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A Convenient Synthesis of Pyridazino[4,5-*b*]quinolines and Pyrrolo[3,4-*b*]quinolines[1)]

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The reaction of N-(1,2-bisethoxycarbonylvinyl)-*o*-aminoacetophenone (IVc) with an excess of hydrazines or guanidines gave 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]-quinolines (Ia,b) or 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinolines (IIIc,d), respectively. It was found that 2,3-bishydrazinocarbonyl-4-methylquinolines (VIa,b) were converted to 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia,b) and 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinolines (IIIa,b) under different reaction conditions.

Keywords—— N-(1,2-bisethoxycarbonylvinyl)-*o*-aminoacetophenone; hydrazine hydrate; methylhydrazine; 1,2-bishydrazinocarbonyl-4-methylquinoline; 2,3-bisalkoxycarbonylquinoline; guanidine; methylguanidine; coloration; ferrous ion

Many studies have been reported concerning the synthesis of maleic hydrazides[3–7)] and other heteroaromatic ring-condensed cyclic hydrazides[8–10)] (pyridazine derivatives). Among the condensed pyridazines, 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia, c) have been synthesized from the reactions of 4-methyl-2,3-bismethoxycarbonylquinoline (IIa),[11)] 2,3-bismethoxycarbonylquinoline (IIb),[12)] and 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline (IIIe)[12)] with hydrazine hydrate. On the other hand, IIa and IIb have been prepared from N-(1,2-bismethoxycarbonylvinyl)-*o*-aminoacetophenone (IVa) and N-(1,2-bismethoxycarbonylvinyl)-*o*-aminobenzaldehyde (IVb),[13,14)] respectively. Recently, we have found that 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia, b) are conveniently produced by the reaction of N-(1,2-bisethoxycarbonylvinyl)-*o*-aminoacetophenone (IVc)[13,14)] with hydrazine

1) A part of this work was reported by Y. Kurasawa and A. Takada, in *Heterocycles*, **14**, 267 (1980).
2) Location: *Shirokane, Minato-ku, Tokyo 108, Japan.*
3) O. Ohashi, M. Mashima, and M. Kubo, *Can. J. Chem.*, **42**, 970 (1964).
4) H.P. Fritz, F.H. Koehler, and B. Lippert, *Chem. Ber.*, **106**, 2918 (1973).
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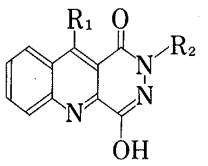
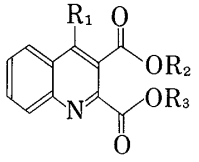
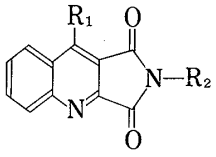
13) E.C. Taylor and N.D. Heindel, *J. Org. Chem.*, **32**, 1666 (1967).
14) J.B. Henderickson, R. Rees, and J.F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).



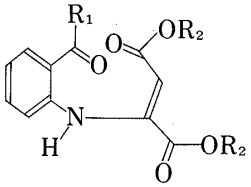
Ia : R_1=Me, R_2=H
Ib : R_1=R_2=Me
Ic : R_1=R_2=H



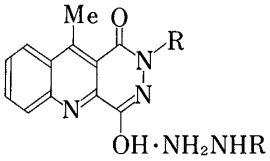
IIa : R_1=R_2=R_3=Me
IIb : R_1=H, R_2=R_3=Me
IIc : R_1=Me, R_2=R_3=Et
IId : R_1=Me, R_2=Et, R_3=H



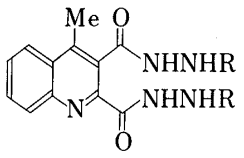
IIIa : R_1=Me, R_2=NH_2
IIIb : R_1=Me, R_2=NHMe
IIIc : R_1=R_2=Me
IIId : R_1=Me, R_2=H
IIIe : R_1=R_2=H



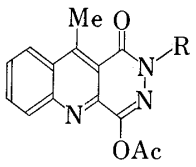
IVa : R_1=R_2=Me
IVb : R_1=H, R_2=Me
IVc : R_1=Me, R_2=Et



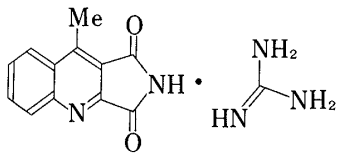
Va : R=H
Vb : R=Me



VIa : R=H
VIb : R=Me



VIIa : R=H
VIIb : R=Me
VIIc : R=Ac



VIII

Chart 1

hydrate and methylhydrazine, and that IVc is also cyclized easily to give 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinolines (IIIc, d) in the presence of guanidines.

Reaction of IVc with Hydrazines

When IVc was allowed to react with a 2-fold molar excess of hydrazine hydrate in ethanol, 4-hydroxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline monohydrazinium salt (Va) was obtained in 13% yield. From the above filtrate, 2,3-bishydrazinocarbonyl-4-methylquinoline (VIa) was obtained in 53% yield. However, the yields of Va and VIa were lower in the reaction of IVc with an equimolar amount of hydrazine hydrate, and hence the above reaction was carried out in the presence of a large excess of hydrazine hydrate. The reaction of IVc with a 30-fold molar excess of hydrazine hydrate predominantly gave Va (88%), and VIa was not obtained. Treatment of Va with acetic acid afforded hydrazine-free compound Ia.

On the other hand, the reaction of IVc with a 2-fold molar excess of methylhydrazine produced 2,3-bisethoxycarbonyl-4-methylquinoline (IIc) in 94% yield. However, the reaction of IVc with a 10-fold molar excess of methylhydrazine provided 4-hydroxy-2,10-dimethyl-1-

oxo-1,2-dihydropyridazino[4,5-*b*]quinoline monomethylhydrazinium salt (Vb) in 30% yield. From its filtrate, 4-methyl-2,3-bis(2′-methylhydrazinocarbonyl)quinoline (VIb) was obtained in 28% yield. Furthermore, the reaction of IVc with a 30-fold molar excess of methylhydrazine exclusively provided Vb in 94% yield. Treatment of Vb with acetic acid gave methylhydrazine-free compound Ib.

Thus, it was found that 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia, b) were conveniently synthesized in good yields by the reaction of IVc with a large excess of hydrazines. This method does not require the preparation and isolation of 2,3-bisalkoxycarbonylquinolines (II) as intermediates.

Compounds VIa and VIb easily cyclized to 2-amino-9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline (IIIa) (76%) and 9-methyl-2-methylamino-1,3-dioxo-1,3-dihydropyrrolo-[3,4-*b*]quinoline (IIIb) (23%), respectively, on refluxing in ethanol. When VIa was dissolved in water and stirred for 30 min, IIIa was produced in 86% yield. When VIb was passed through a silica gel column, IIIb was obtained in 98% yield. Moreover, the reaction of IIIa with an excess of methylhydrazine afforded Vb in 50% yield, and the reaction of IIIb with an excess of hydrazine hydrate provided Va in 30% yield.

Acetylated compounds, 4-acetoxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIa), 4-acetoxy-2,10-dimethyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIb), and 4-acetoxy-2-acetyl-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIc),[12] were also prepared by the ordinary method.

The above results are summarized in Table I and Chart 2. It is suggested that IVc was dehydrated to 2,3-bisethoxycarbonyl-4-methylquinoline (IIc), which was converted to 2,3-bishydrazinocarbonyl-4-methylquinolines (VIa, b) followed by the formation of 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia, b) and (Va, b) in the presence of hydrazines. In addition, it was found that 2,3-bishydrazinocarbonyl-4-methylquinolines (VIa, b) were transformed to 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines (Ia, b) and 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinolines (IIIa, b) under different reaction conditions. The intermediates from IIIa and IIIb to Vb and Va were postulated to be VIb and VIa, respectively.

Table I

Molar ratio		Yield (%)		
IVc :	$NH_2NH_2 \cdot H_2O$	Va	VIa	
1	1	Trace	12	
1	2	13	53	
1	30	88	—	
IVc :	NH_2NHMe	Vb	VIb	IIc
1	2	Trace	—	94
1	10	30	28	—
1	30	94	—	—

While the molecular ion peaks of VIa and VIb [(VIa, b)$^+$] were seen upon in-beam electron impact mass spectrometry,[15] the appropriate fragment ion peaks [(VIa, b-NH_2NHR)$^+$] were observed without the molecular ion peaks in direct inlet electron impact mass spectrometry. The fragmentation patterns of VIa, b were similar to those of Ia, b and IIIa, b (Table II), and hence VIa, b were also found to cyclize to Ia, b and/or IIIa, b during mass spectrometry. The similarity of the fragmentation patterns between Ia, b and IIIa, b may be explained by the

15) M. Ohashi, S. Yamada, H. Kudo, and N. Nakayama, *Biomed. Mass Spectrom.*, **5**, 578 (1978); M. Ohashi, K. Tsujimoto, and A. Yasuda, *Chem. Lett.*, **1976**, 439.

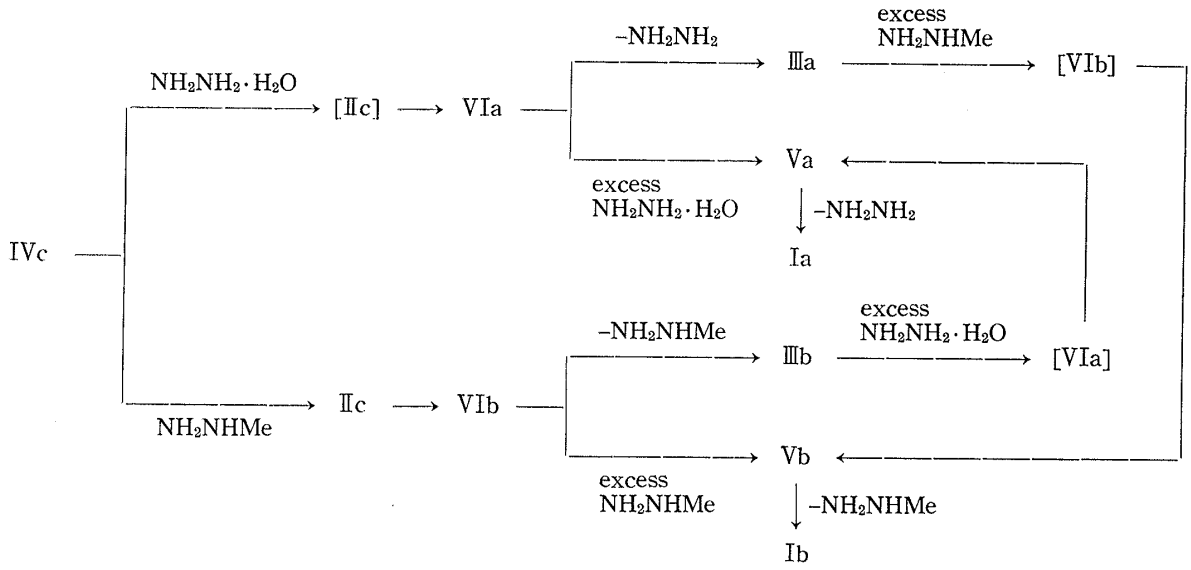


Chart 2

TABLE II

Compound	Molecular and fragment ions (*m/e*)						
VIa	259 (M^+)	227	199	184	170	169	142
Va, IIIa, Ia	227 (M^+)	199	184	170	169	142	
VIb	287 (M^+)	241	213	184	170	169	142
Vb, IIIb, Ib	241 (M^+)	213	184	170	169	142	

formation of fragment species having identical molecular weight, as shown in Chart 3-a. The following fragment species are assumed, as shown in Chart 3-b.[16]

Compounds Ia and VIIa were assigned as the 1-oxo-4-hydroxy forms by analogy with the finding of Godard,[12] who showed Ic to be the 1-oxo-4-hydroxy form. Compounds Ib and VIIb are also assumed to be the 1-oxo-4-hydroxy forms, since the UV spectral patterns of these compounds are similar to those of Ia and VIIa, respectively. This was supported by the NMR spectral data. The chemical shifts for the 10-methyl protons of Ia, Ib, VIIa, and VIIb were almost the same, that is, 3.40 (Ia), 3.38 (Ib), 3.39 (VIIa), and 3.37 (VIIb). Therefore, Ib and VIIb may also be assigned as the 1-oxo-4-hydroxy forms. On the other hand, the signals for the methyl protons of the quinoline nucleus in IIIa and IIIb were observed at 3.03 ppm, about 20 Hz higher than those of Ia, b and VIIa, b. Moreover, coupling between the 2-NHMe and 2-NHMe protons was observed in IIIb, and the signal for the 2-amino protons of IIIa was observed at similar magnetic field to that for the 2-amino proton of IIIb. These data support the above structural assignments for IIIa and IIIb.

Reaction of IVc with Guanidines

The reaction of IVc with a 2-fold molar excess of guanidine in ethanol gave 9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline guanidinium salt (VIII) (21%). From the filtrate, 2-carboxyl-3-ethoxycarbonyl-4-methylquinoline (IId) was obtained in 76% yield. In the

16) J.H. Bowie, R.G. Cooks, P.R. Donaghue, J.A. Halleday, and H.J. Rodda, *Aust. J. Chem.*, **20**, 2677 (1967); B.M. Lynch and S.C. Sharma, *Can. J. Chem.*, **55**, 831 (1977).

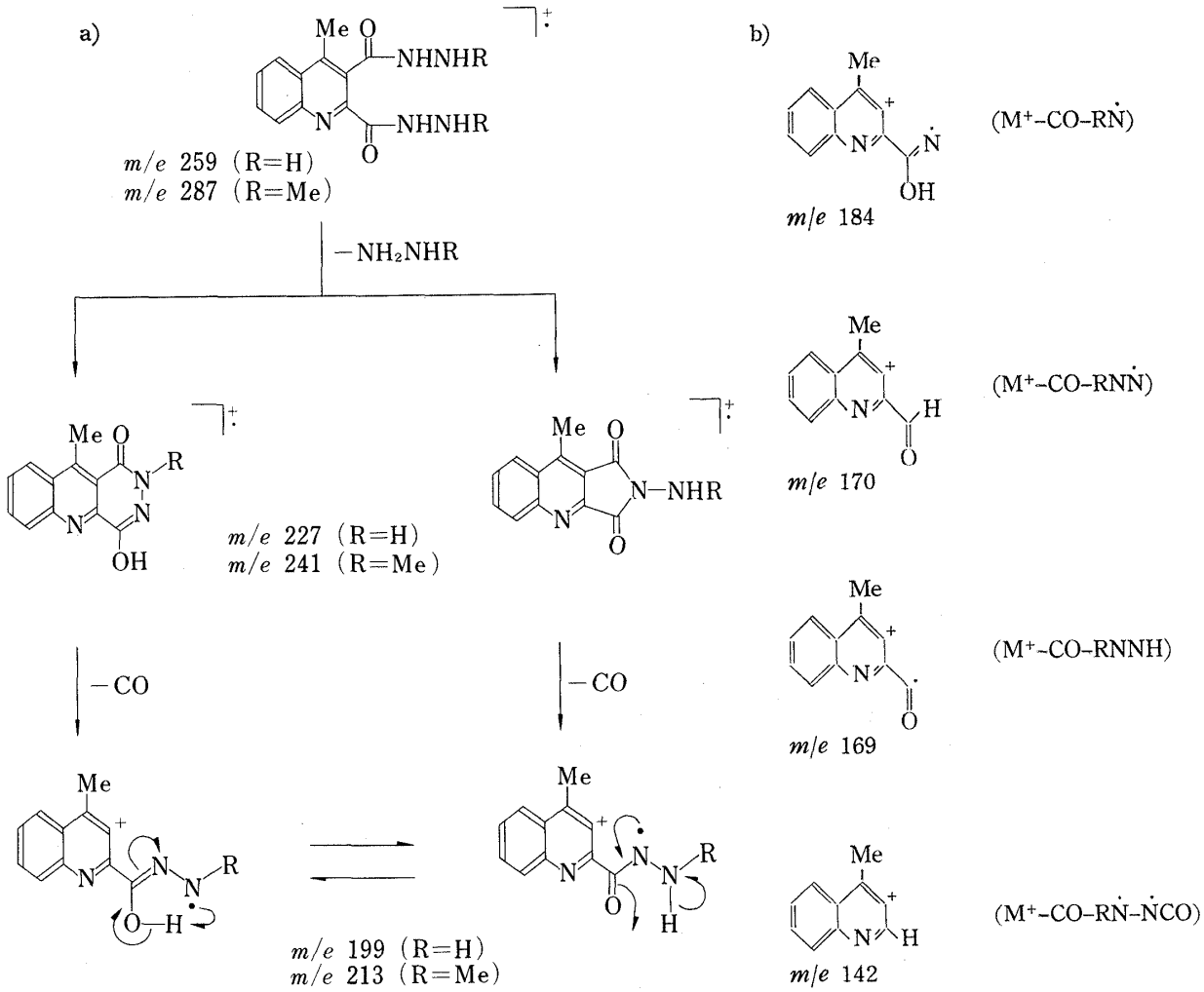


Chart 3

presence of a 30-fold molar excess of guanidine, VIII and IId were obtained in 51% and 36% yields, respectively. On the other hand, the reaction of IVc with a 2-fold molar excess of methylguanidine afforded three compounds, 2,9-dimethyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]-quinoline (IIIc) (10%), IId (21%), and IIc (32%), which were isolated by column chromatography. Treatment of VIII with acetic acid provided guanidine-free compound IIId. The reaction of IIId with an excess of hydrazine hydrate or methylhydrazine produced Va or Vb in 83% or 89% yield, respectively.

The above results are summarized in Table III. It is suggested that IVc was converted to IIc and/or IId, which were attacked by guanidines to provide VIII and IIIc. The mechanism of formation of the pyrrole ring was assumed to be as shown in Chart 4.

The structures of IIIc and IIId were established on the basis of the analytical and spectral data. Their UV spectral patterns were similar to those of IIIa and IIIb. On the other hand,

Table III

Reagent	Molar ratio to IVc	Product (Yield %)		
Guanidine	2-fold	VIII (21)	IId (76)	
	30-fold	VIII (51)	IId (36)	
Methylguanidine	2-fold	IIIc (10)	IId (21)	IIc (32)

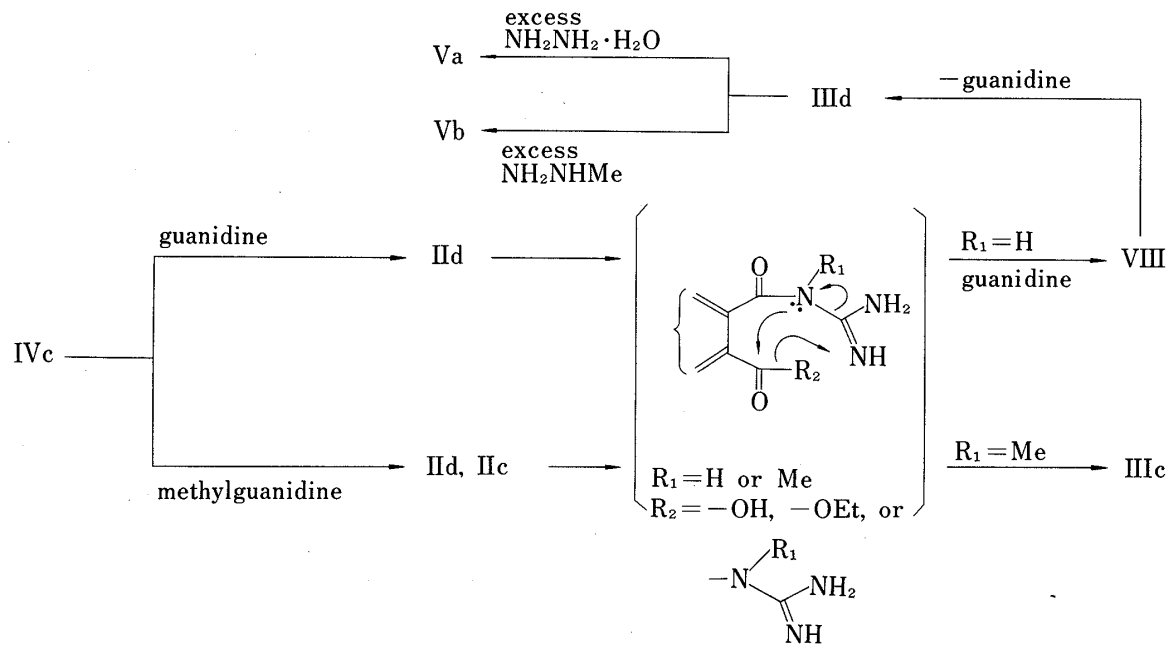
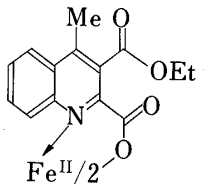


Chart 4

IId was found to contain carboxyl and ethoxycarbonyl groups from its analytical and spectral data, and it gave an immediate red coloration (λ_{max} 506.5 nm) with ferrous ions. This suggests the formation of a chelate (IX) (Chart 5).[17] Therefore, IId was assigned as 2-carboxyl-3-ethoxycarbonyl-4-methylquinoline. Its 3-ethoxycarbonyl group was preserved without hydrolysis, presumably due to the tautomeric character of IV. The mechanism of formation of IId was assumed to be as shown in Chart 6.



IX

Chart 5

In conclusion, it was found that 4-hydroxy-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinolines and 1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]-quinolines were conveniently synthesized by the reaction of IVc with hydrazines and with guanidines, respectively.

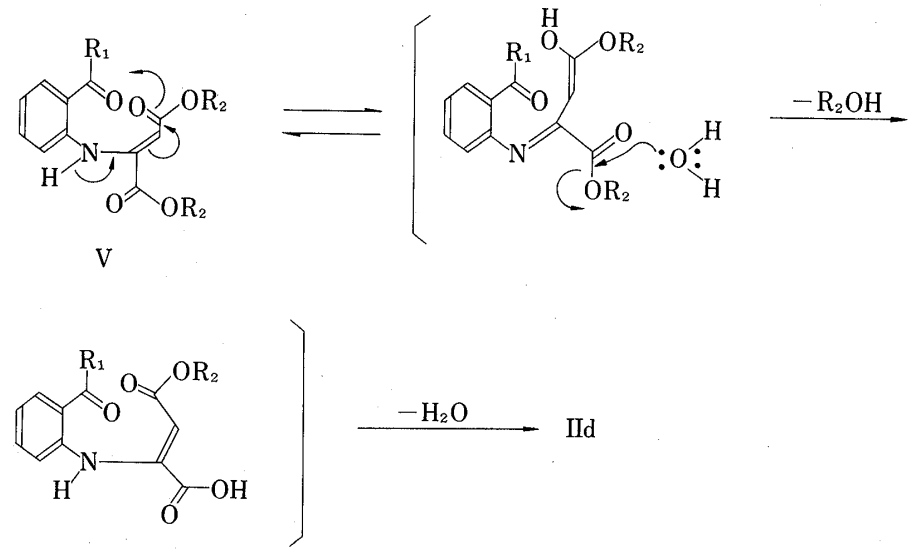


Chart 6

17) G. D'Ascenzo, U.B. Ceipidor, A. Marino, and A. Magri, *Anal. Chim. Acta*, **65**, 105 (1973).

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrophotometer as KBr discs. UV spectra were measured in EtOH on a Hitachi model 200-20 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian T-60 spectrometer with tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. Mass spectra (MS) were determined at 75 eV with a JMS-D100 spectrometer (Japan Electron Optics Laboratory Co. Ltd.). Silica gel used for column chromatography was purchased from Mallinckrodt Chemical Works: 100 mesh silicic acid (analytical reagent).

Reaction of Compound IVc with Hydrazine Hydrate——Compound IVc (1 g, 3.3 mmol) was dissolved in EtOH (15 ml), and a 2-fold molar excess of hydrazine hydrate (0.33 g, 6.6 mmol) was added. The solution was refluxed for 5 hr to precipitate red needles during the reaction. After the reaction, precipitated 4-hydroxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline monohydrazinium salt (Va) was filtered off while the reaction mixture was hot. The red needles collected were further refluxed in a solution of hydrazine hydrate (3 ml) in EtOH (30 ml) to give an analytically pure sample (280 mg, 13%), mp 245° (discoloration), 310—315° (dec.). IR ν_{max} cm^{-1}: 1630 (C=O). UV λ_{max} nm (log ε): 215.0 (4.36), 248.0 (4.72), 287.0 (3.94). MS *m/e*: 227 (M$^+$). *Anal.* Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.02. Found: C, 55.49; H, 5.06; N, 26.91.

The above filtrate was concentrated *in vacuo* to a small volume, and yellow crystals that deposited were recrystallized directly from this filtrate, which was suitably basified with hydrazine hydrate, to afford 2,3-bishydrazinocarbonyl-4-methylquinoline (VIa) as yellow needles (450 mg, 53%), mp 323°. IR ν_{max} cm^{-1}: 3220 (NH), 1665, 1630 (C=O). NMR (DMSO-d_6): 9.22 (2H, br.s, CONHNH$_2$), 8.47—7.50 (4H, m, aromatic), 4.17 (4H, br.s, CONHNH$_2$), 2.65 (3H, s, 4-Me). MS *m/e*: 259 (M$^+$), 227 (M$^+$−NH_2NH_2). *Anal.* Calcd for $C_{12}H_{13}N_5O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C. 63.23; H, 3.94; N, 18.64.

The reaction of compound IVc (1 g, 3.3 mmol) with a 30-fold molar excess of hydrazine hydrate (5 g, 99 mmol) and with an equimolar amount of hydrazine hydrate (0.17 g, 3.3 mmol) under the same conditions as above predominantly afforded compound Va (740 mg, 88%), and compound VIa (280 mg, 12%), respectively.

Reaction of Compound IVc with Methylhydrazine——Compound IVc (1 g, 3.3 mmol) was dissolved in EtOH (15 ml), and a 10-fold molar excess of methylhydrazine (1.5 g, 33 mmol) was added. The solution was refluxed for 5 hr and red needles precipitated during the reaction. After the reaction, precipitated 4-hydroxy-2,10-dimethyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline monomethylhydrazinium salt (Vb) was collected by suction. Compound Vb was further refluxed in a solution of methylhydrazine (3 ml) in EtOH (30 ml) to give an analytically pure sample (280 mg, 30%), mp 210° (discoloration), 260—263°. IR ν_{max} cm^{-1}: 1625 (C=O). UV λ_{max} nm (log ε): 214.0 (4.39), 249.0 (4.71), 293.0 (3.98). MS *m/e*: 241 (M$^+$). *Anal.* Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.55; H, 5.96; N, 24.41.

The above filtrate was concentrated *in vacuo* to give an oily residue, which was treated with benzene and then hexane–EtOH to yield crude 4-methyl-2,3-bis(2′-methylhydrazinocarbonyl)quinoline (VIb) as a powder (258 mg, 28%). MS *m/e*: 287 (M$^+$), 241 (M$^+$−NH_2NHMe). The purification of VIb was difficult because of its ease of cyclization to IIIb, and hence the structure of VIb was assumed on the basis of the mass spectral data and the observation that the reactivity was similar to that of VIa.

The reaction of compound IVc (1 g, 3.3 mmol) with a 30-fold molar excess of methylhydrazine (4.54 g, 99 mmol) under the same conditions as above gave compound Vb (880 mg, 94%).

The reaction of compound IVc (1 g, 3.3 mmol) with a 2-fold molar excess of methylhydrazine (0.31 g, 6.6 mmol) under the same conditions as above afforded a trace amount of compound Vb. This compound was collected by suction, then the filtrate was concentrated *in vacuo* to leave an oily substance, which was subjected to column chromatography on silica gel to afford 2,3-bisethoxycarbonyl-4-methylquinoline (IIc) (895 mg, 94%). The spectral data for this sample were identical with those of an authentic sample.[13,14]

2-Amino-9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline (IIIa)——Compound VIa (200 mg) was dissolved in H_2O (20 ml) and stirred for 30 min to precipitate compound IIIa, which was collected by suction (150 mg, 86%). When a solution of VIa (200 mg) in EtOH (30 ml) was refluxed for 2 hr, and the solution was concentrated *in vacuo* to a small volume, compound IIIa was obtained in 76% yield. Recrystallization from EtOH gave colorless needles, mp 269—271°. IR ν_{max} cm^{-1}: 3220 (NH), 1773, 1700 (C=O). UV λ_{max} nm (log ε): 212.5 (4.30), 261.5 (4.67). NMR (DMSO-d_6): 8.47—7.73 (4H, m, aromatic), 5.15 (2H, s, 2-NH$_2$), 3.03 (3H, s, 9-Me). MS *m/e*: 227 (M$^+$). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.23; H, 3.94; N, 18.64.

9-Methyl-2-methylamino-1,3-dioxo-1,3-dihydropyridazino[3,4-*b*]quinoline (IIIb)——Compound VIb (200 mg) was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave colorless crystals (IIIb) (165 mg, 98%). When a solution of VIb (200 mg) in EtOH (30 ml) was refluxed for 2 hr, and the solution was concentrated *in vacuo* to a small volume, compound IIIb was obtained in 23% yield. Recrystallization from EtOH afforded colorless needles, mp 240—241°. IR ν_{max} cm^{-1}: 3280 (NH), 1770, 1715 (C=O). UV λ_{max} nm (log ε): 212.5 (4.33), 261.5 (4.68). NMR (DMSO-d_6): 8.43—7.63 (4H, m, aromatic), 5.85 (1H, q, J=6 Hz, 2-NHMe), 3.02 (3H, s, 9-Me), 2.60 (3H, d, J=6 Hz, 2-NHMe). MS *m/e*: 241 (M$^+$). *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.43; H, 4.69; N, 17.38.

4-Hydroxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (Ia)——Compound Va (1 g) was pulverized and placed in a flask, then AcOH (100 ml) was added. The solution was heated on a boiling water bath for 3 hr, and then concentrated *in vacuo* to a small volume. H_2O (50 ml) was added, and the crystals that precipitated were collected by suction. Recrystallization from H_2O gave a colorless powder (815 mg, 93%), mp 326° (dec.). IR ν_{max} cm^{-1}: 3150, 3000, 2920 (NH and OH), 1650 (C=O). UV λ_{max} nm (log ε): 216.0 (4.28), 248.5 (4.71), 282.5 (3.93). NMR (DMSO-d_6): 8.67—7.67 (4H, m, aromatic), 3.40 (3H, s, 10-Me). NH and OH protons were not observed because of moisture in the solvent.[2] MS *m/e*: 227 (M^+). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.53; H, 4.01; N, 18.62.

4-Hydroxy-2,10-dimethyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (Ib)——Compound Vb (1 g) was dissolved in AcOH (100 ml). The solution was heated on a boiling water bath for 3 hr, and then evaporated to dryness *in vacuo* to give yellow crystals. These crystals were washed with H_2O and then recrystallized from EtOH to afford yellow needles (800 mg, 95%), mp 239—240°. IR ν_{max} cm^{-1}: 3370 (OH), 1638 (C=O). UV λ_{max} nm (log ε): 215.0 (4.34), 249.0 (4.69), 290.0 (3.98). NMR (DMSO-d_6): 8.67—7.67 (4H, m, aromatic), 3.58 (3H, s, 2-NMe), 3.38 (3H, s, 10-Me). OH proton was not observed because of moisture in the solvent.[2] MS *m/e*: 241 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.94; H, 4.57; N, 17.62.

4-Acetoxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIa)——Compound Va (300 mg) or compound Ia (300 mg) was placed in a flask, and AcOH (30 ml) and Ac_2O (5 ml) were added. The solution was refluxed at 140° for 1 hr. The solvent was evaporated off to leave colorless crystals (VIIa), which were recrystallized from EtOH to give colorless needles (250 mg, 80% from compound Va; 295 mg, 83% from compound Ia), mp 246—247°. IR ν_{max} cm^{-1}: 1762 (acetyl C=O), 1650 (C=O). UV λ_{max} nm (log ε): 228.5 (4.32), 253.5 (4.69), 296.0 (3.87), 340.0 (3.74), 357.5 (3.66). NMR (DMSO-d_6): 12.50 (1H, s, 1-NH), 8.67—7.77 (4H, m, aromatic), 3.39 (3H, s, 10-Me), 2.50 (3H, s, 4-OCOMe). MS *m/e*: 269 (M^+). *Anal.* Calcd for $C_{14}H_{11}N_3O_3$: C, 62.68; H, 3.73; N, 15.66. Found: C, 62.44; H, 4.01; N, 15.83.

4-Acetoxy-2,10-dimethyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIb)——The acetylation procedure was the same as above. The reaction of compound Vb (300 mg) or compound Ib (300 mg) with Ac_2O (5 ml) in AcOH (30 ml) afforded colorless crystals (VIIb). Recrystallization from EtOH provided colorless needles (219 mg, 74% from compound Vb; 267 mg, 76% from compound Ib), mp 196—198°. IR ν_{max} cm^{-1}: 1763 (acetyl C=O), 1650 (C=O). UV λ_{max} nm (log ε): 229.5 (4.30), 254.0 (4.68), 300.0 (3.82), 340.0 (3.77), 360.0 (3.79). NMR (DMSO-d_6): 8.63—7.57 (4H, m, aromatic), 3.70 (3H, s, 2-NMe), 3.37 (3H, s, 10-Me), 2.50 (3H, s, 4-OCOMe). MS *m/e*: 238 (M^+). *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.52; H, 4.60; N, 14.80.

4-Acetoxy-2-acetyl-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-*b*]quinoline (VIIc)——Compound Va (300 mg) or compound Ia (300 mg) was placed in a flask, then AcOH (30 ml), Ac_2O (50 ml), and pyridine (3 ml) were added. The solution was heated on a boiling water bath for 1 hr. Removal of the solvent by evaporation afforded a colorless product. Recrystallization from EtOH gave colorless needles (320 mg, 89% from compound Va; 353 mg, 86% from compound Ia), mp 207—209°. IR ν_{max} cm^{-1}: 1770, 1742 (acetyl C=O), 1682 (C=O). UV λ_{max} nm (log ε): 229.0 (4.24), 255.5 (4.63). NMR (DMSO-d_6): 8.67—7.67 (4H, m, aromatic), 3.30 (3H, s, 10-Me), 2.65 (3H, s, 2-COMe), 2.50 (3H, s, 4-OCOMe). MS *m/e*: 311 (M^+). *Anal.* Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.54; H, 4.23; N, 13.61.

Formation of Compound Va from Compound IIIb——Compound IIIb (200 mg) was dissolved in EtOH (20 ml), and hydrazine hydrate (5 g, excess) was added. The solution was refluxed for 2 hr to precipitate red needles. The solution was concentrated *in vacuo* to a small volume, and compound Va that precipitated was collected by suction (65 mg, 30%).

Formation of Compound Vb from Compound IIIa———The reaction of compound IIIa (200 mg) with methylhydrazine (5 g, excess) in EtOH (20 ml) gave compound Vb (125 mg, 50%).

Reaction of Compound IVc with Guanidine——Na (152 mg) was dissolved in abs. EtOH (30 ml), and guanidine hydrochloride (626 mg, 6.6 mmol) was added. NaCl that deposited was filtered off. Compound IVc (1 g, 3.3 mmol) was added to the filtrate. This solution was refluxed for 3 hr to precipitate 9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline guanidinium salt (VIII) as a colorless powder (186 mg, 21%). IR ν_{max} cm^{-1}: 1700, 1633 (C=O). MS *m/e*: 212 (M^+).

Recrystallization of compound VIII from AcOH gave 9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]-quinoline (IIId) (free from guanidine) as colorless needles, mp 282—284°. IR ν_{max} cm^{-1}: 1770, 1710 (C=O). UV λ_{max} nm (log ε): 213.0 (4.35), 259.0 (4.66). NMR (CF_3COOH–DMSO-d_6): 8.43—7.67 (4H, m, aromatic), 3.10 (3H, s, 9-Me). NH proton was not observed, presumably due to moisture in the solvent. MS *m/e*: 212 (M^+). *Anal.* Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.83; H, 3.86; N, 13.23.

The above filtrate was cooled below 0° to precipitate 2-carboxyl-3-ethoxycarbonyl-4-methylquinoline (IId) (642 mg, 76%). Recrystallization from hexane–acetone gave colorless needles, mp 116—118°. IR ν_{max} cm^{-1}: 1718, 1650 (C=O). UV λ_{max} nm (log ε): 213.0 (4.46), 238.0 (4.62), 287.5 (3.68). NMR (CF_3COOH–DMSO-d_6): 8.47—7.60 (4H, m, aromatic), 4.40 (2H, q, $J=7$ Hz, CH_2), 2.77 (3H, s, 4-Me), 1.37 (3H, t, $J=7$ Hz, Me). OH proton was not observed, presumably due to moisture in the solvent. MS *m/e*: 259 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.68; H, 4.89; N, 5.20.

When a solution of compound IVc (1 g, 3.3 mmol) and guanidine hydrochloride (9.4 g, 99 mmol) in

EtONa (99 mmol)–EtOH (60 ml) was refluxed for 3 hr, compound VIII (450 mg, 51%) and compound IId (300 mg, 36%) were obtained.

Reaction of Compound IVc with Methylguanidine——Methylguanidine hydrochloride (716 mg, 6.6 mmol) was added to a solution of EtONa (6.6 mmol)–EtOH (30 ml), and NaCl that deposited was filtered off. Compound IVc (1 g, 3.3 mmol) was dissolved in this solution, and the whole was refluxed for 3 hr. After the reaction, the solvent was evaporated off *in vacuo* to leave an oily substance, which was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. The column was eluted with $CHCl_3$ to exclude unreacted starting materials. Subsequent elution of the column with $CHCl_3$–EtOH (1 : 2) gave 2,9-dimethyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*b*]quinoline (IIIc) (70 mg, 10%). Recrystallization from EtOH–AcOH gave colorless needles, mp 240—243°. IR ν_{max} cm^{-1}: 1700, 1670 (C=O). UV λ_{max} nm (log ε): 211.0 (4.33), 258.0 (4.71). NMR (DMSO-d_6): 8.43—7.67 (4H, m, aromatic), 3.10 (3H, s, 9-Me), 2.98 (3H, s, 2-Me). MS *m/e*: 226 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.74; H, 4.48; N, 12.37.

Further elution of the column with the same solvent system as above provided 2-carboxyl-3-ethoxycarbonyl-4-methylquinoline (IId) (180 mg, 21%).

Continued elution of the column with the same solvent system afforded 2,3-bisethoxycarbonyl-4-methylquinoline (IIc)[13,14] (300 mg, 32%).

Reaction of Compound IIId with Hydrazines——A solution of compound IIId (200 mg) in EtOH (20 ml) was treated with hydrazine hydrate (5 g, excess), and this solution was refluxed for 2 hr to precipitate compound Va, which was collected by suction (203 mg, 83%).

Compound Vb was obtained (153 mg, 57%) by the reaction of IIId (200 mg) with methylhydrazine (5 g, excess) in EtOH (20 ml).

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