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Isoxazoles. XXI.[1] Ring Conversion Reactions of 2,3,4-Trisubstituted Isoxazolium Salts with Some Nucleophiles

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Ring conversion reactions of the quaternary salts: 2,4-dimethyl-3-phenyl-, 3,4-diphenyl-2-methyl- and 2-methyl-3-phenylisoxazolium perchlorate (Ia, b and c) with some nucleophiles were investigated. Reactions of I with alkyl malonates in the presence of sodium alcoholates gave the corresponding 4-unsubstituted-2-pyridone-3-carboxylates (II) and their 4-hydroxy derivatives (III), along with 2,5-diphenyl-1,3,4-trimethylpyrrole (IV) and alkyl cinnamates (V). Similar reactions of Ia with some active methylene compounds were also examined. Reactions of I with cyclic enamines gave 4-unsubstituted 1-methyl-2,3-trimethylene or tetramethylenepyridinium perchlorates (XIII) besides β-kteo acid amides (XIV). Reactions of Ia with potassium cyanate and with phenylhydrazine in the presence of sodium hydroxide gave 3,5-dimethyl-4-phenyluracil (XV) and 1,5-diphenyl-3-hydroxy-4-methylpyrazole (XVI), respectively. On the contrary, the reaction of Ia with phenylhydrazine in the absence of sodium hydroxide resulted in the formation of 1,5-diphenyl-4-methyl- and 1,3-diphenyl-4-methylpyrazole (XVII and XVIII). A tentative mechanism of these ring conversion reactions of I are presented.

In the preceding paper of this series,[1] it has been shown that 2,3,4-trisubstituted isoxazolium salts are extraordinarily sensitive toward bases and undergo reaction with a variety of bases to afford the ring opening products. We have suggested that the cleavage reaction may proceed through either initial addition of nucleophiles at C-5 or a ketene intermediate arising from abstraction of the proton at C-5. In relation to the elucidation of this cleavage process, the present work was undertaken to examine the possible ring conversions of 2,3,4-trisubstituted isoxazolium salts with various nucleophiles. Although a number of ring conversions of 3-unsubstituted isoxazolium salts with nulceophiles have been reported by Kunst, Mumm[3] and Woodward, Olofson,[4] there has been little reported on the ring conversion of the 2,3,4-trisubstituted isoxazolium salts.

Thus, three quaternary salts: 2,4-dimethyl-3-phenyl-3,4-diphenyl-2-methyl- and 2-methyl-3-phenylisoxazolium perchlorate (Ia, b and c) were prepared by the usual quaternization of the parent bases.[1]

I. Reactions with Some Active Methylene Compounds

Reactions of Ia with alkyl malonates in the presence of sodium alcoholate in alcohol gave the corresponding alkyl 1,5-dimethyl-6-phenyl-2-pyridone-3-carboxylates (IIa, b) and their 4-hydroxy derivatives (IIIa, b), along with 2,5-diphenyl-1,3,4-trimethylpyrrole (IV) and alkyl α-methyl-β-methylaminocinnamates (Va, b).[5] The structure of IIa was assigned by the infrared (IR), ultraviolet (UV), and nuclear magnetic resonance (NMR) spectra, which displayed the bands at 1639, 1544 cm^{-1}, the maximum at 349 mμ (log ε 4.082) and a signal at τ 1.94 corresponding to the γ-proton of the pyridone, respectively. The structure assignment was

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[1] Part XX: I. Adachi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **17**, 2201 (1969).
[2] Location: *Fukushima-Ku, Osaka.*
[3] A. Kunst and O. Mumm, *Chem. Ber.*, **50**, 563 (1917).
[4] R.B. Woodward and R.A. Olofson, *Tetrahedron*, Supplement No. 7, 415 (1966).
[5] The formations of IV and V from Ia were described in the preceding paper.
[6] R.P. Mariella and V. Kvinge, *J. Am. Chem. Soc.*, **70**, 3126 (1948).

confirmed by the alkaline hydrolysis of IIa to a carboxylic acid(VI), which was identified with 1,5-dimethyl-6-phenyl-2-pyridone-3-carboxylic acid. This authentic sample was obtained by the methylation of 3-cyano-5-methyl-6-phenyl-2-pyridone⁶⁾ with dimethyl sulfate in aqueous alkali followed by hydrolysis with aqueous potassium hydroxide. Heating VI with copper powder in quinoline gave a decarboxylated product VII in 71% yield and treatment with diazomethane afforded IIb in 60% yield. Compound III showed the IR and UV spectra similar to those of II, but its NMR spectrum showed the absence of the signal attributable to

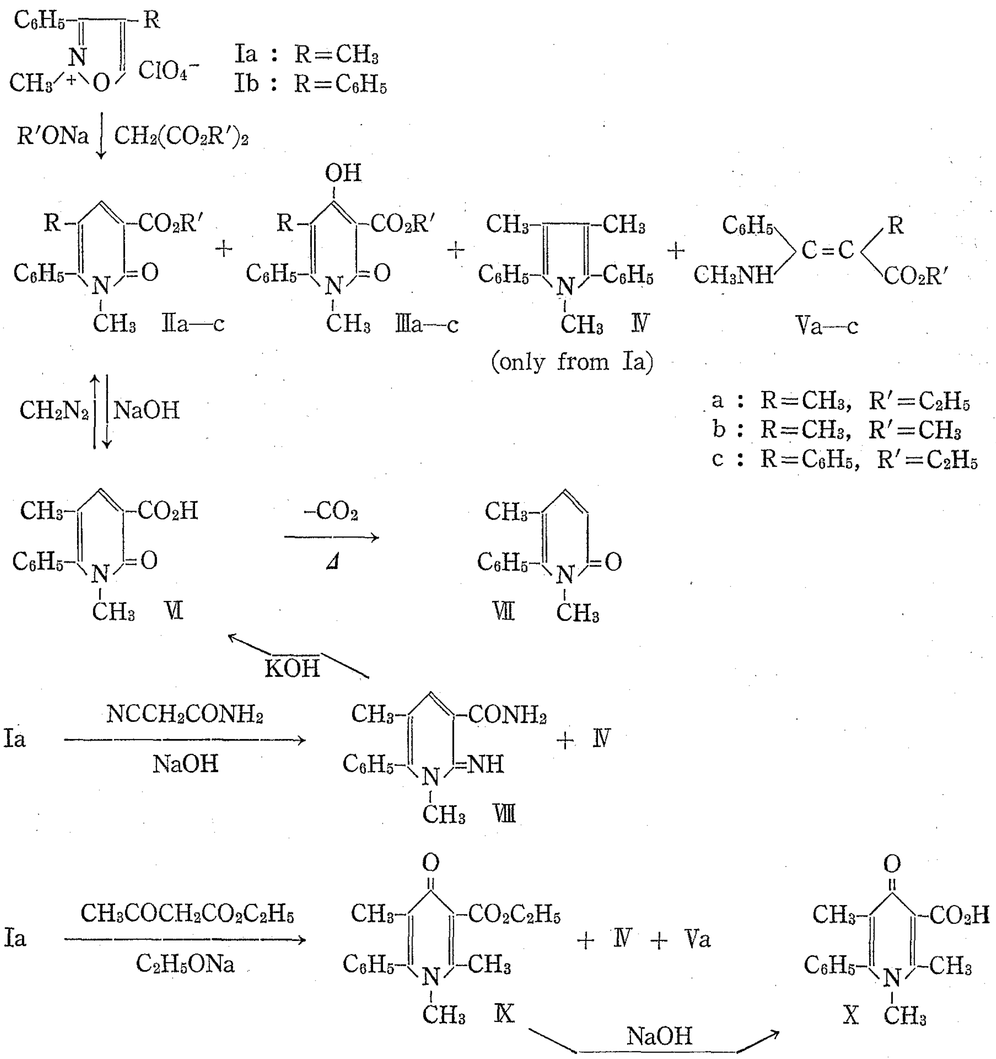

Chart 1

Table I. The Yields of II-V in Varying Reaction Conditions

	Mol. ratio of materials I:	$CH_2(CO_2C_2H_5)_2$:	C_2H_5ONa	II	Yields of products (%) III	IV	V
a	1	1	1	14.1	2.2	3.0	48.2
	1	5	1	9.3	0.8	3.4	47.5
	1	1	3	1.9	6.0	5.7	63.9
	1	1	5	1.7	5.9	5.1	66.5
	1	3	3	19.9	12.4	10.9	27.1
	1	5	5	22.7	16.0	13.3	23.1
b	1	1	2	—	7.6	0	85.8
	1	3	3	2.4	2.9	0	91.4

γ-proton of the pyridone. The assignment was confirmed by an unequivocal synthesis[7] from VII with ethyl malonate. Similar reaction of Ib with ethyl malonate gave the corresponding phenyl analogs (IIc, IIIc, and Vc) of IIa, IIIa and Va.

The yields of each products (II—V) in these reactions in varying conditions were listed in Table I. The data indicated that the use of excess amount of sodium alcoholate causes a marked decrease in the yield of II and increase in the yields of III and V, while the use of large amount of the sodium salt of active methylene compound decrease the yield of V and increase the yields of II and III. It seemed that the formation of each product in these reactions depends on the strength of the base used. Similar reaction of Ia with cyanoacetamide in aqueous sodium hydroxide[8] gave 1,2-dihydro-1,5-dimethyl-2-imino-6-phenylnicotinic acid amide (VIII) and IV in respective yields of 15.8% and 20.2%. Structure of VIII was confirmed by its hydrolysis with alkali to give VI. Reactions of Ia with methyl cyanoacetate or malononitrile in the presence of alkali in various media were unsuccessful only to give tarry substances.

Reaction of Ia with ethyl acetoacetate in the presence of sodium ethylate in ethanol gave ethyl 6-phenyl-1,2,5-trimethyl-4-pyridone-3-carboxylate (IX), IV and Va in respective yields of 5.3%, 32.3% and 26.9%. Structure of IX was proved by its satisfactory analytical and spectral data (see Experimental) and hydrolysis to the corresponding carboxylic acid (X). Similar ring conversions of Ia with acetyl or benzoylacetone did not occur: in aqueous alkali they gave IV and propiophenone in respective yields of 30% and 25%, and gave quantitatively Va in ethanolic sodium ethylate. The results shown in Chart 1 and Table I suggest the following

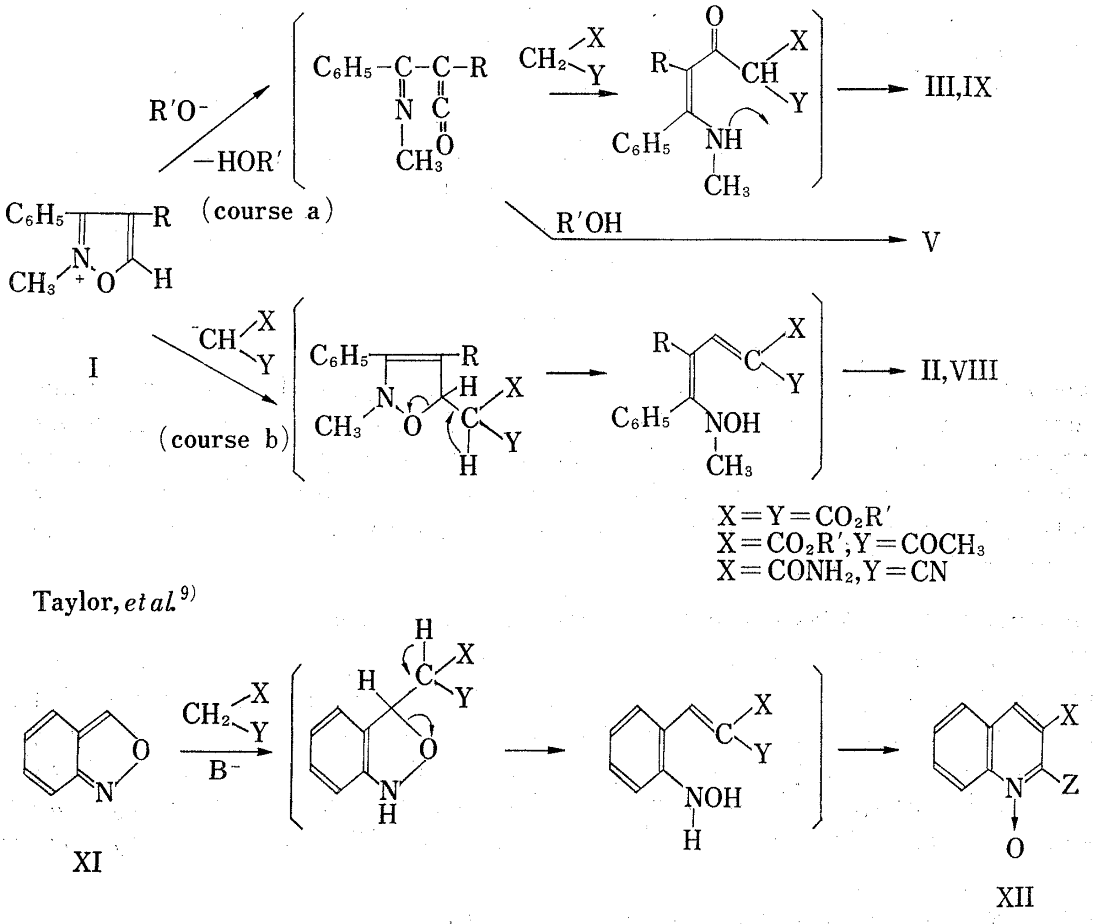

Chart 2

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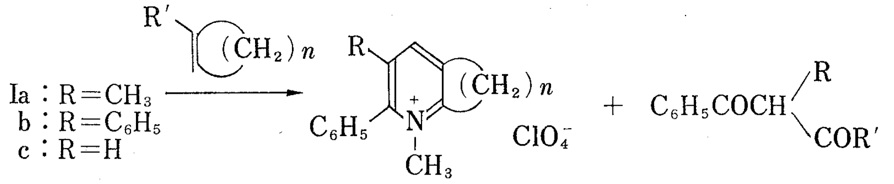
[7] W.F. Bruce and L.A. Perez-Medina, *J. Am. Chem. Soc.*, **69**, 2571 (1947).

[8] Equimolar amount of sodium hydroxide toward cyanoacetamide was used.

two routes for the reaction of I with the active methylene compounds. As shown in Chart 2, in the presence of strong base the reaction may proceed through a ketene intermediate arising from initial abstraction of the proton at C-5 with consequent N–O bond cleavage. Addition of anions to the resulting intermediate followed by ring closure would afford III, IX and V (course a). In the reaction with a relatively weak base, the salt I may undergo initial addition of the nucleophile at C-5 followed by ring opening and subsequent ring closure to 4-unsubstituted pyridine derivatives, II and VIII (course b). Similar reaction with 2,1-benzisoxazole (anthranil XI) was reported by Taylor, *et al.*,[9] which gave 4-unsubstituted quinoline 1-oxides (XII). However, the deoxygenation mechanism in the case of the present paper is not clear.

II. Reactions with Cyclic Enamines

When Ia, b, c were allowed to react with 1-morpholinocyclopentene in acetonitrile, the corresponding 1-methyl-2,3-trimethylenepyridinium perchlorates (XIIIa, b, c) and β-keto acid amides (XIVa, b) were isolated from the tarry reaction mixtures. By the similar reactions of Ia, b with 1-pyrrolidinocyclohexene, 1-methyl-2,3-tetramethylenepyridinium perchlorates (XIIId, e) and amides (XIVc, d) were obtained. The structures of XIII were assigned by their analytical and spectral data, which were showed in Table II. The assignments were confirmed by the unequivocal syntheses, namely quaternization of the respective 6-phenyl-2,3-trimethylene and 2,3-tetramethylenepyridines prepared by Stobbe's procedure.[10]



XIII a : $R=CH_3, n=3$
b : $R=C_6H_5, n=3$
c : $R=H, n=3$
d : $R=CH_3, n=4$
e : $R=C_6H_5, n=4$

XIV a : $R=CH_3$, R'=N◯O
b : $R=C_6H_5$, R'=N◯O
c : $R=CH_3$, R'=N◻
d : $R=C_6H_5$, R'=N◻

Chart 3

The formation of the pyridinium salts (XIII) can be explained by the similar mechanism for the reaction with the active methylene derivatives (course b in Chart 2). However, Diels–Alder type mechanism advanced by Wilk, *et al.*[11] in the reaction of 2,1-benzisoxazole with cycloalkanones, which gave 4-unsubstituted quinoline derivatives, can not be ruled out. The products XIV can arise in a mechanism (course a) similar to that of the reactions of I with amines reported previously.

III. Reactions with Potassium Cyanate and Phenylhydrazine

The reaction of Ia with potassium cyanate in methanol gave 3,5-dimethyl-4-phenyluracil (XV) in yield of 24%, whose structure was proved by an unequivocal synthesis[12] from N-(2-benzoylpropanoyl)urethan with methylamine. The reaction of Ia with phenylhydrazine in the presence of sodium hydroxide in ethanol gave 1,5-diphenyl-3-hydroxy-4-methylpyrazole (XVI) in yield of 91%. This compound was identified with an authentic sample, which was prepared according to the procedure reported by Michaelis.[13] On the contrary, the reaction

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[9] E.C. Taylor and J. Bartulin, *Tetrahedron Letters*, **1967**, 2337.
[10] H. Stobbe and H. Volland, *Chem. Ber*,. **35**, 3973 (1902).
[11] M. Wilk, H. Schwab and J. Rochlitz, *Ann.*, **698**, 149 (1966).
[12] P.K. Ralph, G. Shaw and R.N. Naylor, *J. Chem. Soc.*, **1959**, 1177.
[13] A. Michaelis, *Ann.*, **338**, 267 (1904).

of Ia with phenylhydrazine in methylene chloride gave 1,5-diphenyl-4-methylpyrazole (XVII) and 1,3-diphenyl-4-methylpyrazole (XVIII) in the respective yields of 43% and 47%. The structures of XVII and XVIII were proved by the unequivocal syntheses from 2-benzoylpropionaldehyde with phenylhydrazine and from 1,3-dipolarcycloaddition of diphenylnitrileimine with N-(1-propenyl)piperidine, respectively. The formation of the products XV—XVIII can be rationalized as proceeds according to the similar mechanism mentioned above (as visualized in Chart 2).

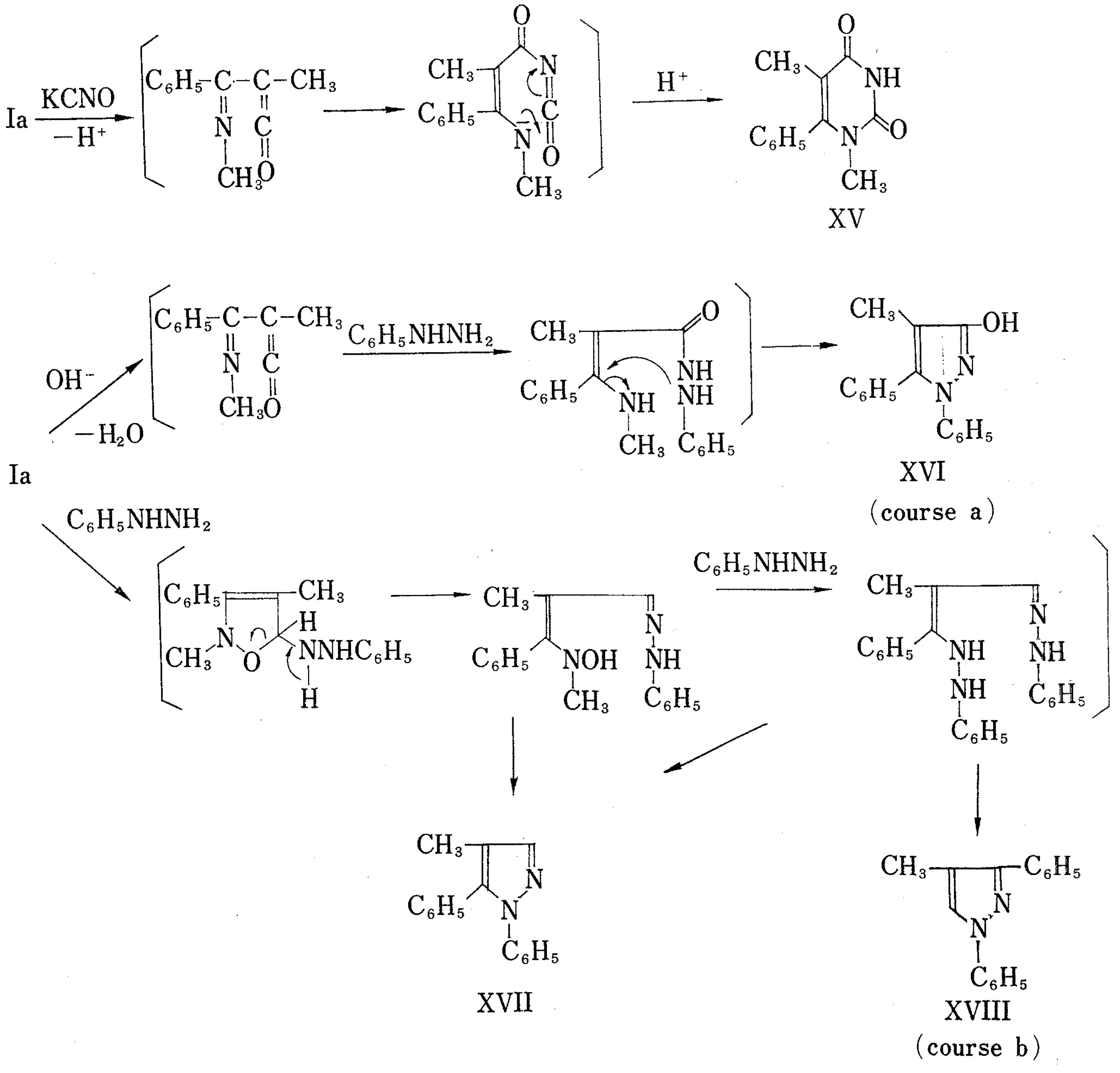


Chart 4

Experimental

All melting points were taken on a Kofler hot stage and are uncorrected. Solvents were removed *in vacuo*. IR spectra were recorded with a Koken Infrared Spectrophotometer, Model IR-S. UV spectra were taken on a Hitachi Recording Spectrophotometer, EPS-2. NMR spectra were measured with a Varian A-60 analytical NMR spectrometer with tetramethylsilane as an internal reference. Chemical shifts were given in τ values and coupling constants (*J*) in cps.

Three Quaternary Salts——2,4-Dimethyl-3-phenyl-, 3,4-diphenyl-2-methyl- and 2-methyl-3-phenylisoxazolium perchlorate (Ia, b and c) were prepared according to the procedure described in the preceding paper.[1]

Reaction of Ia with Ethyl Malonate——To a solution of Et. malonate (3.2 g, 20 mmole) and C_2H_5ONa (1.36 g, 20 mmole) in EtOH (40 ml) was added Ia (5.46 g, 20 mmole) with stirring at 40° and the mixture was refluxed for 2 hr, then evaporated. To the residue was added ice-water and the mixture was shaken with $CHCl_3$ and separated. Concentration of the organic phase left a brown liquid, which was chromatographed on alumina to give the following products: 2,5-diphenyl-1,3,4-trimethylpyrrole (IV) (0.077 g) as 1 st fraction with petr. ether; ethyl α-methyl-β-methylaminocinnamate (Va) (2.11 g) as 2nd fraction with benzene; and ethyl 1,5-dimethyl-6-phenyl-2-pyridone-3-carboxylate (IIa) (0.764 g) as 3rd fraction with $CHCl_3$, which was recrystallized from petr. benzin to give colorless needles, mp 110—111°. UV λ_{max}^{EtOH} mμ (log ε): 349 (4.082), 243 (3.855). IR ν_{max}^{Nujol} cm^{-1}: 1738, 1639, 1544. NMR (in $CDCl_3$) τ: 1.94 (singlet, 4-H), 6.73 (s, N–CH_3), 8.17 (s, 5-CH_3). *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.15; H, 6.16; N, 5.07. The water phase was neutralized with AcOH and the precipitated crystalline product (0.127 g) was filtered and recrystallized from benzene–petr. ether to give ethyl 1,5-dimethyl-4-hydroxy-6-phenyl-2-pyridone-3-carboxylate (IIIa) as colorless needles, mp 148—149°. UV λ_{max}^{EtOH} mμ (log ε): 326 (4.111), 229 (4.232). IR ν_{max}^{Nujol} cm^{-1}: 1650, 1638, 1548. NMR (in $CDCl_3$) τ: 6.88 (s, N–CH_3), 8.30 (s, 5-CH_3). *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.04; H, 5.97; N, 4.97. This reaction was carried out by varying the molar ratios of each materials used and the respective yields of the products were listed in Table I.

Reaction of Ia with Methyl Malonate——A mixture of Ia (2.73 g), Me.malonate (2.64 g) and MeONa (1.1 g) in MeOH (10 ml) was treated by the similar manner as the above to give the following products: IV (0.01 g); methyl α-methyl-β-methylaminocinnamate (Vb) (0.87 g); and methyl 1,5-dimethyl-6-phenyl-2-pyridone-3-carboxylate (IIb) (0.12 g) as colorless scales, mp 146—147°. UV λ_{max}^{EtOH} mμ: 350, 242. IR ν_{max}^{Nujol} cm^{-1}: 1721, 1630, 1539. *Anal.* Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.17; H, 5.97; N, 5.46. This compound (IIb) was identified with an authentic sample prepared by the following procedure by comparison of their infrared spectra. To a solution of CH_2N_2 in ether was added a solution of VI (0.20 g) in tetrahydrofuran dropwise with shaking and the mixture was stood overnight at room temperature, then evaporated. The residue (0.13 g) was recrystallized from EtOH to give colorless scales, mp 144—145°.

Reaction of Ib with Ethyl Malonate——A mixture of Ib (1.68 g), Et. malonate (2.4 g) and EtONa (1.02 g) in EtOH (20 ml) was treated by the similar manner as the above to give the following products: ethyl β-methylamino-α-phenylcinnamate (Vc) (1.28 g); ethyl 5,6-diphenyl-1-methyl-2-pyridone-3-carboxylate (IIc) (0.04 g) as colorless plates, mp 158—159°. UV λ_{max}^{EtOH} mμ: 356, 244. IR ν_{max}^{Nujol} cm^{-1}: 1687, 1658, 1528. *Anal.* Calcd. for $C_{21}H_{19}O_3N$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.62; H, 5.74; N, 4.03; and ethyl 5,6-diphenyl-4-hydroxy-1-methyl-2-pyridone-3-carboxylate (IIIc) (0.05 g) as colorless prisms, mp 164—166°. UV λ_{max}^{EtOH} mμ: 331, 234. IR ν_{max}^{Nujol} cm^{-1}: 1656, 1638, 1535. *Anal.* Calcd. for $C_{21}H_{19}O_4N$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.22; H, 5.51; N, 3.79.

1,5-Dimethyl-6-phenyl-2-pyridone-3-carboxylic Acid (VI)——Method A: A mixture of IIa (0.143 g) and NaOH (0.1 g) in H_2O (5 ml) was heated on a water bath for 1 hr, then cooled and neutralized with aq. HCl. The precipitated crystalline product (0.117 g) was filtered and recrystallized from EtOH to give colorless needles, mp 230—231°. *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.36; H, 5.56; N, 5.82.

MethodB: To a solution of 3-cyano-5-methyl-6-phenyl-2-pyridone$^{6)}$ (2.1 g) and NaOH (4.0 g) in H_2O (50 ml) was added dimethylsulfate (6.3 g) dropwise with stirring at room temperature and the mixture was heated on a water bath for 5 min. After cooling, the precipitated crystalline product was filtered and recrystallized from EtOH to give 3-cyano-1,5-dimethyl-6-phenyl-2-pyridone (2.7 g) as colorless prisms, mp 191—193°. *Anal.* Calcd. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.74; H, 5.37; N, 12.27. This product (0.45 g) was refluxed with a solution of KOH (0.5 g)in 80% aq. EtOH (7 ml) for 9 hr, then evaporated. To the residue was added H_2O and the mixture was washed with $CHCl_3$ and neutralized with aq. HCl. The precipitated crystalline product (0.38 g) was filtred and recrystallized from EtOH to give colorless needles, mp 228—229°. It was identified with the product obtained by Method A by mixed mp determination and comparison of their infrared spectra.

1,5-Dimethyl-6-phenyl-2-pyridone (VII)——A mixture of VI (0.35 g)and Cu powder (0.35 g) in quinoline (2 ml) was refluxed for 1 hr, then cooled and chromatographed on alumina with $CHCl_3$ to give colorless crystals (0.20 g). Recrystallization from *n*-hexane gave colorless prisms, mp 124—125°. UV λ_{max}^{EtOH} mμ: 320, 228. IR ν_{max}^{Nujol} cm^{-1}: 1655, 1539. *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.49; H, 6.71; N, 7.05.

Ethyl 1,5-Dimethyl-4-hydroxy-6-phenyl-2-pyridone-3-carboxylate(IIIa)——By the modification of Bruce's procedure,$^{7)}$ a solution of Va (1.45 g), Et. molonate (1.06 g) and EtONa (0.45 g) in EtOH (10 ml) was heated at 150° for 5 hr in a sealed tube, then evaporated. To the residue was added H_2O and the mixture was washed with ether and neutralized with AcOH. The precipitated crystalline product (0.01 g, 0.3%) was filtered and recrystallized from benzene–petr. ether to give colorless needles, mp 148—149°, which was identified with the product obtained above by mixed mp determination and comparison of their infrared spectra.

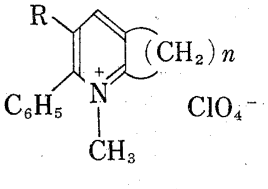
Reaction of Ia with Cyanoacetamide——To a solution of cyanoacetamide (0.84 g) and NaOH (0.4 g) in H_2O (2 ml) was added Ia (1.37 g) portionwise with stirring and cooling in an ice bath and the mixture was stirred at room temperature for 3 hr, then 60° for 10 min. After cooling, the precipitated crystalline product was filtered, washed with ether and recrystallized from EtOH to give perchlorate of VIII (0.27 g) as colorless needles, mp 287° (decomp.). *Anal.* Calcd. for $C_{14}H_{16}O_5N_3Cl$: C, 49.20; H, 4.72; N, 12.30. Found: C, 49.54; H, 4.89; N, 11.81. A suspension of this salt in CH_2Cl_2 was shaken with aq. NaOH and the organic phase was separated. Evaporation of the solvent left a solid, which was recrystallized from EtOH to give 1,2-dihydro-1,5-dimethyl-2-imino-6-phenylnicotinic amide (VIII) as yellow prisms, mp 251—252° (decomp.). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 341 (4.025), 251 (3.994). IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3280—3040 (broad), 1654, 1520. NMR (in $CDCl_3$) τ: 1.79 (s, 4-H), 6.94 (s, N–CH_3), 8.25 (s, 5-CH_3). *Anal.* Calcd. for $C_{14}H_{15}ON_3$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.82; H, 6.37; N, 17.29. Evaporation of the ether washings left a solid, which was recrystallized from petr. ether to give IV (0.172 g).

Hydrolysis of VIII with NaOH to VI——A solution of VIII (0.36 g) with NaOH (0.3 g) in 50% aq. EtOH (10 ml) was refluxed for 6 hr, then evaporated. To the residue was added H_2O and the solution was neutralized with aq. HCl. The precipitated crystalline product (0.104 g) was filtered and recrystallized from EtOH to give colorless needles, mp 228—229°, which was identified with authentic VI by mixed mp determination and comparison of their infrared spectra.

Reaction of Ia with Ethyl Acetoacetate——To a solution of Et. acetoacetate (6.5 g) and EtONa (1.4 g) in EtOH (10 ml) was added Ia (2.73 g) portionwise with stirring and cooling in an ice–bath and the mixture was stirred at room temperature for 1 hr, then refluxed for 3 hr. After cooling, the mixture was neutralized with AcOH, then evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. Evaporation of the solvent and excess Et. acetoacetate left a brown liquid, which was chromatographed on alumina to give following products: IV (0.39 g) as 1st fraction with petr. ether: Va (0.43 g) as 2nd fraction with benzene; and ethyl 6-phenyl-1,2,5, trimethyl-4-pyridone-3-carboxylate (IX) (0.20 g) as 3rd fraction with $CHCl_3$, which was recrystallized from AcOEt to give colorless needles, mp 204—205°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 271 (4.196), 216 (4.361). IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1724, 1617, 1566, 1222, 1180. MNR (in $CDCl_3$) τ: 6.78 (singlet, N–CH_3), 7.63 (s, 2-CH_3), 8.31 (s, 5-CH_3). *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.33; H, 6.69; N, 4.72.

6-Phenyl-1,2,5-trimethyl-4-pyridone-3-carboxylic Acid (X)——A mixture of IX (0.10 g) and NaOH (0.1 g) in H_2O (5 ml) was heated on a water bath for 1 hr, then cooled and neutralized with aq. HCl. The

Table II. 1-Methyl-5-R-6-phenyl-2,3-trimethylene- and Tetramethylenepyridinium Perchlorates



XIII

Compound No.	R	n	mp (°C)	UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε)	NMR (in $CDCl_3$) τ (multiplicity)[a] 4-H	N-CH_3	5-CH_3
XIII-a	CH_3	3	204—205	295 (4.098)	2.01 (s)	6.19 (s)	7.94 (s)
b	C_6H_5	3	210—212	305 (3.953), 245 (4.011)	1.95 (s)	6.05 (s)	
c	H	3	164—165	295 (4.095)	1.91 (d $J=7.9$ cps)	6.03 (s)	
d	CH_3	4	207—209	292 (4.079)	2.02 (s)	6.16 (s)	7.92 (s)
e	C_6H_5	4	184—185	304 (3.924), 244 (3.998)			

Compound No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Yield (%)	Yield of XIV (%)
XIII-a	$C_{16}H_{18}O_4NCl$	59.35	5.60	4.33	59.20	5.56	4.09	38.4	10.4[b]
b	$C_{21}H_{20}O_4NCl$	65.37	5.23	3.63	65.33	5.23	3.34	10.7	18.3[d]
c	$C_{15}H_{16}O_4NCl$	58.16	5.21	4.52	58.50	5.20	4.60	2.3	—
d	$C_{17}H_{20}O_4NCl$	60.44	5.97	4.15	60.34	6.02	3.89	27.4	14.0[c]
e	$C_{22}H_{22}O_4NCl$	66.08	5.55	3.50	65.51	5.54	3.54	8.9	17.1[e]

[a] s=singlet d=doublet
[b] N-(2-benzoylpropanoyl)morpholine
[c] N-(2-benzoylpropanoyl)pyrrolidine
[d] N-(2-benzoyl-phenylacetyl)morpholine
[e] N-(2-benzoyl-phenylacetyl)pyrrolidine

precipitated crystalline product (0.05 g) was filtered and recrystallized from EtOH to give colorless needles, mp 267—268°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 261 (4.023), 220 (4.618). *Anal.* Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.18; H, 5.83; N, 5.33.

Reactions of I with 1-Morpholinocyclopentene or 1-Pyrrolidinocyclohexene——The reactions were undertaken by the following general procedure. To a solution of cyclic enamine (15 mmole) in CH_3CN (15 ml) was added I (10 mmole) portionwise with stirring and cooling in an ice–bath and the mixture was stirred at room temperature for 3 hr, then at 50° for 1 hr and evaporated. To the residue was added small amount of EtOH and the precipitated crystalline product was filtered and recrystallized from EtOH to give 1-methylpyridinium perchlorate derivative (XIII) listed in Table II. The filtrate was concentrated and the residue was chromatographed on alumina with $CHCl_3$ and subsequent AcOEt to give β-keto acid amide (XIV)[1] and added XIII. The compounds XIIIa—e were identified with the authentic samples prepared by the following procedure, respectively. A mixture of Me_2SO_4 (6 mmole) and pyridine derivative (5 mmole), which was prepared by Stobbe's procedure,[10] was heated at 80° for 1 hr, then at 110° for 1 hr. After cooling, the mixture was poured into a solution of $NaClO_4$ (10 mmole) in H_2O (30 ml) and the precipitated crystalline product was filtered and recrystallized from EtOH to give corresponding 1-methylpyridinium perchlorate (XIII).

3,5-Dimethyl-4-phenyluracil (XV)——To a solution of KCNO (3.2 g) in 60% aq. MeOH (40 ml) was added Ia (2.73 g) portionwise with stirring at 50° and the solution was stirred at 50° for 1 hr, then evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. Evaporation of the solvent left a brown solid, which was recrystallized from benzene to give colorless needles (0.52 g), mp 238—240°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.49; H, 5.52; N, 13.11. It was identified with an authentic sample prepared by Ralph's procedure[12] by mixed mp determination and comparison of their infrared spectra.

Reaction of Ia with Phenylhydrazine——A. 1,5-Diphenyl-3-hydroxy-4-methylpyrazole (XVI): To a solution of $C_6H_5NHNH_2$ (1.60 g) and NaOH (0.6 g) in EtOH (20 ml) was added Ia (2.0 g) portionwise with stirring at 50° and the mixture was refluxed for 1 hr, then evaporated. To the residue was added H_2O and the precipitated crystalline product was filtered, washed with H_2O and then ether. Recrystallization from EtOH–benzene gave colorless needles (1.60 g), mp 274—275°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 2800—2350 (broad), 1600, 1532. *Anal.* Calcd. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.93; H, 5.82; N, 11.16. It was identified with an authentic sample prepared by Michaelis' procedure[13] by comparison of their infrared spectra.

B. 1,5-Diphenyl-4-methyl- and 1,3-Diphenyl-4-methylpyrazole (XVII, XVIII): A solution of Ia (1.37 g) and $C_6H_5NHNH_2$ (1.20 g) in CH_2Cl_2 (12 ml) was refluxed for 2 hr, then evaporated. To the residue was added ether and the precipitated solid was filtered off. Concentration of the filtrate left a brown liquid, which was chromatographed on alumina with benzene to give XVIII (0.55 g) as orange liquid (1st fraction) and XVII (0.50 g) as colorless crystals (2nd fraction). Distillation of XVIII *in vacuo* gave orange liquid, bp 175° (0.7 mmHg). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ: 284. NMR (in $CDCl_3$) τ: 7.82 (doublet $J=1.1$ cps, 4-CH_3). *Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Fund: C, 82.36; H, 6.01; N, 11.83. It was identified with an authentic sample prepared by the following procedure by comparison of their infrared spectra. Recrystallization of XVII from petr. ether gave colorless prisms, mp 85—86°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ: 253. NMR (in $CDCl_3$) τ: 2.39 (singlet, 3-H), 7.89 (s, 4-CH_3). *Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.05; H, 5.96; N, 12.12. It was identified with an authentic sample prepared from 2-benzoylpropionaldehyde with phenylhydrazine by comparison of their infrared spectra.

Synthesis of XVIII——To a solution of N-(1-propenyl)piperidine[14] (1.25 g) and NEt_3 (1.01 g)in benzene (10 ml) was added a solution of benzophenylhydrazide chloride[15] (1.15 g) in benzene (20 ml) dropwise with stirring at room temperature and the mixture was stirred at 50° for 1 hr, then cooled and filtered. The filtrate was concentrated and the residue was dissolved in AcOH (10 ml) contained aq. conc. HCl (3 ml). The solution was refluxed for 2 hr, then evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. Evaporation of the solvent left a brown liquid, which was chromatographed on alumina with benzene to give orange liquid. It was distilled *in vacuo* to give XVIII (0.27 g) as orange liquid, bp 173° (0.5 mmHg).

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