A New Synthesis of 6-(Alkyl)amino-3-aryl(alkyl)-1,2,4,5-tetrazines

Anda Counotte-Potman and Henk C. van der Plas

Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

Received June 9, 1980

A new method for the preparation of 6-(alkyl)amino-3-aryl(alkyl)-1,2,4,5-tetrazines is described. Dissolving 3-aryl(alkyl)-1,2,4,5-tetrazines in liquid ammonia or a primary aliphatic amine at −35° to −40°, followed by addition of potassium permanganate gives the title compounds in reasonable to excellent yields.

J. Heterocyclic Chem., **18**, 123 (1981).

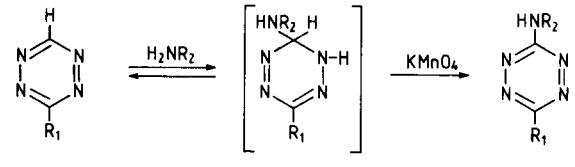
There is strong interest in the synthesis of 6-(substituted)-amino-3-aryl-1,2,4,5-tetrazines since some of these compounds exhibit suppressive antimalarial activity. Several methods for the preparation of these compounds have been described (1-3) but they all show severe limitations.

Very recently an attractive synthesis of these compounds has been published by Werbel, *et al.* (4), involving: i) the thiobenzoylation of hydrazinecarbohydrazonothioic acid methyl ester with (substituted phenyl)thioxomethyl thio acetic acid into a 1,2-dihydro-3-aryl-6-(methylthio)-1,2,4,5-tetrazine; ii) oxidation of this compound with bromine in acetic acid into 3-aryl-6-(methylthio)-1,2,4,5-tetrazine; and iii) treatment with amines (Scheme I).

In most syntheses of the 6-(substituted)amino-3-aryl-1,2,4,5-tetrazines described in the literature so far, the (substituted)amino group is introduced by replacement of X in the 6-X-3-aryl-1,2,4,5-tetrazines. We report in this paper a new approach to the synthesis of 6-(substituted)-amino-3-aryl-1,2,4,5-tetrazines, which differs from the other methods of preparation in this respect that the (substituted)amino group is introduced in a 3-aryl-1,2,4,5-tetrazine being *unsubstituted* at position 6. This method is not limited to aryltetrazines, but can also be applied for the preparation of 6-(substituted)amino-1,2,4,5-tetrazines, containing an *alkyl* group on position 3. The procedure is quite simple and is exemplified with the preparation of 6-amino-3-phenyl-1,2,4,5-tetrazine (**1**).

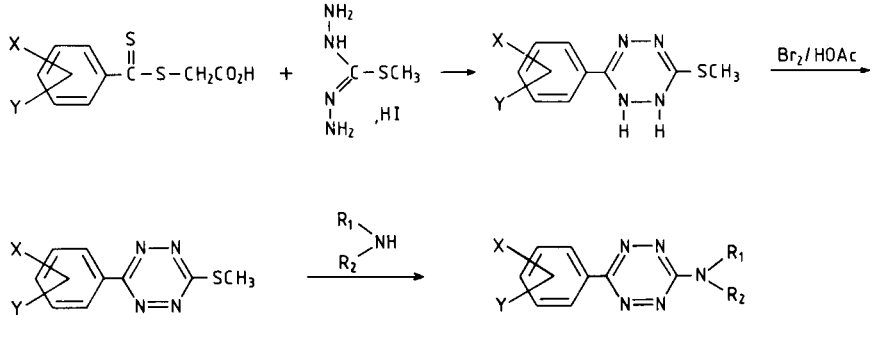
The red 3-phenyl-1,2,4,5-tetrazine (1 equivalent) is dissolved in liquid ammonia. The solution becomes yellow. After addition of 1 equivalent of potassium permanganate to the liquid ammonia solution and working-up 6-amino-3-phenyl-1,2,4,5-tetrazine (**1**) can be isolated in 74% yield. Use of ferric chloride or dichloro-dicyanoquinone instead of potassium permanganate also gave 6-amino-3-phenyl-1,2,4,5-tetrazine but the yields were much lower. With air and oxygen only starting material could be retrieved.

We propose that by dissolving of 3-phenyl-1,2,4,5-tetrazine in liquid ammonia the yellow coloured 1,6-dihydro-6-amino-3-phenyl-1,2,4,5-tetrazine is formed (Scheme II). Dihydro-1,2,4,5-tetrazines are known to be easily oxidized (5). Potassium permanganate added to the liquid ammonia solution (6) is apparently sufficiently active to perform the oxidation at the low temperature. Attempts to isolate the 1,6-dihydrotetrazine derivative met with little success,



$R_1 = CH_3$, t-C_4H_9, C_6H_5, p-Br-C_6H_4
$R_2 = H$, C_2H_5, i-C_3H_7, n-C_4H_9, n-C_8H_{17}

Scheme II



Scheme I

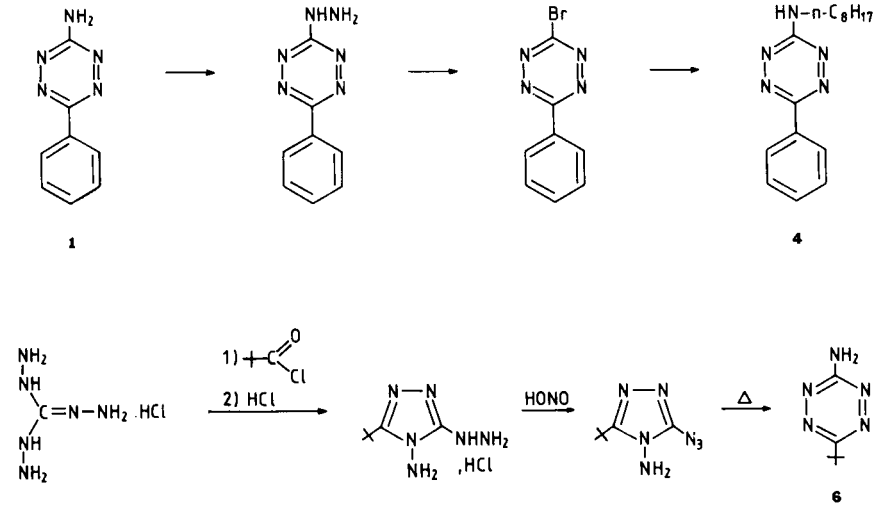
0022-152X/81/010123-05$02.25

Table I

6-(Alkyl)amino-3-aryl(alkyl)-1,2,4,5-tetrazines Obtained by the Method Described in Scheme II

Compound No.	R_1	HNR_2	M.p. °C	Yield %	Analyses % Calcd./Found C	H	^{1}H-NMR δ (f) 3-position	HN	α-CH_2	β-CH_2 (g)	ω-CH_3
1	C_6H_5	NH_2	213.5-214.5(a)	74	55.48	4.07	(i)	7.45			
					55.60	4.12					
2	C_6H_5	HNC_2H_5	143-146	59	59.68	5.51	(i)	6.18	3.69 (h)		1.38
					59.46	5.62					
3	C_6H_5	HN-*n*-C_4H_9	126-127	44	62.86	6.59	(i)	6.23	3.67	1.56	1.00
					63.08	6.53					
4	C_6H_5	HN-*n*-C_8H_{17}	105-108	38	67.33	8.12	(i)	5.83	3.67	1.30	0.86
					67.05	7.95					
5	C_6H_5	HN-*i*-C_3H_7	152-154	18	61.37	6.09	(i)	5.77	4.38		1.38
					61.35	5.99					
6	*t*-C_4H_9	NH_2	114-117	72	47.04	7.24	1.44	6.95			
					46.78	7.35					
7	*t*-C_4H_9	HNC_2H_5	48-50	81	53.01	8.34	1.47	6.35	3.60 (h)		1.31
					53.11	8.54					
8	*t*-C_4H_9	HN-*n*-C_4H_9	oil	47	57.38	9.15	1.50	6.27	3.58	1.50	1.10
					57.64	9.26 (d)					
9	*t*-C_4H_9	HN-*n*-C_8H_{17}	oil	58	63.35	10.25	1.48	6.33	3.57	1.29	0.87
					63.19	10.40 (e)					
10	CH_3	NH_2	170-171 (b)	80	32.43	4.54	2.74	7.00			
					32.53	4.62					
11	CH_3	HNC_2H_5	91-92	76	43.15	6.52	2.83	6.14	3.63 (h)		1.33
					43.38	6.69					
12	CH_3	HN-*n*-C_4H_9	50-51	35	50.28	7.48	2.80	16.00	3.56	1.57	0.98
					50.27	7.85					
13	CH_3	HN-*n*-C_8H_{17}	64-65.5	35	59.16	9.48	2.80	5.65	3.56	1.30	0.90
					59.39	9.49					
14	*p*-Br-C_6H_4	NH_2	241.5-242.5(c)	81	38.11	2.40	*m*. 7.77	7.48			
					38.30	2.41	*o*. 8.31				

(a) 226° (1,2). (b) 171° (2). (c) 247° (4). (d) Exact mass measurement gave for $C_{10}H_{19}N_5$ (M^+) 209.1647 (theoretical 209.1640). (e) Exact mass measurements gave for $C_{14}H_{27}N_5$ (M^+) 265.2275 (theoretical 265.2266). (f) Compounds **1, 6, 10** and **14** are measured in acetone-d_6, all other compounds in deuteriochloroform, (g) β-CH_2 is the total multiplet due to the β-CH_2 and γ-CH_2 group in *n*-C_4H_9 and β, γ, δ, *etc.*, CH_2 groups in *n*-C_8H_{17}. (h) $J_{NH\text{-}CH_2}$ = 5.8 Hz, (i) *meta/para* 7.46-7.60; *ortho* 8.26-8.48.



Scheme III

Table II

Mass Spectrometry (a) of Compounds **1-14** in Table I

R_1	HNR_2	NH_2		HNC_2H_5		$HNn\text{-}C_4H_9$		$HN\text{-}n\text{-}C_8H_{17}$		$HN\text{-}i\text{-}C_3H_7$	
C_6H_5	M^+	173	11	201	21	229	75	285	58	215	23
	a	42	11	70	32	98	24	153 (d)	4	84	25
	b	103	100	103	100	103	100	103	73	103	100
	inlet conditions(b)	probe	150°	h.b.	150°	probe	90°	probe	90°	h.b.	160°
$t\text{-}C_4H_9$	M^+	153	10	181	12	209	10	265	12		
	a	42	31	70	75	98	11	153 (d)	6		
	b-1 (c)	84	33	84	47	84	53	84	58		
	$t\text{-}C_4H_9$	57	100	57	100	57	100	57	79		
	inlet conditions	probe	50°	h.b.	130°	h.b.	150°	h.b.	170°		
CH_3	M^+	111	13	139	27	167	15	223	28		
	a	42	97	70	41	98	3	153 (d)	3		
	b	41	100	41	27	41	55	41	100		
	inlet conditions	h.b.	180°	h.b.	140°	probe	30°	h.b.	180°		
$p\text{-}Br\text{-}C_6H_4$	M^+	253		15							
		251		16							
	a	42	8	11							
	b	183	96								
		181	100								
	b-Br	102	97								
	inlet conditions	h.b.	185°								

(a) Only the most characteristic peaks are given. All mass spectra were measured at 70 eV. For each compound the first figure is the m/e value, the second figure is the intensity of the peak in percentage of the base peak. (b) Inlet conditions: inlet system: all glass heated inlet system (hot box = h.b.); direct inlet (probe); inlet temperature. (c) Fragment **b** is very small (< 1% for compound **6**). (d) (**a**-1), with the *n*-octylamino group no fragment **a** is observed.

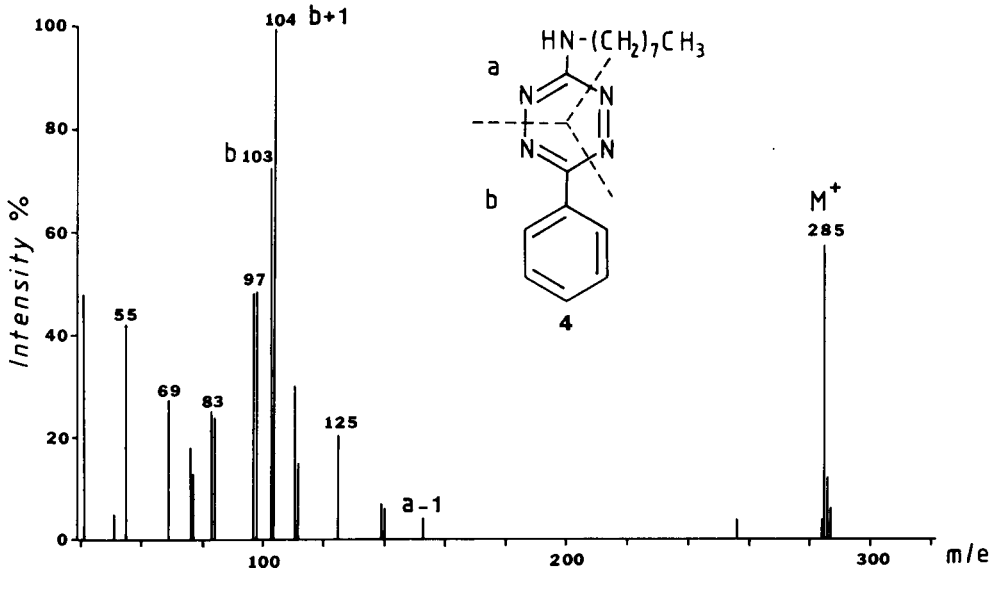


Figure I

only the starting material could be recovered.

Primary aliphatic amines were found to be as active as liquid ammonia. When 3-phenyl-1,2,4,5-tetrazine was dissolved in an excess of primary amine at −35° to −40° and subsequently potassium permanganate was added the corresponding 6-alkylamino-3-phenyl-1,2,4,5-tetrazine could be isolated. The yields vary depending on the size of the alkyl group (Table I). The reactions with the primary amines have to be carried out at low temperature, because otherwise decomposition occurs. Attempts to introduce an arylamino group by performing the reaction with aromatic amines were not successful.

The generality of this reaction can be shown by the 6-(alkyl)amino-1,2,4,5-tetrazines (**1-14**) obtained by this amination-oxidation procedure. They are summarized in Table I, together with the yields, their microanalytical data, melting points and ^{1}H-nmr spectra. The mass spectral data are collected in Table II.

Most of the compounds prepared by this method were not described in the literature before. The already known compounds **1** and **10** were prepared according to published routes (2) and their physical data compared with those of the compounds obtained in this study. They proved to be identical. Two compounds, *i.e.*, 6-*n*-octylamino-3-phenyl-1,2,4,5-tetrazine (**4**) and 6-amino-3-*t*-butyl-1,2,4,5-tetrazine (**6**) were prepared independently according to a different route (Scheme III).

Synthesis of compound **4** involves hydrazinolysis of 6-amino-3-phenyl-1,2,4,5-tetrazine (**1**) into 6-hydrazino-3-phenyl-1,2,4,5-tetrazine, conversion of this 6-hydrazino compound with bromine in acetic acid (7) into 6-bromo-3-phenyl-1,2,4,5-tetrazine and amino-debromination with 2-equivalents of *n*-octylamine at room temperature. Compound **6** was prepared from pivaloyl chloride and triaminoguanidine according to the route given in Scheme III (8). Both compounds proved to be identical with those, obtained by the amination-oxidation method.

Most mass spectra of 1,2,4,5-tetrazines published thusfar comprise 3,6-symmetrical disubstituted 1,2,4,5-tetrazines (9,10). Like symmetrical disubstituted 1,2,4,5-tetrazines the unsymmetrical disubstituted compounds **1-14** show a very simple splitting pattern. Besides the molecular ion M^+ in nearly all our compounds the ion $(M-28)^+$ is observed, due to loss of N_2. The residual species show cleavage between the N-N bond resulting in two different fragments **a** and **b** (and **a** + 1, **a** − 1; **b** + 1, **b** − 1). Then characteristic splitting pattern for the ions **a** and **b** is observed. As an example the mass spectrum of 6-*n*-octylamino-3-phenyl-1,2,4,5-tetrazine (**4**) is given (Figure I).

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. ^{1}H-nmr spectra were recorded on a Varian EM 390 spectrometer or on a Hitachi-Perkin Elmer R-24B spectrometer. TMS was used as internal standard (δ 0 ppm). Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM).

1. Preparation of Starting Materials.

3-Phenyl-1,2,4,5-tetrazine.

This compound was prepared according to the synthesis described by Lang, Johnson and Cohen (11). We modified the oxidation step by using air or oxygen instead of bromine in acetic acid.

3-*t*-Butyl-1,2,4,5-tetrazine.

This compound was prepared analogous to the the synthesis of Lang, *et al.* (11). Accordingly, 16 g. of pivalimido ethyl ether hydrochloride (12), 31 g. for formamidine acetate (13) and 50 ml. of absolute ethanol were cooled at −10°, 70 ml. of hydrazine hydrate were added, keeping the temperature below 5°. The mixture was stirred during 3 hours at 25° and then poured into 500 ml. of water. The water layer was continuously extracted with boiling dichloromethane for 4 days; during this period air was bubbled through the boiling dichloromethane in order to oxidize the dihydrotetrazine.

After column chromatography on silica gel using as eluent pentane-dichloromethane, successively 0.40 g. of 3,6-di-*t*-butyl-1,2,4,5-tetrazine (4%) was obtained, m.p. 95-97° [lit. (10) 95-99°]; ^{1}H-nmr (carbon tetrachloride): δ 1.57 (s, *t*-C_4H_9) [lit. (10) δ 1.57] and 0.63 g. of 3-*t*-butyl-1,2,4,5-tetrazine, a red volatile oil, (4.5%); ^{1}H-nmr (methanol-d_4): δ 1.58 (9H, s, *t*-C_4H_9), 10.45 (1H, s, H_6); ms: M^+ m/e 138. Exact mass measurements gave for $C_6H_{10}N_4$ (M^+) 138.0907 (theoretical 138.0905).

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.15; H, 7.30. Found: C, 52.51; H, 7.59.

3-Methyl-1,2,4,5-tetrazine.

This compound was prepared from 6-amino-3-methyl-1,2,4,5-tetrazine as described previously (14). The preparation of this compound, analogous to the synthesis of Lang, *et al.* (11), was not successful; the yield was poor and it was difficult to separate 3-methyl-1,2,4,5-tetrazine from 3,6-dimethyl-1,2,4,5-tetrazine.

3-(*p*-Bromo)phenyl-1,2,4,5-tetrazine.

This compound was also prepared analogous to the synthesis of Lang, *et al.* (11), overall yield 46%, m.p. 182-184°; ^{1}H-nmr (deuteriochloroform): δ 7.75 (2H, d, *meta* H), 8.50 (2H, d, *ortho* H), 10.25 (1H, s, H_6); ms: M^+, m/e = 238/236.

Anal. Calcd. for $C_8H_5BrN_4$: C, 40.53; H, 2.13. Found: C, 40.61; H, 2.17.

2. Amination-Oxidation Procedure.

As an example, the procedure is given for 3-phenyl-1,2,4,5-tetrazine; the other 1,2,4,5-tetrazines were treated in a similar way.

A. With Liquid Ammonia.

3-Phenyl-1,2,4,5-tetrazine (100 mg., 0.63 mmole) was dissolved in 10 ml. of liquid ammonia; immediately the yellow colour is observed. After 5 minutes, 67 mg. (0.42 mmole = 1 redox equivalent) of potassium permanganate were added at once. After 10 minutes, 25 ml. of ethyl acetate was added slowly. The ammonia is evaporated off, the solution is filtered through silica gel. The ethyl acetate is evaporated off *in vacuo* and the solid residue is crystallized from ether/pentane.

B. With Alkylamines.

The procedure is the same as described under A) using about 3 ml. of liquid alkylamine at low temperature (−35° to −40°). However, when using *n*-octylamine, due to the high melting point (0°) of *n*-octylamine, a 1:1 mixture of *n*-octylamine and ethanol was used.

All compounds **1-14** were crystallized from ether/pentane.

6-*n*-Octylamino-3-phenyl-1,2,4,5-tetrazine (**4**).

A solution of 173 mg. (1 mmole) of **1** in 4 ml. of ethanol was refluxed with 0.10 ml. (2 mmoles) of hydrazine hydrate during 1 hour. After cool-

ing to room temperature 6-hydrazino-3-phenyl-1,2,4,5-tetrazine separated out as crystals; they were filtered off and washed with 1 ml. of ethanol, yield 139 mg. (74%), m.p. 169-171° [lit. (15) 178° dec.] ms: M^+, m/e = 188. It was further characterized as its benzaldehyde hydrazone, m.p. 213-214.5° [lit. (15) 211-212°]; ms: M^+ m/e 276.

Anal. Calcd. for $C_{15}H_{12}N_6$: C, 65.20; H, 4.38. Found: C, 65.07; H, 4.25.

The 6-hydrazino compound was dissolved in 5 ml. of acetic acid and oxidized with bromine according to the procedure published (7). We obtained 149 mg. of 3-bromo-6-phenyl-1,2,4,5-tetrazine (85%), m.p. 126-129° [lit. (1,7) 131°]; ms: M^+ m/e 238/236. To 149 mg. (0.36 mmole) of the 3-bromo compound dissolved in 4 ml. of tetrahydrofuran 0.22 ml. (1.3 mmoles) of *n*-octylamine was added. The mixture was stirred at room temperature during 30 minutes, the solvent was evaporated off and the material was filtered through silica gel. Recrystallization from pentane gave 131 mg. of **4**, yield 73%, m.p. 105.5-107°. Ir, ^{1}H-nmr and mass spectrum are the same as for compound **4** obtained by the amination-oxidation procedure. Mixed melting point determination gave no depression.

6-Amino-3-*t*-butyl-1,2,4,5-tetrazine (**6**).

This compound was prepared from pivaloyl chloride and triaminoguanidine hydrochloride analogous to the preparation of 6-amino-3-phenyl-1,2,4,5-tetrazine as described by Takimoto and Denault (2,8), yield 1%, m.p. 114-119°. ^{1}H-nmr and mass spectrum are identical with those of compound **6** obtained by the amination-oxidation procedure.

Acknowledgement.

We are indebted to Mr. H. Jongejan for carrying out the microanalysis and to Drs. C. A. Landheer and Mr. W. P. Combé for mass spectrometric data.

REFERENCES AND NOTES

(1) V. A. Grakauskas, A. J. Tomasewski and J. P. Horwitz, *J. Am. Chem. Soc.*, **80**, 3155 (1958).

(2) H. H. Takimoto and G. C. Denault, *Tetrahedron Letters*, 5369 (1966).

(3a) E. G. Kovalev, I. Ya. Postovskii and G. L. Rusinov, *Dokl. Akad. Nauk. SSSR*, **241**, 366 (1978); (b) I. Ya. Postovskii, E. G. Kovalev and G. L. Rusinov, *Otkrytiya Izobret., Prom. Obiaztsy, Tovarnye Znaki*, **30**, 95 (1979); *Chem. Abstr.*, **92**, 6564 (1980); (c) V. A. Ershov and I. Ya. Postovskii, *Byull. Izobr.*, **30**, (1973); Inventors Certificate No. 390093.

(4) L. M. Werbel, D. J. McNamara, N. L. Colbry, J. L. Johnson, M. J. Degnan and B. Whitney, *J. Heterocyclic Chem.*, **16**, 881 (1979).

(5a) P. F. Wiley, "The Chemistry of Heterocyclic Compounds, The 1,2,4-triazines, Tetrazines and Pentazines", A. Weissberger, Ed., Interscience, New York, N.Y., 1956, Chapter V; (b) V. P. Wystrach, "Heterocyclic Compounds", Vol. 8, R. C. Elderfield, Ed., John Wiley and Sons, New York, N.Y., 1967, Chapter II; (c) P. F. Wiley, "The Chemistry of Heterocyclic Compounds, Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines and Pentazines", A. Weissberger and E. C. Taylor, Eds., Interscience, New York, N.Y., 1978, Chapter III.

(6) Potassium permanganate in acetone has been used to oxidize dihydrodiazines *isolated* from the reaction of the diazine with phenyllithium; (a)H. Bredereck, R. Gompper and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958); (b) R. E. van der Stoel and H. C. van der Plas, *Rec. Trav. Chim.*, **97**, 116 (1978).

(7) V. A. Ershov and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, **4**, 571 (1971).

(8) This method is described for the synthesis of some 6-amino-1,2,4,5-tetrazines (2). However when 6-amino-3-phenyl- or 6-amino-3-*t*-butyl-1,2,4,5-tetrazine is prepared according to this route the diazotation-step results in our hand largely in the loss of the *N*-amino group, consequently a poor yield is obtained.

(9a) C. Fridh, L. Asbrink, B. V. Johnson and E. Lindholm, *Int. J. Mass Spectrom. Ion Phys.*, **9**, 485 (1972); (b) C. D. Kimble, *Chem. Abstr.*, **73**, 44463 q (1970); (c) S. J. Weininger and E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 2050 (1967); (d) C. Larsen, E. Binderup and J. Møller, *Acta. Chem. Scand.*, **21**, 2855 (1967); (e) P. Yates, O. Meresz and L. S. Weiler, *Tetrahedron Letters*, 3929 (1968).

(10) W. Skorianetz, E. Kovats, *Helv. Chim. Acta*, **54**, 1922 (1971).

(11) S. A. Lang, Jr., B. D. Johnson and E. Cohen, *J. Heterocyclic Chem.*, **12**, 1143 (1975).

(12) G. K. Helmkamp and N. S. Kondo, *Biochim. Biophys. Acta*, **157**, 242 (1968). It took about 2 weeks at 5° to obtain pivalimido ethyl ether hydrochloride in 90% yield.

(13) E. C. Taylor, W. A. Ehrhart and M. Kawanisi, *Org. Synth.*, **46**, 39 (1966).

(14) A. D. Counotte-Potman and H. C. van der Plas, *J. Heterocyclic Chem.*, **15**, 445 (1978).

(15) I. Ya. Postovski, A. P. Novikova and V. A. Ershov, *Zh. Org. Khim.*, **6**, 1104 (1970).