter the redox potential, and the pyridinophanes may serve as models of the active center of NAD(P). On the basis of this hypothesis, we planned the syntheses of [n](2,4)pyridinophanes **C** (where

Scheme I



Scheme II



R^1, R^2 = $(CH_2)_n$) having ester or amide functions (see Scheme II).

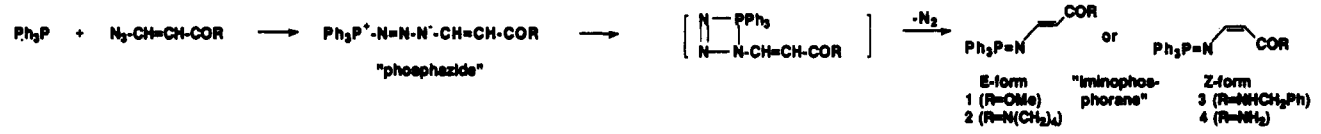
Vinyliminophosphorane. The reactions between α,β-unsaturated cyclic ketones **A** and vinyliminophosphoranes **B** were previously studied by a member of our group and have been reported to give 2,4-disubstituted pyridines **C** (Scheme II).[12] In the present study, [n](2,4)pyridinophanes were synthesized by the reactions of [β-(methoxycarbonyl)vinyl]iminophosphorane (**1**) or (β-carbamoylvinyl)iminophosphoranes **2–4** with cyclic α,β-unsaturated ketones **A** (Scheme II).

Vinyliminophosphoranes **1–4** were prepared in situ from the corresponding vinyl azides[13,14] and triphenylphosphine (Scheme III). When (*Z*)-β-(methoxycarbonyl)vinyl azide and triphenylphosphine were mixed at −78 to −50 °C in ether, the adduct crystals precipitated from the solution. Elemental analysis suggested that the crystalline product was a phosphazide, a 1:1 adduct of the azide and triphenylphosphine. At −10 °C in chloroform solution, the phosphazide gave (*E*)-[β-(methoxycarbonyl)-vinyl]-iminophosphorane (**1**) by the slow liberation of nitrogen. ^{1}H NMR spectra of the phosphazide at variable temperatures (−30 to 30 °C) indicated that the reaction proceeded

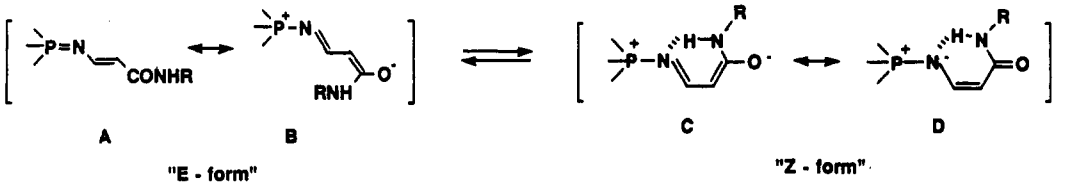
(1) Sund, H. *Nucleotide Dependent Dehydrogenase*; Springer-Verlag: Berlin, New York, 1969.
(2) Eisner, V. *Chem. Rev.* **1972**, *72*, 1.
(3) Kill, R. J.; Widdowson, D. A. *Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. IV, p 239.
(4) Wood, H. C. S. *Comprehensive Organic Chemistry*; Haslam, E., Ed.; Pergamon Press: Oxford, 1979; Vol. 5.
(5) Fukui, S., Ed. *Vitamin*; Tokyo Kagaku Dojin: Tokyo, 1980; Vol. II, p 227.
(6) Gizzi, L. R.; Joullie, M. M. *Tetrahedron Lett.* **1969**, 3117.
(7) Ohnishi, Y.; Teramoto, S. *Tetrahedron Lett.* **1977**, 1909.
(8) Benner, S. A. *Experientia* **1982**, *38*, 633.
(9) Jenneskens, J. W.; Klamer, J. C.; de Boer, H. J. R.; de Wolf, W. H.; Bickelhaupt, F.; Stam, C. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 238.
(10) Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kasai, N. *Tetrahedron* **1986**, *42*, 1851.
(11) Dhanak, D.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* 1987, 2829.
(12) Kanomata, N.; Nitta, M. *Tetrahedron Lett.* **1988**, *29*, 5957; *J. Chem. Soc., Perkin Trans. 1* **1990**, 1119.
(13) Rappe, C. *Acta Chem. Scand.* **1965**, *19*, 31.
(14) Hassner, A.; Fourer, F. W. *J. Org. Chem.* **1968**, *33*, 2686.

0022-3263/93/1958-2046$04.00/0

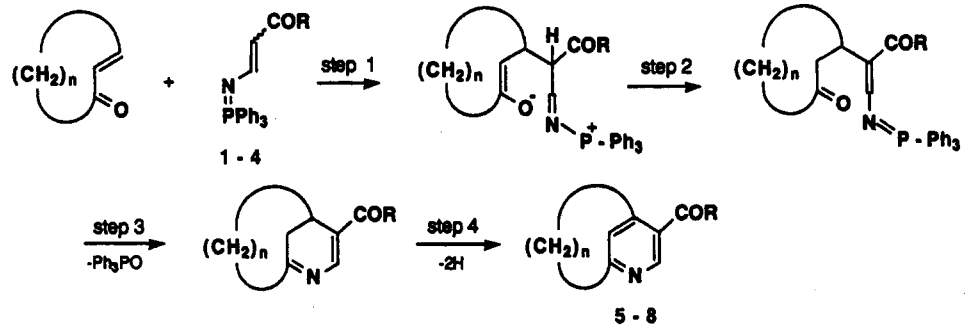
Scheme III



Scheme IV



Scheme V



1, 5 (R=OMe); 2, 6 (R=N(CH$_2$)$_4$); 3, 7 (R=NHCH$_2$Ph); 4, 8 (R=NH$_2$)

Table I. Conditions and Yields for the Reactions of Vinyliminophosphoranes 1–4 and α,β-Unsaturated Ketones

run	product	R	*n*	solvent	yield (%)
1	5	OMe	9	benzene	0
2	5	OMe	9	toluene	11
3	5	OMe	9	xylene	31
4	5	OMe	9	mesitylene	27
5	5	OMe	8	toluene	11
6	5	OMe	8	mesitylene	38
7	5	OMe	7	toluene	6
8	5	OMe	7	xylene	12
9	5	OMe	6	xylene	0
10	6	N(CH$_2$)$_4$	9	xylene	29
11	6	N(CH$_2$)$_4$	8	xylene	22
12	6	N(CH$_2$)$_4$	7	xylene	6
13	7	NHCH$_2$Ph	8	xylene	21
14	7	NHCH$_2$Ph	7	xylene	5
15	8	NH$_2$	9	xylene	14
16	8	NH$_2$	8	xylene	16
17	8	NH$_2$	7	xylene	4

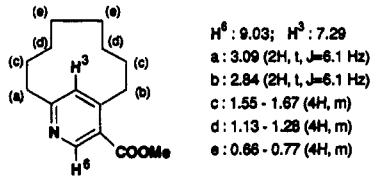


Figure 1. ^{1}H NMR spectrum (400 MHz) of **5**.

by means of the initial formation of (*Z*)-[β-(methoxycarbonyl)vinyl]iminophosphorane by the loss of nitrogen and subsequent thermal isomerization to the *E*-isomer (**1**). Similarly, (*E*)-β-(methoxycarbonyl)- and (*E*)-β-(*N*,*N*-tetramethylenecarbamoyl)vinyl azides gave (*E*)-[β-(methoxycarbonyl)vinyl]- (**1**) and (*E*)-[β-(*N*,*N*-tetramethylenecarbamoyl)vinyl]iminophosphorane (**2**), respectively. (*E*)-β-(*N*-Benzylcarbamoyl) and (*E*)-β-(carbamoyl)vinyl azide, however, gave the isomerized (*Z*)-[β-(*N*-benzylcarbamoyl)-vinyl]- (**3**) and (*Z*)-(β-carbamoylvinyl)iminophosphorane (**4**), respectively. Thus, (*E*)-[β-(methoxycarbonyl)vinyl- (**1**), (*E*)-[β-(*N*,*N*-tetramethylenecarbamoyl)vinyl]- (**2**), (*Z*)-[β-(*N*-benzylcarbamoyl)vinyl]- (**3**), and (*Z*)-(β-*N*-carbamoylvinyl)iminophosphorane (**4**) were exclusively obtained irrespective of the geometry of the starting vinylazides (Scheme III).

The stereochemistry can be accounted for by a facile thermal isomerization and an intramolecular hydrogen bond in the β-(carbamolyvinyl)iminophosphoranes (Scheme IV). In fact, the ^{1}H NMR spectrum of (*Z*)-[β-(*N*-benzylcarbamoyl)vinyl]iminophosphorane (**3**) in deuteriochloroform showed an NH signal at δ 9.7–10.1, and the signal moved to δ 6.7–7.2 when a small quantity of DMSO was added. This shift suggested that cleavage of an intramolecular hydrogen bond (**C** and **D**)[15] followed by a *Z* → *E* isomerization (**C**, **D** → **A**, **B**) (Scheme IV). Vinyliminophosphoranes without an NH group cannot be stabilized in the *Z*-form, and they isomerize into the *E*-form because of the weak double-bond character caused by the contribution of structures **B** and **C** in Scheme IV. Vinyliminophosphoranes **1**–**4** thus prepared were stable.

Since the thermal *E* ⇄ *Z* isomerization takes place easily, either isomer can be a good starting material for the aza-Wittig reaction to form a pyridine ring system.

Syntheses of Pyridinophanes by the Aza-Wittig Reaction. Vinyliminophosphoranes **1**–**4** and cyclic α,β-unsaturated ketones were refluxed in an aromtic hydrocarbon for 48 h in the presence of Pd/C. The reaction gave 2,4-pyridinophane derivatives **5**–**8** in the yields listed in Table I. The structures of the products were deduced from ^{1}H NMR, ^{13}C NMR, and elemental analyses. As illustrated in Figure 1 for pyridinophane **5** (*n* = 8), one

(15) Ouelette, R. J. *Can. J. Chem.* **1965**, *43*, 707.

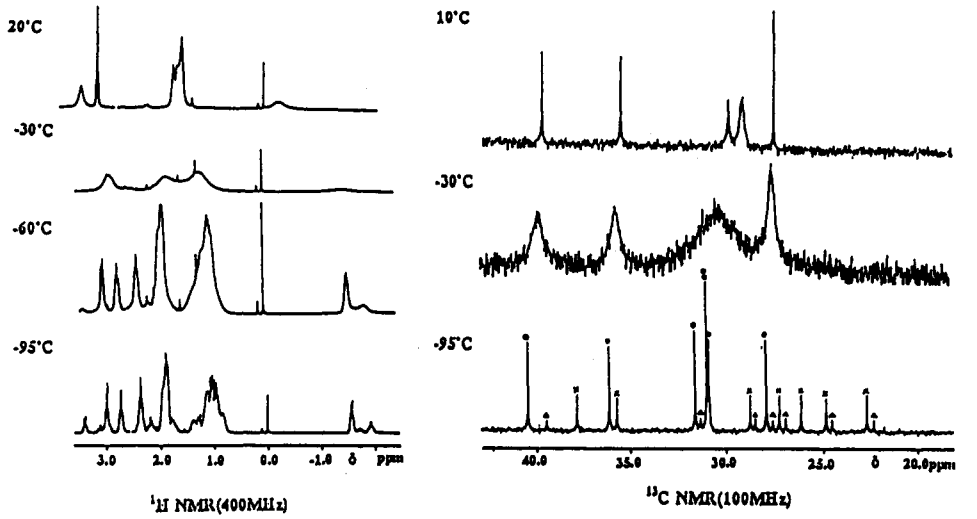


Figure 2. Temperature dependence of NMR spectra of **5** (n = 7).

aromatic hydrogen (H^6) resonates at a lower field (δ 9.03) because of the ring nitrogen and the adjacent ester group, and another aromatic hydrogen (H^3) resonates at a higher field (δ 7.29). The two methylene groups connected to the pyridine ring resonate at δ 3.09 and 2.84 as triplets (J = 6.1 Hz).

The proposed reaction mechanism for these multi-step reactions is outlined in Scheme V. The β-carbon of the vinyliminophosphoranes is electron rich because it is conjugated with the imino nitrogen, and the carbon adds Michael-fashion to the α,β-unsaturated ketone (step 1). Intramolecular proton transfer and ketonization (step 2) followed by the aza-Wittig reaction (step 3) give a dihydropyridinophane. Since the reactions are carried out in the presence of a dehydrogenation catalyst (Pd/C), the aromatization (step 4) to give [n](2,4)pyridinophanes takes place in the same pot.[12]

We sought an adequate solvent for the reaction by using [β-(methoxycarbonyl)vinyl]iminophosphorane as a test compound (runs 1–4) and found boiling xylene to be a convenient reaction medium. The reaction in boiling benzene did not give the product (run 1), and carrying out the reaction in boiling mesitylene did not improve the yields. We were unable to obtain the pyridinophane with a hexamethylene bridge (**5**, n = 6) (run 9). Shortening the oligomethylene bridge decreased the yields of the pyridinophanes in the following order: nonamethylene ≈ octamethylene > heptamethylene ≫ hexamethylene. The effect of the bridge length can be accounted for by the ease of the aza-Wittig reaction and the final aromatization (steps 3 and 4 in Scheme V). This final step introduces strain into the resulting pyridine ring, and the shortening of the oligomethylene bridge lowers the yield. From all of the reactions, 30–60% of the starting ketone was recovered, probably because of the thermal deterioration of vinyliminophosphoranes.

Flipping of the Bridged Oligomethylene Chain. ^{1}H NMR and ^{13}C NMR spectra of heptamethylenepyridinophane **5** (n = 7) varied depending on the temperature. Portions of the spectra, δ −2.5 to 3.5 for ^{1}H NMR and δ 18–45 for ^{13}C NMR, are shown in Figure 2. Protons H_{4x} and H_{4y} (Figure 3) appeard as a single broad signal at ca. −0.3 ppm. Lowering the temperature caused this peak to separate into two groups because the conformational flipping of the heptamethylene bridge was slowed. These signals coalesced at −10.3 °C, and the spectral analysis by

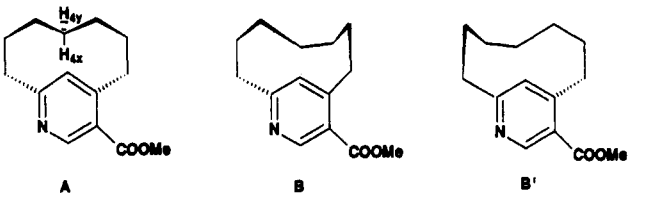


Figure 3. Conformations of **5** at −95 °C.

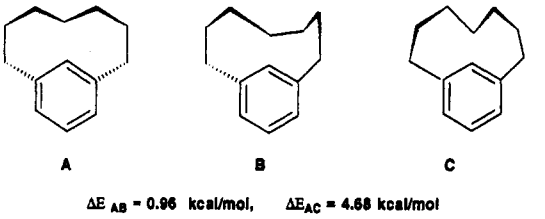


Figure 4. Conformations of [7](1,3)cyclophane.

the coalescence temperature (T_c) method[16] gave a $\Delta G^{\ddagger}$ for the flipping of 11.2 kcal/mol (T_c = −10.3 °C). Similar analyses of amide derivatives **6** and **7** (n = 7) gave $\Delta G^{\ddagger}$ = 10.8 (T_c = 0.2 °C) and $\Delta G^{\ddagger}$ = 10.5 kcal/mol (T_c = −5.2 °C), respectively. The signals due to H_{4x} and H_{4y} were fixed at −95 °C into three sets of paired peaks; one half of each set appeared at approximately δ −1.7 and the other half at approximately δ 1.2. The latter signals were partially buried by the strong signals due to other methylene groups. The higher field set of signals of H_{4x} and H_{4y} (at approximately δ −1.7) showed the existence of three conformers (**A**, **B**, and **B'**) in a frozen state (Figure 3).[12] A ^{13}C NMR spectrum of **5** (n = 7) at −95 °C showed three sets of peaks due to the heptamethylene group of the three conformers (see Figure 2).

Molecular mechanics calculation by Carballeira et al.[17] concluded that the three conformations (**A**, **B**, and **C** in Figure 4) of [7](1,3)cyclophane have energy minima. Because of the lack of symmetry, pyridinophane **5** has two variations, **B** and **B'** (Figure 3), that correspond to conformation **B** of the cyclophane (Figure 4). Because of the energy gaps shown in Figure 4, the amount of the least stable conformer of pyridinophane **5** (n = 7), which

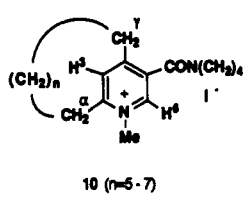
(16) Jackman, L. M., Cotton, F. A., Eds. *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Academic Press: New York, 1975.
(17) Carballeira, L.; Pereiras, A. J.; Rios, M. A. *J. Chem. Phys.* **1984**, *80*, 4387.

Table II. ^{1}H NMR Chemical Shifts of *N*-Methylpyridinium Salts of 5-(*N*,*N*-Tetramethylenecarbamoyl)-[*n*](2,4)pyridinophanes 10 (*n* = 5–7) and 11

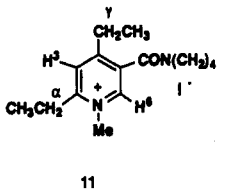
salt	*n*	δ(H^3)	δ(H^6)	NMe	$-CH_2-(\alpha)$	$-CH_2-(\gamma)$
10	5	8.20	9.13	4.32	3.02	2.68
10	6	8.02	9.20	4.46	3.27	2.88
10	7	8.01	9.27	4.50	3.32	2.98
11		7.66	9.07	4.48	3.18	2.93

corresponds to conformation C of the cyclophane (Figure 4), is negligible at −95 °C.

Strain in 5-Substituted [*n*](2,4)Pyridinophane. 5-(*N*,*N*-tetramethylenecarbamoyl)[*n*](2,4)pyridinophane (**6**, *n* = 7–9) and 2,4-diethyl-5-(tetramethylenecarbamoyl)pyridine (**9**) were transformed into methylpyridinium iodides **10** and **11**, respectively.



10 (n=5-7)



11

The chemical shifts of H^3 of pyridinium ions **10** (*n* = 5–7) and **11** are a consequence of the electronic state of C_3 and steric compression around H^3.[18,19] However, the chemical shifts of H^6, NCH_3, α-CH_2, and γ-CH_2 seem to depend on the nature of the pyridinium ring. The shortening of the oligomethylene bridge of **10** pushes the chemical shifts of all the H^6, NCH_3, α-CH_2, and γ-CH_2 groups to higher field. These shifts to higher field can be accounted for by the decrease in aromaticity and the decrease in the ring current effect of the pyridinium ions.

Cyclic voltammetry of these pyridinium ions in acetonitrile gave irreversible reduction waves in the range of ca. −2.0 to −1.0 V vs Ag/AgCl. The half-height potentials of the reduction waves ($E_{1/2*}$) of compounds **10** move into the positive direction when the oligomethylene bridge is shortened: −1.82 (**11**), −1.65 (**10**, *n* = 7), −1.63 (**10**, *n* = 6), and −1.29 V (**10**, *n* = 5). The difference in the reduction potential ($E_{1/2*}$) between heptamethylenepyridinophane **10** (*n* = 5) and the reference compound **11** is 0.53 V. This lowering of the reduction potential is ascribed to the decreased aromaticity of the pyridinium ion due to the steric strain exerted by the bridge. The irreversible nature of the cyclic voltammetry is accounted for by the rapid dimerization of the radicals formed by a single electron reduction, as has been reported for a similar system (Scheme VI).[20,21]

These experimental findings suggest the possibilities for improved NAD(P) models which may effect the oxidation of alcohols.

Experimental Section

Syntheses of β-Substituted Vinyl Azides. β-(Methoxycarbonyl)vinyl and β-carbamoylvinyl azides were synthesized by the reaction of sodium azide with the corresponding 3-chloropropenoates[22] and 3-chloropropenamides.[22,23] (*Z*)-*N*,*N*-Tetramethylene-3-chloropropenamide,[22] (*Z*)-*N*-benzyl-3-chloropropenamide, and (*Z*)-3-chloropropenamide[23] did not react with sodium azide under similar conditions.

A typical procedure for the preparation of (*Z*)-β-(methoxycarbonyl)vinyl azide is described. Methyl (*Z*)-3-chloropropenoate (300 mg, 2.5 mmol) and NaN_3 (325 mg, 5.0 mmol) in 25 mL of DMSO were stirred for 12 h at rt and then treated with 30 mL of ether. The reaction mixture was extracted with chloroform (50 mL × 3), and the extracts were dried over Na_2SO_4. Evaporation of the solvent gave the crude product. Silica gel chromatography ($CHCl_3$) removed polar materials to give 251 mg (79%) of (*Z*)-β-(methoxycarbonyl)vinyl azide.[13] Other azides were obtained by the same procedure, and the solvents for chromatography are shown in parentheses along with spectroscopic data.

(*Z*)-β-(Methoxycarbonyl)vinyl azide (chloroform):[13] mp 64.0–64.5 °C (benzene–hexane (1:2)).

(*E*)-β-(Methoxycarbonyl)vinyl azide (chloroform):[14] mp 50.6–51.1 °C (ethyl acetate–hexane (1:2)). (*E*)-β-(*N*,*N*-Tetramethylenecarbamoyl)vinyl azide (EtOAc): mp 95.1–96.3 °C (EtOAc–hexane (1:2)); key signals of ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.92 (1 H, d, *J* = 12.7 Hz), 7.34 (1 H, d, *J* = 12.7 Hz); IR ($CHCl_3$) 2134, 1706 cm^{-1}. Anal. Calcd for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.71. Found: C, 50.78; H, 6.08; N, 33.64.

(*E*)-β-(*N*-Benzylcarbamoyl)vinyl azide (ether–hexane 4:1)): mp 118.0–119.6 °C (EtOAc–hexane (1:1)); key signals of ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.53 and 4.46 (NH), 5.72 (1 H, d, *J* = 13.5 Hz), 7.31 (1 H, d, *J* = 13.5 Hz); IR ($CHCl_3$) 3450 (br), 2138, 1668 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.68; H, 4.92; N, 27.64.

(E)-β-Carbamoylvinyl azide (EtOAc): mp 115.8–117.3 °C ($CHCl_3$–ethanol (5:1)); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.40–6.50 (2 H, br, NH_2), 5.70 (1 H, d, *J* = 13.2 Hz), 7.25 (1 H, d, *J* = 13.2 Hz); IR ($CHCl_3$) 3495, 3280, 2150, 1685 cm^{-1}. Anal. Calcd for $C_3H_4N_4O$: C, 32.15; H, 3.60; N, 49.98. Found: C, 32.40; H, 3.41; N, 50.18.

β-(Methoxycarbonyl)vinyl Phosphazide (cf. Scheme III). (*Z*)-β-(Methoxycarbonyl)vinyl azide (63 mg, 0.5 mmol) in 50 mL of ether was cooled to −78 °C, and triphenylphosphine (131 mg, 0.5 mmol) dissolved in 10 mL of ether was added. The mixture was allowed to warm slowly, and the yellow crystals of the phosphazide, which precipitated at about −50 °C, were separated by filtration at low temperature and dried under vacuum to give yellow crystals, mp 68.0–69.5 °C dec. The crystals decomposed by loss of nitrogen at the mp. Anal. Calcd for $C_{22}H_{20}N_3O_2P$; C, 67.86; H, 5.18; N, 10.79. Found: C, 68.16; H, 5.30; N, 10.40.

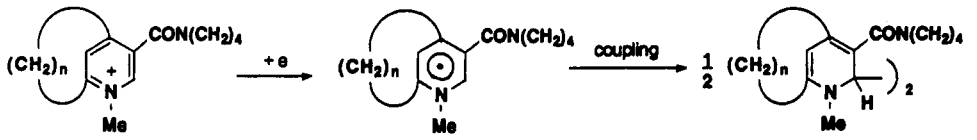
^{1}H NMR spectrum of this phosphazide in $CDCl_3$ at −10 °C gave the following signals along with those due to the (*Z*)-[β-(methoxycarbonyl)vinyl]- and (*E*)-[β-(methoxycarbonyl)vinyl]-iminophosphorane (1): ^{1}H NMR (400 MHz, −10.2 °C, $CDCl_3$) δ 3.73 (3 H, s), 4.82 (1 H, dd, *J* = 7.7 and 4.4 Hz (J_p)), 7.06 (1 H, dd, *J* = 7.7 and 27.2 Hz (J_p)), 7.44–7.77 (15 H, m), 7.46 (1 H, d, *J* = 9.3 Hz). The spectrum at rt showed only the signals due to the iminophosphorane (1) (see text).

β-Substituted Vinyliminophosphoranes. Vinyliminophosphoranes 1–4 were prepared directly from the vinyl azides and triphenylphosphine, and a typical procedure is described for the synthesis of (*E*)-[β-(methoxycarbonyl)vinyl]iminophosphorane (1).

(*Z*)- or (*E*)-β-(Methoxycarbonyl)vinyl azide (247 mg, 1.9 mmol) in 10 mL of ether was treated with triphenylphosphine (511 mg, 1.9 mmol) in 10 mL of ether at rt. The mixture was stirred for 1 h after the completion of gas evolution, and the precipitated crystals were filtered to give 549 mg (80%) of (*E*)-[β-(methoxycarbonyl)vinyl]iminophosphorane (1): mp 137.5–138.4 °C (benzene–hexane (1:1)); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.60 (3 H, s), 5.41 (1 H, dd, *J* = 12.3 and 1.1 Hz (J_p)), 7.30–7.88 (15 H, m), 7.95 (1 H, dd, *J* = 12.3 and 27.7 Hz (J_p)); IR ($CHCl_3$) 1665, 1588 cm^{-1}. Anal. Calcd for $C_{22}H_{20}NO_2P$: C, 73.12; H, 5.59; N, 3.89. Found: C, 73.34; H, 5.73; N, 3.94.

(18) Winstein, S.; Carter, P., Anet, F. A. L.; Brown, A. J. R. *J. Am. Chem. Soc.* **1965**, *87*, 5247.
(19) Baldwin, J. E.; Pinchmidt, R. K., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 5247.
(20) Cunningham, A. J.; Underwood, A. L. *Biochemistry* **1967**, *6*, 266.
(21) Ohnishi, Y.; Kitami, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2674.
(22) Ohta, A.; Inagawa, Y.; Okuwaki, Y.; Shimazaki, M. *Heterocycles* **1984**, *22*, 2369.
(23) Kurz, A. N.; Billups, W. E. *J. Org. Chem.* **1965**, *30*, 3131.

Scheme VI



(*E*)-[β-(*N*,*N*-Tetramethylenecarbamoyl)vinyl]-iminophosphorane (**2**) (69% from the azide): mp 164.1–165.0 °C (benzene–hexane (1:1)); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.60–2.13 (4 H, m), 3.45 (4 H, t, *J* = 6.7 Hz), 5.74 (1 H, dd, *J* = 12.1 and 1.0 Hz (J_p)), 7.28–7.82 (15 H, m), 7.97 (1 H, dd, *J* = 12.1 and 25.0 Hz (J_p)); IR ($CHCl_3$) 1608, 1540 cm^{-1}. Anal. Calcd for $C_{25}H_{25}N_2OP$: C, 74.98; H, 6.29; N, 7.00. Found: C, 75.20; H, 6.15; N, 7.00.

(*Z*)-[β-(*N*-Benzylcarbamoyl)vinyl]iminophosphorane (**3**) (80% from the (*E*)-azide): mp 167.0–168.1 °C ($CHCl_3$–hexane (1:5)). ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.63 (2 H, d, *J* = 5.3 Hz), 4.98 (1 H, dd, *J* = 7.9 and 4.2 Hz (J_p)), 6.79 (1 H, dd, *J* = 7.9 and 22.6 Hz (J_p)), 7.20–7.80 (20 H, m), 9.95 (1 H, s, NH); IR ($CHCl_3$) 1649, 1623, 1572 cm^{-1}. Anal. Calcd for $C_{28}H_{25}N_2OP$: C, 77.05; H, 5.77; N, 6.40. Found: C, 76.79; H, 5.77; N, 6.40.

(*Z*)-(β-Carbamoylvinyl)iminophosphorane (**4**) (88% from the (*E*)-azide): mp 194.9–195.8 °C ($CHCl_3$–hexane (1:1)); ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.78 (1 H, m), 5.20 (1 H, br, NH), 6.84 (1 H, dd, *J* = 7.7 and 23.5 Hz (J_p)), 7.25–7.77 (15 H, m), 8.88–9.30 (1 H, br, NH); IR ($CHCl_3$) 3460, 3250, 1620, 1575 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_2OP$: C, 72.82; H, 5.53; N, 8.09. Found: C, 72.85; H, 5.53; N, 7.88.

Syntheses of 5-(Methoxycarbonyl)[*n*](2,4)pyridinophane 5. Pyridinophanes **5** (*n* = 9, 8, and 7) were synthesized by the same procedure in the yields listed in Table I. The procedure used for [7](2,4)pyridinophane (**5**, *n* = 7) is described as an example.

A mixture of (*E*)-[β-(methoxycarbonyl)vinyl]iminophosphorane (**1**) (2.39 g, 6.9 mmol), cyclodec-2-enone (1.01 g, 6.6 mmol), and 10% Pd/C (200 mg) in 10 mL of xylene was refluxed for 48 h under nitrogen. Filtration of the cooled mixture and evaporation of the solvent gave the crude products. Polar materials were removed by silica gel chromatography (EtOAc–hexane (3:4)), and the eluate was subjected to preparative TLC (SiO_2, EtOAc–hexane (2:5)). Bulb to bulb distillation (Kugelrohr) gave 86 mg (12%) of [7](2,4)pyridinophane **5** (*n* = 7): bp 110 °C/1.0 Torr; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ −0.30 to 0.13 (2 H, br, s), 1.34–1.48 (4 H, m), 1.53 (2 H, quint, *J* = 5.2 Hz), 1.59 (2 H, quint, *J* = 6.1 Hz), 2.88 (2 H, t, *J* = 6.1 Hz), 3.14 (2 H, br, s), 3.90 (3 H, s), 7.46 (1 H, s), 8.94 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 27.2, 28.7, 28.8, 28.9, 29.5, 35.3, 39.6, 51.7, 121.7, 126.8, 152.1, 154.0, 165.1, 166.6; IR ($CHCl_3$) 1722, 1600, 1552 cm^{-1}; UV (EtOH) λ_{max} (log ε) 217 (4.01), 232 (3.98), 273 nm (3.54).

Picrate: mp 160.0–162.0 °C (EtOH). Anal. Calcd for $C_{20}H_{22}N_4O_9$: C, 51.95; H, 4.80; N, 12.12. Found: C, 51.68; H, 4.97; N, 12.04.

5 (*n* = 8): bp 120.0 °C/1.0 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66–0.77 (4 H, m), 1.13–1.28 (4 H, m), 1.55–1.68 (4 H, m), 2.84 (2 H, t, *J* = 6.1 Hz), 3.09 (2 H, t, *J* = 6.1 Hz), 3.91 (3 H, s), 7.29 (1 H, s), 9.03 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 23.8, 25.8, 26.9, 27.6, 27.8, 33.9, 38.3, 52.0, 122.0, 126.3, 152.4, 153.4, 165.0, 166.5; IR ($CHCl_3$) 1730, 1598, 1550 cm^{-1}; UV (EtOH) λ_{max} (log ε) 216 (3.83), 233 (3.99), 270 (3.54).

Picrate: mp 136.5–138.0 °C (EtOH). Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.11; H, 5.37; N, 11.57.

5 (*n* = 9): bp 120 °C/1.0 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81–0.96 (4 H, m), 1.03–1.17 (6 H, m), 1.76 (2 H, quint, *J* = 6.3 Hz), 1.80 (2 H, quint, *J* = 6.1 Hz), 2.91 (2 H, *J* = 6.1 Hz), 3.10 (2 H, t, *J* = 6.3 Hz), 3.92 (3 H, s), 7.25 (1 H, s), 9.04 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 25.0, 25.5, 25.6, 25.7, 25.9, 26.6, 33.4, 36.8, 52.0, 122.0, 126.7, 152.0, 152.6, 164.7, 166.6; IR ($CHCl_3$) 1720, 1602, 1550 cm^{-1}; UV (EtOH) λ_{max} (log ε) 215 (3.84), 232 (3.98), 269 nm (3.58).

Picrate: mp 140.0–141.5 °C (EtOH). Anal. Calcd for $C_{22}H_{26}N_4O_9$: C, 53.8; H, 5.34; N, 11.42. Found: C, 53.75; H, 5.33; N, 11.29.

Syntheses of 5-(*N*,*N*-Tetramethylenecarbamoyl)[*n*](2,4)-pyridinophanes 6. Aza-Wittig reactions of [β-(*N*,*N*-tetramethylenecarbamoyl)vinyl]iminophosphorane (**2**) with α,β-unsaturated cyclic ketones were carried out in the manner described for the synthesis of **5** (*n* = 7), and the crude products were purified by preparative TLC (SiO_2, EtOAc) to afford the pure products in the yields listed in Table I. However, pyridinophanes **6** were synthesized more conveniently by the treatment of 5-(methoxycarbonyl)[*n*](2,4)pyridinophane **5** with pyrrolidine. Thus, a mixture of ester **5** (*n* = 7) (93.1 mg) and 3 mL of pyrrolidine was refluxed for 24 h, treated with 10 mL of water, and extracted with CH_2Cl_2 (30 mL × 3). Evaporation of the solvent after washing (aqueous NH_4Cl) and drying ($MgSO_4$) gave a crude product. Preparative TLC (SiO_2, EtOAc–hexane (2:5)) gave 102 mg (94%) of 5-(*N*,*N*-tetramethylenecarbamoyl)[7](2,4)-pyridinophane (**6**, *n* = 7): oil; ^{1}H NMR (400 MHz, CD_2Cl_2) δ −0.60 to 0.50 (2 H, br, s), 1.03–1.58 (18 H, m), 1.78 (2 H, quint, *J* = 6.6 Hz), 1.86 (2 H, quint, *J* = 6.6 Hz), 2.61 (2 H, m), 2.76 (2 H, t, *J* = 5.9 Hz), 3.18 (2 H, t, *J* = 6.6 Hz), 3.51 (2 H, t, *J* = 6.6 Hz), 7.41 (1 H, s), 8.23 (1 H, s); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 23.7, 25.3, 26.6, 27.8, 27.9, 28.5 (2 C), 33.6, 38.3, 44.8, 48.2, 125.3, 129.6, 145.8, 148.5, 161.0, 166.0; IR ($CHCl_3$) 1615, 1550 cm^{-1}.

Picrate: mp 157.5–158.3 °C (EtOH). Anal. Calcd for $C_{23}H_{27}N_5O_8$: C, 55.09; H, 5.43; N, 13.96. Found: C, 54.87; H, 5.51; N, 14.00.

6 (*n* = 8): oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.48–0.91 (4 H, m), 0.98–1.45 (4 H, m), 1.45–1.80 (4 H, m), 1.70–2.10 (4 H, m), 2.69 (2 H, t, *J* = 6.0 Hz), 2.83 (2 H, t, *J* = 5.9 Hz), 3.27 (2 H, t, *J* = 6.0 Hz), 3.66 (2 H, t, *J* = 6.0 Hz), 7.30 (1 H, s), 8.41 (1 H, s); IR ($CHCl_3$) 1616, 1550 cm^{-1}.

Picrate: mp 159.5–160.3 °C (EtOH). Anal. Calcd for $C_{24}H_{29}N_5O_8$: C, 55.92; H, 5.67; N, 13.52. Found: C, 55.75; H, 5.76; N, 13.52.

6 (*n* = 9): oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.50–1.41 (10 H, m), 1.49–2.18 (8 H, m), 2.76 (2 H, t, *J* = 6.6 Hz), 2.90 (2 H, t, *J* = 6.2 Hz), 3.25 (2 H, t, *J* = 6.4 Hz), 3.66 (2 H, t, *J* = 7.0 Hz), 7.29 (1 H, s), 8.39 (1 H, s); IR ($CHCl_3$) 1620, 1552 cm^{-1}.

Picrate: mp 153.1–154.0 °C (EtOH). Anal. Calcd for $C_{25}H_{31}N_5O_8$: C, 56.70; H, 5.90; N, 13.23. Found: C, 55.41; H, 5.41; N, 13.24.

Syntheses of 5-(*N*-Benzylcarbamoyl)[*n*](2,4)-pyridinophane 7. The reactions between (*Z*)-[β-(*N*-benzylcarbamoyl)vinyl]iminophosphorane (**3**) and α,β-unsaturated ketones were carried out in the manner described previously for the synthesis of **5** (*n* = 7), and the crude products were purified by preparative TLC (Al_2O_3, EtOAc–hexane (3:2)).

7 (*n* = 7): oil; ^{1}H NMR (400 MHz, CD_2Cl_2) δ −0.55 to 0.10 (2 H, br), 1.30–1.48 (4 H, m), 1.48–1.61 (4 H, m), 2.86 (2 H, t, *J* = 5.9 Hz), 2.85–3.20 (2 H, m), 6.48–6.63 (1 H, NH), 7.26–7.34 (3 H, m), 7.36 (2 H, d, *J* = 4.4 Hz), 7.52 (1 H, s), 8.51 (1 H, s); IR ($CHCl_3$) 3445, 1662, 1598, 1552 cm^{-1}.

Picrate: mp 176.7–179.5 °C (EtOH). Anal. Calcd for $C_{26}H_{27}N_5O_8$: C, 58.10; H, 5.06; N, 13.03. Found: C, 57.94; H, 5.30; N, 12.95.

7 (*n* = 8): oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.36–0.92 (4 H, m), 0.92–1.36 (4 H, m), 1.36–1.80 (4 H, m), 2.50–3.05 (4 H, m), 4.61 (2 H, d, *J* = 5.7 Hz), 6.35–6.80 (1 H, NH), 7.27 (1 H, s), 7.33 (5 H, s), 8.51 (1 H, s); IR ($CHCl_3$) 3445, 1658, 1598, 1550 cm^{-1}.

Picrate: mp 174.2–175.1 °C (EtOH). Anal. Calcd for $C_{27}H_{29}N_5O_8$: C, 58.80; H, 5.30; N, 12.70. Found: C, 58.55; H, 5.32; N, 12.68.

Syntheses of 5-Carbamoyl[*n*](2,4)pyridinophanes 8. The reactions of (*Z*)-(β-carbamoylvinyl)iminophosphorane (**4**) with α,β-unsaturated cyclic ketones were carried out in the manner described for the synthesis of **5** (*n* = 7), and the crude products were purified by preparative TLC (SiO_2, EtOAc).

8 (*n* = 7): mp 185.1–186.3 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ −0.45 to 0.00 (2 H, br), 1.00–1.80 (8 H, m), 2.65–3.03 (4 H, m), 7.05–7.50 (1 H, NH), 7.61 (1 H, s), 7.60–8.00 (1 H, NH), 8.45 (1 H, s); IR ($CHCl_3$) 3510, 3400, 1675, 1587 cm^{-1}.

Picrate: mp 185.1–186.3 °C (EtOH). Anal. Calcd for $C_{19}H_{21}N_5O_8$: C, 51.01; H, 4.73; N, 15.65. Found: C, 51.39; H, 5.01; N, 15.98.

8 (n = 8): mp 180.2–181.5 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 0.45–0.92 (4 H, m), 0.92–1.35 (4 H, m), 1.35–1.83 (4 H, m), 2.53–3.05 (4 H, m), 7.20–7.70 (1 H, NH), 7.41 (1 H, s), 7.70–8.03 (1 H, NH), 8.50 (1 H, s); IR ($CHCl_3$) 3510, 3400, 1675, 1587 cm^{-1}.

Picrate: mp 180.2–181.5 °C (EtOH). Anal. Calcd for $C_{20}H_{23}N_5O_8$: C, 52.06; H, 5.02; N, 15.18. Found: C, 52.52; H, 5.21; N, 15.33.

Synthesis of 4,6-Diethyl-3-(*N,N*-tetramethylenecarbamoyl)pyridine 9. Pyridine derivative **9** was prepared by the radical alkylation reported by us.[24] A mixture of 3-(*N,N*-tetramethylenecarbamoyl)pyridine (151 mg, 0.86 mmol), propanoic acid (0.32 mL, 4.3 mmol), silver(I) nitrate (58 mg, 0.34 mmol), and 1 mL of a 1:1 mixture of H_2O and acetonitrile was heated to 75 °C and treated with ammonium peroxodisulfate (780 mg, 3.4 mmol) in 2 mL of water. The reaction mixture was kept at the same temperature for 4.5 h, and then concd aqueous NH_3 was added until the reaction mixture became alkaline. The reaction mixture was extracted with CH_2Cl_2 (20 mL × 3). The CH_2Cl_2 extracts were washed with aqueous $NaHCO_3$ and dried over $MgSO_4$ to afford the crude product, which was subjected to preparative TLC (SiO_2) developed twice with EtOAc–hexane–$CHCl_3$ (3:5:1). This procedure gave 34.2 mg (17%) of 2,4-diethyl-3-(*N,N*-tetramethylenecarbamoyl)pyridine (**9**) as a yellow oil. This oil was directly used for the preparation of *N*-methylpyridinium iodide **11**.

9: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.23 (3 H, t, J = 7.7 Hz), 1.30 (3 H, t, J = 7.5 Hz), 1.58–2.05 (4 H, m), 2.66 (2 H, q, J = 7.7 Hz), 2.81 (2 H, q, J = 7.5 Hz), 3.20 (2 H, t, J = 6.4 Hz), 3.66 (2 H, t, J = 7.0 Hz), 7.07 (1 H, s), 8.34 (1 H, s); IR ($CHCl_3$) 2980, 2875, 1625 cm^{-1}.

Syntheses of *N*-Methylpyridinium Iodides 10 of 5-(*N,N*-Tetramethylenecarbamoyl)[7](2,4)pyridinophane 6 (n = 9–7) and *N*-Methyl-2,4-diethyl-5-(*N,N*-tetramethylenecarbamoyl)pyridinium Iodide 11. *N*-Methylpyridinium iodides **10** (n = 7–9) were synthesized by warming a mixture of 5-(*N,N*-tetramethylenecarbamoyl)[n](2,4)pyridinophane **6** (250–310 mg) and methyl iodide (3 mL) at 40 °C for 40 h. The precipitated salts were collected by filtration, recrystallized from $CHCl_3$–hexane (1:1), and dried under vacuum. These salts were hygroscopic, and their melting points were not determined.

10 (n = 5): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.96–1.83 (14 H, m), 2.68 (2 H, t, J = 6.1 Hz), 3.02 (2 H, t, J = 6.0 Hz), 3.23–3.59 (4 H, m), 4.32 (3 H, s), 8.20 (1 H, s), 9.13 (1 H, s).

10 (n = 6): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.85–2.10 (16 H, m), 2.88 (2 H, t, J = 6.2 Hz), 3.27 (2 H, t, J = 6.0 Hz), 3.40–3.73 (4 H, m), 4.46 (3 H, s), 8.02 (1 H, s), 9.20 (1 H, s).

10 (n = 7): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90–2.10 (18 H, m), 2.98 (2 H, t, J = 6.7 Hz), 3.32 (2 H, t, J = 6.0 Hz), 3.40–3.70 (4 H, m), 4.50 (3 H, s), 8.01 (1 H, s), 9.29 (1 H, s), 8.01 (1 H, s), 9.29 (1 H, s).

Pyridinium iodide **11** (126 mg, 65% yield) was synthesized from **9** (120 mg, 0.52 mmol) and methyl iodide (0.2 mL, 3.1 mmol) in the manner described for **10**, except that 3 mL of THF was used as a solvent.

11: mp 169.8–170.5 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.34 (3 H, t, J = 7.5 Hz), 1.48 (3 H, t, J = 7.5 Hz), 1.89–2.11 (4 H, m), 2.89 (2 H, q, J = 7.5 Hz), 3.18 (2 H, J = 7.5 Hz), 3.50–3.80 (4 H, m), 4.48 (3 H, s), 7.66 (1 H, s), 9.07 (1 H, s). Anal. Calcd for $C_{15}H_{23}N_2O$: C, 48.14; H, 6.19; N, 7.48. Found: C, 48.01; H, 6.26; N, 7.51.

Cyclic Voltammetry of Pyridinium Salts 10 and 11. Reduction potentials of the salts **10** and **11** were determined by means of a CV-27 voltammetry controller (BAS Co.) using a platinum disk electrode. An acetonitrile solution (3 mL) of the pyridinium salt (0.24 mM) and Bu_4NClO_4 (0.1 M) was deaerated by bubbling argon through the solution for 15 min. Scanning started from 0.0 V toward −2.0 V and returned to +0.3 V at a rate of 100 mV/s. The potentials were corrected by the $E_{1/2}$ of ferrocene. All the pyridinium iodides showed common irreversible reduction waves of pyridinium ions. The half-height potentials, $E_{1/2}$*(red), of the reduction wave were −1.29 (**10**, n = 5), −1.63 (**10**, n = 6), −1.65 (**10**, n = 7), and −1.82 V (**11**) vs Ag/AgCl.

Acknowledgment. This work was supported by an Annual Project organized by Waseda University, 1991–1992, and also by the Shoraikagaku Foundation.

(24) Tada, M.; Yokoi, Y. *J. Heterocycl. Chem.* 1989, *26*, 45.