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Studies on Ketene and Its Derivatives. LIV.[1] Reaction of Diketene with Ketene Acetals

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The reaction of diketene with ketene acetals (Ia—f) has been studied on cycloaddition reaction to form 4-pyrone derivatives (II and III). Cyanoketene diethylacetal reacted with diketene to give 3-cyano-4-ethoxy-6-methyl-2-pyrone besides the formation of IIIf. IIa, b and IIIa, b, c, d, f were converted in good yields to corresponding 2-ethoxy-6-methyl-3-substituted-4-pyridone (V), respectively, whereas VI was converted to VIII and IX by treatment with ammonia.

Milward[3] and Hünig[4] reported that diketene reacts with the C=C double bond of enamine giving the chromone derivative. While investigating some potential uses of diketene, it occured to us that the reaction of diketene with ketene acetal, which has the active C=C double bond in its structure, might afford O-heterocycles. The present paper reports the reaction of diketene with a variety of ketene acetals to give pyrone derivatives.

When the mixture of ketene diethyl acetal (Ia) and diketene was heated in benzene, an oily product of bp 83—84° (3 mmHg), $C_{10}H_{16}O_4$ (IIa) was obtained. In the infrared (IR) spectrum of IIa a characteristic absorption band due to the carbonyl streching can be observed at 1660 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum in $CDCl_3$ shows the presence of methyl protons (2.20 ppm, s), methylene protons (2.73 ppm, s), an olefinic proton (5.35 ppm, s) and two O-ethyl groups. These spectral data are consistent with the dihydropyrone structure of 2,2-diethoxy-2,3-dihydro-6-methyl-4-pyrone (IIa).

When this reaction was carried out at room temperature in the presence of a trace of triethylamine as a catalyst, crystals of mp 44—46°, $C_8H_{10}O_3$ (IIIa), were obtained besides the formation of IIa. Also, compound (IIIa) was formed when IIa was allowed to stand at room temperature for several months. The IR spectrum of IIIa shows carbonyl band at 1660 cm^{-1}. The NMR spectrum shows the presence of methyl group at 2.20 ppm (s), two olefinic protons at 5.40 ppm (d, $J=3$) and 5.93 ppm (m), and an O-ethyl group. These data are consistent with the structure of IIIa as 2-ethoxy-6-methyl-4-pyrone.

Similarly, the pyrone derivatives (II and III) were obtained from Ib—e with the exception of IIc and IIe. The results of these reactions are summarized in Table I. Comparing with IIa and IIb compound (IId) was unstable and completely lost EtOH at room temperature in three days to give IIId. The physical properties of II and III are shown in Table II.

Ammonolysis of IIa yielded crystals of mp 170—171°, $C_8H_{11}O_2N$ (Va), and crystals of mp 320° (decomp.), $C_6H_7O_2N$ (IVa). Compound (IVa) was identified as 2,4-dihydroxy-6-methylpyridine by spectral comparison with an authentic sample prepared according to the literature.[5] Compound (Va), whose NMR spectrum shows the presence of an O-ethyl group, was obtained by ammonolysis of IIIa. Hydrolysis of Va with HCl gave IVa. These data are consistent with the structure of Va as 2-ethoxy-4-hydroxy-6-methylpyridine. On the

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[1] Part LIII: T. Kato and N. Katagiri, *Chem. Pharm. Bull.* (Tokyo), 21, 729 (1973).
[2] Location: *Aobayama, Sendai, 980, Japan.*
[3] B. Milward, *J. Chem. Soc.*, **1960**, 26.
[4] S. Hünig, E. Benzing, and K. Hübner, *Ber.*, **94**, 486 (1961).
[5] S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Japan*, **39**, 281 (1966).

other hand, treatment of IIb with ammonia gave the γ-pyrone (IIIb) in 43% yield and the pyridin-2,4-dione (IVb) in 43% yield, both of which were confirmed by spectral data.

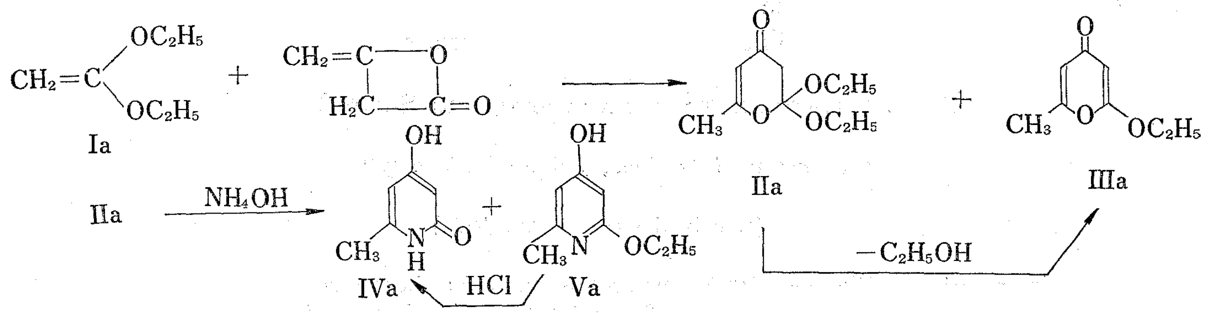

Chart 1

Table I. Reaction of Diketene with Ketene Acetal in Benzene

Ketene acetal RCH =C(OC$_2$H$_5$)$_2$	R	Reaction time (day)	Reaction temperature	Catalyst	Product II bp(°C) /mmHg	Product II Yield (%)	Product III mp(°C)	Product III Yield (%)	Product III Appearance (solvent)
Ia	H	2	room temp.	Et$_3$N	83—84/3	29	44—46	27	colorless needles(ether)
Ib	CH$_3$	7	room temp.	Et$_3$N	95—96/3	55	71—73	9	colorless prisms (ether)
Ic	C$_6$H$_5$	4	room temp.	Et$_3$N	——	—	72—73	17	colorless needles (ether)
Id	Cl	6	room temp.	Et$_3$N	103—105/3	27	135—136	10	colorless prisms (ethyl acetate)
Ie	Br	3	room temp.	Et$_3$N	——	—	131—132	10	pale yellow needles (ether)
If	CN	1.5	reflux	none	——	—	165—167	14	pale yellow leaflets (chloroform)

Reaction of cyanoketene diethylacetal (If) with diketene gave crystals of mp 165—167° (IIIf) and mp 175—176° (VI), both of which had the same empirical formula, $C_9H_9O_3N$. The IR spectrum of IIIf indicates the presence of C≡N at 2240 cm^{-1} and C=O at 1670 cm^{-1}. The NMR spectrum shows signals due to O-ethyl protons, methyl protons (2.32 ppm, s) and an olefinic proton (6.05 ppm, s). These spectral data suggested the structure of IIIf being 3-cyano-2-ethoxy-6-methyl-4-pyrone. Treatment of IIIf with ammonia afforded 3-cyano-2-ethoxy-6-methyl-4-pyridone (Vf).

The NMR and IR data of VI are essentially similar in every respects with those of IIIf except the carbonyl absorption band in the IR spectrum: *i.e.*, in the IR spectrum of VI absorption bands due to C≡N and C=O can be observed at 2240 cm^{-1} and 1730 cm^{-1}, respectively. The higher frequency of the carbonyl absorption of VI is well consistent with the α-pyrone structure, 3-cyano-4-ethoxy-6-methyl-2-pyrone, but not with the γ-pyrone structure.

Treatment of VI with 28% ammonium hydroxide afforded VIII as a main product with a small amount of IX. Compound (VIII) was identified as 2-amino-4-ethoxy-6-methylpyridine by the mixture melting point test and the spectral comparison with an authentic sample prepared from 2-amino-4-chloro-6-methylpyridine (VII)$^{6)}$ and sodium ethoxide.

The IR spectrum of IX indicates absorption bands due to C≡N group at 2240 cm^{-1} and C=O group at 1720 cm^{-1}. The NMR spectrum shows signals owing to methyl protons (2.20 ppm, s), methylene protons (3.49 ppm, s), an olefinic proton (4.50 ppm, s) and O-ethyl protons. These data supports the structure of IX being 5-cyano-4-ethoxy-4-penten-2-one. The formation of VIII from VI can be explained as following; that is, the first stage would be ammonolysis of VI to give the ringopening intermediate (X) and the next stage might well involve the ringformation between the amino nitrogen and nitril carbon giving VIII, which is shown in Chart 2.

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6) R. Urban and O. Schnider, *Helv. Chim. Acta*, 47, 363 (1964).

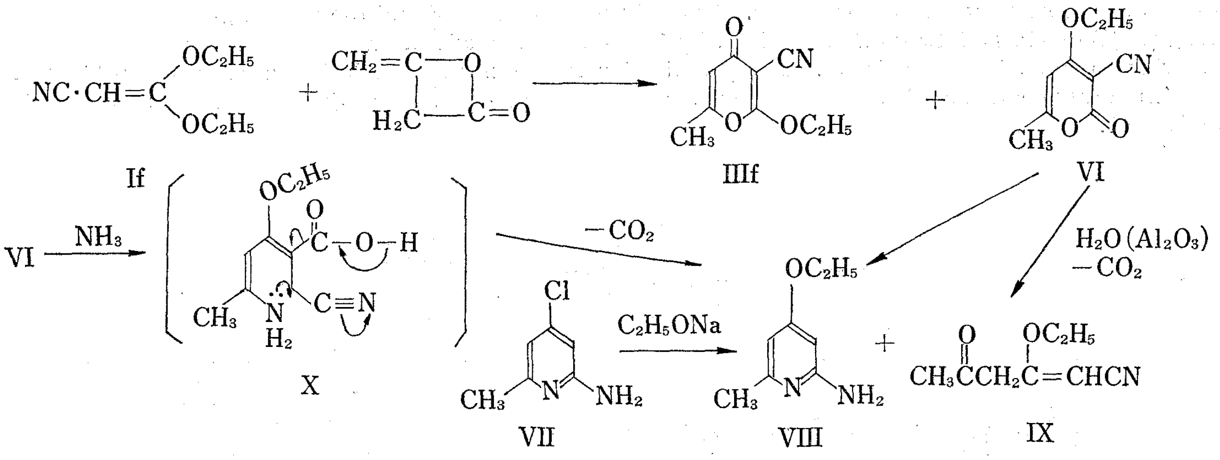

Chart 2

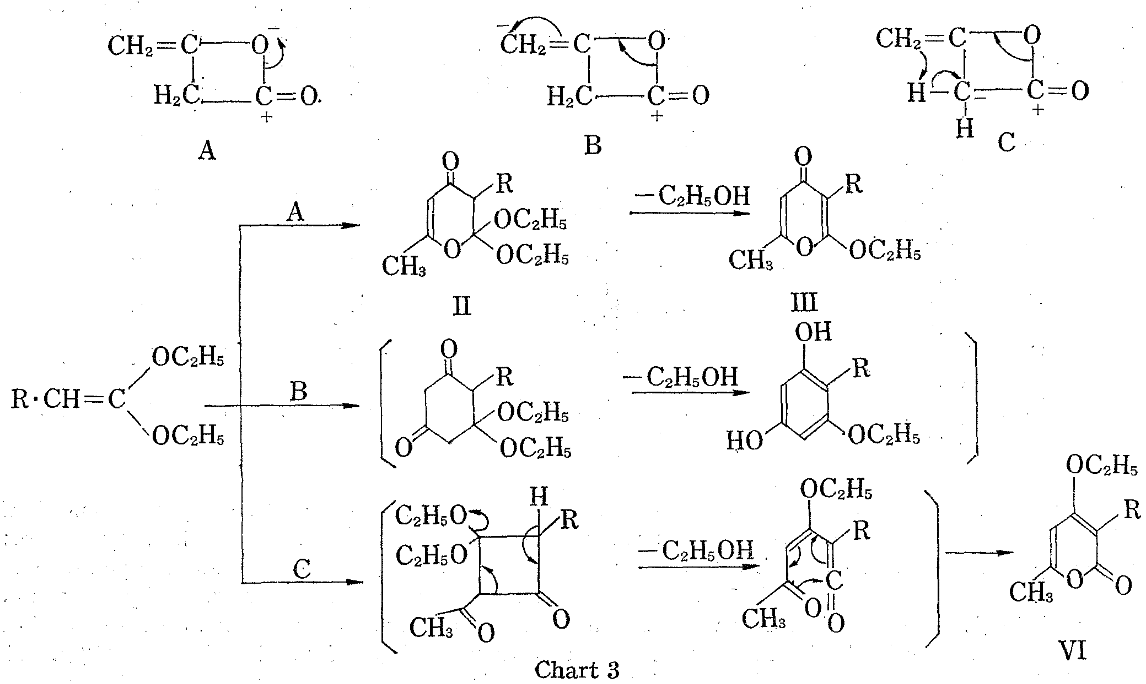

Chart 3

Although the details of the mechanism of the formation of these pyrone derivatives from diketene and ketene acetals are not always clear at present, some likely pathways are shown in Chart 3. Namely the reactivity of diketene can be elucidated by its three limited formulae as listed in Chart 3. Though none of the resorcinol derivatives which might be expected to form by the B formula of diketene was not isolated, reactions of A and B gave rise to γ-pyrone and α-pyrone derivatives (II, VI), respectively.

Experimental[7]

Reaction of Diketene with Ketene Diethylacetal (Ia)——1) To a solution of 5 g (0.043 mole) of ketene diethylacetal (Ia) in 10 ml of benzene was added dropwise 4 g (0.043 mole) of diketene and the mixture was refluxed for 8 hr. The solvent was evaporated, and the residual liquid was distilled under reduced pressure to give 2.5 g (29%) of IIa as a pale yellow oil, bp 83—84° (3 mmHg).

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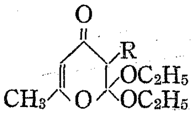
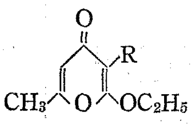
[7] Melting points are uncorrected. NMR spectrum was recorded at 60 MHz. Chemical shifts are expressed in ppm downfield from TMS as internal reference and coupling constants (*J*) in Hz. Abbreviation: s=singlet, d=doublet and m=multiplet.

2) A mixture of 5 g of Ia, 4 g of diketene and 2 drops of triethylamine in 10 ml of benzene was allowed to stand at room temperature for 2 days. The solvent was removed and the residue gave after distillation 2.5 g (29%) of IIa and 1.8 g (27%) of IIIa, bp 105—115° (0.5 mmHg). Product (IIIa) was solidified after allowing to stand in a refrigirater. Recrystallization from ether gave colorless needles of mp 44—46°.

The other compound (II and III) were made by similar procedures and these reactions are summarized in Table I.

TABLE II


II


III

	R	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)	NMR (CDCl$_3$·TMS)ppm		Formula	Analysis					
							Calcd.			Found		
				6-CH$_3$	5-H		C	H	N	C	H	N
IIa	H	1660	—	2.01	5.34	$C_{10}H_{16}O_4$	60.14	8.05	—	59.98	8.05	—
IIb	CH$_3$	1665	—	2.00	5.28	$C_{11}H_{18}O_4$	61.03	8.23	—	61.66	8.47	—
IId	Cl	1680	—	2.05	5.22	$C_{10}H_{15}O_4Cl \cdot \frac{1}{3}H_2O$	49.90	6.57	—	50.39	6.43	—
IIIa	H	1660	241 (4.04)	2.20	5.95	$C_8H_{10}O_3 \cdot \frac{1}{2}H_2O$	58.47	6.64	—	58.88	6.80	—
IIIb	CH$_3$	1665	259 (3.98)	2.21	5.96	$C_9H_{11}O_3$	64.18	7.66	—	64.27	7.19	—
IIIc	C$_6$H$_5$	1660	260 (4.00)	2.25	6.10	$C_{14}H_{14}O_3$	73.18	6.18	—	73.02	6.13	—
IIId	Cl	1660	262 (3.96)	2.30	6.13	$C_8H_9O_3Cl$	50.78	4.72	—	50.94	4.82	—
IIIe	Br	1660	264 (3.95)	2.29	6.10	$C_8H_9O_3Br$	41.44	4.09	—	41.22	3.89	—
IIIf	CN	1670	248 (3.83)	2.31	6.10	$C_9H_9O_3N$	60.33	5.06	7.82	60.01	5.16	7.67
VI	CN	1730	310 (3.95)	2.36	6.10	$C_9H_9O_3N$	60.33	5.06	7.82	60.22	5.17	7.58

Reaction of Diketene with Cyanoketene Diethylacetal (If)——A mixture of 4 g of cyanoketene diethylacetal (If) and 7.2 g of diketene in 10 ml of benzene was refluxed for 40 hr. After cooling, crystals formed were taken up by suction. Recrystallization from CHCl$_3$ gave 0.72 g (14%) of IIIf as pale yellow leaflets, mp 165—167°. The filtrate was condensed *in vacuo* and the resulting solid was purified by column chromatography (Al$_2$O$_3$). Ether and AcOEt were used as eluent. From the ether eluent, a colorless oil of bp 80—83° (3 mmHg) (IX) was obtained after purification by vacuum distillation. Yield, 0.05 g (1%). *Anal.* Calcd. for $C_8H_{11}O_2N$ (IX): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.88; H, 7.47; N, 9.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1720 (C=O). NMR (in CDCl$_3$) ppm: 1.36 (3H, t, J=7), 2.20 (3H, s), 3.49 (2H, s), 3.85 (2H, q, J=7), 4.50 (1H, s). From the AcOEt eluent crystaline substance was obtained. Recrystallization from benzene gave 0.31 g (6.3%) of VI, pale yellow needles, mp 175—176°. *Anal.* Calcd. for $C_9H_9O_3N$ (VI): C, 60.33; H, 5.60; N, 7.82. Found: C, 60.22; H, 5.17; N, 7.58. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1730 (C=O). UV λ_{max}^{EtOH} mμ(log ε): 310 (3.95). NMR (in CDCl$_3$) ppm: 1.50 (3H, t, J=7), 2.36 (3H, s), 4.05 (2H, q, J=7), 6.10 (1H, s).

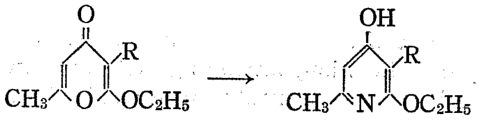
4-Hydroxy-6-methyl-2-pyridone (IVa) and 2-Ethoxy-4-hydroxy-6-methylpyridine (Va)——A mixture of 0.78 g of IIa in 3 ml of EtOH and 5 ml of 28% NH$_4$OH was heated on a steam bath for 30 min and condensed *in vacuo*. The residue was purified by recrystallization to give 0.11 g (19%) of Va as colorless prisms, mp 170—171°, and 0.22 g (46%) of IVa as colorless needles, mp 320° (decomp.), latter of which was identified by the comparison of its IR spectrum with that of an authentic sample.[5]

4-Hydroxy-6-methyl-2-pyridone (IVa) from 2-Ethoxy-4-hydroxy-6-methylpyridine (Va)——A mixture of 0.05 g of Va and 0.5 ml of conc. HCl was heated in a sealed glass tube at 130—140° for 3 hr. The mixture was made alkaline with ammonia and condensed *in vacuo*. Recrystallization of the residual solid from EtOH gave 0.03 g (70%) of IVa, mp 320° (decomp.), whose IR spectrum was identical in every respects with that of a sample obtained in the above run.

Preparation of 2-Ethoxy-4-hydroxy-6-methylpyridine (Va) from 2-Ethoxy-6-methyl-4-pyrone (IIIa)——A mixture of 0.82 g of IIIa and 10 ml of liq. NH$_3$ was placed in a sealed tube and allowed to stand at room temperature for 2 days. After evaporation of ammonia, the resulting residue was purified by recrystallization from EtOH to give 0.59 g (72%) of Va as colorless prisms, mp 170—171°, undepressed on admixture with a sample prepared in the above run.

Following the similar fashion given for the above run IIIb—f were treated with NH_3 giving Vb—f. Results are summarized in Table III.

TABLE III

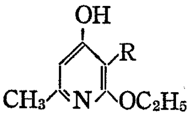


III V

Starting material (g)	R	liq.NH_3 (ml)	Reaction Time & temperature (°C)		Product V mp (°C)	Product V Yield (%)	Appearance (solvent)
IIIa (0.82)	H	10	2 days	room temp.	170—171	72	colorless prisms (ethanol)
IIIb (0.63)	CH_3	10	6 hr	60[a]	137—138	13	colorless prisms (ethanol)
IIIc (0.22)	C_6H_5	10	3 days	room temp.	155—156	84	colorless needles (ether)
IIId (0.32)	Cl	10	3 days	room temp.	52— 53	75	colorless prisms (ether)
IIIf (0.10)	CN	2[b]	1 hr	100	165—166	41	colorless needles (ethyl acetate)

a) IIIb did not react with ammonia at room temperature. b) 28% NH_4OH (ml)

TABLE IV



V

	R	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)	NMR (CF_3COOH·TMS)ppm		Formula	Analysis					
							Calcd.			Found		
				6-CH_3	5-H		C	H	N	C	H	N
Va	H	1630(sh) 1615	250 (4.06)	2.60	6.72(m)	$C_8H_{11}O_2N$	62.72	7.24	9.14	62.71	7.10	8.70
Vb	CH_3	1610(sh) 1600	263 (3.54)	2.60	6.80	$C_9H_{13}O_2N$	64.65	7.84	8.38	64.19	7.98	8.15
Vc	C_6H_5	1615[a] 1585	255 (4.02)	2.39	6.39[b]	$C_{14}H_{15}O_2N$	73.34	6.59	6.11	73.32	6.77	6.18
Vd	Cl	1590[a]	265 (3.42)	2.39	6.39[b]	$C_8H_{19}O_2NCl$	51.43	5.71	7.48	51.25	5.34	7.45
Vf	CN	1655 1600	245 (3.87)	2 70	6.95	$C_9H_{10}O_2N_2 \cdot \frac{2}{3}H_2O$	56.47	5.70	14.70	56.83	6.01	14.73

m: multiplet a) in $CHCl_3$ b) in $CDCl_3$

Treatment of IIb with Ammonia——A mixture of 1.25 g of IIb in 10 ml of liq. NH_3 was placed in a sealed tube and allowed to stand at room temperature for 4 days. After evaporation of NH_3, the residue was purified by recrystallization from ether to give 0.35 g (43%) of IVb as colorless prisms, mp 276—283° (decomp.). *Anal.* Calcd. for $C_7H_9O_2N$ (IVb): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.38; H, 6.61; N, 10.15. IR ν_{max}^{KBr} cm^{-1}: 1645 (sh), 1630. UV ${}_{max}^{EtOH}$ mμ(log ε): 283 (4.02). NMR (in CF_3COOH) ppm: 2.21 (3H, s), 2.55 (3H, s), 6.70 (1H, s). Mother liquor was condensed, and distilled to give 0.42 g (43%) of a yellow oil, bp 114° (3 mmHg), which was solidified and recrystallized from ether giving colorless prisms of mp 71—73°, whose IR and NMR spectra were identical with those of IIIb.

Reaction of 3-Cyano-4-ethoxy-6-methyl-2-pyrone (VI) with Ammonia——To a solution of 0.24 g of VI in 2 ml of EtOH was added 3 ml of 28% NH_4OH and the mixture was heated on a steam bath for 30 min. After removal of the solvent, the resulting residue was purified by column chromatography (Al_2O_3). The ether eluted fraction was evaporated to give 0.05 g (24%) of IX as a colourless oil, bp 80—83° (3 mmHg). From the AcOEt eluent crystalline substance was obtained. Recrystallization from ether gave 0.08 g (40%) of VIII as colorless prisms, mp 107—108°, undepressed on admixture with an authentic sample. *Anal.* Calcd. for $C_8H_{12}ON_2$ (VIII): C, 63.13; H, 7.95; N, 18.22. Found: C, 63.31; H, 8.22; N, 18.34. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3410. NMR (in $CDCl_3$) ppm: 1.35 (3H, t, $J=7$), 2.30 (3H, s), 3.95 (2H, q, $J=7$), 4.2—6.1 (2H, broad), 5.76 (1H, d, $J=3$), 6.07 (1H, d, $J=3$).

Preparation of VIII from 2-Amino-4-chloro-6-methylpyridine (VII)——Sodium metal (5 mg) was dissolved in absolute EtOH (1 ml) and 2-amino-4-chloro-6-methylpyridine (80 mg) was added. The mixture was heated at 130—140° for 12 hr in a sealed tube. The mixture was evaporated *in vacuo* and the resulting residue was purified by column chromatography (Al_2O_3). From the AcOEt eluent, 30 mg (35%) of VIII as colorless prisms, mp 106—108° (ether), was obtained.

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