N,N′-Bis(4-quinolyl-, 4-quinaldinyl-, 4-quinazolinyl-, or 9-acridinyl)polymethylenediamine (I)——Bis-amine dihydrochloride[11,12] was basified with 10—15% NaOH and the precipitated oil was taken up in chloroform, washed with distilled water, dried over anhydrous potassium carbonate, stripped of solvent to afford a pasty mass, which solidified on scratching. It was recrystallized from chloroform. Yields and melting points of the respective compounds are given in Table I. IR (Nujol): 3300 cm^{-1} (NH).

N,N′-Bis(4-quinolyl-, 4-quinaldinyl-, 4-quinazolinyl-, 9-acridinyl-, or arenesulfonyl)polymethylenediamine (II)——Bis-amine and aromatic sulfonyl chloride, taken in the molar proportion of 1: 2, were dissolved in dry pyridine using 10 ml of pyridine/g of the bis-amine, and the mixture was gently heated for 3—4 hr, at 130—135°. After the reaction was over, solvent was removed under reduced pressure, and the residue was triturated with cold water to get a solid, which on crystallization from hot water gave analytical sample. Yields and physical constants are given in Table III.

Acknowledgement Thanks are due to Dr. A.K. Mukerjee, Applied Chemistry Section, Institute of Technology, B.H.U., Varanasi, for his interest in this work. The biological screening of the compounds was carried out under the direction of Dr. T. Ramakrishnan, Indian Institute of Science, Bangalore, which is gratefully acknowledged. Competent technical assistance by Mr. V.N. Muley, Mr. P.S. Gurjar, and R.C. Bipin is appreciated.

[Chem. Pharm. Bull. 23(8)1873—1879(1975)]

UDC 547.867.04 : 547.823.057

Synthesis of Methylpyridine Derivatives. XXX.[1] Reaction of Active Methylene Compounds with 6-Methyl-2-phenyl-4H-1,3-oxazin-4-one and 2-Ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one to give 3-Acetylpyridone Derivatives[2]

TETSUZO KATO, YUTAKA YAMAMOTO, and MASATSUGU KONDO

Pharmaceutical Institute, Tohoku University[3]

(Received September 27, 1974)

Reaction of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) with active methylene compounds, such as diethyl malonate (IIIa), acetylacetone (IIIb), cyclohexane-1,3-dione (IIIc), malononitrile (IIId), ethyl acetoacetate (IIIe), ethyl cyanoacetoacetate (IIIf), and cyanoacetophenone (IIIg) afforded pyridone derivatives, such as 3-acetyl-5-ethoxycarbonyl-4-hydroxy-6-phenyl-2(1H)-pyridone (IVa), 3,5-diacetyl-4-methyl-6-phenyl-2(1H)-pyridone (IVb), 4-acetyl-1-phenyl-6,7-dihydro-3,8-(2H, 5H)-isoquinolinedione (IVc), 3-acetyl-4-amino-5-cyano-6-phenyl-2(1H)-pyridone (IVd), 3-acetyl-5-ethoxycarbonyl-4-methyl 6-phenyl-2(1H)-pyridone (IVe), 3-acetyl-5-cyano-4-hydroxy-6-phenyl-2(1H)-pyridone (IVf), and 3-acetyl-5-cyano-4,6-diphenyl-2(1H)-pyridone (IVg), respectively.

Similarly, 2-ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one (II) reacted with IIIa—f under the same conditions to give the corresponding pyridone derivatives (Va—f).

We have previously reported that diketene reacted with imidates to give 1,3-oxazin-4-one derivatives.[4,5] The present paper reports a continuation of our study of those products related to the reaction with active methylene compounds to give pyridine derivatives.

Oxazines used in this reaction are 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) and 2-ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one (II), prepared by the reaction of diketene with ethyl benzimidate and ethyl acetimidate, respectively.

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1) Part XXIX: T. Kato and N. Niitsuma, *Yakugaku Zasshi*, **94**, 766 (1974).
2) This forms Part LXX of "Studies on Ketene and Its Derivatives," by T. Kato.
3) Location: *Aobayama, Sendai, 980, Japan.*
4) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1334 (1967).
5) T. Kato, H. Yamanaka, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972).

When 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) was allowed to react with diethyl malonate (IIIa) in absolute ethanol in the presence of sodium ethoxide, a crystalline substance of mp 180—182° (decomp.), $C_{16}H_{15}O_5N$ (IVa), was obtained in 44% yield. The use of potassium *tert*-butoxide in place of sodium ethoxide increased the yield of IVa to 60%.

Infrared (IR) and nuclear magnetic resonance (NMR) spectra suggested the structure being the pyridone derivative. Hydrolysis of IVa with diluted alkalies gave rise to phenylacetyl-hydroxypyridone (VI), mp>350° (decomp.), which was treated with conc. sulfuric acid to afford the deacetylated product, 4-hydroxy-6-phenyl-2(1H)-pyridone (VII). An authentic sample of VII was prepared by the ammonolysis of 4-hydroxy-6-phenyl-2-pyrone (IX), which was prepared from 5-acetyl-4-hydroxy-6-phenyl-2-pyrone (VIII) according to the literature.[6] Ammonolysis of VIII gave the known compound, 5-acetyl-4-hydroxy-6-phenyl-2(1H)-pyridone (X), mp 310° (decomp.),[6] whose IR and NMR spectra were different from those of VI.

The observations described above are well consistent with the structure of IVa as ethyl 3-acetyl-4-hydroxy-6-phenyl-2(1H)-pyridone-5-carboxylate.

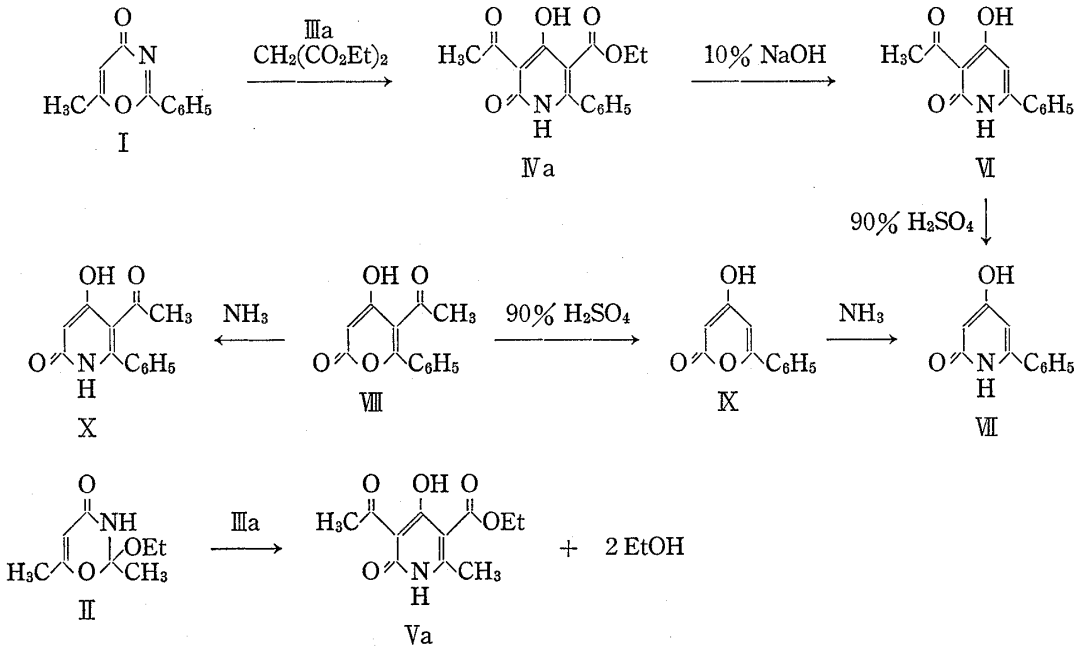


Chart 1

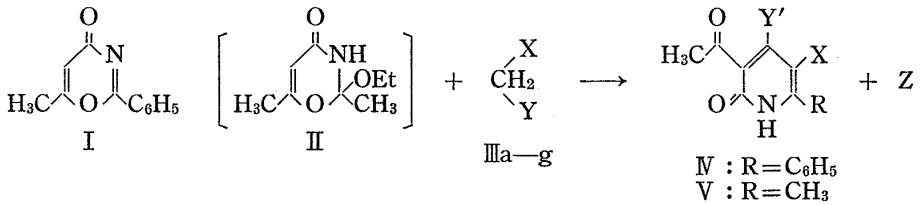
Similarly, acetylacetone (IIIb) and cyclohexane-1,3-dione (IIIc) were allowed to react with I under the same condition to give 3,5-diacetyl-4-methyl-6-phenyl-2(1H)-pyridone (IVb) and 4-acetyl-1-phenyl-6,7-dihydro-3,8-(2H, 5H)-isoquinolinedione (IVc), respectively. Elemental analysis and spectral data are consistent with these structures (Table II and III).

Similar reaction of malononitrile (IIId) with I afforded the 1:1 adduct, $C_{14}H_{11}O_2N_3$ (IVd), whose spectral data were consistent with the structure as 3-acetyl-4-amino-5-cyano-6-phenyl-2(1H)-pyridone.

Although details of the mechanism of the formation of these products are obscure at present, likely pathways are shown in Chart 2. Nucleophilic attack of active methylene of III to the 2 position of I gives rise to N-acetoacetylanil derivatives (XI), as intermediates. For instance, diethyl malonate (IIIa) adds to I to give the ring-opened anil (XIa, X=CO_2Et) as an intermediate. Cyclization of XIa by the elimination of ethanol gives the pyridone (XIIa, X=CO_2Et), which, by prototropy, is transformed to IVa (path-a).

6) M. Aslam Butt and J.A. Elridge, *J. Chem. Soc.*, **1963**, 4483.

Table I. Reaction of I(II) with Active Methylene Compound (III)



Oxazine I(II)	g	Active methylene comp. (III)	g	IV(V)	Yield of IV(V) Method A g	Method A %	Method B g	Method B %	X	Y	Y′	Z
I	3.7	diethyl malonate (IIIa)	3.2	IVa	2.6	44	3.6	60	CO_2Et	CO_2Et	OH	EtOH
I	3.7	acetylacetone (IIIb)	2.0	IVb	2.0	39	4.6	86	$COCH_3$	$COCH_3$	CH_3	H_2O
I	3.7	cyclohexanedione (IIIc)	2.2	IVc			5.0	90	$-CO(CH_2)_3CO-$		$-(CH_2)_3CO-$	H_2O
I	3.7	malononitrile (IIId)	1.3	IVd	3.5	70			CN	CN	NH_2	
I	3.7	ethyl acetoacetate (IIIe)	2.6	IVe	3.5	60	5.0	83	CO_2Et	$COCH_3$	CH_3	H_2O
I	3.7	ethyl cyanoacetate (IIIf)	2.3	IVf	3.3	66	4.0	80	CN	CO_2Et	OH	EtOH
I	3.7	cyanoacetophenone (IIIg)	2.9	IVg	4.0	65	5.7	90	CN	$CO\cdot C_6H_5$	C_6H_5	H_2O
II	3.4	diethyl malonate (IIIa)	3.2	Va	1.4	30	2.4	50	CO_2Et	CO_2Et	OH	EtOH
II	3.4	acetylacetone (IIIb)	2.0	Vb			1.4	35	$COCH_3$	$COCH_3$	CH_3	H_2O
II	3.4	cyclohexanedione (IIIc)	2.2	Vc			1.4	32	$-CO(CH_2)_3CO-$		$-(CH_2)_3CO-$	H_2O
II	3.4	malononitrile (IIId)	1.3	Vd	2.9	76			CN	CN	NH_2	
II	3.4	ethyl acetoacetate (IIIe)	2.6	Ve	3.5	75	3.8	80	CO_2Et	$COCH_3$	CH_3	H_2O
II	3.4	ethyl cyanoacetate (IIIf)	2.3	Vf			1.9	50	CN	CO_2Et	OH	EtOH
II	3.4	cyanoacetophenone (IIIg)	2.9	Vg	4.1	82	4.0	80	CN	COC_6H_5	C_6H_5	H_2O

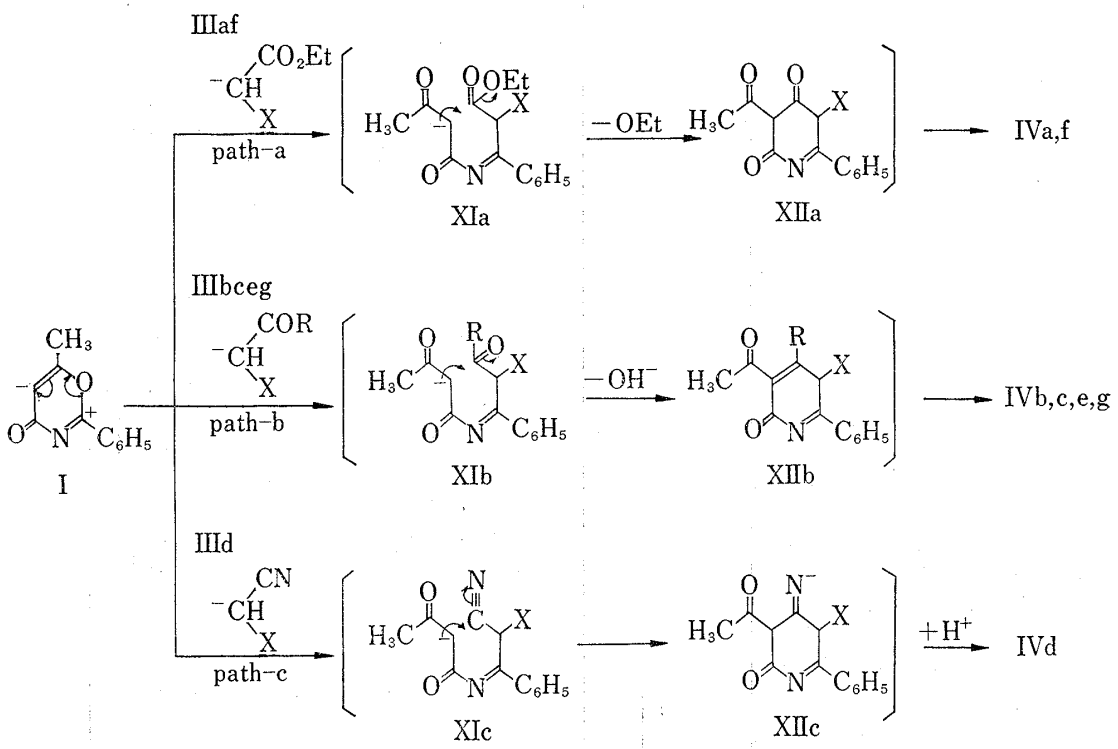


Chart 2

Table II. Crystal Forms, Melting Points and Elemental Analysis of IV and V

	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	colorless needles (AcOEt)	180—182 (d)[a]	$C_{16}H_{15}O_5N$	63.78	5.02	4.65	64.00	5.10	4.73
IVb	colorless needles (MeOH)	266—268 (d)	$C_{16}H_{15}O_3N$	71.36	5.61	5.20	71.57	5.74	5.18
IVc	colorless needles (EtOH)	230—233 (d)	$C_{17}H_{15}O_3N$	72.58	5.37	4.98	72.76	5.47	4.69
IVd	pale yellow needles (AcOH)	>350 (d)	$C_{14}H_{11}O_2N_3$	66.39	4.38	16.59	66.55	4.35	16.78
IVe	colorless prisms (AcOEt)	181—183	$C_{17}H_{17}O_4N$	68.21	5.73	4.68	68.49	5.87	4.82
IVf	colorless prisms (AcOH)	287—289 (d)	$C_{14}H_{10}O_3N_2$	66.13	3.96	11.02	65.94	3.99	11.31
IVg	colorless needles (CH_3CN)	281—283 (d)	$C_{20}H_{14}O_2N_2$	76.42	4.49	8.91	76.25	4.54	8.89
Va	colorless needles (AcOEt)	177—178 (d)	$C_{11}H_{13}O_5N$	55.23	5.48	5.86	55.54	5.56	5.83
Vb	colorless needles (EtOH)	232—235 (d)	$C_{11}H_{13}O_3N$	63.75	6.32	6.76	64.01	6.61	6.91
Vc	colorless needles (EtOH)	200—203 (d)	$C_{12}H_{13}O_3N$	65.74	5.98	6.39	65.57	6.18	6.15
Vd	colorless needles (H_2O)	260—262 (d)	$C_9H_9O_2N_3$	56.54	4.75	21.98	56.41	4.71	21.61
Ve	colorless needles (AcOEt)	180—181	$C_{12}H_{15}O_4N$	60.75	6.37	5.90	60.89	6.34	5.97
Vf	colorless plates (EtOH)	246—247 (d)	$C_9H_8O_3N_2$	56.25	4.20	14.58	56.17	4.37	14.74
Vg	colorless plates (MeOH)	221—222	$C_{15}H_{12}O_2N_2$	72.41	4.80	11.11	71.09	4.94	10.77

a) d: decomposition

Table III. Spectral Data of IV and V

	R	X	Y′	NMR ppm						IR cm^{-1}	
				Solvent	Ac[a]	R[b]	NH[c]	X	Y′	Solvent	CN, CO
IVa	C_6H_5	CO_2Et	OH	$CDCl_3$	2.48	7.50	11.80—12.40	1.00(3H, t) 4.10(2H, q)	16.32(1H, s)	$CHCl_3$	1720, 1645
IVb	C_6H_5	$COCH_3$	CH_3	DMSOd-6	2.45	7.40	11.70—12.50	1.80(3H, s)	2.00(3H, s)	KBr	1685, 1620
IVc	C_6H_5	$-CO(CH_2)_3-$		$CDCl_3$	2.31	7.35—7.50	11.80—12.90	1.70—2.20(2H, broad q) 2.20—2.70(2H, broad t) 2.70—3.10(2H, broad t)		$CHCl_3$	1686, 1655(sh)
IVd	C_6H_5	CN	NH_2	CF_3CO_2H	2.88	7.70	—	—	—	KBr	2230, 1638
IVe	C_6H_5	CO_2Et	CH_3	$CDCl_3$	2.36	7.44	12.50—13.10	0.94(3H, t) 4.00(2H, q)	2.26(3H, s)	$CHCl_3$	1712, 1642
IVf	C_6H_5	CN	OH	CF_3CO_2H	2.92	7.73	—	—	—	KBr	2230, 1655(sh), 1634
IVg	C_6H_5	CN	C_6H_5	DMSOd-6	2.20	7.39	12.30—13.50	—	7.45—7.90 (5H, m)	$CHCl_3$	2240, 1705, 1640
Va	CH_3	CO_2Et	OH	$CDCl_3$	2.45	2.70	11.90—12.70	1.35(3H, t) 4.35(2H, q)	16.31(1H, s)	$CHCl_3$	1716, 1654
Vb	CH_3	$COCH_3$	CH_3	DMSOd-6	2.42	2.42	11.80—12.90	2.18(3H, s)	2.00(3H, s)	KBr	1685, 1646
Vc	CH_3	$-CO(CH_2)_3-$		$CDCl_3$	2.60	2.78	12.80—13.20	1.70—2.20(2H, m) 2.20—3.10(4H, m)		KBr	1679, 1644
Vd	CH_3	CN	NH_2	DMSOd-6	2.40	2.05	11.50—13.00	—	2.70—4.50(2H,b)	KBr	2240, 1660
Ve	CH_3	CO_2Et	CH_3	$CDCl_3$	2.40	2.52	13.00—13.36	1.35(3H, t) 4.32(2H, q)	2.22(3H, s)	$CHCl_3$	1705, 1640
Vf	CH_3	CN	OH	DMSOd-6	2.42	2.60	11.90—12.70	—	16.20—17.10 (1H, b)	KBr	2240, 1660
Vg	CH_3	CN	C_6H_5	$CDCl_3$	2.19	2.67	12.90—13.70	—	7.25—7.60 (5H, m)	$CHCl_3$	2240, 1705, 1640

a) 3H, s. *b*) IV: 5H, s (IVc, 5H, m), V: 3H, s. *c*) 1H, broad

Addition of acetylacetone (IIIb) affords the ring-opened intermediate (XIb, R=CH_3, X=$COCH_3$), dehydration of which gives rise to IVb via a cyclic product (XIIb) (path-b).

Similarly, malononitrile (IIId) adds to I to give the intermediate (XIc, X=CN), followed by prototropy to cyclize to 4-amino-pyridone derivative (XIIc), prototropy of which affords IVd (path-c).

In the case of active methylene compounds, such as ethyl acetoacetate (IIIe), ethyl cyanoacetate (IIIf), and cyanoacetophenone (IIIg), two pyridones are possible. However, the sole product was isolated in each reaction. For instance, similar reaction of I with ethyl acetoacetate (IIIe) afforded a single product (IVe). Its empirical formula, $C_{17}H_{17}O_4N$ indicated the structure being ethyl 3-acetyl-4-methyl-6-phenyl-2(1H)-pyridone-5-carboxylate (IVe) formed by dehydration along path-b. The result is in contrast with the expective 3,5-diacetyl-4-hydroxy-6-phenyl-2(1H)-pyridone, produced by the elimination of ethanol along pathway-a.

Reaction of ethyl cyanoacetate (IIIf) did not give the adduct corresponding to XIIc (X=CO_2Et) along path-c, but gave IVf *via* the condensation product (XIIa, X=CN) by the elimination of ethanol along path-a. Similar reaction of cyanoacetophenone (IIIg) did not afford the adduct (XIIc, X=COC_6H_5) along path-c, but gave IVg *via* the dehydrated product (XIIb, X=CN) along path-b. These structures (IVe, f, g) were established by IR and NMR spectral data (see Table III).

Similar, reaction of 2-ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one (II) with IIIa—g gave the corresponding products (Va—g).

Experimental

Melting points were determined by a calibrated Yanagimoto melting point apparatus. IR spectra were measured by a JASCO DS-301 spectrometer, and NMR spectra were measured on a Hitachi-Perkin Elmer R-20, and reported as δ value (ppm) relative to tetramethylsilane as an internal standard. Abreviations are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad.

General Procedure——Method A: Sodium metal (0.5 g, 0.02 g atom) was dissolved in abs. EtOH (30 ml), and III (0.02 mole) was added to the mixture with stirring. Stirring was continued for an additional 30 min at room temperature, then the oxazine (0.02 mole) was added. After allowing to stand overnight at room temperature, the mixture was diluted with H_2O (300 ml) and neutralized with 10% HCl. Crystals precipitated were collected, dried, and purified by recrystallization.

Method B: Potassium metal (0.8 g, 0.02 g atom) was dissolved in abs. *tert*-BuOH (40 ml) under mild heating (*ca.* 50°), and III (0.02 mole) was added to the mixture. The solution was stirred for 30 min, and oxazine (0.02 mole) was then added. The reaction mixture was heated at 50° overnight. Similar treatment as above afforded the corresponding pyridones.

These results are summarized in Table I, II and III.

3-Acetyl-4-hydroxy-6-phenyl-2(1H)-pyridone (VI)——A suspension of IVa (3 g) in 10% NaOH (20 ml) was heated for 2 hr. The reaction mixture was neutralized with 10% HCl. Crystals precipitated were collected. Recrystallization from MeOH gave colorless needles of mp>350° (decomp.). Yield, 2.1 g (92%). *Anal.* Calcd. for $C_{13}H_{11}O_3N$ (VI): C, 68.11; H, 4.84; N, 6.11. Found: C, 68.17; H, 4.88; N, 6.13. IR ν_{max}^{KBr} cm^{-1}: 3100, 3000, 1655 (sh), 1633, 1608. NMR (CF_3COOH) ppm: 2.90 (3H, s), 6.90 (1H, s), 7.68 (5H, s).

4-Hydroxy-6-phenyl-2(1H)-pyridone (VII)——1) 3-Acetyl-6-phenyl-2(1H)-pyridone (VI) (1 g) was suspended in 90% H_2SO_4 (10 ml), and the mixture was heated in an oil bath at 160° for several minutes. The reaction mixture was poured into ice-water, and neutralized with 10% Na_2CO_3. Crystals precipitated were collected, washed with H_2O, and recrystallized from 70% AcOH to give colorless needles of mp 317—318° (decomp.). Yield, 0.5 g (60%). *Anal.* Calcd. for $C_{11}H_9O_2N$ (VII): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.66; H, 5.04; N, 7.27. IR ν_{max}^{KBr} cm^{-1}: 3400, 3080, 2920, 2600, 1610, 1590, 1570. NMR (CF_3COOH) ppm: 6.70 (1H, broad s), 7.05 (1H, broad s), 7.65 (5H, s).

2) A mixture of 4-hydroxy-6-phenyl-2-pyrone[6] (IX, 0.4 g) in 28% NH_4OH (30 ml) was placed in a sealed tube, and heated at 100° for 12 hr. The resulting solution was condensed *in vacuo*. The crystalline residue was purfied by recrystallization from 70% AcOH to give colorless needles, mp 317—318° (decomp.), whose IR and NMR spectra were identical in every respect with those of a sample (VII) obtained in the above run. Yield, 0.2 g (51%).

5-Acetyl-4-hydroxy-6-phenyl-2(1H)-pyridone (X)——According to the literature,[6] a mixture of 5-acetyl-4-hydroxy-6-phenyl-2-pyrone (VIII, 0.3 g) in 28% NH_4OH (20 ml) was placed in a sealed tube and heated for 15 hr at 100°. After evaporation, the residue was recrystallized from EtOH to give colorless prisms of mp 310—311° (decomp.) (lit.[6] mp 320 (decomp.)). Yield, 0.2 g (60%). *Anal.* Calcd. for $C_{13}H_{11}O_3N$ (X):

C, 68.11; H, 4.84; N, 6.11. Found: C, 68.06; H, 5.21; N, 5.73. IR ν_{max}^{KBr} cm^{-1}: 3400, 2960—2880, 2680—2560, 1660, 1595. NMR (CF_3COOH) ppm: 2.50 (3H, s), 6.80 (1H, s), 7.40—8.10 (5H, m).

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[Chem. Pharm. Bull. 23(8)1879—1881(1975)]

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Syntheses of 1-Alkoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinones and Related Compounds[1]

Shozo Kamiya and Masayuki Tanno

National Institute of Hygienic Sciences[2]

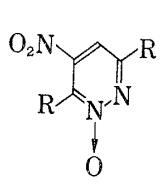
(Received December 4, 1974)

1-Alkoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinones (VIIa, b) were synthesized by the nitration of 3,6-dimethyl-4-hydroxypyridazine 1-oxide (IV), followed by alkylation with alkyl halides. The catalytic hydrogenation of the nitro compound VIIa gave 1-methoxy-3,6-dimethyl-5-amino-4(1H)-pyridazinone (IX).

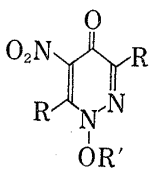
1-Methoxy-3,6-dimethyl-5-bromo-4(1H)-pyridazinone (XI) was similarly synthesized by the bromination of IV, followed by alkylation.

5-Nitropyridazine 1-oxides (A) have mutagenic and prophage-inducing activities for bacteria.[3]

This paper describes the syntheses of 1-alkoxy-5-nitro-4(1H)-pyridazinones (B), in which the aromaticity is considerably reduced as compared with that of A, and related compounds.



A



B

The starting material, 3,6-dimethyl-4-hydroxypyridazine 1-oxide (IV) was first synthesized by Sako[4] from 3,6-dimethyl-4-chloropyridazine. In this experiment we synthesized compound IV from 3,6-dimethyl-4-nitropyridazine 1-oxide (I) according to the synthetic route shown in Chart 1.

The predominance of the hydroxy form in the prototropic tautomers of compound IV is supported by its ultraviolet (UV) spectrum (Fig. 1). Namely, the absorption curve of IV

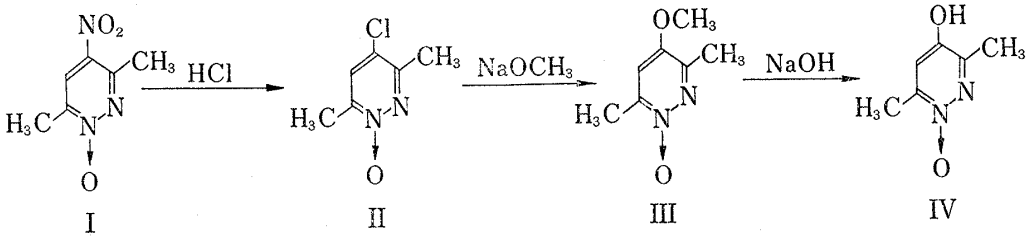


Chart 1

1) S. Kamiya and M. Tanno, *Chem. Pharm. Bull.* (Tokyo), **23**, 923 (1975).
2) Location: *Kamiyoga, 1-18-1, Setagaya, Tokyo.*
3) S. Kamiya, T. Nakashima, S. Sueyoshi, M. Tanno, I. Suzuki, K. Yanagimachi, K. Yoshikawa, and H. Kurata, the 94th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts No. III, p. 104.
4) S. Sako, *Chem. Pharm. Bull.* (Tokyo), **11**, 337 (1963).