Tetrazolo–Azido Isomerization in Heteroaromatics. I. Syntheses and Reactivities of Some Tetrazolopolyazines[1]

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The tetrazolo–azido transformation for eight model compounds (**3**, **4a–c**, **5–8**) are discussed. The tetrazolo–azido equilibrium in **3a,b** is much influenced by the solvent, but the pyridazine derivatives (**4a–c**) exist entirely as the tetrazoles in various solvents. Compounds **5** and **6** are demonstrated to exist exclusively as the azido form in the solid state because of the destabilization of the fused rings by electron-attracting tetrazolo and triazolo moieties. The tetrazolo–azido equilibrium in *as*-triazine derivatives **7** and **8** is observed in chloroform, but the tetrazolo form is predominant. Photochemical and thermal reactions of **3** give the imidazoles.

The chemistry of heteroaromatic nitrenes has received little attention[2] compared to that of arylnitrenes generated from aromatic azides[3] and aromatic nitro compounds,[4] although several heterocycles bearing an azido group adjacent to the annular nitrogen have been investigated with regard to cyclization to a fused tetrazolo ring in order to establish their structures.[5]

In continuation of our recent studies on the syntheses of bicyclo heteroaromatics such as benzo-1,2,4-triazines, polyazaindolidines, and pyrazolopyridines,[6] this paper presents spectral evidence for tetrazolo–azido isomerizations in some bicyclic tetrazolopolyazines and chemical properties of these systems.

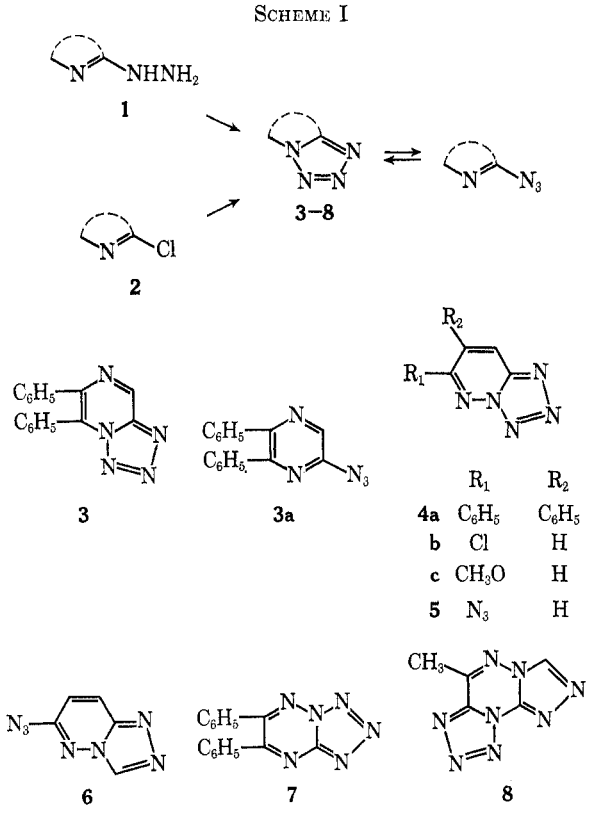
Results and Discussion

Syntheses and Spectral Studies of Tetrazolopolyazines.—The compounds (**3–8**) were synthesized from the corresponding hydrazino compound (**1**) with sodium nitrite and/or the corresponding halogeno compounds (**2**) with sodium azide as shown in Scheme I.

Marked differences in the ir are observed between the solid state and dimethyl sulfoxide solution, and other solutions; azido absorptions in the solid state and DMSO solution are shown by strong bands at 2160 and 2144 cm^{-1} for **5** and **6**, respectively, but are absent for **3**, **4a–c**, **7**, and **8**. In chloroform, tetrahydrofuran, and trifluoroacetic acid solutions, **3**, **5**, and **6** show the strong azido bands at 2145, 2160, and 2144 cm^{-1}, but **7** and **8** indicate only the weak bands at 2160 and 2170 cm^{-1}, respectively. These data are summarized in Table I.

The nmr spectrum of **3** discloses the presence of the tetrazolo–azidoazomethine equilibrium (10:3 ratio) in chloroform solution which is indicated by two singlet signals at τ 0.29 and 1.77. However, in DMSO-d_6, exclusively the tetrazolo tautomer was present as shown by a singlet at τ 0.04; in trifluoroacetic acid only the azido tautomer was present (τ 1.72). These spectral results are in good accordance with observations in 2-azidopyrimidines.[7]

SCHEME I



Since the ir spectra of **4b** and **4c** show no azido absorptions in chloroform, the signals at τ 2.26 and 1.44 for **4b**, and those at τ 2.74 and 1.68 for **4c**, were attributable to the ring protons at C_5 and C_6 of the tetrazolopyridazines. On the other hand, **5** and **6** retain the corresponding azido structures **5a** and **6a** but not tricyclic structures such as **5a** and **6a**, probably because of the destabilization of the fused rings by electron-attracting tetrazolo and triazolo groups, on the basis of the spectral data described above (Scheme II). It is to be noted that the isomerization of 6-azido-7-methyltetrazolo[1,5-*b*]pyridazine to 6-azido-8-methyltetrazolo-[1,5-*b*]pyridazine is demonstrated by means of the nmr spectrum,[8] and the existence of the monocyclic 3-azidopyridazine 1-oxide is explained by the influence with the electron-attracting *N*-oxide group.[9]

The tetrazolo:azido ratios at the equilibrium for **3**, **4b–c**, **5**, and **6** in the various solvents determined by

(1) Part XLIX. Studies on Heteroaromaticity. For part XLVIII see T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc. C*, in press.

(2) For recent reviews, see (a) W. D. Crow and C. Wentrup, *Chem. Commun.*, 1387 (1969); (b) R. Huisgen and K. von Fraunberg, *Tetrahedron Lett.*, 2595, 2599 (1969), and references cited therin.

(3) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966).

(4) R. J. Sundberg, B. P. Das, and R. H. Smith Jr., *J. Amer. Chem. Soc.*, **91**, 658 (1969); R. J. Sundberg and S. R. Suter, *J. Org. Chem.*, **35**, 827 (1970).

(5) For recent brief reviews, see (a) G. L'abbé, *Chem. Rev.*, **69**, 345 (1969); (b) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969), and references cited therin.

(6) (a) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, submitted to *J. Org. Chem.*; (b) T. Sasaki and M. Murata, *Chem. Ber.*, **102**, 3818 (1969).

(7) C. Temple and J. A. Montgomery, *J. Org. Chem.*, **30**, 286 (1965).

(8) Calculation for the temperature dependence of the equilibrium constants in the isomerization of the 7-methyl to the 8-methyl compound gives the values ΔH = −5.9 kcal/mol (at 89 and 94°), and E_a = 20.5 kcal/mol; see ref 5b.

(9) T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)*, **11**, 348 (1963).

TABLE I

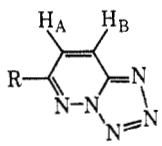
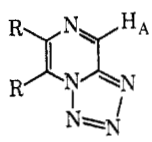
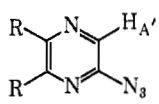
IR SPECTRA OF TETRAZOLOPOLYAZINES

	Absorption bands,[a] cm^{-1}						
	3	**4a**	**4b**	**4c**	**5**	**6**	**7**	**8**
KBr ν_{N_3}					2160	2144		
KBr $\nu_{C=N}$	1530	1610	1615	1612	1609	1605	1580	1627
$CHCl_3$ ν_{N_3}	2145 (s)				2160 (s)	2144 (s)		
							2160 (w)	2170 (w)
THF ν_{N_3}	2150 (s)				2160 (s)	2144 (s)	2160 (w)	2170 (w)
DMSO ν_{N_3}					2160 (s)	2144 (s)		
CF_3COOH ν_{N_3}	2148 (s)				2160 (s)	2144 (s)	2160 (w)	2170 (w)

[a] s = strong, w = weak.

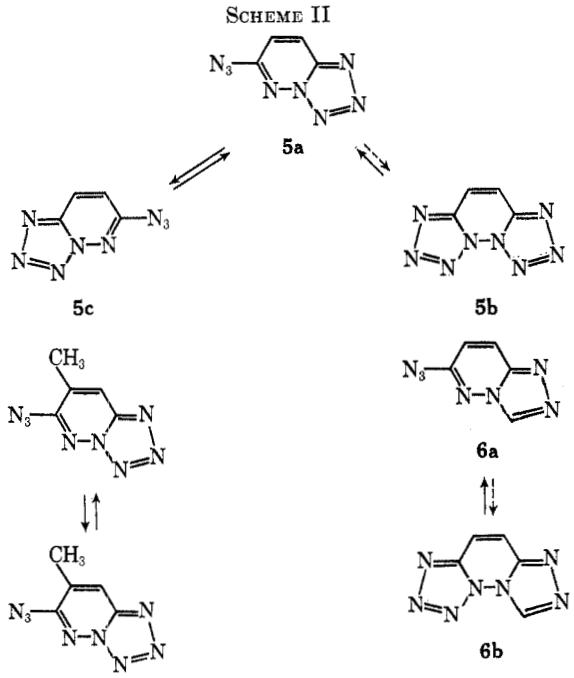
TABLE II

RATIOS OF THE TETRAZOLO–AZIDO EQUILIBRIUM COMPOUNDS IN VARIOUS SOLVENTS BY NMR

Compd no.	Solvent	Concn, w/v %	Azido:tetrazolo ratios	Chemical shifts, τ H_A	$H_{A'}$	H_B	J_{AB}, Hz
3	$CDCl_3$	7	3:10	0.29	1.77		
	DMSO-d_6	8	0:10	0.04			
	CF_3COOH	7	10:0		1.72		
4b	$CDCl_3$	7	0:10	2.26		1.44	9.0
	DMSO-d_6	8	0:10	1.93		1.03	9.0
	CF_3COOH	8	0:10	1.93		1.16	9.0
	CD_3OD	7	0:10	2.11		1.36	9.0
4c	$CDCl_3$	8	0:10	2.74		1.68	9.2
	DMSO-d_6	9	0:10	2.45		1.30	9.2
	CF_3COOH	7	0:10	2.30		1.36	9.2
	CD_3OD	8	0:10	2.61		1.73	9.2
5	$CDCl_3$	10	0:10	2.68		1.49	9.5
6	$CDCl_3$	10	0:10	3.20		1.85	9.5

SCHEME II



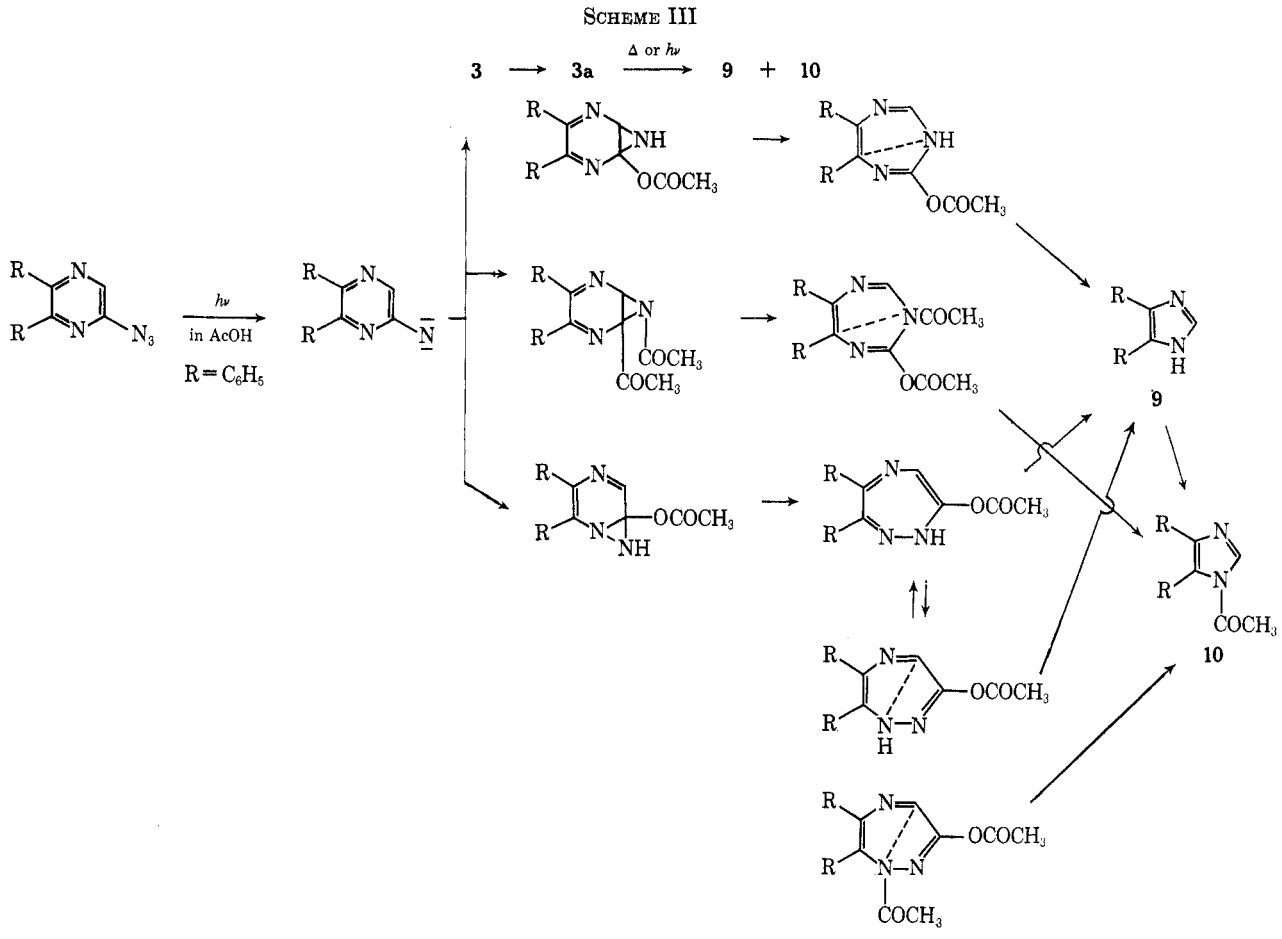
nmr are listed in Table II. In summary, electron-withdrawing substituents appear to be effective not only in destabilizing the electron-attracting tetrazolo ring, but also in stabilizing the electron-donating azido group. In addition to these factors, the stabilization of the tetrazolo and/or the azido form is influenced by the solvent effects.

Chemical Reactivities of Tetrazolopolyazines.—The existence of the reactive tautomeric azido forms in tetrazolopyridine, -pyrimidine, -triazine, and -benzothiazole by the reactions of enamines have been disclosed,[10] and recently Huisgen, *et al.*,[2] reported on the thermal decomposition and the cycloaddition reactions of 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine and tetrazolo[1,5-*a*]pyridine.

Reflux of 7,8-diphenyltetrazolo[1,5-*a*]pyrazine (**3**) in acetic acid for 11 hr afforded two products, **9** (56%) and **10** (13%). Similar treatment of **3** in acetic anhydride containing 14% acetic acid gave also **9** and **10** in 24 and 36% yields, respectively. In contrast to the thermolysis, the photochemical reaction of **3** in acetic acid using a 300-W high-pressure mercury lamp for 32 hr afforded **9** in only 10% yield together with 7% yield of benzoic acid and considerable amounts of recovered **3**. Compound **10**, which was also obtained by the treatment of **9** with acetic anhydride and sodium acetate, shows an ir absorption at 1735 cm^{-1} due to an acetyl group, and the nmr spectrum shows signals at τ 7.74 (3 H, s, $COCH_3$), 2.54, 2.62 (10 H, broad s, $2C_6H_5$), and 1.72 (1 H, s, olefinic proton). On the other hand, **9** shows signals at τ 2.62, 2.82 (10 H, each broad singlet, $2C_6H_5$), and 2.28 (1, H, s, olefinic proton). From this spectral

(10) R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965), and references cited therein.

SCHEME III



and chemical evidence, compounds **9** and **10** were assigned as 4,5-diphenylimidazole and 1-acetyl-4,5-diphenylimidazole, respectively (Scheme III).

The mechanisms for the formation of 4,5-diphenylimidazole (**9**) could be explained by suggesting a nitrene intermediate, which may give rise probably to two kinds of bicyclic intermediates by addition of an acetoxyl group followed by the valence bond isomerization to the triazepine isomers to the imidazole, because of the thermal instability of the bicyclic ring.

By contrast, the mechanisms for the conversions of the pyrazine *N*-oxide to imidazoles have been proposed to proceed *via* the oxazirane intermediate,[11] while, in the case of 2,3-dihydropyrazines, the reaction proceeds *via* the irreversibly formed endiimine intermediate.[12]

Attempts to effect the thermal and photochemical isomerization of the tetrazolopyridazines, **4b** and **4c**, and the tetrazolo-*as*-triazines, **7** and **8**, in acetic acid were unsuccessful even under more drastic conditions, probably because of the absence or low concentration of the azido tautomer even at higher temperatures.

Treatment of **3** with dimethyl acetylenedicarboxylate in chloroform afforded a cycloadduct in 15% yield at 62°. The product was characterized as a triazole derivative **12** by the nmr and ir [1740, 1717 cm^{-1} ($COOCH_3$)]. The analogous reaction of **5** gave **13** in 40% yield but under more drastic conditions (boiling toluene), indicating the existence of the reactive tautomeric azido forms as a function of the temperature (Scheme IV). However, the cycloaddition reaction of **4b** and **4c**, which show no azide form, did not occur even in refluxing toluene or quinoline.

(11) N. Ikekawa and Y. Honma, *Tetrahedron Lett.*, 1197 (1967).
(12) P. Beak and J. L. Miesel, *J. Amer. Chem. Soc.*, **89**, 2375 (1967).

Experimental Section[13]

7,8-Diphenyltetrazolo[1,5-*a*]pyrazine (3).—To a solution of 2-hydrazino-5,6-diphenylpyrazine[14] (0.8 g), acetic acid (16 ml), and ethanol (2 ml) were added sodium nitrite (0.5 g) and water (5 ml) under at 0° for 30 min. The mixture was then stirred for 1 hr. The reaction mixture was poured into water and the precipitated material was filtered. Recrystallization from methanol gave pale yellow needles (0.8 g, 96%): mp 171–173°; $\lambda_{max}^{CHCl_3}$ 250 nm (sh) (log ε 4.18), 270 (4.14), 322 (sh) (3.88); λ_{max}^{EtOH} 248 nm (sh) (log ε 4.18), 275 (4.14), 318 (3.88); $\lambda_{max}^{EtOH\text{-}HCl}$ 290 nm (sh) (log ε 3.81), 324 (3.92).

Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.56; H, 3.97; N, 25.42.

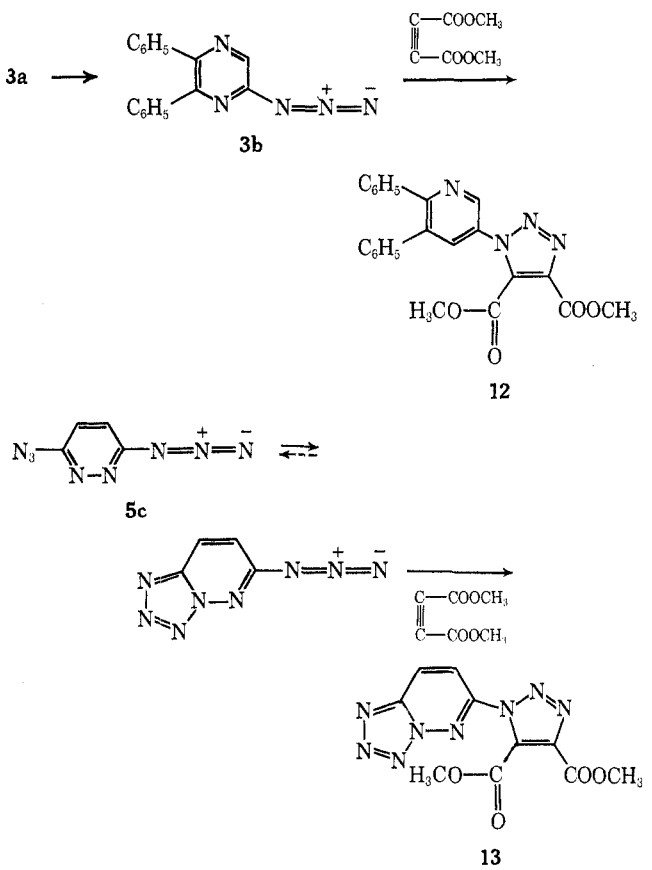
3,4-Diphenyl-6-chloropyridazine.—A solution of 3,4-diphenylpyridazone-6[15] (0.8 g) in phosphorus oxychloride (0.5 ml) was heated on a steam bath for 10 min and the reaction mixture was added to cracked ice water. The precipitated material was dissolved in chloroform, and then water was added to the chloroform solution. The solution was neutralized with aqueous sodium hydroxide (10%) under cooling. The chloroform layer was concentrated *in vacuo*, and the residue was recrystallized from ether to give colorless needles (0.65 g, 75%), mp 111–112°.

Anal. Calcd for $C_{16}H_{11}N_2Cl$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.45; H, 4.02; N, 10.89.

3,4-Diphenyl-6-hydrazinopyridazine.—A mixture of 3,4-diphenyl-6-chloropyridazine (0.65 g), pyridine (2 ml), ethanol (1

(13) The melting points were measured with a Yanagimoto micromelting point apparatus and were uncorrected. Microanalyses were performed on a Yanagimoto CHN-Corder, Model MT-1. The nmr spectra were taken with a JEOLCO, Model JNM-MH-60 nmr spectrometer and with a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ values. The ir spectra were taken with a JASCO Model IR-S spectrophotometer.
(14) P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **27**, 3234 (1962).
(15) G. K. Almström, *Justus Liebigs Ann. Chem.*, **400**, 138 (1913).

SCHEME IV



ml), and 80% hydrazine hydrate (1 ml) was refluxed for 40 min. The solvent was removed *in vacuo* and the residue was poured into cracked ice. The precipitated material was filtered and was recrystallized from the organic solvent such as ethanol, chloroform, and benzene. However, the crystals were hygroscopic and were used in the following reactions without further purification (one spot by tlc).[16]

6,7-Diphenyltetrazolo[1,5-*b*]pyridazine (**4a**).—To 3,4-diphenyl 6-hydrazinopyridazine was added acetic acid (10 ml) and ethanol (2 ml). Then to the solution were added sodium nitrite (0.25 g) and water (0.5 ml) under cooling at 0°, and the reaction mixture was stirred for 2 hr. The precipitate was filtered and recrystallized from methanol to give a colorless powder (0.4 g, 77%): mp 166–167°; $\lambda_{max}^{CHCl_3}$ 244 nm (log ϵ 4.35), 309 (3.78); λ_{max}^{EtOH} 245 nm (log ϵ 4.31), 306 (3.69); $\lambda_{max}^{EtOH\text{-}HCl}$ 243 nm (log ϵ 4.24), 306 (3.66).

Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.33; H, 3.80; N, 25.21.

6-Chlorotetrazolo[1,5-*b*]pyridazine (**4b**).—This compound was prepared by treatment of 3-chloro-6-hydrazinopyridazine with nitrous acid by the method of Takabayashi,[17] mp 108–109° (lit. 107°).

6-Methoxytetrazolo[1,5-*b*]pyridazine (**4c**).—This compound was prepared by the method of Takabayashi,[17] mp 155–157° (lit. 154.5°).

6-Azidotetrazolo[1,5-*b*]pyridazine (**5**).—This compound was prepared by treatment of 3,6-dichloropyridazine and sodium azide by the method of Takabayashi,[17] mp 130–131° (lit. 128–129°).

6-Azido-*s*-triazolo[4,3-*b*]pyridazine (**6**).—A mixture of 6-chloro-*s*-triazolo[4,3-*b*]pyridazine[17] (0.57 g), sodium azide (0.3 g), ethanol (6 ml), and water (6 ml) was refluxed for 18 hr. The solvents were evaporated to dryness, and the resulting mixture was extracted with hot chloroform for several times. The extracted chloroform solution was then evaporated to dryness. The residue was recrystallized from ethanol to give colorless needles (0.45 g, 77%): mp 168–170°; nmr ($CDCl_3$) τ 0.98 (s, H_3), 3.20 (d, H_7, J = 9.5 Hz), 1.85 (d, H_8, J = 9.5 Hz).

Anal. Calcd for $C_5H_3N_7$: C, 37.27; H, 1.88; N, 60.86. Found: C, 37.05; H, 2.01; N, 60.54.

5,6-Diphenyltetrazolo[1,5-*b*]-*as*-triazine (**7**).—This compound was prepared by the method of Takabayashi:[17] mp 201–202° (lit. 198°); $\lambda_{max}^{CHCl_3}$ 249 nm (log ϵ 4.07), 342 (3.82); λ_{max}^{EtOH} 248 nm (log ϵ 4.24), 333 (3.96); $\lambda_{max}^{EtOH\text{-}HCl}$ 240 nm (log ϵ 3.90), 330 (3.76).

4-Methyltetrazolo[1,5-*d*]-*s*-triazolo[4,3-*b*]-*as*-triazine (**8**).—This compound was prepared by the method of Sasaki, *et al.*,[18] mp 185–187°.

Thermal Reaction of Compound 3. A.—A solution of 7,8-diphenyltetrazolo[1,5-*a*]pyrazine (0.5 g) in acetic acid (10 ml) was refluxed in an oil bath for 11 hr. After the reaction mixture was left standing at room temperature for 10 hr, the precipitated crystals (**3**, 0.1 g) were filtered and the filtrate was concentrated *in vacuo*. Purification by chromatography (silic acid) using chloroform as an eluent followed by recrystallization from ethanol gave **9**[19] (mp 235–237°, 0.226 g, 56%) and **10** (mp 153–155°, 0.063 g, 13%).

9: ν_{max} (KBr) 2980 (NH), 1068 cm^{-1} (C=N); τ (CD_3OD) 2.28 (1 H, s), 2.62–2.82 (10 H, multiplet, $2C_6H_5$); λ_{max}^{EtOH} 216 nm (log ϵ 4.10), 252 (3.78), 282 (3.97); mass spectrum M^+ *m/e* 220.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.81; H, 5.25; N, 12.61.

10: ν_{max} (KBr) 1735 cm^{-1} (C=O); nmr τ ($CDCl_3$) 1.72 (1 H, s), 2.54–2.62 (10 H, multiplet, $2C_6H_5$), 7.74 (3 H, CH_3, s); mass spectrum M^+ *m/e* 262.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.55; H, 4.93; N, 10.86.

B.—A solution of **3** (0.6 g) in acetic anhydride (12 ml) and acetic acid (2 ml) was refluxed for 25 hr. Work-up as described above afforded **9** (0.118 g, 24%) and **10** (0.2111 g, 36%).

Photolysis of Compound 3.—A solution of **3** (1.13 g) in acetic acid (400 ml) was irradiated using a high-pressure mercury lamp (300 W) for 32 hr. The solution was concentrated *in vacuo*, and work-up as described above afforded **9** (10%), benzoic acid (7%), and recovered **3** (0.78 g).

1,3-Dipolar Cycloaddition of 3 with Dimethyl Acetylenedicarboxylate.—A mixture of **3** (0.28 g), dimethyl acetylenedicarboxylate (0.15 g), and chloroform (4 ml) was heated at 70° in an oil bath for 15 hr. After cooling, work-up involved filtration, evaporation of the solution, and chromatography (silic acid) of the residue using chloroform as a eluent.

Colorless needles of **12** (0.075 g, 15%), mp 194–196°, were obtained from the eluent: ν_{max} (KBr) 1740, 1717, 1253, 1210, 1170 cm^{-1} ($COOCH_3$).

Anal. Calcd for $C_{22}H_{17}N_5O_4$: C, 63.61; H, 4.13; N, 16.86. Found: C, 63.81; H, 4.00; N, 16.72.

1,3-Dipolar Cycloaddition of 5 with Dimethyl Acetylenedicarboxylate.—A solution of **5** (0.3 g), dimethyl acetylenecarboxylate (0.26 g), and toluene (10 ml) was heated at 120° for 47 hr. The solution was concentrated *in vacuo*, and work-up as described above of the residue afforded **13** (0.23 g, 39%): mp 153–155°; ν_{max} (KBr) 1740, 1710, 1275, 1240 cm^{-1} ($COOCH_3$).

Anal. Calcd for $C_{10}H_8N_8O_4$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.50; H, 2.80; N, 36.59.

Registry No.—**3**, 27062-47-1; **4a**, 27062-48-2; **4b**, 21413-15-0; **4c**, 27062-50-6; **5**, 14393-79-4; **6**, 14393-80-7; **7**, 2762-35-8; **8**, 21119-79-9; **9**, 668-94-0; **10**, 27062-55-1; **12**, 27062-56-2; **13**, 27062-57-3; 3,4-diphenyl-6-chloropyridazine, 27062-58-4.

(16) Thin layer chromatography was carried out on alumina and silica plates by using a benzene–methanol mixture as developing solvents and iodine as a developing reagent.

(17) N. Takabayashi, *Yakugaku Zasshi*, **75**, 1242 (1955).

(18) T. Sasaki, K. Minamoto, and M. Murata, *Chem. Ber.*, **101**, 3969 (1968).

(19) D. Davison, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).