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TETRAZOLO-AZIDO ISOMERIZATION IN HETEROAROMATICS—II[1]

SYNTHESES AND CHEMICAL REACTIVITIES OF TETRAZOLOPYRIDINES[2]

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Abstract—The tetrazolo-azido transformations of four model compounds (**4**, **5**, **6** and **7**) are examined by spectral means. The heats of isomerization as a function of temperature have been determined for **5** and **6** from NMR spectral data. Chemical reactivities of tetrazolo-pyridines with aniline and dimethyl acetylene-dicarboxylate have been examined.

THE CHEMISTRY of heteroaromatic nitrenes has received little attention[3] compared with that of phenyl nitrene, although several N-heterocycles bearing an azido group adjacent to the annular nitrogen have been investigated from their spectral point of view.[4]

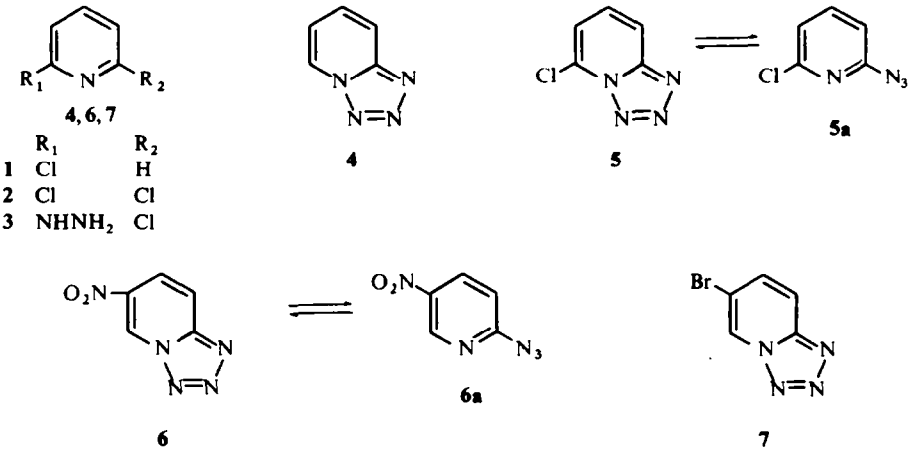
Recently, we reported the tetrazolo-azido transformation, and photochemical and thermal reactions of tetrazolopyrazines, tetrazolopyridazines and tetrazolo-*as*-triazines.[2] While, Wentrup described the isomerizations of tetrazolopyrimidines, tetrazolopyridazines and tetrazolopyridines, and provided evidence for nitrene formation in the gas-phase.[5]

As a continuation of the work, this paper deals with the NMR spectral evidence for tetrazolo-azido isomerization in the pyridine ring and some chemical properties of these systems.

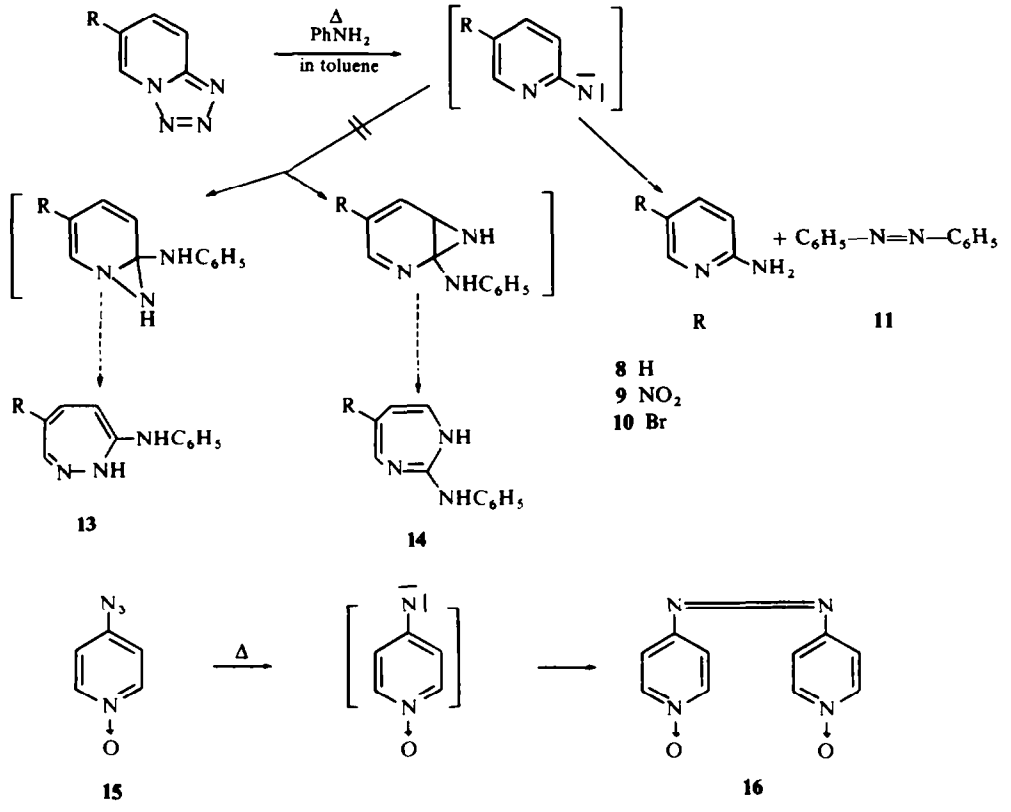
RESULTS AND DISCUSSION

Syntheses and spectral studies of tetrazolopyridines. Tetrazolo[1,5-a]pyridines **4** and **5** were prepared from either the corresponding halogeno compounds and sodium azide in the presence of HCl or the corresponding 2-hydrazinopyridines and $NaNO_2$ by the modified method of Boyer *et al.*[6] Nitration of **4** at 120° gave 6-nitrotetrazolo-[1,5-a]pyridine (**6**) in 90% yield, which was identified by the spectroscopic comparison with a specimen prepared by the unambiguous method[6] from 5-nitro-2-chloropyridine and NaN_3 in HCl. Analogously, bromination of **4** at 75° gave 6-bromotetrazolo-[1,5-a]pyridine (**7**) in 56% yield, the structure of which was assigned as above by NMR comparison with **6**.

Since the presence of an equilibrium between azido and tetrazolo group in some tetrazolopyridines with electron withdrawing and/or electron donating substituents in the pyridine ring has been confirmed by IR and UV spectral inspections,[6,7] we re-examined the substituted tetrazolopyridine systems (**4**–**7**) by both IR and NMR spectral analyses. These spectral data are summarized in Table 1 and 2.



SCHEME 1



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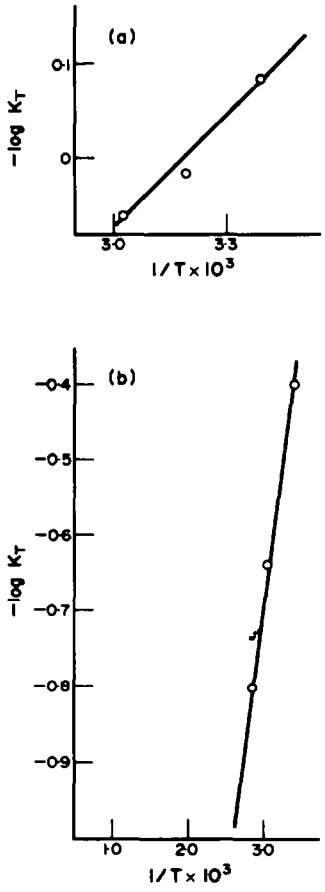


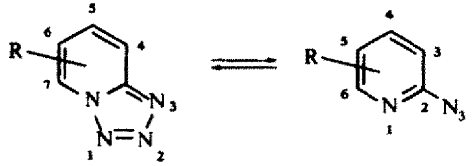
FIG 1. Temperature dependences on the equilibrium constants (K_T) for **5** in DMSO-d_6 (**Ia**) and for **6** in $CDCl_3$ (**Ib**).

TABLE 1. IR SPECTRAL DATA OF TETRAZOLOPYRIDINES

IR cm^{-1} / Compound No.	4	5	6	7
$\nu_{N_3}^{KBr}$	—	—	—	—
$\nu_{C=N}^{KBr}$	1630	1620	1646	1623
$\nu_{N_3}^{CHCl_3}$	—	2150 (s)*	2155 (w)*	—
$\nu_{C=N}^{CHCl_3}$	1630	1587	1640	1626
$\nu_{N_3}^{CF_3COOH}$	—	2150 (s)	2155 (w)	—
$\nu_{C=N}^{CF_3COOH}$	1630	1592	1640	1628
$\nu_{N_3}^{DMSO}$	—	2150 (s)	—	—
$\nu_{C=N}^{DMSO}$	1630	1590	1645	1623
$\nu_{N_3}^{(CH_3)_2CO}$	—	2150 (s)	2160 (w)	—
$\nu_{C=N}^{(CH_3)_2CO}$	1630	1587	1640	1625

* s = strong, w = weak

TABLE 2. EQUILIBRIUM CONSTANTS, HEATS OF ISOMERIZATION AND NMR SPECTRAL ASSIGNMENTS



Compound No.	Solvent	Concn. w/v%	Probe temp	KT†	ΔH‡ (kcal/mol)	τ-values							
						Tetrazolo tautomer*					Azido tautomer*		
						H_4	H_5	H_6	H_7	H^3	H_4	H_5	H_6
4	$CDCl_3$	7	23			1·89	2·26	2·62	1·09				
			60			1·88	2·27	2·65	1·13				
	CF_3COOH	7	23			1·50	1·56	2·08	0·72				
	CD_3OD	7	23			1·85	2·14	2·57	0·86				
	$(CD_3)_2CO$	6	23			1·83	1·90	2·53	0·84				
	pyridine	5	23			1·87	2·37	2·79	0·81				
	DMSO-d_6	6	23			1·71	2·09	2·51	0·68				
		6	80			1·79	2·13	2·56	0·73				
		6	120			1·83	2·17	2·60	1·07				
	DMSO-d_6/CF_3COOH (1:1)	5	23			1·89	2·21	2·65	0·96				
5	$CDCl_3$	7	23	18·0		2·00	2·30–2·60	—	2·64	2·96	2·43	—	3·30
			40	only azido form									
	DMSO-d_6	7	25	2·51		1·75	1·95–2·25	—	2·39	2·66	2·09	—	3·01
		7	57	4·32	3·4 ± 0·5	1·70	1·90–2·20	—	2·32	2·55	2·05	—	2·94
		7	80	6·37		1·70	1·90–2·20	—	2·32	2·50	2·02	—	2·90

TABLE 2—*continued*

Compound No.	Solvent	Concn. w/v%	Probe temp	K_T†	ΔH‡ (kcal/mol)	τ-values: Tetrazolo tautomer* H_4	H_5	H_6	H_7	Azido tautomer* H_3	H_4	H_5	H_6
6	$CDCl_3$	5	23	0·83	4·2 ± 0·5	1·87	1·59	—	0·19	3·12	1·66	—	0·87
		5	40	1·04		1·86	1·56	—	0·22	3·23	1·64	—	0·88
		5	60	1·15		1·89	1·61	—	0·24	3·16	1·68	—	1·02
	CF_3COOH	5	23	3·84		1·53	1·17	—	−0·05	2·08	0·83	—	0·50
	CD_3OD	5	23			1·74	1·42	—	−0·30				
	DMSO-d_6	5	23			1·63	1·43	—	−0·58				
		5	120			1·68	1·48	—	−0·59				
7	$CDCl_3$	7	23			2·33	2·04	—	1·05				
			40			2·33	2·06	—	1·03				
	DMSO-d_6	7	60			2·35	2·06	—	1·06				
		12	80			2·21	2·05	—	0·57				
		12	120			2·23	2·07	—	0·59				

* Ratios of the integrated proton intensities of the azido tautomer to those of the tetrazolo tautomer

† The estimated mean deviation in K_T was less than ±0·02

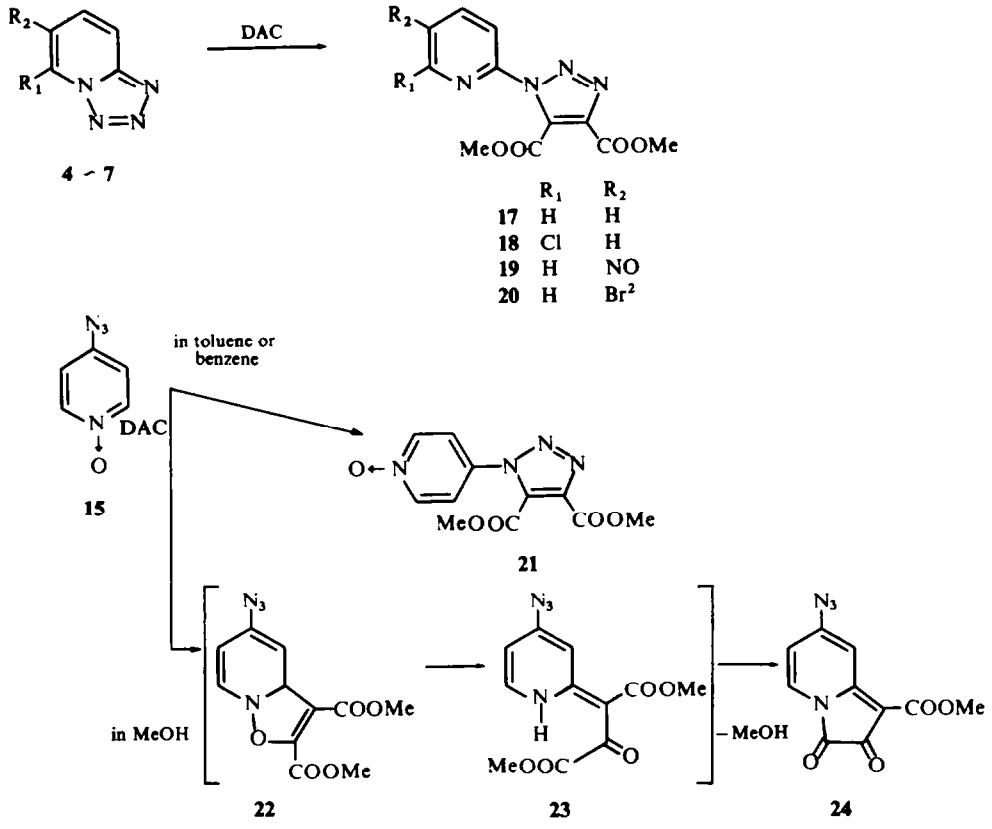
‡ ΔH = the heat of isomerization (*cf.* Fig. 1); Each value was determined by the mean value of three runs at the specified temperature. The least-squares standard deviation in K_T was less than ±0·01.

Remarkable differences are observed by the IR spectral comparison of compound **5** with **6**; the former showed a strong azido absorption at 2150 cm^{-1}, but the latter exhibited a weak one at 2155 cm^{-1} in both $CHCl_3$ and TFA solutions. However, **4** and **7** showed no such absorptions. From these results, **4** and **7** are concluded to exist entirely as the tetrazole forms indifferent from the solvents. Furthermore, the NMR spectrum of **5** discloses the existence of a tetrazolo-azidoazomethine equilibrium in DMSO-d_6. The effects of the temperature on the equilibrium constants (K_T) are calculated to be 2·51 at 25°, 4·32 at 57°, and 6·37 at 80° from the ratios of the integrated intensities of the ring proton signals of the azido tautomer to that of the tetrazolo tautomer. Thus, from the variation of the equilibrium constants with several temps in DMSO-d_6 the heat of isomerization is found to be endothermic with $\Delta H = 3{\cdot}4 \pm 0{\cdot}5$ kcal/mol (Fig. 1). While the azidoazomethine-tetrazole equilibrium of **5** is observed at 23° in $CDCl_3$, the azido tautomer is exclusively present at above 40°. The spectrum of **6** also discloses the presence of the azidoazomethine-tetrazole equilibrium in $CDCl_3$ and TFA solutions, but in DMSO-d_6 the tetrazolo tautomer is predominant. The temp dependence on the equilibrium constants (K_T) in $CDCl_3$ are calculated to be 0·83 at 23°, 1·04 at 40°, and 1·15 at 60°, from the ratios of the equilibrium and thus, the ΔH value is given as $4{\cdot}2 \pm 0{\cdot}5$ kcal/mol (Fig. 1). It has been stated[5] that the heat of isomerization of tetrazolo[1,5-a]pyrimidine in DMSO was $5{\cdot}1 \pm 0{\cdot}1$ kcal/mol and *ca.* 2 kcal/mol more for the 5,7-dimethyl derivative. It appears that the heat of isomerization is generally less than 12 kcal/mol, and therefore, azide tautomerization might be the first step in pyrolysis of the tetrazoles.[8]

Chemical reactivities of tetrazolopyridines. The existence of the reactive tautomeric azido forms in tetrazolopyridines has been confirmed by cycloadditions with enamines.[9] The thermal cycloaddition reactions of tetrazolo[1,5-a]pyridine with dipolarophiles at 150–180°,[10] and its thermal conversion to 2-cyanopyrrole, 2-aminopyridine and glutaconitrile[11] have been explained by the intermediacy of 2-pyridylnitrene, and furthermore, 2-pyridylnitrene and 2-pyridylcarbene are reported to be ring-expanded in the gas phase.[11]

The present investigation was to determine the limit and scope of this type of cycloaddition reaction using substituted tetrazolopyridines.

Reactions of tetrazolopyridines **4**, **6** and **7** with aniline in toluene in the presence or in the absence of cupric acetylacetonate were carried out, and the results summarized in Table 3 and Scheme II. When the reaction was carried out in the presence of cupric acetylacetonate in boiling toluene, 2-aminopyridine derivatives **8**, **9** and **10** were produced in 55–60% yields together with azobenzene in about 10% yield, but the reactions proceeded with difficulty in the absence of catalyst at below 160°. The mechanism for the formation of these compounds might be explained by suggesting 2-pyridylnitrene intermediates (probably the triplet) which could be produced by the thermal decomposition of the reactive azido tautomer (as a function of the moderate temperature in the presence of the catalyst), followed by hydrogen abstraction. Neither 1,2- (**13**), nor 1,3-diazepines (**14**) were detected, though these products could be produced by the ring enlargements through nitrene insertion by analogy with the decomposition of phenyl azide in the presence of amine bases.[12] All attempts to effect the photochemical reactions of the tetrazolopyridines with aniline and diethylamine in C_6H_6 or AcOH were unsuccessful.



SCHEME 3

TABLE 3. REACTIONS OF TETRAZOLOPYRIDINES AND 4-AZIDOPYRIDINE 1-OXIDE IN ANILINE AND TOLUENE

Compound No.	Reaction temp	Reaction time hr	Catalyst	Products Compound No.	Products (Yield, %)
4	80	10	none	—	—
	120	10	none	—	—
	170	10	none	**8** (10)	**11** (trace)
	120	10	$Cu(acc)_2$	**8** (15)	**11** (trace)
	120	30	$Cu(acc)_2$	**8** (59)	**11** (10)
6	170	10	none	**9** (20)	**11** (trace)
	120	10	$Cu(aac)_2$	**9** (50)	**11** (10)
	125	13	$Cu(aac)_2$	**9** (58)	**11** (10)
7	170	10	none	**10** (18)	**11** (10)
	120	10	$Cu(aac)_2$	**10** (48)	**11** (trace)
	125	30	$Cu(aac)_2$	**10** (56)	**11** (15)
15	120	10	$Cu(aac)_2$	**16** (5)	
	120	30	$Cu(aac)_2$	**16** (10)	

$Cu(aac)_2$ = Cupric Acetylacetonate

In contrast, the reaction of 4-azidopyridine 1-oxide (**15**) with aniline in toluene in the presence of cupric acetylacetonate resulted in the formation of **16**. The structure of **16** was assigned as 4,4'-azopyridine 1,1'-dioxide in comparison with a specimen prepared by the reduction of 4-nitropyridine 1-oxide.[13]

TABLE 4. 1,3-DIPOLAR CYCLOADDITION OF TETRAZOLO[1,5-a]PYRIDINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

Compound No.	Reaction temps	Reaction time hr	Solvent	Products Compound No.	m.p.	Yield %	$\nu_{C=O}^{KBr}$ (cm^{-1})
4	150	7	none	**17**	120–121[a]	46	1722 1708
5	60	11	$CHCl_3$	**18**	80–83[b]	44	1738
6	140	3	none	**19**	148–150[c]	90	1730 1705
7	145	3	none	**20**	149–151[d]	88	1724

[a] Lit. (m.p. 112–114°), see ref. 10.
[b] Found: C, 44·58; H, 2·95; N, 18·68. Requires C, 44·54; H, 3·06; N, 18·88%
[c] Found: C, 43·13; H, 2·90; N, 22·65. Requires C, 43·01; H, 2·95; N, 22·79%
[d] Found: C, 38·63; H, 2·72;, N, 16·48. Requires C, 38·73; H, 2·66; N, 16·42%

Treatment of **4** with dimethyl acetylenedicarboxylate (DAC) gave no cycloadduct even in refluxing $CHCl_3$, but under the more drastic condition of absence of solvent at 150° afforded a cycloadduct (**17**) as suggested by Huisgen *et al.*[10] The analogous reactions of **5**, **6** and **7** with DAC gave the corresponding cycloadducts, **18**, **19** and **20** in about 50–90% yields.

On the other hand, treatment of **15** with DAC in toluene or C_6H_6 at 80° afforded **21** in about 7% yield, but in MeOH at room temperature gave 7-azido-2,3-dioxopyrazolo[2,1-a]pyridine (**24**) in 5% yield. In both cases, intractable tarry materials always accompanied these products. These results are summarized in Scheme III and Table 4.

EXPERIMENTAL

All m.ps were measured on a Yanagimoto micromelting point apparatus and uncorrected. The microanalyses were performed on a Perkin–Elmer 240 Elemental Analyser, while the IR and UV spectra were obtained on a JASCO Model IR-S and a ORD/UV-5 spectrometers, respectively. The NMR spectra were recorded with a JEOL Model C-60-XL spectrometer, TMS as internal standard.

Tetrazolo[1,5-a]pyridine (4). Compound **4** was prepared by the method of Boyer *et al.*[6]; m.p. 158–160° (lit.[6] 156–158°), UV (EtOH) max 260 nm (ε 3,610).

5-Chloro-tetrazolo[1,5-a]pyridine (5). Compound **5** was prepared by the method of Reimlinger[14]; m.p. 126–127° (decomp.) (lit.[14] 120°), UV (EtOH) max 240 nm (ε 30,560), 260 (18,370).

6-Nitro-tetrazolo[1,5-a]pyridine (6). A solution of **4** (10·0 g, 0·083 mol) in conc H_2SO_4 (60 ml) fuming HNO_3 (6·5 ml) was heated at 110–120° for 9 hr. After cooling, the mixture was poured into ice-water and neutralized with Na_2CO_3. The precipitated product was filtered and recrystallized from EtOH acidified with few drops of HCl to give colorless needles (**6**), m.p. 147–148° (80–90%), UV (EtOH) max 233 nm (ε 12,970), 308 (5,130) and 397 (2,740), identified by spectroscopic and m.m.ps with a specimen prepared from 5-nitro-2-chloropyridine and NaN_3 in HCl.[6]

6-Bromo-tetrazolo[1,5-a]pyridine (7). To a solution of **4** (3·0 g, 0·025 mol) in AcOH (30 ml) was added dropwise a mixture of Br_2 (12 ml) in AcOH (10 ml) and the solution heated at 75° for 18 hr in a sealed tube. After neutralization with 20% NaOH (30 ml), the precipitated crystals were recrystallized from EtOH to give **7**, m.p. 155–157°, (2·8 g, 56%), UV (EtOH) max 266 nm (ε 3,520). (Found: C, 30·40; H, 1·68; N, 28·25. $C_5H_3N_4Br$ requires C, 30·14; H, 2·01; N, 28·14%).

Thermal decompositions of tetrazolo[1,5-a]pyridines and 4-azido-pyridine 1-oxide in the presence of aniline and cupric acetylacetonate. General Method. A mixture of tetrazolo[1,5-a]pyridine (0·1 mol) and/or 4-azidopyridine 1-oxide (0·1 mol) in aniline (0·1 mol), cupric acetylacetonate (0·2 mol) and toluene (20 ml) was heated in a sealed tube. The solvent was removed under reduced pressure and the tarry residue chromatographed on silica gel using C_6H_6:EtOH (5:1) as eluent. These results are summarized in Table 3.

1,3-Dipolar cycloadditions of tetrazolo[1,5-a]pyridines with dimethyl acetylenedicarboxylate. A mixture of tetrazolo[1,5-a]pyridines (**4–7**) (0·01 mol) and dimethyl acetylenedicarboxylate (0·012 mol) was heated in an oil bath. After cooling, work-up involved filtration, evaporation of solution, and chromatography (silicic acid) of the residue using $CHCl_3$ as eluent. These results are summarized in Table 4.

1,3-Dipolar cycloaddition of 4-azido-pyridine 1-oxide with dimethyl acetylenedicarboxylate. (a) A solution of **15** (0·4 g), dimethyl acetylenedicarboxylate (0·42 g) and toluene (20 ml) of C_6H_6 (20 ml) was heated at 80° for 1·5 hr. The solution was concentrated *in vacuo*, and work-up of the residue as described above afforded **21** (0·054 g, 6·6%): m.p. 205–208°; ν_{max}^{KBr} 1760, 1730 cm^{-1} ($COOCH_3$). (Found: C, 47·30; H, 3·78; N, 20·02. $C_{11}H_{10}N_4O_5$ requires C, 47·40; H, 3·62; N, 20·14%). (b) A solution of **15** (0·4 g) and dimethyl acetylenedicarboxylate (0·42 g) in MeOH (20 ml) was stirred at room temp overnight. The solution was concentrated *in vacuo*, and work-up of residue as described above afforded **24** (0·04–0·06 g): m.p. 194–196°; ν_{max}^{KBr} 2160 (N_3), 1713 ($COOCH_3$ and C=O), 1645 cm^{-1} (CO—N<). (Found: C, 48·53; H, 2·29; N, 22·95. $C_{10}H_6N_4O_4$ requires: C, 48·78; H, 2·46; N, 22·76%).

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