Novel Synthesis of Unsymmetrically Substituted *s*-Tetrazines

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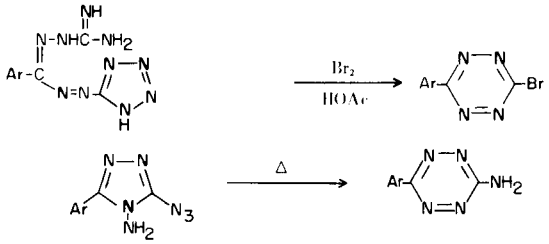
The synthesis of unsymmetrical 3-aryl and 3-heterocyclic *s*-tetrazines has been examined and the scope of the reaction and the product distribution is discussed. The products included unsymmetrical and symmetrical *s*-tetrazines, hydrazines, diimides, tetrazoles and triazoles with the composition of the mixtures with respect to structural type varying with the individual reactions. Some transformations with the system are discussed.

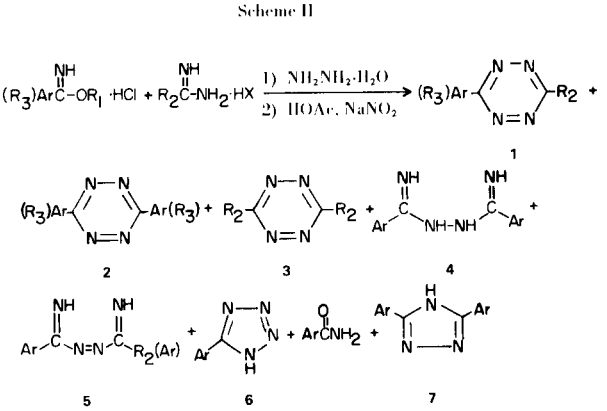
The syntheses of unsymmetrically substituted *s*-tetrazines generally have been long and tedious or involved unstable intermediates (1,3) (Scheme I). A synthesis of 3-phenyl-*s*-tetrazines from methyl iminobenzoates, formamidines, and hydriazine hydrate (4,5) offered a sequence which produced the *s*-tetrazines in one step (Scheme II).

Scheme I



We investigated this latter reaction (Scheme II) for the preparation of *s*-tetrazines and discovered that in addition to the desired phenyl-*s*-tetrazines (**1**), *bis*-3,6-*s*-tetrazines (**2**), tetrazoles (**6**), triazoles (**7**), hydrazines (**4**), diimides (**5**) and amide by-products were also formed. The composition of the reaction mixtures with respect to the structural types varied with individual reactions. Separation could be effected by chromatography on silica gel (200-325 mesh), eluting with methylene chloride. The *bis*-3,6-phenyl-*s*-tetrazine eluted first, the 3-phenyl-*s*-tetrazine next, and the *bis*-3,6-alkyl-*s*-tetrazine third. The more polar materials were eluted with varying amounts of methanol (1-5%) in methylene chloride. The symmetrical *bis*-3,6-alkyl-*s*-tetrazines were generally volatile and were lost on *in vacuo* evaporation of solvent. The product distribution is believed to involve subtle energy factors, solubility variables, and steric considerations. We extended this synthetic method to include substituted amidines and iminoesters and extended the synthetic utility.

Scheme II



Several modification in this sequence were successful although the number of products remained the same, but the yields were generally lower. These conditions were advantageous when the precursor nitriles were labile to acidic conditions (Pinner conditions), or when the iminoesters were difficult to form or would not form at all. Amides or nitriles could be activated by the use of methyl fluorosulfonate. The reactions (Scheme III) were highly

Scheme III

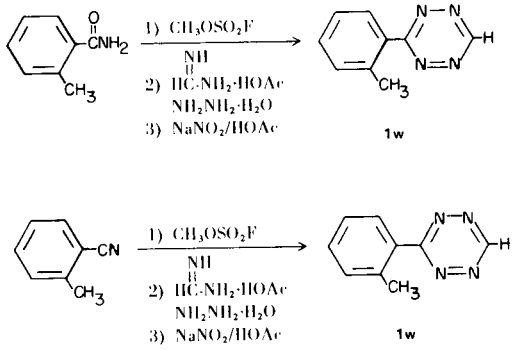


Table I

Unsymmetrical Phenyl-*s*-tetrazines Prepared

Compound	Ar(R_3)	R_2	Formula	M.p., °C	Yield, (a) %	Method of Preparation	Anal: Calcd. Found or Lit. (b)
1a	C_6H_5	H	$C_8H_6N_4$	126-129	30	B	125-127° (c)
b	*p*-Cl-C_6H_4	H	$C_8H_5ClN_4$	164-167	45	A	C, 49.88; H, 2.62; N, 29.09 C, 49.79; H, 2.71; N, 29.46
c	*p*-Cl-C_6H_4	CH_3	$C_9H_7ClN_4$	143-145	32	A	C, 52.31; H, 3.43; N, 27.19 (d) C, 52.16; H, 3.36; N, 26.73
d	*p*-F-C_6H_4	H	$C_8H_6FN_4$	144-146	31	C	C, 54.54; H, 2.86; N, 31.81; F, 10.79 C, 54.26; H, 2.86; N, 31.54; F, 10.99
e	*p*-F-C_6H_4	CH_3	$C_9H_7FN_4$	123-126	22	A	C, 56.84; H, 3.71; N, 29.46; F, 9.99 C, 56.88; H, 3.78; N, 29.33; F, 10.13
f	*m*-$CH_3C_6H_4$	H	C_9H_8N	75-78	38	F	C, 62.78; H, 4.68; N, 32.54 C, 62.84; H, 4.62; N, 32.35
g	*p*-$CH_3SC_6H_4$	H	$C_9H_8N_4S$	145-148	12	A	C, 52.92; H, 3.95; N, 27.42 C, 52.70; H, 4.00; N, 27.59
h	*p*-HOC_6H_4	H	$C_8H_6N_4O$	242-244	32	A	C, 55.17; H, 3.47; N, 32.17 C, 54.99; H, 3.51; N, 32.33
i	*p*-HOC_6H_4	CH_3	$C_9H_8N_4O$	224-226	36	A	C, 57.44; H, 4.28; N, 29.77 C, 57.75; H, 4.28; N, 29.78
j	3-Cl,4-$CH_3C_6H_3$	H	$C_{10}H_7N_4Cl$	110-111	18	B	C, 52.31; H, 3.42; N, 27.11; Cl, 17.16 C, 52.44; H, 3.52; N, 26.72; Cl, 17.25
k	*m*-$CF_3C_6H_4$	H	$C_9H_5N_4F_3$	60-62	18	D	C, 47.79; H, 2.23; N, 24.77; F, 25.20 C, 47.60; H, 2.35; N, 24.91; F, 24.91
l	*m*-$CF_3C_6H_4$	CH_3	$C_{10}H_7N_4F_3$	46-48	16	D	C, 50.00; H, 2.94; N, 23.33; F, 23.73 C, 50.14; H, 2.96; N, 23.18; F, 23.60
m	*p*-$CH_3OC_6H_4$	H	$C_9H_8N_4O$	152-154	27	A	C, 57.44; H, 4.28; N, 29.77 C, 57.08; H, 4.45; N, 29.39
n	*p*-$CH_3OC_6H_4$	CH_3	$C_{10}H_{10}N_4O$	103-106	15	A	C, 59.39; H, 4.98; N, 27.71 C, 59.31; H, 5.08; N, 27.38
o	*p*-FC_6H_4	C_2H_5	$C_{10}H_9FN_4$	134-135	22	D	C, 58.81; H, 4.45; N, 27.44; F, 9.30 C, 58.81; H, 4.42; N, 27.44; F, 9.31
p	*p*-$CH_3C_6H_4$	C_2H_5	$C_{11}H_{12}N_4$	44-46	11	D	C, 65.98; H, 6.04; N, 27.98 C, 66.08; H, 6.03; N, 27.90
q	3,4-di-$CH_3C_6H_3$	CH_3	$C_{10}H_{10}N_4$	75-77	12	E	C, 65.98; H, 6.04; N, 27.98 C, 66.12; H, 6.09; N, 28.05
r	*m*-$CH_3OC_6H_4$	H	$C_9H_8N_4O$	96-98	18	E	C, 57.44; H, 4.28; N, 29.77 C, 57.26; H, 4.43; N, 29.99
s	3,4-di-$CH_3C_6H_3$	H	$C_{11}H_2N_4$	80-83	18	E	C, 64.50; H, 5.41; N, 30.09 C, 64.45; H, 5.41; N, 30.05
t	3,4,5-tri-$CH_3OC_6H_2$	H	$C_{11}H_9N_4O_3$	138-140	55	E	C, 53.22; H, 4.87; N, 22.57 C, 53.16; H, 4.80; N, 22.55

Table I (continued)

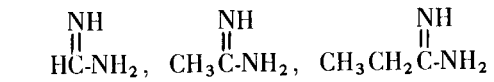
Compound	Ar(R_3)	R_2	Formula	M.p., °C	Yield, (a) %	Method of Preparation	Anal: Calcd. or Lit. (b) Found
u	3,4,5-tri-$CH_3OC_6H_2$	CH_3	$C_{12}H_{11}N_4O_3$	165-168	16	E	C, 54.95; H, 5.38; N, 21.36 C, 54.57; H, 5.51; N, 21.43
v	*o*-FC_6H_4	H	$C_8H_5FN_4$	36-38	16	G	C, 54.54; H, 2.86; N, 31.81; F, 10.79 (d) C, 54.48; H, 3.05; N, 31.58; F, 10.30
w	*o*-$CH_3C_6H_4$	H	$C_8H_5FN_4$	liq.	6	G	C, 62.78; H, 4.68; N, 32.54 C, 62.51; H, 4.73; N, 32.23
x	*o*-ClC_6H_4	H	$C_8H_5ClN_4$	48-50	1.2	G	C, 49.88; H, 2.62; N, 29.09; Cl, 18.41 C, 49.83; H, 2.66; N, 29.07; Cl, 18.69
y	*o*-FC_6H_4	CH_3	$C_9H_7FN_4$	38-40	11	E	C, 56.84; H, 3.71; N, 29.46; F, 9.99 C, 57.05; H, 3.76; N, 29.56; F, 9.77

(a) Isolated and purified yields. (b) All new compounds had supporting spectral data. (c) Reference 6. (d) $> \pm 0.40\%$.

exothermic and caution was neccessary. The formed "iminoester" was treated with an amidine acetate and hydrazine hydrate (with cooling and extreme caution). The "*N*-alkylnitriles" were treated with methanol (exothermic) before treatment with an amidine acetate and hydrazine hydrate (highly exothermic) (Scheme III). The normal workup then followed for both of these modifications.

The use of anhydrous hydrazine as a reactant gave slightly improved yields of *s*-tetrazines but the increased exothermic character made this pathway less advantageous. The use of an inert solvent, such as alcohol, gave similar yields and product mixtures.

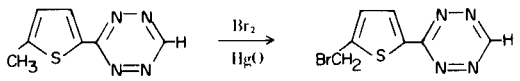
The yields of 3-aryl-*s*-tetrazines were generally lower when the steric size of the amidine was increased; *i.e.*



etc. and when *o*-iminoesters were used.

The *s*-tetrazines were remarkeably unreactive at the alkyl or H, or Ar residue. Many methods of bromination or chlorination were unsuccessful. In only one select case, halogenation of a methyl group on the aryl moiety was successful (Scheme IV).

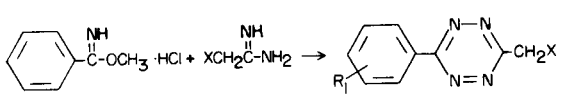
Scheme IV



3f **3x**

Extremely harsh conditions led to ring degradation and the formation of dimeric and polymeric materials. For instance, the attempted bromination of 3-phenyl-*s*-tetrazine using *n*-butyl lithium or trityl lithium and ethylene dibromide (8) gave a homogeneous dimer which we did not identify. We were successful with modification of the alkyl residue by using iminoesters of substituted acetonitriles. However, with increasing steric bulk, the yield of the desired 3-aryl-6-alkyl-*s*-tetrazine was minuscule and the 3,6-*bis*-aryl-*s*-tetrazine was the predominate product (Scheme V).

Scheme V



8, X = OCH_3, OPh, SCH_3, SPh

We were able to perform certain transformations within these systems. The thio group could be oxidized to the sulfone and **8b** could be cleaved with boron tribromide to a relatively unstable alcohol **8i** plus traces of a bromide

Table II

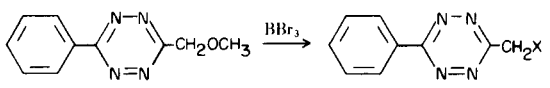
3,5-*Bis*-Aryl-*s*-tetrazines Prepared

Compound	Ar	Formula	M.p., °C	Anal.: Calcd. Found or Lit.
2a	C_6H_5	$C_{14}H_{10}N_4$	188-191	189-192° (a)
b	*p*-$CH_3C_6H_4$	$C_{16}H_{14}N_4$	230-234	C, 72.26; H, 5.38; N, 21.36 C, 72.99; H, 5.45; N, 21.49
c	*o*-FC_6H_4	$C_{14}H_8F_2N_4$	138-140	C, 62.22; H, 2.98; N, 20.73; F, 14.06 C, 61.92; H, 3.03; N, 20.38; F, 14.38
d	*m*-$CH_3C_6H_4$	$C_{16}H_{14}N_4$	135-138	C, 73.26; H, 5.38; N, 21.36 C, 73.56; H, 5.53; N, 21.12
e	*o*-$CH_3C_6H_4$	$C_{16}H_{14}N_4$	118-121	C, 73.26; H, 5.38; N, 21.36 C, 72.99; H, 5.18; N, 20.98
f	*p*-ClC_6H_4	$C_{14}H_8Cl_2N_4$	228-231	229-230° (b)

(a) Reference 3h and 7. (b) Reference 10.

8p (Scheme VI). The alcohol yielded an acetate **8k** when treated with acetic anhydride but when it was reacted with tosyl chloride, the tosylate was so labile that it could not be isolated. The acetate failed to displace with cyanide but the hydroxyl reacted with thionyl chloride to give an unstable chloride **8m** (Scheme VI).

Scheme VI

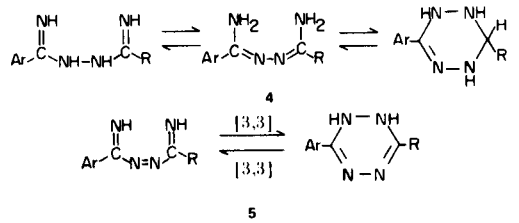


8b

8i, X = OH
k, X = OAc
l, X = $O_2CC_6H_5$
m, X = Cl
p, X = Br

The diimide side products are tautomeric with dihydro-*s*-tetrazines and the benziminoyl hydrazines with tetrahydro-*s*-tetrazines. It is on the basis of spectral analysis and the fine points therein that the ring opened from is believed to be the predominate form (Scheme VII).

Scheme VII



4

5

The mass spectrum of **4c** (Figure I) shows the loss of NH_2 from the parent ion, a protonated nitrile radical, a phenyl radical, and splitting of the central N-N bond with a proton shift. The nmr (DMSO-d_6-deuteriochloroform) of **4c** shows the CH_3 at 2.42 δ, 4-NH's at 6.25 δ, a doublet at 7.26 δ (8 Hz), a doublet of doublets at 7.78 δ (2 Hz and 8 Hz), and a doublet at 7.92 δ (2 Hz).

The mass spectrum of **5a** (Figure II) shows the parent ion and the ion for the protonated nitrile as the only significant ions. The nmr (TFA) of **5g** shows the usual pyridine coupling at 8.40 δ (3) and 8.8 δ (m) with other minor coupling. A broad singlet exists at 8.32 δ (-N^{NH}H). For **5b** the nmr (DMSO-d_6) has signals at 7.5 δ (m, 2) 7.92 δ (m, 4), 8.6 δ (m, 2) and 8.9 δ (NH's, exchangeable).

EXPERIMENTAL

All melting points are uncorrected and were observed on a Mel-Temp ®. Nmr were recorded on a Varian HA 100 and are reported as ppm from TMS. Ir were recorded on a Perkin-Elmer 137 and unless otherwise noted were recorded as a potassium bromide pellet.

All solvents were dried before use, and all reagents, unless otherwise noted, were used as received. For nmr solvents, DMSO refers to DMSO-d_6. The silica gel used for chromatography was 200-325 mesh (Grade 922) obtained from the Grace Division Chemical Company. Mass spectra were obtained on a AEI MS 902 Instrument.

Preparation of Iminoester Hydrochloride (Pinner Conditions).

A suspension or solution of 100 g. of arylnitrile (arylacetonitrile) in 250 ml. of ether and 50 ml. of methanol (alcohol) was cooled to 0-5° and a stream of dry hydrogen chloride gas introduced through the stirred solution. When saturation was reached, the gas flow was discontinued and the solution stored at 0-5° for 1-5 days (at room temperature for iminoesters of pyridines). The crystals were collected by filtration, washed well with ether, and recrystallized from ethanol.

In some cases, a suspension of arylnitrile (50 g.) in 100 ml. of methanol was treated with 25 ml. of methanol saturated with dry hydrogen chloride gas and the solution stirred at 0-5° for 6 hours and then stored at 0-5° for 1 day. The solution was treated with 250 ml. of ether and the crystals which formed were collected and recrystallized from ethanol.

Figure I

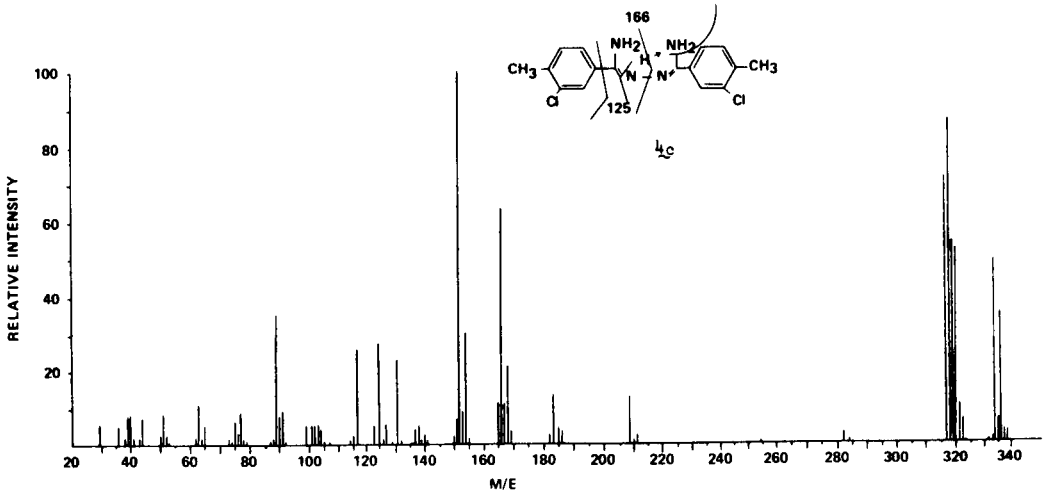
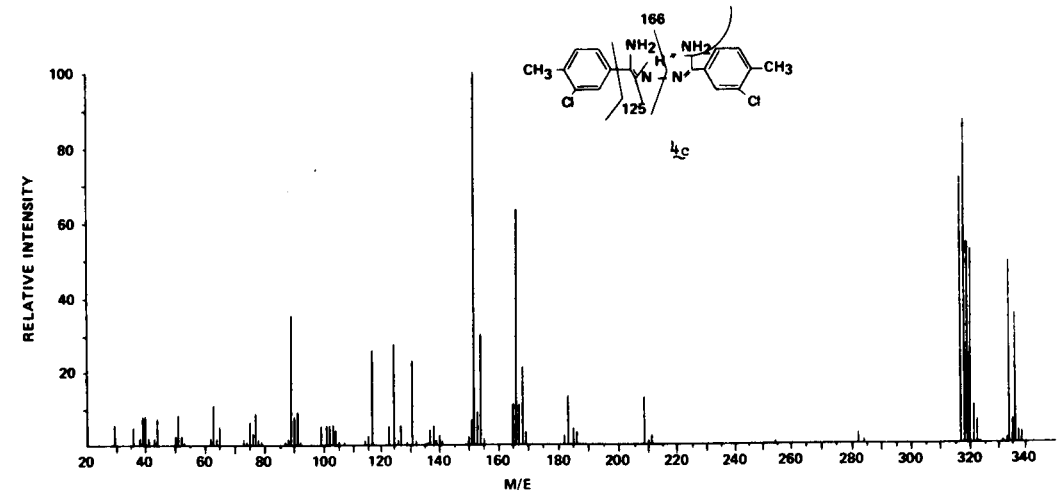


Figure I



Preparation of Iminoesters by the Action of Sodium Borohydride.

A solution of heterocyclic nitrile (50 g.) in 150 ml. of ethanol was treated with (1/16 mole) sodium borohydride and the resultant was refluxed for 5-16 hours. The ethanol was removed *in vacuo* or distilled off and the resultant iminoester was purified by distillation at reduced pressure (9).

Method A.

3-(*p*-Chlorophenyl)-*s*-tetrazine (**1b**).

A suspension of 10 g. (0.053 mole) of ethyl *p*-chloroiminobenzoate hydrochloride and 15 g. (0.15 mole) of formamidine acetate in 35 ml. of hydrazine hydrate was stirred at room temperature for 2-3 hours. The now yellow suspension was poured into 250 ml. of water and the resulting solid was collected by filtration and sucked as dry as possible. The damp solid was dissolved in 80 ml. of glacial acetic acid and placed in a cooling bath at 5-10°. Sodium nitrite (~5 g.) was slowly added with vigorous stirring. After addition (~10-15 minutes), the dark purple solution was poured into water (300 ml.) and the solid was collected and air dried.

The solid was chromatographed on silica gel, eluting with methylene chloride. The initial fraction yielded 3,6-*bis*-*p*-chlorophenyl)-*s*-tetrazine (**2f**), m.p. 228-231° (220 mg.). The second fraction yielded the desired material, 3-(*p*-chlorophenyl)-*s*-tetrazine (**1b**), 4.5 g. (44.1%), m.p. 164-167°.

Further elution (methylene chloride-5% methanol) gave a yellow solid (chloroform), m.p. 180-183° (-gas), which resolidified and then melted 278-281°. This was identified as *sym*-1,2-*bis*-(*p*-chlorobenziminoyl)hydrazine.

In other runs, a white material eluted with 5% methanol-methylene chloride. This material, m.p. 278-281°, was identified as 3,5-*di*-(*p*-chlorophenyl)-1,2,4-triazole.

Method B.

3-Phenyl-*s*-tetrazine (**1a**).

Table III

Aryl and Alkyl-*s*-tetrazines Prepared

Compound	R_1	R_2	Formula	M.p., °C	% Yield (a)	Method (a) of Preparation	Anal.: Calcd. Found or Lit. (b)
3a	1-Naphthyl	H	$C_{12}H_8N_4$	105-108	3	E	C, 69.22; H, 3.87; N, 26.91 C, 68.97; H, 4.03; N, 27.21
b	1-Naphthyl	H	$C_{12}H_8N_4$	198-201	21	E	C, 69.22; H, 3.87; N, 26.91 C, 68.93; H, 3.90; N, 27.02
c	2-Naphthyl	CH_3	$C_{13}H_{10}N_4$	128-130	28	E	C, 70.25; H, 4.54; N, 25.21 C, 70.28; H, 4.51; N, 25.24
d	2-Thienyl	CH_3	$C_7H_6N_4S$	132-135	34	A	C, 47.17; H, 3.39; N, 31.44; S, 17.99 C, 46.96; H, 3.38; N, 31.79; S, 18.36
e	2-Thienyl	H	$C_6H_4N_4S$	103-105	46	A	C, 43.89; H, 2.45; N, 34.13; S, 19.53 C, 43.88; H, 2.51; N, 34.35; S, 19.86
f	5-Methyl	H	$C_7H_6N_4S$	113-114	6	A	C, 47.17; H, 3.38; N, 31.44; S, 18.00 C, 47.03; H, 3.53; N, 31.81; S, 17.93
g	5-Methyl-2-thienyl	CH_3	$C_8H_8N_4S$	118-120	22	A	C, 49.99; H, 4.06; N, 29.15; S, 16.68 C, 50.25; H, 4.07; N, 28.86; S, 16.68
h	5-Methyl-2-thienyl	5-Methyl 2-thienyl	$C_{12}H_{10}N_4S_2$	208-210			C, 52.53; H, 3.67; N, 20.42; S, 23.39 C, 52.49; H, 3.63; N, 20.07; S, 23.32
i	2-Pyridyl	CH_3	$C_8H_7N_5$	61-64	6	D	C, 55.28; H, 4.07; N, 40.45 C, 55.32; H, 3.98; N, 40.08
j	5-Chloro-2-thienyl	H	$C_6H_3ClN_4S$	124-126	2	E	C, 36.27; H, 1.52; N, 28.20; Cl, 17.85; S, 16.14 C, 36.63; H, 1.61; N, 28.31; Cl, 17.56; S, 16.31
k	5-Bromo-2-furyl	H	$C_6H_3BrN_4O$	160-163	15	E	C, 31.73; H, 1.33; N, 24.68; Br, 35.20 C, 31.59; H, 1.48; N, 24.64; Br, 35.08
l	5-Bromo-2-furyl	H	$C_7H_5N_5$	100-102	20	E	C, 34.88; H, 2.09; N, 23.24; Br, 33.15 C, 34.46; H, 2.18; N, 23.19; Br, 32.82
m	2-Pyridyl	H	$C_7H_5N_5$	100-102	3	A	C, 53.82; H, 3.15; N, 44.01 C, 53.62; H, 3.41; N, 44.07
n	5-Bromo-2-furyl	5-Bromo-2-furyl	$C_{10}H_4Br_2N_4O_2$	260-262			C, 32.29; H, 1.08; N, 15.06; Br, 42.97 C, 32.32; H, 1.13; N, 15.02; Br, 43.06
o	3-Pyridyl	CH_3	$C_8N_7N_5$	92-94	11	D	C, 55.48; H, 4.07; N, 40.45 C, 55.23; H, 4.06; N, 40.09
p	1-Adamantyl	1-Adamantyl	$C_{20}H_{30}N_4$	170-173			C, 75.39; H, 8.63; N, 15.99 C, 75.33; H, 8.99; N, 16.12
q	1-Cyclohexyl	1-Cyclohexyl	$C_{14}H_{22}N_4$	35-38			C, 68.25; H, 9.00; N, 22.74 C, 67.98; H, 8.96; N, 22.28
r	1-Adamantyl	CH_3	$C_{13}H_{18}N_4$	68-71	8	A	C, 67.89; H, 7.88; N, 24.33 C, 67.81; H, 8.03; N, 23.92
s	1-Adamantyl	H	$C_{12}H_{16}N_4$	112-114	10	A	C, 66.64; H, 7.46; N, 25.91 C, 66.24; H, 7.32; N, 25.59
t	1-Cyclohexyl	H	$C_8H_{12}N_3$	red oil	8	A	C, 58.51; H, 7.37; N, 34.12 C, 58.24; H, 7.59; N, 34.11

Table III (continued)

Compound	R_1	R_2	Formula	M.p., °C	% Yield (a)	Method (a) of Preparation	Anal.: Calcd. Found or Lit. (b)
3u	1-Cyclohexyl	CH_3	$C_9H_{14}N_4$	red oil	8	A	C, 60.65; H, 7.92; N, 31.44 C, 60.47; H, 8.18; N, 31.03
v	1-Cycloheptyl	1-Cyclo-heptyl	$C_{16}H_{26}N_4$	43-45			C, 70.03; H, 9.55; N, 20.42 C, 69.72; H, 9.56; N, 20.07
w	1-Cycloheptyl	H	$C_9H_{14}N_4$	red oil	5	A	C, 60.68; H, 7.42; N, 31.44 C, 60.44; H, 7.86; N, 31.69
x	5-Bromomethyl-2-thienyl	H	$C_7H_5BrN_4S$	130-132	55 (c)		C, 32.70; H, 1.96; N, 21.79; S, 12.47; Br, 31.08 C, 32.96; H, 2.01; N, 21.91; S, 12.67; Br, 31.28
y	*p*-$BrC_6H_4CH_2$	H	$C_9H_7BrN_4$	53-56	40	A	C, 43.05; H, 2.81; N, 22.32; Br, 31.83 C, 43.16; H, 2.74; N, 22.24; Br, 32.21
z	*p*-$BrC_6H_4CH_2$	CH_3	$C_{10}H_9BrN_4$	65-67	23	A	C, 45.30; H, 3.42; N, 21.13; Br, 30.14 C, 44.98; H, 3.30; N, 21.09; Br, 30.17
aa	*p*-$BrC_6H_4CH_2$	*p*-$BrC_6H_4CH_2$	$C_{16}H_{12}Br_2N_4$	154-156	16		C, 45.74; H, 2.88; N, 13.34; Br, 38.04 C, 45.54; H, 2.76; N, , 3.35; Br, 38.19
bb	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{16}H_{14}N_4$	72-75	2.4		C, 73.26; H, 5.38; N, 21.36 C, 73.56; H, 5.42; N, 21.30
cc	$C_6H_5CH_2$	H	$C_9H_8N_4$	red oil	12	A	C, 62.78; H, 4.68; N, 32.54 C, 62.76; H, 4.78; N, 32.72
dd	*p*-$ClC_6H_4CH_2$	H	$C_9H_7ClN_4$	47-49	7.8	A	C, 52.31; H, 3.41; N, 27.11; Cl, 17.17 C, 52.16; H, 3.40; N, 27.17; Cl, 17.10
eee	*p*-$ClC_6H_4OH_2$	CH_3	$C_{10}H_9BrN_4$	39-42	9	A	C, 54.43; H, 4.11; N, 25.39; Cl, 16.07 C, 54.30; H, 4.15; N, 25.37; Cl, 16.06
ff	2-Thienyl-CH_2	H	$C_7H_6N_4S$	red oil (d)	12	A	C, 47.14; H, 3.39; N, 31.44; S, 17.00 C, 47.32; H, 3.62; N, 31.58; S, 16.88
gg	2-Thienyl-CH_2	CH_3	$C_8H_8N_4S$	red oil (e)	8	A	C, 49.98; H, 4.19; N, 29.15; S, 16.68 C, 50.28; H, 4.25; N, 29.20; S, 16.45
hh	2-Thienyl	C_2H_5	$C_8H_8N_4S$	69-71	15	D	C, 49.99; H, 4.19; N, 29.15; S, 16.68 C, 49.89; H, 4.07; N, 29.48; S, 17.03

(a) Yields and methods of preparation are recorded for 3-aryl-6-alkyl-*s*-tetrazines only. (b) All compounds have supporting spectral data. (c) Formed by other transformation. (d) Decomposes violently when heated neat and moderately when stored at room temperature. (e) Decomposes slowly when heated or stored at room temperature for long periods.

Table IV

3-Phenyl-6-substituted-methyl-*s*-tetrazines Prepared

Compound	Ar	X	Formula	M.p., °C	% Yield	Anal.: Calcd. Found (b)
8a	*p*-FC_6H_4	OCH_3	$C_{10}H_9FN_4O$	97-98	19 (a)	C, 54.54; H, 4.12; N, 25.45; F, 8.63 C, 54.48; H, 4.26; N, 25.78; F, 8.52
b	C_6H_5	OCH_3	$C_{10}H_{10}N_4O$	59-60	24 (a)	C, 59.39; H, 4.98; N, 27.71 C, 59.15; H, 5.08; N, 27.81
c	*p*-ClC_6H_4	OCH_3	$C_{10}H_9ClN_4O$	123-125	13 (a)	C, 51.42; H, 3.75; N, 23.84; Cl, 14.55 C, 51.03; H, 3.91; N, 24.00; Cl, 14.40
d	*p*-$CH_3C_6H_4$	OCH_3	$C_{11}H_{12}N_4$	46-48	26 (a)	C, 61.09; H, 5.59; N, 25.91 C, 61.20; H, 5.61; N, 26.11
e	*m*-ClC_6H_4	OC_6H_5	$C_{15}H_{11}ClN_4O$	102-103	8 (a)	C, 60.31; H, 3.71; N, 18.76; Cl, 11.87 C, 60.07; H, 3.74; N, 18.63; Cl, 11.61
f	*p*-ClC_6H_4	OC_6H_5	$C_{15}H_{11}ClN_4O$	152-153	15 (a)	C, 60.31; H, 3.71; N, 18.76; Cl, 11.87 C, 59.91; H, 3.78; N, 18.74; Cl, 11.91
g	*p*-FC_6H_4	OC_6H_5	$C_{15}H_{11}FN_4O$	142-143	18 (a)	C, 63.82; H, 3.93; N, 19.85; F, 6.73 C, 63.57; H, 4.15; N, 20.04; F, 6.68
h	C_6H_5	SCH_3	$C_{10}H_{10}N_4S$	96-98	32 (a)	C, 55.02; H, 4.61; N, 25.67; S, 14.69 C, 54.82; H, 4.64; N, 25.82; S, 14.76
i	C_6H_5	OH	$C_9H_8N_4O$	92-95	50	C, 57.44; H, 4.29; N, 29.77 C, 57.36; H, 4.93; N, 30.08
j	C_6H_5	$O_2SC_6H_5$	$C_{15}H_{12}N_4O_2S$	134-135	66	C, 57.68; H, 3.87; N, 17.94; S, 10.27 C, 57.87; H, 3.95; N, 17.88; S, 10.09
k	C_6H_5	O_2CCH_3	$C_{11}H_{10}N_4O_2$	85-86	66	C, 57.38; H, 4.38; N, 24.34 C, 57.81; H, 4.47; N, 24.62
l	C_6H_5	$O_2CC_6H_5$	$C_{16}H_{12}N_4O_2$	115-117	92	C, 65.75; H, 4.14; N, 19.17 C, 65.59; H, 3.80; N, 19.45
m	C_6H_5	Cl	$C_9H_7ClN_4$	102-103	41	C, 52.31; H, 3.41; N, 27.12; Cl, 17.16 C, 52.33; H, 3.49; N, 27.06; Cl, 17.06
n	C_6H_5	O_2SCH_3	$C_{10}H_{10}N_4O_2S$	194-195	62	C, 47.99; H, 4.03; N, 22.39; S, 12.81 C, 47.98; H, 3.86; N, 22.70; S, 12.81
o	C_6H_5	OC_6H_5	$C_{15}H_{12}N_4O$	122-124	20 (a)	C, 68.17; H, 4.58; N, 21.20 C, 68.05; H, 4.53; N, 21.22
p	C_6H_5	Br	$C_9H_7N_4Br$	125-126	(c)	C, 43.05; H, 2.81; N, 22.32; Br, 31.29 C, 42.81; H, 2.87; N, 22.58; Br, 31.29
q	$C_6H_5SCH_2$	SC_6H_5	$C_{16}H_{14}N_4S_2$	93-95 (a)	23	C, 58.87; H, 4.32; N, 17.16; S, 14.65 C, 59.06; H, 4.23; N, 17.09; S, 14.82
r	CH_3SCH_2	SCH_3	$C_6H_{10}N_4S_2$	61-63 (a)	32	C, 35.62; H, 4.98; N, 27.70; S, 31.70 C, 35.56; H, 5.17; N, 27.78; S, 31.78
s	2-Thienyl	SCH_3	$C_7H_8N_4S_2$	99-101 (a)	13	C, 42.83; H, 3.59; N, 24.98; S, 28.60 C, 43.03; H, 3.87; N, 24.85; S, 28.78
t	2-Thienyl	SC_6H_5	$C_{12}H_{10}N_4S_2$	77-79 (a)	4	C, 54.52; H, 3.52; N, 19.57; S, 22.39 C, 54.84; H, 3.66; N, 19.19; S, 22.17
u	$C_6H_5OCH_2$	OC_6H_5	$C_{14}H_{14}N_4O_2$	122-124	10	C, 65.29; H, 4.80; N, 19.04 C, 65.68; H, 4.96; N, 19.37
v	2-Thienyl	OC_6H_5	$C_{13}H_{10}N_4OS$	97-99 (a)	17	C, 57.76; H, 3.73; N, 20.94; S, 12.26 C, 57.69; H, 3.64; N, 20.94; S, 12.26

(a) Prepared by Method A. (b) All new compounds have supporting spectral data. (c) Isolated in trace amounts from synthesis of **8i**, see Experimental.

A suspension of ethyl iminobenzoate hydrochloride (5 g.) and formamidine acetate (10 g.) was treated with 15 ml. of 95% hydrazine (highly exothermic). After stirring for 15 minutes, the mixture was diluted with water (30 ml.) and the solid was collected, sucked as dry as possible, and suspended in acetic acid. The solution was cooled to 0-5° and treated with 4 g. of sodium nitrite (in small batches) over a 10 minute period. After stirring 10 additional minutes, the mixture was diluted with water and the solid was collected and dried.

The red solid was chromatographed on silica gel, eluting with methylene chloride, to give as the first eluting material, 3,5-*bis*-phenyl-*s*-tetrazine (**2a**), m.p. 196-198° (3h,7). The second eluting material is 3-phenyl-*s*-tetrazine, m.p. 155-160°, lit. m.p. 158-159° (10,11). Further elution with 5% methanol-methylene chloride gave 1,2-*bis*-(benzimidoyl)hydrazine, m.p. 189-192° (**4a**).

Method C.

3-(*p*-Fluorophenyl)-*s*-tetrazine (**1d**).

Table V

Benziminoyl Hydrazines Observed

Compound	R	M.p., °C	Anal. Calcd. / Found or Other
4a	H	189-192	lit. m.p. 190-191°
b	*m*-CF_3	174-175	C, 51.34; H, 3.23; N, 14.97; F, 30.36 C, 51.25; H, 3.32; N, 15.17; F, 29.87
c	3-Cl, 4-CH_3	199-202	C, 57.32; H, 4.81; N, 16.71; Cl, 21.15 C, 57.04; H, 4.60; N, 16.93; Cl, 21.03

Benziminoyldiimides Observec

Compound	Ar	R	M.p., °C	Anal. Calcd. / Found or Other
5a	3-Pyridyl	H	140-142	m/e calcd. 161 (a) obs 161
b	2-Pyridyl	2-Pyridyl	210-215	m/e calcd. 238 (b) obs 238
c	2-Pyridazyl	2-Pyridazyl	230-233	C, 50.00; H, 3.36; N, 46.65 C, 49.96; H, 3.37; N, 46.76

(a) C $>\pm 0.40\%$. (b) N $>\pm 0.40\%$.

Tetrazoles Observed

Compound	Ar	M.p., °C	Anal. Calcd. / Found
6a	5-Chloro-2-thienyl	210-212	C, 32.17 (a); H, 1.62; N, 30.02; Cl, 19.00; S, 17.18 C, 32.69; H, 1.71; N, 29.97; Cl, 18.95; S, 17.34
b	*p*-IC_6H_4	270-272	C, 30.91; H, 1.85; N, 20.60; I, 49.65 C, 31.07; H, 2.00; N, 20.98; I, 49.66

(a) $>\pm 0.40\%$.

Triazoles Observed

Compound	Ar	M.p., °C	Anal. Calcd. / Found
7a	*p*-$CH_3C_6H_4$	249-250	C, 77.08; H, 6.06; N, 16.86 C, 76.95; H, 6.34; N, 16.78
b	*m*-$CF_3C_6H_4$	213-215	C, 53.79; H, 2.54; N, 11.76; F, 31.91 (a) C, 53.32; H, 2.37; N, 11.57; F, 31.82

(a) $>\pm 0.40\%$.

A suspension of methyl *p*-fluoroiminobenzoate (6.5 g.) and formamidine acetate (12 g.) were treated with 20 ml. of hydrazine hydrate and stirred for 15 minutes. The reaction mixture was poured into 50 ml. of acetic acid and the remaining manipulations were as outlined in Method A, yield 1.9 g. (32%), m.p. 144-146°.

Method D.

3-Ethyl-6-*p*-tolyl-*s*-tetrazine (**1p**).

A suspension of methyl *p*-methyliminobenzoate hydrochloride (10 g., 0.054 mole) and propionamidine acetate (20 g.) was treated with 30 ml. of hydrazine hydrate. After stirring for 15 minutes, the addition of water gave an oil which was extracted with chloroform. After solvent removal, the residue was dissolved in acetic acid (50 ml.) and cooled to 0-5°. Sodium nitrite (7.5 g.) was added in small batches over a 15 minute period. Dilution with water gave an oil which was extracted with chloroform. Solvent removal gave a purple semi-solid which was chromatographed on silica gel, eluting with dichloromethane. The first eluting material was identified as 3,6-*bis*-(*p*-tolyl)-*s*-tetrazine (**2b**). The second fraction was 3-ethyl-6-*p*-tolyl-*s*-tetrazine, m.p. 44-46° (1.65 g., 15%).

Further elution with 5% methanol-methylene chloride gave 2,5-*bis*-(*p*-tolyl)-1,2,4-triazole, m.p. 249-252° (**7a**).

Method E.

3-(*m*-Methoxyphenyl)-*s*-tetrazine (**1r**).

A suspension of *m*-methoxybenzamide (25 g., 0.17 mole) in 50

ml. of dichloromethane and 15 ml. (excess) of methylfluorosulfonate was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo* and the residue dissolved in dichloromethane. Methanol (10 ml.) was added slowly with cooling and the excess solvent and reagent were removed *in vacuo*.

The remaining residue was mixed well with formamidine acetate and placed in an ice bath. Hydrazine hydrate (60 ml.) was cautiously added and after the exotherm the ice bath was removed and the mixture was stirred for 30 minutes. Water was added and the residue was collected and treated as in Method A or D, yield 5.4 g. (19%), m.p. 96-98°.

Method F.

3-*o*-Tolyl-*s*-tetrazine (**1w**).

A solution of *o*-toluonitrile (10 g. 0.085 mole) in 50 ml. of dichloromethane and 15 ml. (excess) of methylfluorosulfonate was stirred at room temperature overnight. The solvent and excess reagent were removed *in vacuo* and the residue dissolved in dichloromethane. Methanol (10 ml.) was added slowly with cooling and the excess solvent and reagent were removed *in vacuo*.

Acetamidine acetate (20 g.) was added and the components mixed well. The flask was placed in an ice bath and hydrazine hydrate (35 ml.) was added with extreme caution as the reaction was highly exothermic. After all the hydrazine hydrate was added, the ice bath was removed and stirring was continued for 30 minutes. Water was added and the oily residue was treated as in Method D, yield 400 mg. (2.5%) of red oil.

Method G.

3-(*o*-Tolyl)-*s*-tetrazine (**1w**).

A solution of 25 g. of *o*-toluamide and 30 ml. of methyl fluorosulfonate in 100 ml. of chloroform was refluxed for 5 hours. Solvent removal *in vacuo* gave an oily residue which was treated as outlined in Method D, to give a deep red oil.

3-Chloromethyl-6-phenyl-*s*-tetrazine (**8m**).

A solution of 0.95 g. (5 mmoles) of 6-phenyl-*s*-tetrazine-3-methanol in 10 ml. of thionyl chloride was allowed to stand for 24 hours. Then the reaction was taken to a solid *in vacuo* without the application of heat. This was extracted with boiling hexane. After filtration, the hexane solution was allowed to go to dryness in an air stream, and the solid was chromatographed with methylene chloride on silica gel to give 420 mg. (40.7%) of the product, which melted at 102-103°.

6-Phenyl-*s*-tetrazine-3-methanol (**8i**).

To a solution of 10.1 g. (0.05 mole) of 3-(methoxymethyl)-6-phenyl-*s*-tetrazine in 100 ml. of methylene chloride cooled in a dry ice-acetone bath was added in a dropwise fashion a solution of 7.2 ml. (18.75 g., 0.075 mole) of boron tribromide in 25 ml. of methylene chloride. Stirring and cooling were continued for 6 hours, then 100 ml. of water was added dropwise. The solution was warmed to room temperature, allowed to stand overnight and the layers were separated. The aqueous layer was extracted with 2-50 ml. portions of methylene chloride. The combined methylene chloride layers were dried and the solution added to a column of grade 922 silica gel. Elution was effected with methylene chloride. The first eluting material was 4.13 g. of starting material, followed by 4.65 g. (49.5%; 83.8% based on starting material consumed) of the desired product, which melted at 95-96°. The analytical sample was purified by recrystallization from ethyl acetate-hexane, m.p. 92-95°.

Besides the alcohol, traces of the bromomethyltetrazine, **8p**, melting at 125-126° could be isolated; nmr (deuteriochloroform, 60 Hz): 5.18 (s, 2), 7.70 (m, 3), 8.72 (m, 2).

6-Phenyl-*s*-tetrazine-3-methanol Benzoate (**8l**).

A 4 ml. portion of benzoyl chloride was added to a 3.76 g. (0.02 mole) portion of 6-phenyl-*s*-tetrazine-3-methanol in 25 ml. of pyridine. After stirring for about ¾ hour, 10 ml. of methanol was added to quench the reaction. Addition of 100-150 ml. of methanol gave 3.79 g. of crystals, 116-119°. The filtrate was allowed to go to dryness in an air stream, and addition of methanol to this gave an additional 1.54 g. of product, melting at 115-117°, total yield, 5.34 g. (91.5%). The analytical sample was purified by chromatography on silica gel eluting with methylene chloride followed by recrystallization from ethyl acetate-hexane, m.p. 116-119°.

6-Phenyl-*s*-tetrazine-3-methanol Acetate (**8k**).

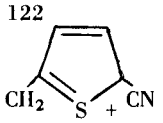
A 3.7 g. (0.02 mole) portion of 6-phenyl-*s*-tetrazine-3-methanol in 20 ml. of acetic anhydride was cooled in an ice bath and 5 ml. of pyridine was added slowly dropwise. After stirring and cooling for half an hour, 200 ml. of water was added, giving a solid. This was filtered and chromatographed on silica gel eluting with methylene chloride to give 3.03 g. (66%) of the product, m.p. 90-92°. The analytical sample was purified by recrystallization from ethyl acetate-hexane, m.p. 85-86°.

3-(Methylsulfonyl)methyl-6-phenyl-*s*-tetrazine (**8n**).

An 86 ml. portion of 30% hydrogen peroxide was added to 31.09 g. (0.143 mole) of 3-(methylthio)methyl-6-phenyl-*s*-tetrazine in 480 ml. of acetic acid. After stirring overnight, the resulting solid was filtered and recrystallized from acetic acid to give 22.11 g. (61.9%) of the product, m.p. 194-195°.

3-(5-Bromomethyl-2-thienyl)-*s*-tetrazine (**3x**).

A solution of tetrazine (500 mg., 0.0028 mole), and NBS (510 mg., 0.0029 mole) in 15 ml. of carbon tetrachloride was refluxed and irradiated with a 500 W Hanovia for 2 hours. Cooling to 0°, filtration and solvent removal gave a red residue which was chromatographed on silica gel, eluting with dichloromethane. The first eluting material, m.p. 130-131° dec. was identified as 3-(5-bromomethyl-2-thienyl)-*s*-tetrazine; nmr (deuteriochloroform, 60 M Hz): 4.91 (s, 2), 7.40 (d, 1, J = 5 Hz), 8.35 (d, 1, J = 5 Hz), 10.28 (s, 1). M/e 256, 258 (m^+), 177 (*m*-Br), 122



A suspension of *s*-tetrazine (1 g.), bromine (1 g.) and mercuric oxide (2 g.) in 15 ml. of carbon tetrachloride was stirred at room temperature for 4 hours. Filtration and solvent removal gave material identical to that reported above.

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