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Studies on Heterocyclic Compounds. XXII.[1)] The Reaction of Oxazolo[3,2-*b*]pyridazinium Perchlorates with Hydroxylamines[2)]

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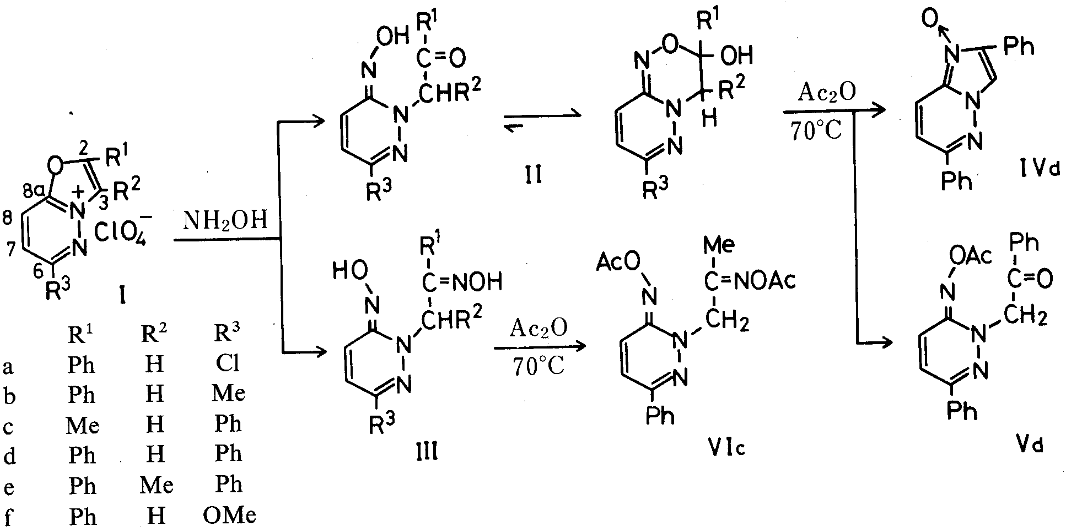
The reaction of oxazolo[3,2-*b*]pyridazinium perchlorates (I) with hydroxylamine hydrochloride and potassium hydroxide in *N*,*N*-dimethylformamide afforded 2-(2,3-dihydro-3-hydroxyimino-2-pyridazinyl)ethanones (II) and 2-(2,3-dihydro-3-hydroxyimino-2-pyridazinyl)-ethanone oximes (III), from both of which imidazo[1,2-*b*]pyridazine 1-oxides (IV) were synthesized by heating in meneral acid. The *N*-oxides were characterized by converting them into the corresponding imidazopyridazines by deoxygenation.

Keywords——oxazolo[3,2-*b*]pyridazinium salt; 2-(2,3-dihydro-3-hydroxyimino-2-pyridazinyl)ethanone; 2-(2,3-dihydro-3-hydroxyimino-2-pyridazinyl)ethanone oxime; 3,4-dihydro-3-hydroxypyridazino[3,2-*c*][1,2,4]oxadiazine; imidazo[1,2-*b*]pyridazine 1-oxide; imidazo[1,2-*b*]-pyridazine; nucleophilic addition

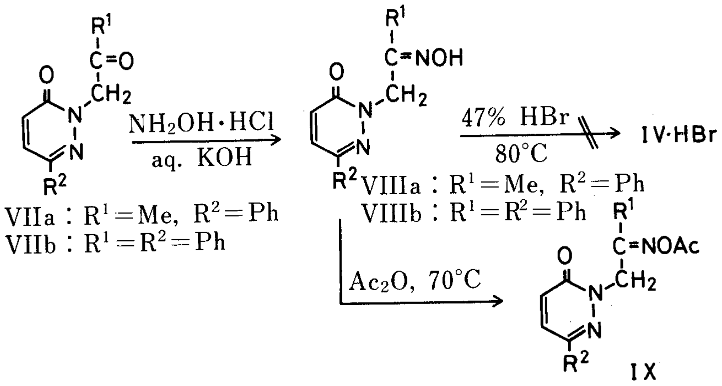
In the course of our studies on the reaction of pi-deficient condensed thiazolium salts with nucleophiles,[1,3-5)] it was found that the reagents attack at the C_2, C_7, C_8, and C_{8a} positions of thiazolo[3,2-*b*]pyridazinium salts[3)] depending upon the class of nucleophiles used. In the case of oxazolo[3,2-*b*]pyridazinium salts (I)[6)] with such nucleophiles as carbanions[6)] and hydrazines,[7)] however, the reagents attack exclusively at C_{8a}, which can be assumed to be the most electron-deficient position of the salts, to afford new ring-transformed products. We have now examined the reaction of the salts (I) with hydroxylamines, which have an ambident character (*N*-nucleophile and *O*-nucleophile).

In the reaction of oxazolo[3,2-*b*]pyridazinium salts (I) with hydroxylamine, two addition products, monoximes (II) and dioximes (III), were obtained. For example, 2,6-diphenyloxazolo[3,2-*b*]pyridazinium perchlorate (Id) was treated with hydroxylamine hydrochloride in the presence of potassium hydroxide in *N*,*N*-dimethylformamide (DMF) at room temperature for 20 h. After purification by silica gel column chromatography, two crystalline products, 1-phenyl-2-(2,3-dihydro-3-hydroxyimino-6-phenyl-2-pyridazinyl)ethanone (IId) and 1-phenyl-2-(2,3-dihydro-3-hydroxyimino-6-phenyl-2-pyridazinyl)ethanone oxime (IIId), were obtained. Treatment of the isolated IId for a longer period of time with hydroxylamine did not give IIId, but the starting material was recovered quantitatively. In the nuclear magnetic resonance (NMR) spectrum of IId, 78% of the methylene protons were observed as two sets of doublets at 3.96 and 4.11 ppm and 22% of the methylene protons as a singlet at 5.45 ppm. The infrared (IR) spectrum of IId showed no bands of the carbonyl group[6)] but exhibited a strong hydroxyl absorption at 3060 cm^{-1} (at 3000—3580 cm^{-1} in chloroform). These spectral data indicated that the major part of the monoxime (IId) was present as 3,4-dihydro-3-hydroxypyridazino[3,2-*c*][1,2,4]oxadiazine, a cyclized hemiketal. The structure of the monoxime (IId) was further confirmed by comparing its ultraviolet (UV) spectrum with that of an alternative monoxime, 1-phenyl-2-(2,3-dihydro-3-oxo-6-phenyl-2-pyridazinyl)ethanone oxime (VIIIb): the ketoxime (VIIIb) prepared from 2-phenacyl-3-pyridazinone (VIIb) showed a UV absorption maximum at 248 nm (log ε 4.45) in methanol, similar to that of VIIb (λ_{max} 247.5 nm), whereas IId showed an absorption maximum at 268 nm (log ε 4.45) and IIId at 247 (log ε 4.22) and 268 nm (log ε 4.25). The NMR spectrum of VIIIb (two methylene signals and two hydroxyl signals in the ratio of 1 : 4) suggested that VIIIb consisted of both *syn*- and *anti*-oximes. In the case of the dioxime (IIId), the NMR spectrum shows a methylene signal as a singlet and two hydroxyl signals as two singlet peaks. However, IIIc shows two methylene signals at 4.60 and 4.80 ppm and two pairs of hydroxyl signals at 9.33 and 9.43 ppm and 10.73 and 10.68 ppm, respectively, in the ratio of 72 : 28. In the case of IIIa, b, the presence of two isomeric oximes could not be detected in the NMR spectra. The reaction of the quaternary salts (Ia—f) with hydroxylamine proceeded in a manner similar to that of Id to give the results shown in Table I. Even in the case of Ia (R^3=Cl) and If (R^3=OMe), hydroxylamine attacked at the C_{8a} position and no displacement reaction of the C–Cl bond was observed.



	R^1	R^2	R^3
a	Ph	H	Cl
b	Ph	H	Me
c	Me	H	Ph
d	Ph	H	Ph
e	Ph	Me	Ph
f	Ph	H	OMe

Chart 1



VIIa : R^1=Me, R^2=Ph
VIIb : R^1=R^2=Ph

VIIIa : R^1=Me, R^2=Ph
VIIIb : R^1=R^2=Ph

Chart 2

When IId was heated in acetic anhydride at 70 °C for an hour, the monoacetate (Vd) and 2,6-diphenylimidazo[1,2-*b*]pyridazine 1-oxide (IVd) were isolated. The NMR spectrum of Vd showed the methyl signal of an acetoxyl group at 2.12 ppm and the methylene signal at 5.59 ppm as a singlet. The IR spectrum of Vd showed the acetoxyl band (1750 cm^{-1}) and the ketone carbonyl band (1700 cm^{-1}). The above spectral data ruled out the possibility that Vd was the *O*-acetyl derivative of the cyclized oxadiazinopyridazine. When IId was heated in acetic anhydride at 80 °C, the *N*-oxide (IVd) was the only product. On acetylation of the dioxime (IIIc) in the same manner, the acetate (VIc) was isolated.

Table I. Reaction Products II and III Prepared from the Quaternary Salts (I)

No.	mp (°C)	Appearance	Yield (%)	NMR δ (DMSO-d_6)		IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}		
				CH$_2$ $\left\{\begin{matrix}\text{q (\%)}\\ \text{s (\%)}\end{matrix}\right.$	OH			
IIa	123—124	Yellow needles	25	3.93 (78) 5.33 (22)	7.30	3080	1560	930 920
IIb	140—142	Yellow flakes	52	3.87 (86) 5.26 (14)	7.04	3060	1570	930
IId	177—180	Yellow plates	38	4.04 (78) 5.45 (22)	7.22	3060	1560	930 920
IIe	209—210	Yellow prisms	56	4.22 (m)	7.15[a]	3050	1555	945 928
IIf	179—180	Yellow needles	65	3.89 (94)[b] 5.15 (6)	7.00	3100	1570	930
IIIa	159—162	Orange needles	36	4.91 (s)	9.56 11.50	3340	1650 1580	960 938 930
IIIb	178—179	Orange needles	10	4.96 (s)	9.10 11.43	3400	1655 1590	960 938 930
IIIc	167—168	Orange needles	61	4.60 (s)	9.33 10.73	3270	1655 1600	940 900
IIId	183—184	Orange red needles	16	5.12 (s)	9.40 11.55	3300	1645 1590	950 935

a) Doublet, $J = ca.$ 4 Hz. *b)* Multiplet.

Table II. Analytical Data for II and III

No.	Formula	Analysis (%) Calcd (Found)		
		C	H	N
IIa	$C_{12}H_{11}ClN_4O_2$	51.72 (52.07	3.98 3.91	20.10 20.29)
IIb	$C_{13}H_{13}N_3O_2$	64.18 (64.43	5.39 5.24	17.28 17.26)
IId	$C_{18}H_{15}N_3O_2$	70.80 (70.73	4.95 4.86	13.76 13.82)
IIe	$C_{19}H_{17}N_3O_2$	71.45 (71.11	5.37 5.32	13.17 12.92)
IIf	$C_{13}H_{13}N_3O_3$	60.22 (60.36	5.05 5.24	16.21 16.15)
IIIa	$C_{12}H_{11}ClN_4O_2$	51.72 (52.07	3.98 3.91	20.10 20.29)
IIIb	$C_{13}H_{14}N_4O_2$	60.45 (60.62	5.46 5.45	21.70 21.58)
IIIc	$C_{13}H_{14}N_4O_2$	60.45 (60.75	5.46 5.71	21.70 21.53)
IIId	$C_{18}H_{16}N_4O_2$	67.48 (67.24	5.03 4.98	17.49 17.46)

TABLE III. The Hydrobromides of Imidazo[1,2-*b*]pyridazine 1-Oxides (IV)

IV·HBr	R^1	R^2	R^3	mp (°C)	Yield (%)[a]	NMR (δ)[b]			IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}		
						C_3–H	C_7–H	C_8–H[c]			
a	Ph	H	Cl	205—207	81	9.25	8.00	8.74	2400	1570 1490	1240 1190
b	Ph	H	Me	210—211	76	9.22	7.90	8.70	2400	1578 1490	1240 1205
c	Me	H	Ph	185—186	70[d]	8.62	8.40	8.70	2500	1590 1480	1220 1200
d	Ph	H	Ph	205—206	83	9.47	8.57	8.86	2400	1575 1485	1240 1208
e	Ph	Me	Ph	188—190	78	2.75[e]	8.49	8.76	2480	1585 1575 1485	1240 1200
f	Ph	H	OMe	192—193	74	9.04	7.58	8.54	2400	1590 1490	1245 1200

a) From II. *b*) Solvent: DMSO-d_6. *c*) $J_{7,8}=ca.$ 10 Hz. *d*) From III. *e*) C_3–CH_3.

TABLE IV. Analytical Data for IV·HBr

No.	Formula	Analysis (%) Calcd (Found)		
		C	H	N
a	$C_{12}H_9BrClN_3O$	44.13 (44.26	2.78 2.71	12.87 12.88)
b	$C_{13}H_{12}BrN_3O$	51.00 (51.24	3.95 3.88	13.73 13.73)
c	$C_{13}H_{14}BrN_3O_2$	48.17 (48.47	4.36 4.37	12.97 12.98)
d	$C_{18}H_{14}BrN_3O$	58.72 (58.59	3.83 3.93	11.41 11.29)
e	$C_{19}H_{16}BrN_3O$	59.83 (59.77	4.23 4.20	11.02 10.93)
f	$C_{13}H_{12}BrN_3O_2$	48.46 (48.60	3.76 3.68	13.04 13.42)

TABLE V. Imidazo[1,2-*b*]pyridazine 1-Oxides (IV)

IV	R^1	R^2	R^3	mp (°C)	Yield[a] (%)	NMR δ (CD_3OD)			IR $\nu_{\max}$ (cm^{-1})
						C_3–H (s)	C_7–H (d)	C_8–H[b]	
a	Ph	H	Cl	214—215 (dec.)	51	8.40	7.33	8.27	1255
b	Ph	H	Me	275—277 (dec.)	56	8.39	7.27	8.13	1250
c	Me	H	Ph	224—225 (dec.)	54	8.06[c]	7.87	8.23	1195 1180
d	Ph	H	Ph	249—250 (dec.)	56	8.42	7.82	8.23	1250
e	Ph	Me	Ph	226—229 (dec.)	51	2.74[d]	7.89	8.28	1230
f	Ph	H	OMe	223—224 (dec.)	50	8.30	7.00	8.10	1260

a) The figures cited are the yields from I through the rapid preparation procedure.
b) $J_{7,8}=ca.$ 10 Hz. *c*) Quartet, $J=1$ Hz. *d*) C_3–CH_3.

Table VI. Imidazo[1,2-*b*]pyridazines (Xa—d)

No.	mp (°C)	Yield (%)	NMR δ ($CDCl_3$)		
			C_3–H	C_7–H[a)]	C_8–H[a)]
a	195—196	76	8.22	7.04	7.91
			8.85	7.40	8.19[b)]
b	157—158	85	8.13	6.83	7.79
c	152—154	70	7.86	7.47	7.95
d	164—165	85	8.31	7.46	8.00

a) $J_{7,8}$ = *ca.* 10 Hz. *b)* Solvent: DMSO-d_6.

Table VII. Analytical Data for IV and X

No.	Formula	Analysis (%) Calcd (Found)		
		C	H	N
IVa	$C_{12}H_8ClN_3O$	58.67	3.28	17.10
		(58.57	3.21	16.83)
IVb	$C_{13}H_{11}N_3O$	69.32	4.92	18.66
		(69.01	4.79	18.90)
IVc	$C_{13}H_{11}N_3O \cdot 1/2H_2O$	66.66	5.16	17.94
		(66.96	5.04	17.74)
IVd	$C_{18}H_{13}N_3O$	75.24	4.56	14.63
		(75.11	4.45	14.68)
IVe	$C_{19}H_{15}N_3O$	75.71	5.02	13.95
		(75.28	5.03	13.72)
IVf	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42
		(65.21	4.56	17.85)
Xa	$C_{12}H_8ClN_3$	62.76	3.51	18.30
		(62.48	3.51	18.27)
Xb	$C_{13}H_{11}N_3$	74.62	5.30	20.08
		(74.69	5.28	20.02)
Xc	$C_{13}H_{11}N_3$	74.62	5.30	20.08
		(74.90	5.16	19.82)
Xd	$C_{18}H_{13}N_3$	79.68	4.83	15.49
		(79.84	4.90	15.73)

Imidazo[1,2-*b*]pyridazine 1-oxides (IV) were also formed by treatment of II, III or VIc with mineral acid such as conc. sulfuric acid, 20% hydrochloric acid or 47% hydrobromic acid. Preparative scale experiments were carried out by heating II or III in 47% hydrobromic acid at 80 °C for half an hour to furnish the hydrobromides of the *N*-oxides (IV) as colorless crystals in 70—80% yields (Table III). These salts were then treated with an aqueous solution of an alkali such as sodium bicarbonate or sodium hydroxide to give the free *N*-oxides (IV). The NMR spectra of IV showed an aromatic methine signal at around 8.2 ppm instead of the methine signal of the starting materials, II and III. The N–O-stretching vibration was observed in the region of 1190—1250 cm^{-1} in the IR spectra[8,9)] (Table V).

The *N*-oxides (IV) can be rapidly prepared by a simplified procedure in onestep from the quaternary salts (I) (see "Experimental"). This procedure constitutes an efficient method for the synthesis of condensed azole *N*-oxides with a bridgehead nitrogen, on which very few articles have been published.[9)]

The deoxygenation of the *N*-oxides (IV) was carried out in the usual way by heating with a slight excess of phosphorus trichloride in chloroform for an hour to furnish the corresponding imidazo[1,2-*b*]pyridazines (X) in good yields (Table VI). The deoxygenated pyridazine (Xc) was identical with the specimen derived from 3-amino-6-phenylpyridazine and chloroacetone.10)

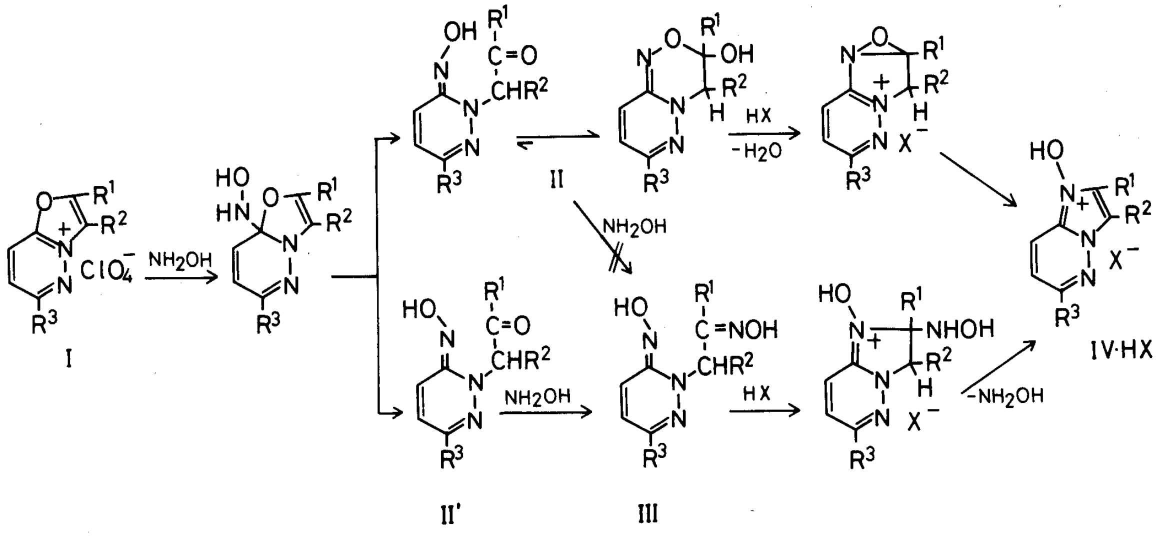
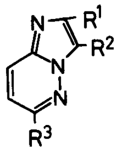


Chart 3

A plausible mechanism for the formation of the *N*-oxides (IV) by the reaction of the quaternary salts (I) with hydroxylamine is shown in Chart 3. Nucleophilic attack of the reagent at the C_{8a} position affords the *syn*-monoxime (II) and the *anti*-monoxime (II′), of which the former is no longer attacked by the reagent. The *syn*-monoxime (II) isomerizes to the intramolecularly cyclized oxadiazinopyridazine followed by dehydration to form the *N*-oxide (IV) on treatment with an acid. The *anti*-monoxime (II′) gives the dioxime (III) through the attack of another molecule of the reagent, and also yields the *N*-oxide (IV) by the elimination of hydroxylamine on treatment with the acid.



X

An attempt to oxidize the imidazo[1,2-*b*]pyridazines (X) with *m*-chloroperbenzoic acid furnished only traces of the *N*-oxides (IV). Thus the newly prepared *N*-oxides (IV) are of interest as possible precursors of physiologically active imidazo[1,2-*b*]pyridazines which have been reported in recent years.11) We believe that our simple procedure for the preparation of the *N*-oxides (IV) offers a new way to approach potentially useful imidazopyridazine derivatives.

Experimental

All melting points were measured in capilally tubes and are uncorrected. The ^{1}H-NMR spectra were measured with a Hitachi R-22 90MC NMR spectrometer and a JNM-FX100 (4167 Hz) spectrometer, using tetramethylsilane (TMS) as an internal reference. The IR and UV spectra were measured on a JASCO IRA-I spectrometer and a Hitachi EPS-3 spectrometer, respectively.

2,6-Diphenyl-3-methyloxazolo[3,2-*b*]pyridazinium Perchlorate (Ie)——This compound was prepared by the method already described,[6] 84% yield, mp 280—281 °C (dec.). *Anal.* Calcd for $C_{19}H_{15}ClN_2O_5$: C, 59.06; H, 3.92; N, 7.25. Found: C, 58.78; H, 3.84; N, 7.11.

General Procedure for the Reaction of Oxazolo[3,2-*b*]pyridazinium Perchlorates (I) with Hydroxylamine. Formation of 2-(2,3-Dihydro-3-hydroxyimino-2-pyridazinyl)ethanones (II) and 2-(2,3-Dihydro-3-hydroxyimino-2-pyridazinyl)ethanone Oximes (III)——KOH (18 mmol) was added to a solution of oxazolo[3,2-*b*]pyridazinium perchlorate (I, 3 mmol) and $NH_2OH \cdot HCl$ (15 mmol) in 15 ml of DMF, and the mixture was stirred for 20 h. KCl precipitated, and was separated by filtration. The filtrate was evaporated *in vacuo* to remove DMF. The residue was chromatographed on a silica gel column (3% MeOH–$CHCl_3$). The first fraction afforded II as yellow crystals and the second fraction gave III as orange crystals. Physical properties and analytical data are shown in Table I and in Table II, respectively.

General Procedure for the Reaction of II or III with 47% Hydrobromic Acid. Formation of the Hydrobromides of Imidazo[1,2-*b*]pyridazine 1-Oxides (IV)——A solution of 100 mg of II or III in 2 ml of 47% HBr was heated at 80 °C for 30 min. The mixture was evaporated to dryness *in vacuo*. Recrystallization from EtOH gave the hydrobromide. Physical properties and analytical data are shown in Table III and in Table IV, respectively.

Reaction of IIIc with 20% Hydrochloric Acid. Formation of IVc——A solution of 200 mg of IIIc in 3 ml of 20% HCl was heated at 80 °C for 1 h. The mixture was poured into ice water and made alkaline with Na_2CO_3. The resultant yellow precipitate was collected by filtration and recrystallized from benzene to give the imidazopyridazine 1-oxide (IVc), 125 mg (69% yield).

Reaction of IId with conc. Sulfuric Acid. Formation of IVd——A solution of 100 mg of IId in 2 ml of conc. H_2SO_4 was allowed to stand at room temperature for 20 h. The mixture was poured into ice water and made alkaline with aqueous NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Recrystallization from EtOH gave imidazopyridazine 1-oxide (IVd), 65 mg (68% yield).

Reaction of IIIc with conc. Sulfuric Acid. Formation of IVc——IVc was prepared by the same procedure as described above. The crude product was recrystallized from benzene to give IVc, in 61% yield.

Acetylation of IId——A solution of IId (150 mg) in 3 ml of acetic anhydride was heated at 70 °C for 1 h. The mixture was poured into ice water to deposit a yellow precipitate, which was collected by filtration. The yellow crystals were chromatographed on a silica gel column (3% MeOH–$CHCl_3$). The first crystalline fraction was recrystallized from benzene–hexane to give 90 mg (53% yield) of the monoacetate of IId as yellow scales, mp 158—159 °C (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1765, 1760, 1700, 1640, 1225. NMR ($CDCl_3$) δ: 2.12 (3H, s), 5.59 (2H, s), 7.33—7.80 (10H, arom), 8.00—8.15 (2H, arom). *Anal.* Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.37; H, 4.81; N, 12.34. The second crystalline fraction was recrystallized from EtOH to give 20 mg (14% yield) of IVd as red needles.

Acetylation of IIIc——A solution of IIIc (100 mg) in 2 ml of acetic anhydride was heated at 70 °C for 1 h. The mixture was poured into ice water to deposit a yellow precipitate, which was collected by filtration and recrystallized from EtOH to give 80 mg (60% yield) of the diacetate of IIIc as yellow needles, mp 144—146 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1780—1760, 1640, 1560, 1380, 1245, 1205. NMR ($CDCl_3$) δ: 2.04 (3H, s), 2.16 (3H, s), 2.19 (3H, s), 4.95 (2H, s), 7.28—7.80 (7H, arom). *Anal.* Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.55; H, 5.53; N, 16.17.

Reaction of 2-Acetonyl-6-phenyl-3(2*H*)-pyridazinone (VIIa) with Hydroxylamine——Method a) KOH (560 mg) was added to a mixture of VIIa (456 mg) and $NH_2OH \cdot HCl$ (690 mg) in 10 ml of H_2O, and the mixture was heated under reflux for 17 h. After cooling, the precipitate was collected by filtration and recrystallized from EtOH to give the oxime (VIIIa) quantitatively as colorless needles, mp 175—176 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3080, 2880, 1660, 1590, 1575. NMR (DMSO-d_6) δ: 1.81 (3H, s), 4.85 (2H, s), 7.05 (1H, d, $J=10$ Hz), 8.03 (1H, d, $J=10$ Hz), 10.75 (1H, s, O$\underline{\text{H}}$). *Anal.* Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.23; H, 5.41; N, 17.56. Method b) KOH (560 mg) was added to a solution of VIIa (456 mg) and $NH_2OH \cdot HCl$ (690 mg) in 10 ml of DMF, and the mixture was stirred at room temperature for 20 h. The precipitate (KCl) was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with a small amount of EtOH and the precipitate was separated by filtration. Recrystallization from EtOH afforded 300 mg (62% yield) of the oxime (VIIIa).

Reaction of 2-Phenacyl-6-phenyl-3(2*H*)-pyridazinone (VIIb) with Hydroxylamine——KOH (560 mg) was added to a mixture of VIIb (580 mg) and $NH_2OH \cdot HCl$ (690 mg) in 10 ml of H_2O, and the whole mixture was heated under reflux for 10 h. After cooling, the precipitate was collected by filtration and recrystallized from EtOH to give the oxime (VIIIb) quantitatively as colorless needles, mp 172—175 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3200, 1660, 1590. NMR (DMSO-d_6) δ: 5.20 (1/5H, s), 5.45 (4/5H, s), 6.96 (1H, d, $J=10$ Hz), 7.90 (1H, d, $J=10$ Hz), 11.10 (1/5H, s, O$\underline{\text{H}}$), 11.58 (4/5H, O$\underline{\text{H}}$). *Anal.* Calcd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.53; H, 4.97; N, 14.06.

Acetylation of VIIIb——A solution of VIIIb (150 mg) in 2 ml of acetic anhydride was heated at 70 °C for 1 h. The mixture was poured into ice water and the resultant white crystals were separated by filtration. Recrystallization from EtOH gave the monoacetate of VIIIb (IX), 135 mg (80% yield), mp 154—155 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1775, 1670, 1600, 1205. NMR ($CDCl_3$) δ: 2.22 (3H, s), 5.64 (2H, s), 6.95 (1H, d, $J=10$ Hz), 7.61 (1H, d, $J=10$ Hz). *Anal.* Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 68.97; H, 4.88; N, 12.23.

General Procedure for the Rapid Preparation of Imidazo[1,2-*b*]pyridazine 1-Oxides (IV)——KOH (18 mmol) was added to a stirred solution of the perchlorate (I, 3 mmol) and $NH_2OH \cdot HCl$ (15 mmol) in 15 ml of DMF, and the mixture was stirred at room temperature for 20 h. The precipitate (KCl) was filtered off and the filtrate was evaporated to dryness *in vacuo*, then 47% HBr (10 ml) was added to the residue and the whole mixture was heated at 80 °C for 30 min. After cooling, the mixture was poured into ice water containing NaOH. The resultant precipitate was collected by filtration and the filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated to dryness *in vacuo*, and the residue was combined with the above crystals. Recrystallization from EtOH or benzene gave the corresponding *N*-oxide (IV) in moderate yields. Physical properties and analytical data are shown in Table V and in Table VII, respectively.

Deoxygenation of Imidazo[1,2-*b*]pyridazine 1-Oxides (IV) with Phosphorus Trichloride——PCl_3 (1.2 eq) in $CHCl_3$ (1 ml) was added to a solution of the *N*-oxide (IV, 200 mg) in 6 ml of $CHCl_3$, and the mixture was heated under reflux for 1 h. After cooling, the mixture was shaken with 10% Na_2CO_3 solution, and the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was recrystallized from benzene–hexane to give the corresponding imidazo[1,2-*b*]pyridazine (X). Physical properties and analytical data are shown in Table VI and in Table VII, respectively.

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References and Notes

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