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2,5-Dicarbonyl Sugars: New Intermediates for Synthesising Heterocyclic Rings. II.[1] Synthesis of N-Substituted 5-Oxidopyridazinium Derivatives from 2,5-Diketo-D-gluconate[2]

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2,5-Diketo-D-gluconate (I) (D-*threo*-2,5-hexodiulosonate) reacted with mono substituted hydrazines yielding anhydro 1-substituted 3-hydroxymethyl-5-hydroxypyridazinium hydroxides (IIa—g) which were a type of zwitterionic heterocyclic compounds, relatively unknown. Their structures were confirmed by their microanalytical results and spectroscopic evidences.

The intermediate in the formation of anhydro 3-hydroxymethyl-5-hydroxy-1-phenylpyridazinium hydroxide was obtained.

The structure (VIIc) (tautomeric 5-phenylhydrazone of 4-deoxy-2,5-hexodiulosonate-3-ene) could be substantiated by spectral data.

The formation of IIa—g might be accounted for in terms of mono phenylhydrazone formation, enediol formation, β-hydroxycarbonyl elimination, decarboxylation and cyclization.

It was reported in the previous paper that 2,5-dicarbonyl sugars (5-keto-D-fructose and 2,5-diketo-D-gluconate) reacted with hydrazine hydrate yielding 4(1*H*)-pyridazinone derivatives.[1]

In this report, the preparation and characterization of the products obtained in the reaction of calcium 2,5-diketo-D-gluconate (I) (calcium D-*threo*-2,5-hexodiulosonate) with methyl- and arylhydrazines are described. The present reaction is widely applicable and provides a new synthetic route to a series of N-substituted 5-oxidopyridazinium derivatives.

It was originally expected that the reaction of I with the mono substituted hydrazines would give N-substituted 4(1*H*)-pyridazinone derivatives, as is analogized from the reaction of I with hydrazine.

Treatment of I with methyl- or arylhydrazine in a buffer solution composed of pyridine, acetic acid and water (2: 1: 2), however, gave anhydro 3-hydroxymethyl-5-hydroxy-1-methyl- or arylpyridazinium hydroxides (IIa—g) respectively, in 50—85% yield, accompanied with carbon dioxide liberation.

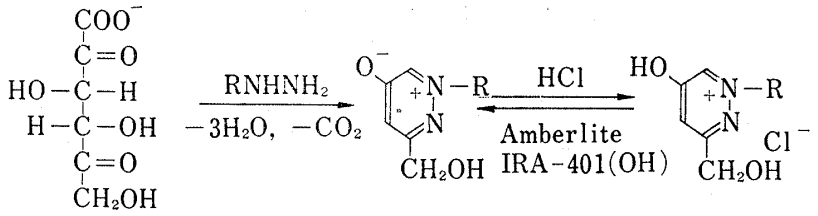
The products are a type of zwitterionic heterocyclic compound. There are apparently only two references in literature reporting syntheses of zwitter ionic pyridazine derivatives.[4,5]

Treatment of IIa,b with HCl gave corresponding hydrochlorides (IIIa,b), respectively.

The structure of the reaction products of I with methyl- and phenylhydrazine were estimated from the products obtained from the reaction of I with hydrazine hydrate[1] and confirmed by their microanalytical results and spectroscopic evidences.

The IR spectrum of IIa showed bands at 3200 (OH), 2830 cm^{-1} (N–CH_3), and 1630, 1600 and 1530 cm^{-1} (oxo–pyridazine ring mode).[6] The infrared (IR) spectrum of IIb showed

1) Part I: K. Imada and K. Asano, *Chem. Pharm. Bull.* (Tokyo), **22**, 1961 (1974).
2) Preliminary communication of this study: K. Imada, *Chem. Commun.*, **1973**, 796.
A part of this work was presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973.
3) Location: *2810, Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) K. Eichenberger, R. Rometsch and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).
5) T. Yamazaki, M. Nagata, F. Nohara and S. Urano, *Chem. Pharm. Bull.* (Tokyo), **19**, 159 (1971).
6) I. Ichimoto, K. Fujii and C. Tatsumi, *Agr. Biol. Chem.*, **31**, 979 (1967).



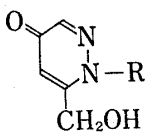
I IIa–g IIIa, b

	products	
R=methyl	IIa	IIIa
R=phenyl	IIb	IIIb
R=*p*-tolyl	IIc	
R=*p*-chlorophenyl	IId	
R=*p*-bromophenyl	IIe	
R=α-naphthyl	IIf	
R=β-naphthyl	IIg	

Chart 1

bands at 3100 cm^{-1} (OH), and 1630, 1600 and 1520 cm^{-1} (oxo–pyridazine ring mode).[6] The compounds (IIa,b) showed no IR absorption corresponding to a carboxyl and carbonyl band.

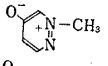
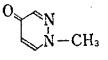
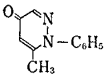
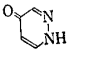
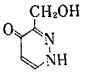
The nuclear magnetic resonance (NMR) spectrum of IIIa showed the presence of two protons of meta-coupling (δ 6.65, 8.27, each 1H, d, J=2.5), $C\underline{H}_2OH$ (δ 4.67, 2H) and $N-CH_3$ (δ 3.53, 3H).[7a,b] The NMR spectrum of IIb showed the presence of two protons of meta-coupling (δ 6.75, 8.50, each 1H, d, J=2.5), $C\underline{H}_2OH$ (δ 4.43, 2H, s) and $N-C_6\underline{H}_5$ (δ 7.40—8.00, 5H, m).[7a] These spectral data remained only two structural possibility of IIa,b or ketonic structure (IV) for their products. However, the structure (IV) was eliminated by ultraviolet (UV) spectral data. Comparison of the UV spectral data with those of authentic 4(1*H*)-pyridazinone derivatives[6,8] and 5-hydroxy-pyridazinium hydroxide[4] are shown in Table I. The UV absorption of



IV : R=CH_3, C_6H_5

Chart 2

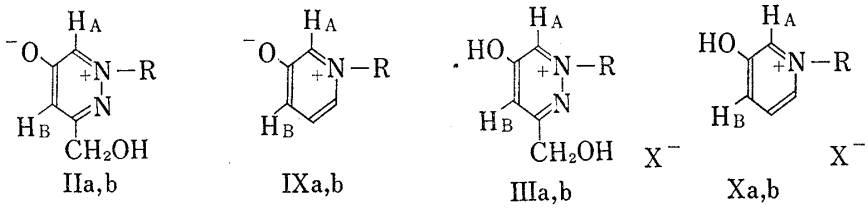
Table I. UV Spectral Data

Solv. / Compds.	2N HCl		EtOH		H_2O		MeOH		1N NaOH	
	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
IIa	235 272	3.53 3.66	258 313	3.79 3.64	257 303	3.89 3.74	258 310	3.81 3.63	255 303	3.85 3.73
IIb	235 285	sh. 4.06	255 325 285	4.30 3.78 sh.	255 315 285	4.30 sh. sh.				
	234 271	3.60 3.64	258 313	3.91 3.62	254 302	3.89 3.64	257 313	3.91 3.62	253 303	3.90 3.65
	252	4.03	269	4.17						
	260	4.06	277	4.24						
	247	3.97	261	4.12						
	250	3.92					267	4.13	248 276	3.97 3.72

7) *a*) Solvent: DMSO-d_6 (+D_2O); *b*) The chemical shifts and coupling constant of IIIa are in a good agreement with those of authentic 5-hydroxy-1-methylpyridazinium hydrochloride.

8) A. Staehelin, K. Eichenberger and J. Druey, *Helv. Chim. Acta*, **39**, 1741 (1956).

TABLE II. NMR Data



IIa,b IXa,b IIIa,b Xa,b

R=Me, Ph

Compounds	R	X	H_A	H_B	N-CH_3	N-C_6H_5
IIa	Me	—	8.27	6.65	3.35	—
IIIa	Me	Cl	9.50	7.92	4.45	—
IXa	Me	—	7.30	6.70	3.73	—
Xa	Me	I	8.63	8.10	4.48	—
IIb	Ph	—	8.50	6.75	—	7.40—8.00
IIIb	Ph	Cl	9.70	8.03	—	7.60—8.10
IXb	Ph	—	7.50	7.08	—	7.50
Xb	Ph	Cl	8.91	8.35	—	7.75

Ph=phenyl

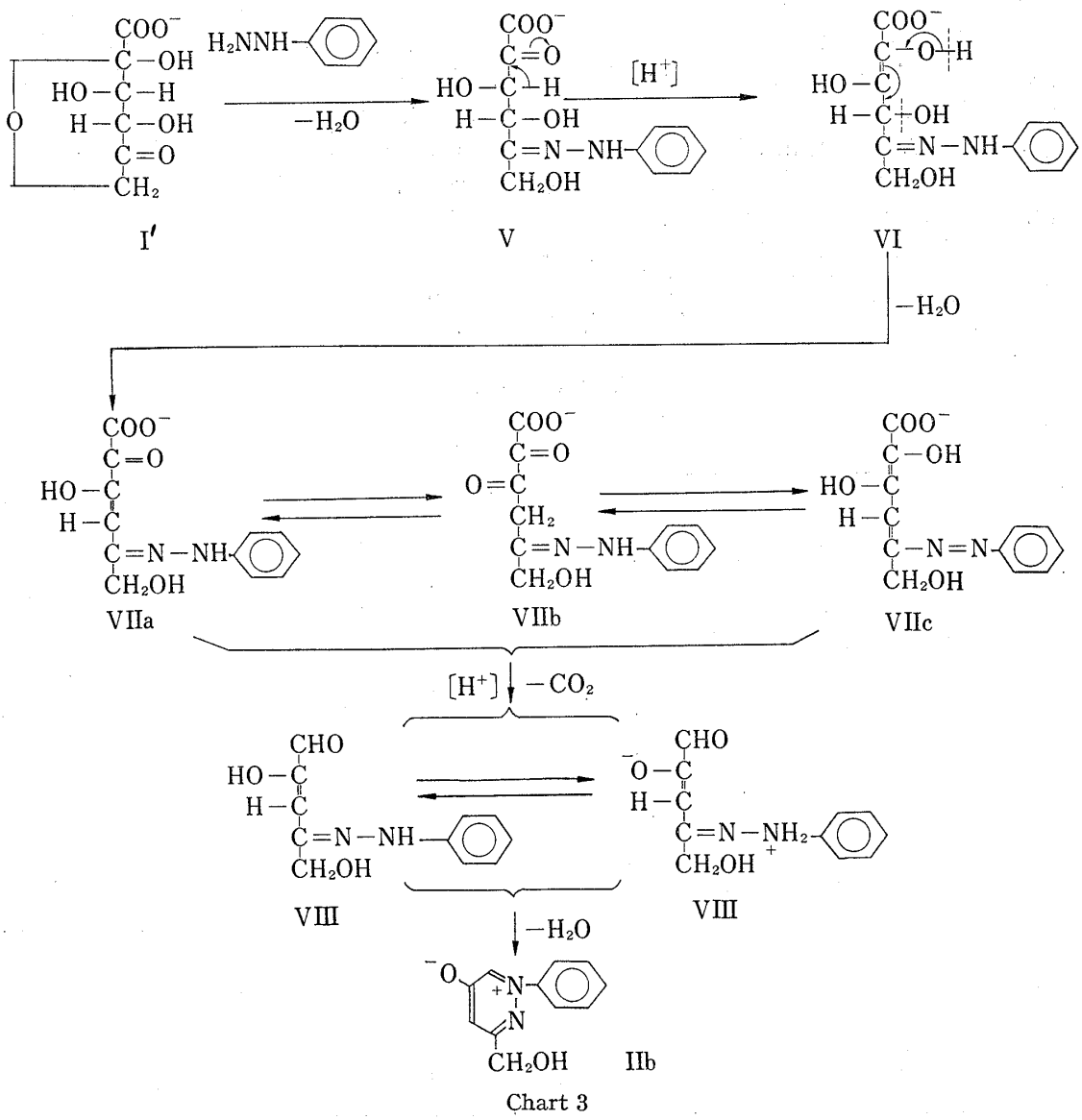


Chart 3

IIa,b were closely similar to those of authentic anhydro 5-hydroxy-1-methylpyridazinium hydroxide and completely different from those of 1-methyl-4(1*H*)-pyridazinone[8] and 1-phenyl-6-methyl-4(1*H*)-pyridazinone.[8]

A comparison of the NMR data for IIa,b and IIIa,b with those for 5-oxidopyridinium betaines and hydrohalides[8,9] is shown in Table II. The NMR spectra of IIa,b show a significant upfield shift for the pyridazine ring protons as compared with those of their hydrochloride, indicating that negative charge from the oxygen atoms is delocalized into the pyridazine ring. The upfield shifts were similar to those between 5-oxidopyridinium betaines and hydrohalides.

Thus the structure (IIa and IIb) were established as anhydro 3-hydroxymethyl-5-hydroxy-1-methyl- and -phenylpyridazinium hydrochlorides, respectively, eliminating the ketonic structure (IV).

The reaction mechanism in the formation of IIb from pyranose form (I′) of 2,5-diketo-D-gluconate and phenylhydrazine, might be proposed as shown in Chart 3. The formation of IIb can be accounted for in terms of mono phenylhydrazone formation, enediol formation,[10] β-hydroxy–carbonyl elimination,[10] decarboxylation and cyclization.

This mechanism can be partially substantiated by the separation of an intermediate which is spontaneously converted into IIb (80% yield) upon treatment with hot aqueous acids.

Treatment of I with phenylhydrazine in pyridine and water containing a small amount of acetic acid at room temperature, gave the intermediate, yellow amorphous, mp 180° (decomp.), in 70% yields along with a small amount (5% yield) of rearranged product (IIb).

The structure of the intermediate was confirmed by its microanalytical result, spectroscopic evidences and by successive acid treatment to yield IIb, to be a tautomeric 5-phenylhydrazone[11] (VIIc) of 4-deoxy-2,5-hexodiulosonate-3-ene (XIa).[12]

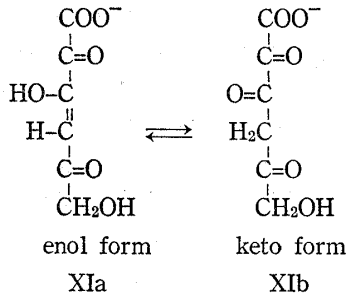


Chart 4

The IR spectrum of VIIc showed bands at 3350 and 1620 cm^{-1} respectively assigned to OH and C=C groups, and at 1570 and 1410 cm^{-1} assigned to COO^- group. No absorption showed in the 1700 cm^{-1} region corresponding to a carbonyl band. The UV absorption of VIIc in water showed at 316.5 mμ characteristic of azo groups.[11,13]

The NMR spectrum of VIIc in D_2O showed two singlets (δ 7.19, 1H and δ 4.72, 2H) and a multiplet (δ 7.30—7.65, 5H) assigned respectively to $-C\underline{H}=$, $-C\underline{H}_2OH$ and $-C_6\underline{H}_5$. All of these spectral data thus consistent with the structure given to VIIc.

However, the observation of the NMR spectrum in DMSO-d_6 suggested that the intermediate may be a mixture composed of VIIa,b,c.

8) A.R. Katrizky and Y. Takeuchi, *J. Chem. Soc.* (*C*), **1971**, 874.
9) Y. Takeuchi, N. Dennis, A.R. Katrizky and I. Taulov, Abstracts of Papers, Second International Congress of Heterocyclic Chemistry, Sendai, Japan, p. 232, and personal communication by Y. Takeuchi.
10) These terms have been proposed for explanation of the formation mechanism of deoxyhexosulose from either aldoses or ketoses. C.D. Hurd and L.L. Isenhour, *J. Am. Chem. Soc.*, **54**, 317 (1932); M.L. Wolfrom, R.D. Schuetz and L.F. Cavalieri, *J. Am. Chem. Soc.*, **70**, 514 (1948); *idem*, *ibid.*, **71**, 3518 (1949).
11) R.H. Wiley and C.H. Jarboe, Jr., *J. Am. Chem. Soc.*, **77**, 403 (1955).
12) Free (XIa) has not yet been obtained from I. XIa may be in tautomeric equilibrium with its keto form, as is analogized from an equilibrium between 3-deoxy-D-*erythro*-hexosulose and 3-deoxy-D-*erythro*-hexos-2-ene. M.L. Wolfrom, "Advances in Carbohydrate Chemistry" Vol. 19, Academic Press, New York, 1964, p. 182.
13) O.H. Wheeler and L.A. Kaplan, "Organic Electronic Spectral Data," Vol. III, Interscience Publisher, A Division of John Wiley & Son, New York, p. 333.

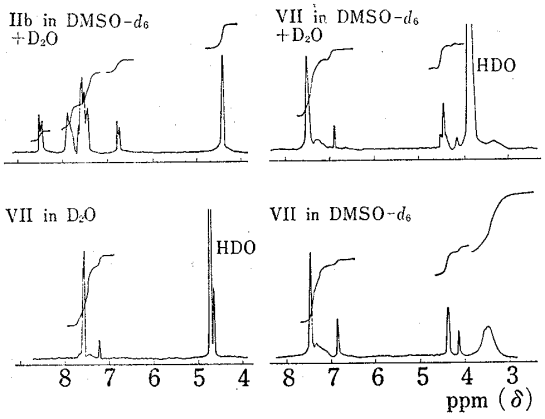


Fig. 1. The NMR Spectra of IIb and VII

This NMR spectrum showed a multiplet (δ 7.0—7.7, 5H) and four singlets (δ 6.89, 0.5H; δ 4.41, 2H; δ 4.15, 0.5H; δ 3.1—3.9, 5H), assigned to $-C_6\underline{H}_5$, $-C\underline{H}=$, $-C\underline{H}_2=$ and O$\underline{H}$,[14] respectively. The singlet at δ 4.15, decreased gradually when D_2O was added, may be attributable to an active methylene of 4-position of VIIb.

These data suggest that the intermediate exsists in aqueous solution as VIIc but in DMSO or probably crystal form, as an equimolar mixture of VIIb and VIIc, or VIIb and VIIa, or of VIIb and VIIa,c.[15]

The first step of the reaction of I with phenylhydrazine must be the formation of mono phenylhydrazone, after which the pyranose ring opens, affording V having a free carbonyl group at 2-position of the hexodiulosonate. The assumed compound (V) may be dehydrated to give VIIa via enolic form VI, as is analogized from the well-known elimination[10] of a hydroxyl group in a position β to a carbonyl group of aldoses or ketoses. Based on the decarboxylation mechanism of α-keto acids[16] and unsaturated α-oxy acids,[16] the intermediate (VIIa,b,c) would be decarboxylated to give the possible aldopentose derivatives (VIII), which may immediately cyclize to afford IIb.

The proposed scheme may also be assumed to apply to the formation of IIa,c—g from I and mono substituted hydrazines (methyl-, *p*-tolyl-, *p*-chlorophenyl-, *p*-bromophenyl-, α-naphthyl- and β-naphthylhydrazine).

The assigned structures of IIc—g were confirmed by the microanalytical results and spectroscopic evidences.

From the reaction of I with *p*-nitro- or 2,4-dinitrophenylhydrazines, corresponding 5-oxidopyridazinium derivatives were not obtained.

Experimental

All melting points were uncorrected. IR, UV and NMR spectra were recorded with a Hitachi EPI-G 2 spectrometer, Hitachi 124 spectrometer and Hitachi 20-B spectrometer, respectively.

1-Methyl-3-hydroxymethyl-5-oxidopyridazinium Hydrochloride (IIIa)——Methylhydrazine (4.6 ml) was added dropwise at room temperature to a stirred solution of I (22.8 g) in a buffer solution (100 ml) composed of pyridine, acetic acid and water (2: 1: 2). The solution was heated at 90—95° for 2 hr, and then evaporated to dryness *in vacuo*. The residue was extracted with hot methanol. The brown syrup obtained by evaporation of the extract, was dissolved in ethanol (50 ml). By addition of 10% HCl–EtOH (40 ml) and ethyl acetate (20 ml), crude crystals of IIIa were obtained which crystallized from EtOH–EtOAc (4: 1) as faintly yellow needles (yield, 9.6 g), mp 176° (decomp.).

1-Methyl-3-hydroxymethyl-5-oxidopyridazinium Hydroxide (IIa)——IIIa (8.8 g) in distilled water (200 ml) was passed through an Amberlite IRA-401 (OH type) column, followed by water until the eluate was neutral. Evaporation of the combined eluate gave IIa (yield 6.3 g).

1-Phenyl-3-hydroxymethyl-5-oxidopyridazinium Hydroxide (IIb)——Phenylhydrazine (10.8 g) was added dropwise to a stirred solution of I (22.8 g) in a buffer solution (100 ml) described above. The solution was heated at 90—95° for 2 hr. The reaction mixture was extracted with hot methanol. Concentration of the extract yielded IIb (10.7 g) as a crude crystal mass which crystallized from MeOH as a white fine needle, (yield 8 g), mp 211° (decomp.).

14) This broad singlet may be assigned to 2 × O$\underline{H}$ of mono hydrate and 3 × (OH or/and NH) of a tautomeric mixture (VIIa,b,c).
15) Further experiments may be required to discuss on these matter.
16) Saul Patai, "The Chemistry of Carboxylic Acids and Esters," Interscience-Publishers, a division of John Wiley & Sons Ltd., New York, p. 591; R.T. Arnold, O.C. Elmer and R.M. Dodson, *J. Am. Chem. Soc.*, **72**, 4359 (1950).

1-Phenyl-3-hydroxymethyl-5-oxidopyridazinium Hydrochloride (IIIb)——A solution of IIb (20.2 g) in 10%HCl–EtOH (40 ml) and EtOH (200 ml) was heated under reflux for 20 min. The reaction mixture was condensed to give a solid mass, which was recrystallized from MeOH affording IIIb as a white fine needle (20 g).

General Procedure for the Syntheses of 1-Aryl-3-hydroxymethyl-5-oxidopyridazinium Hydroxides (IIc—g)——A mixture of I (0.1 mole) and arylhydrazine described in chart 1, in a buffer solution (100 ml) composed of pyridine, acetic acid and water (2: 1: 2), was heated at 90—95° for 2—3 hr. Then the reaction mixture was concentrated to dryness *in vacuo*. The residue was extracted with MeOH. The extract was concentrated to give a crude crystal mass. Recrystallization from a suitable solvent gave the pure sample. Data of IIc—g are summarized in the Table III.

Table III

Compds.	mp[a] (°C)	RS[b]	Yd[c] (%)	$UV_{2N\ HCl}$ λ_{max} (log ε)	IR[d]	Formula	Analyses Calcd. C	H	N	Found C	H	N
IIa	188	M		235(3.53) 272(3.66)	1530 1600 1630	$C_6H_8O_2N_2$	51.42	5.71	20.00	51.02	5.80	19.89
IIIa	176	E–A	54		1490 1520 1590	$C_6H_8O_2N_2 \cdot HCl$	40.80	5.10	15.85	40.55	5.01	15.96
IIb	211	M	53	235(sh) 385(4.56)	1520 1600 1630	$C_{11}H_{10}O_2N_2$	65.35	4.95	13.86	65.79	5.09	13.47
IIIb	176	M–W			1480 1590 1610	$C_{11}H_{10}O_2N_2 \cdot HCl$	55.35	4.61	11.74	55.63	4.68	12.07
IIc	239	M	85	240(sh) 300(4.01)	1500 1585 1600 1610	$C_{12}H_{12}O_2N_2$	66.70	5.56	12.95	66.51	5.63	12.93
IId	245	M	50	211(4.76) 245(s) 290(4.08)	1485 1590	$C_{11}H_9O_2N_2Cl$	55.81	3.81	11.84	56.01	3.89	11.68
IIe	247	E	51	211(4.74) 245(sh) 293(4.39)	1515 1585 1595 1610	$C_{11}H_9O_2N_2Br$	47.00	3.20	9.97	47.34	3.18	9.84
IIf	216	M	71	278(4.04) 314(sh)	1515 1585 1605	$C_{15}H_{12}O_2N_2$	71.42	4.76	11.11	71.14	4.68	10.80
IIg	220	M	67	278(4.24) 314(4.04)	1500 1510 1585 1600 1600	$C_{15}H_{12}O_2N_2$	71.42	4.76	11.11	71.47	4.77	10.76

a) Melting point (decomp.) were not corrected.
b) recrystallizing solvent (RS); M=methanol, E=ethanol, A=ethyl acetate, W=water
c) Yields (Yd) were based on crude product
d) absorption in the 1485—1630 cm^{-1} region

1-Methyl-5-oxidopyridazinium Hydrochloride——A suspension of 4(1*H*)-pyridazinone-3,6-dicarboxylic acid[1] (10 g) in diphenyl ether (50 ml) was heated at 290—300° for 30 min. The reaction mixture was extracted with hot water and the aqueous layer was concentrated to dryness *in vacuo* affording 4(1*H*)-pyridazinone as a crystal mass. Recrystallization from EtOH gave pure 4(1*H*)-pyridazinone as a white hexagonal, mp 250°, which was identical in all respects (IR spectrum and elementary analysis) with authentic sample.[4] A mixture of the product (1.92 g) in absolute EtOH containing Na (0.46 g) and dimethylsulfate (2.1 ml) was heated under reflux for 30 min. After cooling, sodium methylsulfate formed was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in a small amount of water and neutrallized with K_2CO_3 and then extracted with $CHCl_3$. The chloroform solution was dried over Na_2SO_4 and evaporated. The residue was dissolved in EtOH and then 10% HCl–EtOH was added affording a crude crystal mass. Recrystallization from EtOH gave 1-methyl-5-oxidopyridazinium hydrochloride (0.6 g)

as faintly yellow needles, mp 234° (decomp.). *Anal.* Calcd. for $C_5H_6ON_2 \cdot HCl$: C, 40.97; H, 4.78; N, 19.12; Cl, 24.25. Found: C, 40.84; H, 5.08; N, 19.20; Cl, 24.00. IR ν_{max}^{KBr} cm^{-1}: 2840 (N–CH_3), 1625, 1600 and 1510 (oxopyridazine ring mode). NMR (DMSO-d_6, +D_2O) δ: 4.45 (3H, s, N–CH_3), 9.05 (1H, d, J=7.0 Hz, C_3–H), 7.80 (1H, d,d, J=2.5, 7.0 Hz, C_4–H) 9.50 (1H, d, J=2.5 Hz, C_6–H).

Separation of Intermediate (VIIc) in the Formation of IIb——Phenylhydrazine (1.08 g) was added dropwise at room temperature to a stirred solution of I (2.29 g) in a solution composed of pyridine (40 ml), water (40 ml) and acetic acid (2 ml). The solution was allowed to stand for 5 days at room temperature and then evaporated to dryness *in vacuo*. The residue was well washed with cold MeOH (100 ml). Resulting residue was extracted with warmed water (30 ml). The extract was concentrated to dryness *in vacuo*. The residue was chromatographed on avicel (*n*-BuOH: EtOH: H_2O=4: 1: 4). The eluate was evaporated and the residue was recrystallized from H_2O–MeOH (1: 1) to afford yellow amorphous of VII (2.1 g), mp 180° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_5N_21/2Ca \cdot H_2O$: C, 47.90; H, 4.32; N, 9.32. Found: C, 48.39; H, 4.21; N, 8.93. UV $\lambda_{max}^{H_2O}$ mμ(log ε): 316.5 (4.05).

The solution, extracted with cold MeOH (described above), was decolorized and then concentrated to heavy syrup to give a crude crystal of IIb (0.1 g).

IIb from VII——A mixture of VII (3 g) and 1% acetic acid was heated at 50—60° for 1 hr. After evaporating the solvent *in vacuo*, the residue was crystallized from MeOH to yield IIb (2 g) as crude crystals. Recrystallization from MeOH afforded pure IIb as white needles.

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