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Studies on Heterocyclic Compounds. XX.[1] The Reaction of the Oxazolo-[3,2-*b*]pyridazinium Perchlorates with Hydrazines

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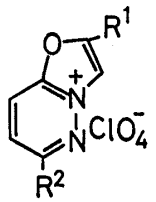
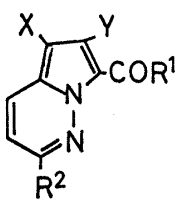
On treatment with hydrazine hydrate (80%) and methylhydrazine, oxazolo[3,2-*b*]-pyridazinium perchlorates (I) furnish hemi-perchlorates of 4*H*-pyridazino[6,1-*c*][1,2,4]-triazines (VI) and 1-methyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazinium perchlorates (VIII), respectively. On reaction with phenylhydrazine by refluxing in acetonitrile, I affords an osazone (XII), a phenylazopyridazine (XIII) and its hydrazo derivative (XIV), which are also formed from *N*-phenylamino-6-chloro-2-phenacyl-2,3-dihydropyridazin-3-ylidene-imine phenylhydrazone (XV) by refluxing with phenylhydrazine in acetonitrile. In the reaction of I with hydrazines, it has been shown that the initial attack of the reagent always occurs at the C_{8a}-position to furnish various condensed pyridazine derivatives.

Keywords——oxazolo[3,2-*b*]pyridazinium salt; 4*H*-pyridazino[6,1-*c*][1,2,4]triazine; 1-methyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazinium perchlorate; imidazo[1,2-*b*]pyridazine; methylglyoxal bis(phenylhydrazone); phenylglyoxal bis(phenylhydrazone); phenylazopyridazine; phenylhydrazopyridazine; nucleophilic addition

In the course of our investigation on the reaction of pi-deficient condensed azolium salts with nucleophiles, the reagents were proved to attack at the C_7-, C_8-, and C_{8a}-positions of thiazolo[3,2-*b*]pyridazinium salts[1,2] depending upon the class of nucleophiles used. However, in the case of oxazolo[3,2-*b*]pyridazinium salts (I), almost all *C*-, *O*-, and *S*-nucleophilies tested were found to attack at the C_{8a}- position, the most electron-deficient position, to furnish new heterocyclic systems. For example, the reaction of I with carbanion gave 3-acylpyrrolo[1,2-*b*]-pyridazine (II).[3] On treatment with hydroxylamine, the salts (I) gave two addition products, a pyridazino[6,1-*c*][1,2,4]oxadiazine (III) and a dioxime (IV), both of which gave an imidazo-[1,2-*b*]pyridazine 1-oxide (V) on being heated in mineral acid.[4]



I



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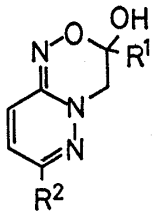

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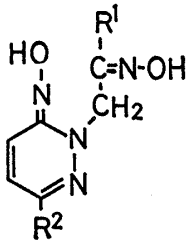
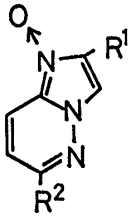


IV

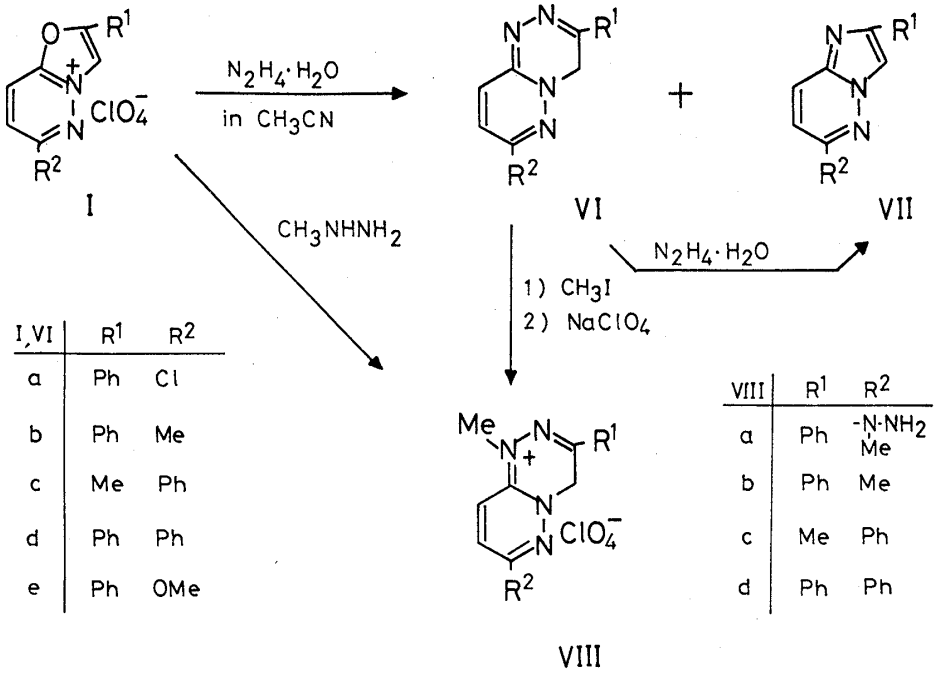


V

We have now examined the reaction mode of the salts (I) with hydrazines, which are simultaneously *N*-nucleophiles and bifunctional nucleophiles.

On reaction of 2-methyl-6-phenyloxazolo[3,2-*b*]pyridazinium perchlorate (Ic) with 5 equivalents of hydrazine hydrate (80%) in acetonitrile at room temperature for 5 h, two products were obtained. Pale yellow crystals, separated from the ethanol-insoluble part, gave analytical data in good agreement with the formula $C_{13}H_{12}N_4 \cdot 1/2HClO_4$. The nuclear magnetic resonance (NMR) spectrum showed a methylene signal at δ 4.88 ppm as a singlet

and methine signals of the pyridazine nucleus at δ 7.44 and 8.13 ppm as an AB quartet. The above results implied a hemi-perchlorate of 4*H*-pyridazino[6,1-*c*][1,2,4]triazine (VIc). White crystals, separated from the ethanol-soluble part, gave analytical data in good agreement with the formula $C_{13}H_{11}N_3$ after purification by column chromatography on silica gel. The NMR spectrum showed two signals at δ 2.57 ppm (–CH=C–C$\underline{H}_3$, J=1 Hz) and at δ 7.86 ppm (CH_3–C=C$\underline{H}$–, J=1 Hz) and methine proton signals at δ 7.47 and 7.95 ppm (pyridazine C_7–$\underline{H}$ and C_8–$\underline{H}$, ABq, J=9 Hz). These data and direct comparison with an authentic sample[5] proved that the structure was 2-methyl-6-phenylimidazo[1,2-*b*]pyridazine (VIIc). Imidazopyridazine (VIIc) was also formed from pyridazinotriazine (VIc), after treatment with excess hydrazine hydrate at room temperature. This suggested that VIIc was formed through VIc as a secondary product of pyridazinotriazine (VIc) (Chart 1).



I, VI	R^1	R^2
a	Ph	Cl
b	Ph	Me
c	Me	Ph
d	Ph	Ph
e	Ph	OMe

VIII	R^1	R^2
a	Ph	$-\underset{\text{Me}}{\overset{}{N}}-NH_2$
b	Ph	Me
c	Me	Ph
d	Ph	Ph

Chart 1

TABLE I. Reaction of I with Hydrazine Hydrate.[a] Formation of VI

VI	R^1	R^2	mp (°C)	Free or HX	React. time (h)	Yield (%)	NMR δ (in DMSO-d_6) 4-C$\underline{H}_2$	C_8–$\underline{H}$	$C_9\underline{H}$[e]	IR ν_{max}^{KBr} cm^{-1} νC=C, C=N		
a	Ph	Cl	160—170[b]	Free	2	31	4.90	6.78	7.10[f,g]	1620	1540	1500
			214—217 (dec.)	$HClO_4$	2	61	5.54	7.80	8.16	1640	1625	1540
			300[c]	HBr	—	—	5.54	7.94	8.23	1640	1625	1540
b	Ph	Me	169—170 (dec.)	Free	—	—	4.97	7.09	7.09	1640	1540	1500
			226—228	$1/2HClO_4$	1.5	83	5.23	7.40	7.63	1630	1540	1495
c	Me	Ph	113—115	Free	—	—	4.56	7.02	7.56	1635	1600	1500
			180—183 (dec.)	$1/2HClO_4$	5	51[d] (65)	4.88	7.44	8.13	1630	1590	1495
			227—229 (dec.)	$HClO_4$	—	—	5.09	7.86	8.15	1630	1555	1545
d	Ph	Ph	173—176	Free	—	—	5.13	7.35	7.73	1630	1520	1495
			198—199	$1/2HClO_4$	2	73	5.42	7.61	8.27	1630	1540	1520
e	Ph	OMe	142—143 (dec.)	Free	—	—	4.87	6.64	7.14[f]	1635	1560	1500
			177—180 (dec.)	$1/2HClO_4$	1.5	66	5.13	7.34	7.60	1650	1575	1550

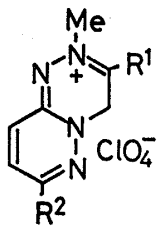
a) 5 Equivalents of $N_2H_4 \cdot H_2O$ were used. *b*) lit. 4): mp 165—167°C (dec.). *c*) lit. 4): mp 320°C. *d*) VI: 51%, VII: 14%. *e*) $J_{8,9}$=*ca.* 10 Hz. *f*) in $CDCl_3$ *g*) lit. 4): 4.93 (4-C$\underline{H}_2$), 6.81 (C_8–$\underline{H}$), 7.11 (C_9–$\underline{H}$).

Table II. Analytical Data for VI

VI	R^1	R^2	Free or HX	Formula	Analysis (%) Calcd (Found) C	H	N
a	Ph	Cl	Free	$C_{12}H_9ClN_4$	58.91	3.71	22.90
					(58.74	3.71	22.79)
a	Ph	Cl	$HClO_4$	$C_{12}H_{10}Cl_2N_4O_4$	41.76	2.92	16.23
					(42.02	2.99	16.71)
a	Ph	Cl	HBr	$C_{12}H_{10}BrClN_4$	44.26	3.10	17.21
					(44.55	3.16	17.53)
b	Ph	Me	Free	$C_{13}H_{12}N_4$	69.62	5.39	24.99
					(69.79	5.36	24.77)
b	Ph	Me	$1/2HClO_4$	$C_{13}H_{12}N_41/2HClO_4$	56.89	4.59	20.41
					(56.97	4.67	20.79)
c	Me	Ph	Free	$C_{13}H_{12}N_4$	69.62	5.39	24.99
					(69.70	5.50	24.50)
c	Me	Ph	$1/2HClO_4$	$C_{13}H_{12}N_41/2HClO_4$	56.89	4.59	20.41
					(57.30	4.58	20.64)
c	Me	Ph	$HClO_4$	$C_{13}H_{13}ClN_4O_4$	48.08	4.04	17.25
					(47.87	4.19	17.45)
d	Ph	Ph	Free	$C_{18}H_{14}N_4$	75.50	4.93	19.57
					(75.29	5.05	19.62)
d	Ph	Ph	$1/2HClO_4$	$C_{18}H_{14}N_41/2HClO_4$	64.23	4.34	16.65
					(63.98	4.56	16.88)
e	Ph	OMe	Free	$C_{13}H_{12}N_4O$	64.98	5.03	23.32
					(64.65	5.11	23.28)
e	Ph	OMe	$1/2HClO_4$	$C_{13}H_{12}N_4O1/2HClO_4$	53.75	4.34	19.30
					(53.71	4.37	19.23)

The perchlorates (Ib, d, e) bearing various kinds of substituents reacted in the same manner with 5 equivalents of hydrazine hydrate in acetonitrile to afford hemi-perchlorates of VIb, d, e (Table I). These hemi-perchlorates gave the free base (VIa—e) as red-orange crystals on shaking with aqueous sodium carbonate or sodium hydroxide solution. The free base (VIc) furnished the corresponding monoperchlorate of VIc as pale yellow crystals on treatment with 70% perchloric acid. In the case of Ia, free base of VIa partly deposited as red crystals and the mono-perchlorate of VIa was obtained as the major product from the filtrate. On reaction of Ic with 1.5 equivalents of hydrazine hydrate in dimethylformamide (DMF) at room temperature, only the mono-perchlorate of VIc was obtained. Even in acetonitrile, the free base of VIc was obtained in 52% yield as red crystals from the reaction mixture. The hydrobromides of compounds VIa and VIb were identical with the corresponding authentic specimens derived from 3-hydrazinopyridazine and α-haloketone by the procedure reported by La Noce *et al.*[6]

When methylhydrazine was used as a nucleophile on the perchlorate (I), 4*H*-pyridazino-[6,1-*c*][1,2,4]triazinium perchlorate (VIII) was obtained. The NMR spectrum of VIIIc showed



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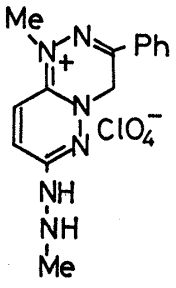
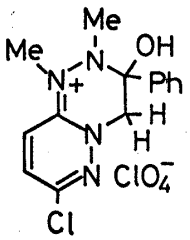


X



XI

Table III. Reaction of I with Methylhydrazine.[a] Formation of VIII

VIII	R^1	R^2	mp (°C)	React. time (h)	Yield (%)	NMR (in DMSO-d_6) δ: N–C<u>H</u>$_3$	4-C<u>H</u>$_2$	C_8–<u>H</u>	C_9–<u>H</u>
a	Ph	–N(NH$_2$)–Me	285—287	20	46	3.26, 3.77	5.33	8.00	8.26
b	Ph	Me	215—216	5	65	3.77	5.53	8.14	8.14
c	Me	Ph	185—186	7	57	3.69	5.13	8.30	8.74
d	Ph	Ph	226—228	5	59	3.89	5.70	8.40	8.80

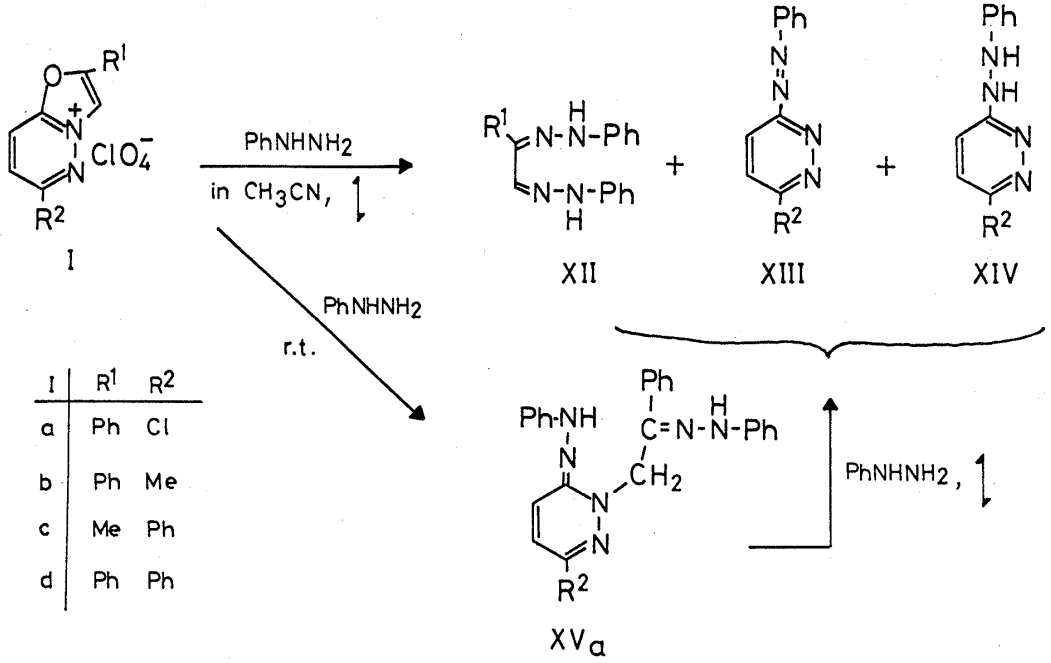
a) 2 Equivalents of CH_3NHNH_2 were used. 3 Equivalents of CH_3NHNH_2 were used in the case of Ia.

Table IV. Analytical Data for VIII

VIII	R^1	R^2	Formula	Analysis. (%) Calcd (Found) C	H	N
a	Ph	–N(NH$_2$)–Me	$C_{14}H_{17}ClN_6O_4$	45.60	4.65	22.79
				(45.54	4.75	22.42)
b	Ph	Me	$C_{14}H_{15}ClN_4O_4$	49.64	4.46	16.54
				(49.34	4.46	16.65)
c	Me	Ph	$C_{14}H_{15}ClN_4O_4$	49.64	4.46	16.54
				(49.35	4.75	16.47)
d	Ph	Ph	$C_{19}H_{17}ClN_4O_4$	56.93	4.28	13.98
				(56.68	4.58	13.86)

signals at δ 3.69 ppm (3H, s, N–C<u>H</u>$_3$) and at δ 5.13 ppm (2H, s, C<u>H</u>$_2$–), indicating an *N*-methyl 4*H*-pyridazino[6,1-*c*]triazinium system. However, the 2-methyl compound (IX), the alternative isomer, could also be produced, depending upon which nitrogen of methylhydrazine attacked first at the C_{8a}-position. When Ia was treated with *N*,*N*′-dimethylhydrazine, 7-chloro-3,4-dihydro-1,2-dimethyl-3-hydroxy-2*H*-pyridazino[6,1-*c*]-triazinium perchlorate (XI) was isolated. The infrared (IR) spectrum of XI showed no absorption band in the frequency region higher than 1638 cm^{-1}. The NMR spectrum exhibited *N*-methyl signals at δ 2.48 and 3.63 ppm, the chemical shift of the latter signal being close to that of the *N*-1 methyl signal of pyridazinotriazinium compounds (VIII: *ca.* δ 3.8 ppm). Methylene signals (δ 4.82 and 5.19 ppm, ABq, J=14 Hz) and a hydroxy proton signal (δ 7.16 ppm) were also observed. From the above data, the 1-methyl compound (VIII) seems to be more reasonable than the 2-methyl compound (IX). Methylation of VId with methyl iodide also gave VIIId, providing further support for the presence of a 4*H*-pyridazino[6,1-*c*]triazine ring system. In the course of the reaction, Ia, having a good leaving group at the C_6-position, suffered another attack of the reagent to give 1-methyl-7-(1-methylhydrazino)-3-phenylpyridazino[6,1-*c*]triazinium perchlorate (VIIIa). The NMR spectrum of VIIIa showed N<u>H</u>$_2$ protons of the methylhydrazino group at the C_7-position at δ 5.13 ppm as a singlet.

On treatment with phenylhydrazine (3 equiv.) at room temperature, the perchlorate (Ia) gave dark purple needles (XVa), mp 140—142°C, almost quantitatively. The analytical data were in good agreement with the formula $C_{24}H_{21}ClN_6$. The IR spectrum [3270 cm^{-1} (νNH)] and the NMR spectrum [δ 5.24 (s, –C<u>H</u>$_2$), 8.47 (s, N<u>H</u>), 10.11 (s, N<u>H</u>)] suggested the structure to be *N*-phenylamino-6-chloro-2-phenacyl-2,3-dihydropyridazin-3-ylidenimine phenylhydrazone. After prolonged treatment with phenylhydrazine at room temperature, Ib—d were recovered unchanged. On treatment with 3 equivalents of phenylhydrazine in refluxing acetonitrile and subsequent separation by silica gel column chromatography, the perchlorate (Ia) gave three compounds: yellow crystals (XIIa), orange crystals (XIIIa) and ivory crystals



I	R^1	R^2
a	Ph	Cl
b	Ph	Me
c	Me	Ph
d	Ph	Ph

Chart 2

(XIVa) (Chart 2). These products were also obtained by heating the dihydrazone (XVa) with phenylhydrazine. These results suggested that the adduct (XVa) was an intermediate in the reaction to give the compounds XIIa, XIIIa and XIVa. The structure of the compound (XIIa) was suggested on the basis of elemental analysis ($C_{20}H_{18}N_4$), the mass (MS) spectrum [*m/e* 314 (M^+), 221 [M^+—93 ($C_6H_5NH_2$)], 91] and the NMR spectrum [δ 8.24 (s, =CH–), 10.74 (s, NH), 12.72 (s, NH), loss of nuclear protons of pyridazine irng] to be the phenylosazone or an alternative structure, tetrahydro-1,2,3,4-tetrazine (XVI; R^1=Ph). As spectral and analytical data of the compound (XIIa) were actually identical with those of the authentic specimen of phenylglyoxal bis(phenylhydrazone), the alternative structure (XVI) was ruled out. Heating the perchlorate (Ic) with 3 equivalents of phenylhydrazine in refluxing acetonitrile for 15 h and subsequent separation by silica gel column chromatography gave three products, XIIc, XIIIc and XIVc. Yellow crystals of XIIc, with the formula $C_{15}H_{16}N_4$, showed a methyl signal (δ 2.13, s), a methine signal (δ 7.62, s) and two NH-protons (each 1H, δ 9.30 and 10.18) in the NMR spectrum.[7] The MS showed a molecular peak (*m/e* 252) and fragment peaks [*m/e* 160 (M^+—92), 93, 92, 91]. The compound (XIIc) was identical with authentic methylglyoxal bis(phenylhydrazone) prepared by the reported method.[8a] Pechmann[8b] reported that colorless crystals of diacetyl bis(phenylhydrazone) prepared from diacetyl and phenylhydrazine were oxidized with potassium dichromate to afford a wine-colored osotetrazine (XVII). Reinvestigation by the present authors gave the same results. The ultraviolet (UV) spectrum of XIIc showed a pattern similar to that of diacetylosazone presented by Engel.[9] An

Table V. Products from the Reaction of I with Phenylhydrazine

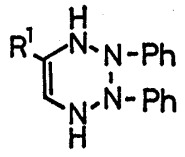
I	R^1	R^2	React. time (h)	XII	R^1	Yield (%)	XIII XIV	R^2	Yield (%) XIII	Yield (%) XIV
a	Ph	Cl	20	a	Ph	70	a	Cl	5	37
b	Ph	Me	19	a	Ph	75	b	Me	13	Trace
c	Me	Ph	15	c	Me	54	c	Ph	5	13
d	Ph	Ph	30	a	Ph	30	c	Ph	23	Trace

Table VI. Physical and Analytical Data for XIII and XIV

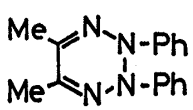
Compd. No.	R^2	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	NMR δ (in $CDCl_3$)	Formula	Analysis (%) Calcd (Found) C	H	N
XIIIa	Cl	119—120	1560 1500 1400	7.70 (1H, d) 7.95 (1H, d) J=10 Hz	$C_{10}H_7ClN_4$	54.94 (55.25	3.23 3.30	25.63 25.45)
XIIIb	Me	119—120	1590 1430	2.83 (3H, s) 7.50 (1H, d) 7.84 (1H, d)	$C_{11}H_{10}N_4$	66.65 (66.66	5.09 5.04	28.27 28.68)
XIIIc	Ph	181—182	1580 1420	7.50—7.70 (6H, arom.) 8.00—8.30 (6H, arom.)	$C_{16}H_{12}N_4$	73.83 (73.37	4.65 4.65	21.53 21.91)
XIVa	Cl	153—154	3280 3210 3040 1600 1500 1418	7.92 (s, NH) 9.11 (s, NH)	$C_{10}H_9ClN_4$	54.43 (54.57	4.11 4.09	25.39 24.98)
XIVc	Ph	162—164	3360 3240 3060 1610 1470	7.20 (1H, d) 7.67 (1H, d)	$C_{16}H_{14}N_4$	73.26 (73.61	5.38 5.66	21.36 21.27)

attempted oxidation of XIIa with potassium dichromate was unsuccessful, and the starting materials were recovered.

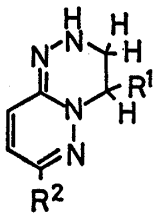
A plausible mechanism for the reaction of the oxazolo[3,2-*b*]pyridazinium salt (I) with hydrazine hydrate and methylhydrazine is shown in Chart 3. Our recent observations on the reaction of thiazolo[3,2-*b*]pyridazinium salt with hydrazine hydrate revealed that initial attack of the reagent occurred at the C_{8a}-position of the salt to afford 2*H*-pyridazino[6,1-*c*]-triazine (XVIII) with elimination of hydrogen sulfide.[10] In the case of oxazolium salts (I), water was eliminated. Presumably, hydrogen sulfide was connected with the formation of XVIII as a redox system in the reaction of thiazolium salts. The formation of VII from VI is also shown in Chart 3. In the course of the reaction of I with hydrazine hydrate, quaternary salts bearing a phenyl group at the C_2-position, such as Ia, b, d, e, gave only trace amounts of imidazopyridazines (VIIa, b, d, e) in addition to VI. A bulky substituent at the C_3-position of VI seems to prevent the attack of another molecule of the reagent.



XVI



XVII



XVIII

A plausible mechanism for the reaction of the perchlorate (I) with phenylhydrazine is shown in Chart 4. Nucleophilic addition of the reagent at the C_{8a}-position and subsequent ring-opening afford the intermediate *N*-phenylamino-2,3-dihydro-2-(2-oxoalkyl)pyridazin-3-ylideneimine (C), which is susceptible to reaction with another molecule of the phenylhydrazine to give the monocyclic dihydrazone (XV) rather than undergoing recyclization to the bicyclic system. Fragmentation of XV by excess reagent seems to proceed as indicated by the solid arrows to give 3-phenyazopyridazine (XIII) and the side chain fragment (XII) through a conventional process of osazone formation. The possibility of bond fission for the direct

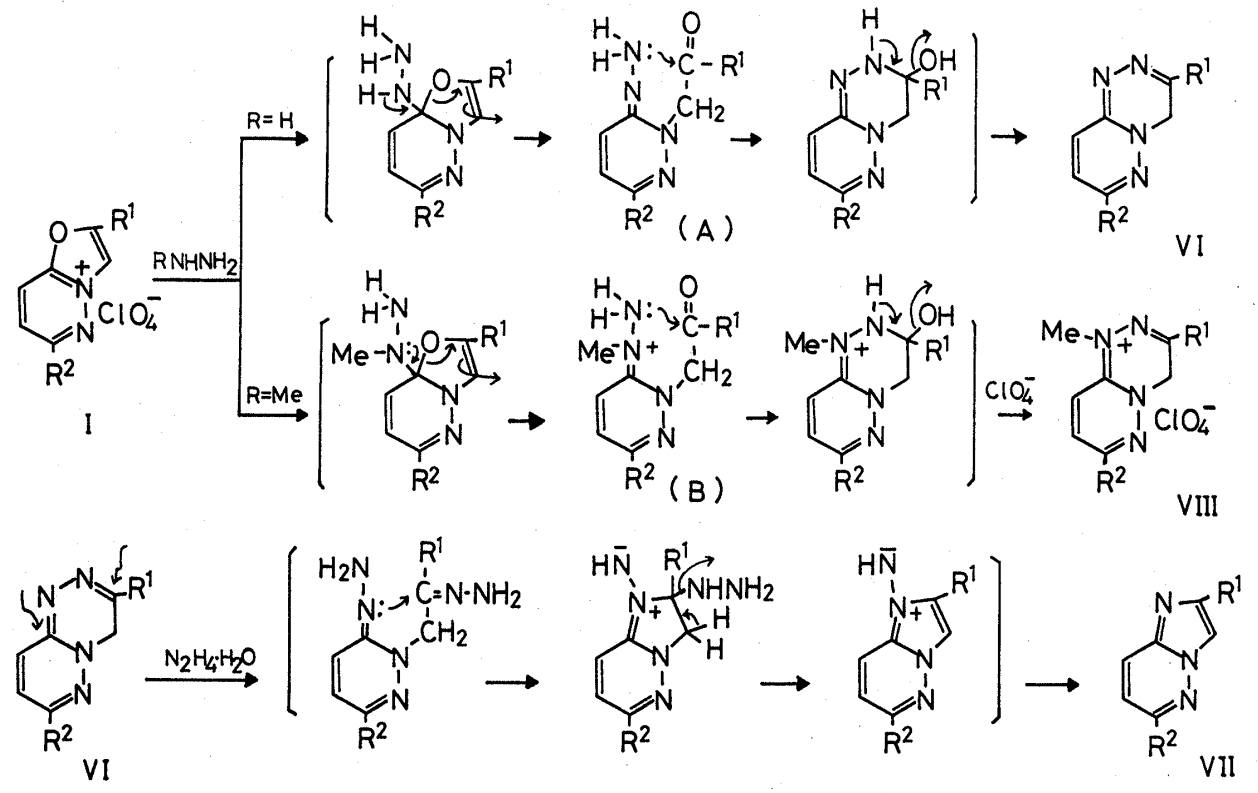


Chart 3

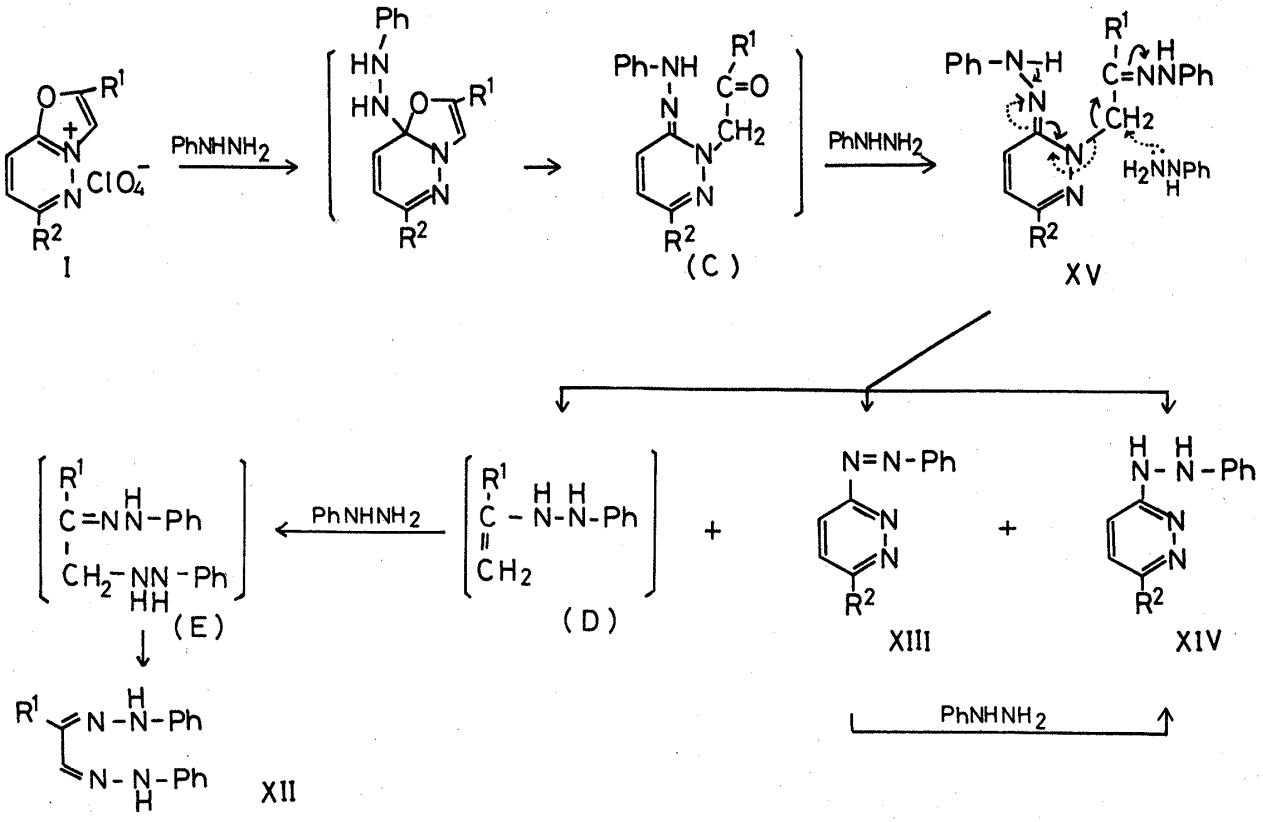


Chart 4

formation of 3-phenylhydrazopyridazine (XIV) as indicated by the dotted arrows cannot be ruled out, although in a separate experiment, heating of XIII with phenylhydrazine in acetonitrile furnished XIV in a quantitative yield.

Among the three ring-opened intermediates A, B and C (Charts 3 and 4), the intermediate (C) underwent fragmentation rather than recyclization probably due to the poor nucleophilicity of the *N*-phenylamino group, which permitted intermolecular attack of the reagent to occur to form the dihydrazone (XV).

Experimental

All melting points were measured in capillary tubes and are uncorrected. The ^{1}H-NMR spectra were measured with a Hitachi R-22 90MC NMR spectrometer, using TMS as an internal reference. The IR and UV spectra were measured with a JASCO IRA-I spectrometer and a Hitachi EPS-3 spectrometer, respectively. Mass spectra were recorded on a JEOL D-300 instrument.

General Procedure for the Reaction of Oxazolo[3,2-*b*]pyridazinium Perchlorate (I) with 80% Hydrazine Hydrate. Formation of 4*H*-Pyridazino[6,1-*c*][1,2,4]triazine (VI) Hemi-perchlorate——To a stirred solution of I (1 mmol) in 10 ml of acetonitrile, 80% hydrazine hydrate (5 mmol) was added at room temperature. The mixture was stirred for 1.5—2 h then concentrated. The residue was crystallized from EtOH to give 4*H*-pyridazino[6,1-*c*]triazine hemi-perchlorate. Physical and analytical data are given in Tables I and II.

Reaction of Ic (R^1=Me, R^2=Ph) with 80% Hydrazine Hydrate. Formation of VIc and 2-Methyl-6-phenylimidazo[1,2-*b*]pyridazine (VIIc)——To a solution of Ic (310 mg, 1 mmol) in 10 ml of CH_3CN, 80% hydrazine hydrate (312 mg, 5 mmol) was added, and the mixture was stirred at room temperature for 5 h. The mixture was evaporated to dryness and a small amount of EtOH was added to the residue. The resultant precipitate was collected by filtration and recrystallized from EtOH to afford light yellow needles of the hemi-perchlorate of VIc, 140 mg (51% yield). The filtrate was chromatographed on SiO_2 with $CHCl_3$ containing 3% MeOH to afford crystals. Recrystallization from benzene–hexane gave 30 mg (14%) of 2-methyl-phenylimidazo[1,2-*b*]pyridazine (VIIc). mp 151.5—153.5°C. IR ν_{max}^{KBr} cm^{-1}: 1540, 1430. NMR (in $CDCl_3$) δ: 2.57 (3H, d, J=*ca.* 1 Hz), 7.47 (1H, d, J=9 Hz), 7.86 (1H, q, J=*ca.* 1 Hz), 7.95 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.90; H, 5.16; N, 19.82. This product showed no melting point depression when mixed with an authentic sample of 2-methyl-6-phenylimidazo[1,2-*b*]-pyridazine and gave an IR spectrum identical with that of the authentic sample. When the above experiment was carried out using 2 equivalents of 80% hydrazine hydrate at room temperature for 25 h, the mono-perchlorate of VIc (28%) and an imidazopyridazine (VIIc) (36%) were obtained.

Reaction of Ic (R^1=Me, R^2=Ph) with 80% Hydrazine Hydrate in DMF——To a solution of Ic (620 mg) in 10 ml of DMF, 80% hydrazine hydrate (190 mg, 1.5 eq) was added, and the mixture was stirred at room temperature for 16 h. After removal of the solvent by evaporation, the residue was triturated with a small amount of EtOH to deposit crystals. Recrystallization from EtOH gave light yellow flakes of the mono-perchlorate of VIc, 330 mg (51%). This was identified by comparing its IR spectrum with that of the specimen which was prepared from VIc with 70% $HClO_4$.

Reaction of Id (R^1=R^2=Ph) with 80% Hydrazine Hydrate in DMF——To a solution of Id (300 mg) in 5 ml of DMF, 80% hydrazine hydrate (250 mg, 5 eq) was added, and the mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was chromatographed on SiO_2 with $CHCl_3$ containing 3% MeOH to afford red crystals. Recrystallization from benzene–hexane gave red-orange needles of VId, 90 mg (39%), mp 173—176°C. This product showed no melting point depression when mixed with the specimen which was prepared from 3,7-diphenylpyridazino[6,1-*c*]triazine (VId) hemi-perchlorate by treatment with Na_2CO_3. Both specimens gave identical IR spectra.

Reaction of VIa with 47% Hydrobromic Acid. Formation of the Hydrobromide of VIa——A solution of VIa (70 mg) in 2 ml of 47% HBr was heated at 80°C for 5 min. The mixture was poured into ice-water and the resultant precipitate was collected by filtration. Recrystallization from EtOH gave yellow needles of the hydrobromide of VIa, 55 mg (59%), mp>300°C. lit. 320°C.[4] The IR and NMR spectra of this product were identical with those of an authentic sample prepared from 6-chloro-3-hydrazinopyridazine with α-bromoacetophenone in refluxing acetic acid.

Reaction of Hemi-perchlorate of VIb with 47% Hydrobromic Acid. Formation of the Hydrobromide of VIb——A solution of the hemi-perchlorate of VIb (80 mg) in 2 ml of 47% HBr was heated at 80°C for 5 min. The mixture was poured into ice-water and the resultant precipitate was collected by filtration. Recrystallization from EtOH gave yellow needles of the hydrobromide of VIb, mp 275—277°C (d). lit. mp 270°C (AcOH).[4]

Reaction of Pyridazino[6,1-*c*]triazine (VIc) with 70% Perchloric Acid. Formation of Mono-perchlorate of VIc——A sample of VIc (100 mg) in 2 ml of 70% $HClO_4$ was heated on a steam bath for a few minutes until it dissolved. The solution was poured into ice-water and the resultant white precipitate was collected by filtration. Recrystallization from EtOH gave light yellow flakes, 80 mg (55%), mp 227—229°C (d).

Reaction of the Hemi-perchlorate of VIc with 80% Hydrazine Hydrate. Formation of 2-Methyl-6-phenylimidazo[1,2-*b*]pyridazine (VIIc)——A mixture of the hemi-perchlorate of VIc (200 mg) and 80% hydrazine hydrate (400 mg) in 10 ml of CH_3CN was stirred at room temperature for 2 d. The mixture was evaporated to dryness and the residue was chromatographed on SiO_2 with $CHCl_3$ containing 3% MeOH to give crystals. Recrystallization from benzene–hexane afforded white needles. This product was identified by comparing its IR spectrum with that of the specimen prepared from Ic by treatment with 80% hydrazine hydrate.

Reaction of Ia (R^1=Ph, R^2=Cl) with 80% Hydrazine Hydrate——To a solution of Ia (331 mg, 1 mmol) in CH_3CN (10 ml), 80% hydrazine hydrate (312 mg, 5 mmol) was added at 10°C, and the mixture was stirred for 2 h. The red crystals that precipitated were collected by filtration. Recrystallization from benzene–hexane afforded 75 mg (31%) of 7-chloro-3-phenylpyridazino[6,1-*c*]triazine (VIa). Five drops of 70% $HClO_4$ were added to the filtrate and the mixture was concentrated to dryness. The residue was crystallized from EtOH to give yellow crystals of 7-chloro-3-phenylpyridazino[6,1-*c*]triazine (VIa) hemi-perchlorate, 210 mg (61%).

General Procedure for the Reaction of Oxazolo[3,2-*b*]pyridazinium Perchlorate (I) with Methylhydrazine. Formation of 1-Methyl-4*H*-pyridazino[6,1-*c*][1,2,4]triazinium Perchlorate (VIII)——To a stirred solution of I (1 mmol) in 10 ml of CH_3CN, methylhydrazine (2 mmol) was added at room temperature. The mixture was stirred for 5 h, then concentrated. A small amount of EtOH was added to the residue, and the precipitated crystals were collected by filtration. Recrystallization from EtOH afforded yellow needles (VIII). Physical and analytical data are given in Tables III and IV.

Methylation of Pyridazino[6,1-*c*]triazine (VId)——Methyl iodide (500 mg) was added to 5 ml of methanolic suspension of VId (100 mg) and the solution was heated under reflux for 4 h, then concentrated. The residue was taken up in a small amount of EtOH. Trituration with 5 drops of a concentrated solution of $NaClO_4$ gave yellow crystals. Recrystallization from EtOH gave yellow needles, 65 mg (47%). The product did not show any melting point depression when mixed with an authentic specimen of VIIId prepared from Id with methylhydrazine. The identity of the product was also confirmed by comparing its IR spectrum with that of the authentic sample.

Reaction of Ia (R^1=Ph, R^2=Cl) with *N*,*N*′-Dimethylhydrazine. Formation of 7-Chloro-3,4-dihydro-1,2-dimethyl-3-hydroxy-2*H*-pyridazino[6,1-*c*][1,2,4]triazinium Perchlorate (XI)——A solution of powdered KOH (672 mg) and *N*,*N*′-dimethylhydrazine dihydrochloride (798 mg) in 20 ml of CH_3CN was stirred at room temperature for 1 h. Potassium chloride separated, and was filtered off, then Ia (500 mg) was added to the filtrate. The reaction mixture was stirred at room temperature for 20 h, then concentrated *in vacuo*. The residue was recrystallized from EtOH to afford yellow crystals (XI), 60 mg (10%), mp 186—187°C (d). IR ν_{max}^{KBr} cm^{-1}: 3380, 3120, 1638, 1560. NMR (in DMSO-d_6) δ: 2.48 (3H, s), 3.63 (3H, s), 4.82 (1H, d, J= 14 Hz), 5.19 (1H, d, J=14 Hz), 7.16 (1H, br s, D_2O-exchangeable), 7.40—7.80 (5H, arom.), 8.17 (2H, s, pyridazine nucleus). *Anal.* Calcd for $C_{14}H_{16}Cl_2N_4O_5$: C, 42.98; H, 4.12; N, 14.32. Found: C, 43.24; H, 4.13; N, 14.23.

General Procedure for Reaction of Oxazolo[3,2-*b*]pyridazinium Perchlorate (I) with Phenylhydrazine——A mixture of I (2 mmol) and phenylhydrazine (6 mmol) in CH_3CN (15 ml) was heated under reflux for 20—30 h. After removal of the solvent by evaporation, the residue was chromatographed on SiO_2 with $CHCl_3$ containing 3% MeOH. The first fraction gave the osazone (XII), which was recrystallized from benzene–hexane. The second fraction gave orange needles of the phenylazopyridazine (XIII) after recrystallization from benzene–hexane. The third fraction gave ivory crystals of the phenylhydrazopyridazine (XIV) after recrystallization from benzene–hexane. Physical and analytical data for XIII and XIV are shown in Table VI.

Reaction of Phenylglyoxal (Monohydrate) with Phenylhydrazine. Formation of XIIa——To a solution of phenylglyoxal (monohydrate) (272 mg) in AcOH (6 ml), phenylhydrazine (432 mg, 2 eq) was added and the mixture was heated under reflux for 30 min, then cooled. The resulting precipitate was filtered off and dried *in vacuo*. The crude yellow crystals (496 mg, 79%) were recrystallized from benzene–hexane to afford yellow needles (XIIa), 453 mg (72%), mp 147—148°C. IR ν_{max}^{KBr} cm^{-1}: 3300, 1605, 1590 (sh), 1540, 1500 (br s), 1280, 1260, 760, 700. NMR (in DMSO-d_6) δ: 8.24 (1H, s), 10.74 (1H, s, NH), 12.72 (1H, s, NH). *Anal.* Calcd for $C_{20}H_{18}N_4$: C, 76.40; H, 5.77; N, 17.82. Found: C, 76.34; H, 5.80; N, 18.10.

Reaction of Monochloroacetone with Phenylhydrazine. Formation of XIIc——Phenylhydrazine (1620 mg, 3 eq) was added to a solution of monochloroacetone (465 mg) in CH_3CN (20 ml), and the mixture was heated under reflux for 5 h. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on SiO_2 with $CHCl_3$ containing 5% MeOH. The major fraction was crystallized from benzene–hexane to afford light yellow needles, 880 mg (70%), mp 147—148°C. The product did not show any melting point depression when mixed with the specimen prepared from Ic with phenylhydrazine, and its identity was also confirmed by comparing the IR spectra. IR ν_{max}^{KBr} cm^{-1}: 3350, 3300, 1600, 1580, 1510, 1495, 1260, 1130, 760. NMR (in DMSO-d_6) δ: 2.13 (3H, s), 7.62 (1H, s), 9.30 (1H, s, NH), 10.18 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.71; H, 6.42; N, 21.81.

Reaction of 3-Phenylazo-6-phenylpyridazine (XIIIc) with Phenylhydrazine. Formation of 3-Phenylhydrazo-6-phenylpyridazine (XIVc)—— A solution of XIII c(30 mg) and phenylhydrazine (30 mg) in 3 ml of

CH_3CN was heated under reflux for 3 h. After removal of the solvent by evaporation, the residue was crystallized from benzene–hexane to give XIVc in quantitative yield. mp 162—164°C.

Reaction of Ia (R^1=Ph, R^2=Cl) with Phenylhydrazine. Formation of XVa——Phenylhydrazine (648 mg, 3 eq) was added to a suspension of Ia (662 mg) in 10 ml of CH_3CN, and the mixture was stirred at room temperature for 24 h. The resultant brown precipitate was collected by filtration. The crude product, obtained in an almost quantitative yield, was recrystallized from benzene–hexane to afford dark purple needles, 770 mg (90%), mp 140—142°C. IR ν_{max}^{KBr} cm^{-1}: 3270, 3060, 2930, 1630 (sh), 1600, 1582, 1570, 1555, 1500, 1450, 1370, 1268, 1160. NMR (in $CDCl_3$) δ: 5.35 (2H, s), (in DMSO-d_6) δ: 5.24 (2H, s), 8.47 (1H, s, D_2O-exchangeable), 10.11 (1H, s, D_2O exchangeable). *Anal.* Calcd for $C_{24}H_{21}ClN_6$: C, 67.20; H, 4.93; N, 19.59. Found: C, 67.39; H, 4.94; N, 19.94.

Oxidation of Diacetyl Bis(phenylhydrazone). Formation of XVII——An aqueous solution of $K_2Cr_2O_7$ (5 ml) was added to a stirred solution of diacetyl bis(phenylhydrazone) (665 mg) in 50% AcOH (4 ml). The mixture was heated at 90°C for 30 min. The precipitate was collected by filtration and the crude product was recrystallized from EtOH to afford dark violet needles, 460 mg (70% yield), mp 159°C. lit. mp 169°C (Acetone or EtOH).[7b] NMR (in $CDCl_3$) δ: 2.60 (3H, s), 7.40—7.65 (3H, arom.), 7.85—8.07 (2H, arom.). IR ν_{max}^{KBr} cm^{-1}: 1465, 1430, 1370, 1115, 770, 680. *Anal.* Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.77; H, 6.24; N, 21.16.

Reaction of XVa with Phenylhydrazine——A solution of XVa (200 mg) and phenylhydrazine (70 mg) in 10 ml of CH_3CN was heated under reflux for 3 h. The solvent was evaporated off, and the residue was chromatographed on SiO_2 with $CHCl_3$ containing 5% MeOH. The first fraction gave the crude osazone (XIIa) in a quantitative yield. It was rechromatographed on SiO_2 with $CHCl_3$ to give 60 mg of XIIc. The second fraction gave the phenylhydrazopyridazine (XIVa) quantitatively.

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References and Notes

1) Part XIX: K. Satoh, T. Miyasaka, and K. Arakawa (the late), *Chem. Pharm. Bull.*, **30**, 35 (1982).
2) *a*) K. Arakawa, T. Miyasaka, and K. Satoh, *Chem. Pharm. Bull.*, **25**, 299 (1977); *b*) K. Satoh, T. Miyasaka, and K. Arakawa, *ibid.*, **25**, 307 (1977).
3) K. Satoh, T. Miyasaka, and K Arakawa, *Yakugaku Zasshi*, **97**, 422 (1977)
4) K Satoh, T. Miyasaka, and K. Arakawa, *Chemistry Letters*, **1977**, 1501.
5) VIIc was prepared from 3-amino-6-phenylpyridazine and chloroacetone.
6) T. La Noce, E. Bellasio, A. Vigevani, and E. Testa, *Ann. Chim.* (Rome), **59**, 552 (1969).
7) O.L. Chapman, R.W. King, W.J. Welstead, Jr., and T.J. Murphy, *J. Am. Chem. Soc.*, **86**, 4968 (1964). [Methylglyoxal bisphenylhydrazone (in DMSO-d_6) δ: 9.28 and 10.22 (solvent-bonded NH), 7.65 (aldimine CH)], [phenylglyoxal bisphenylhydrazone (in DMSO-d_6) δ: 10.90 (solvent-bonded NH), 12.75 (chelate NH), 8.25 (aldimine CH). (in $CDCl_3$) δ: 12.60 (chelate NH), Under aromatic CH (solvent-bonded NH), 7.68 (aldimine CH).
8) *a*) H.v. Pechmann, *Chem. Ber.*, **20**, 2539 (1887); *b*) *Idem*, *ibid.*, **21**, 2751 (1888).
9) L.L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935).
10) K. Satoh and T. Miyasaka, *Chemistry Letters*, **1981**, 1153.