[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF ILLINOIS INSTITUTE OF TECHNOLOGY AND THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH]

IV. Some 3,6-Unsymmetrically Disubstituted 1,2,4,5-Tetrazines[1a,b,c]

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A synthetic route to some hitherto inaccessible 3,6-unsymmetrically disubstituted 1,2,4,5-tetrazines is described which is based on the observation that C-phenyl-N-guanyl-N′-5-tetrazolylformazan (Ia) reacts with bromine in acetic acid to afford 3-bromo-6-phenyl-1,2,4,5-tetrazine (IIIa). The presence of a 1,2,4,5-tetrazine ring is indicated from visible absorption measurements λ_{max} (ethanol) 530 mμ, log ϵ_{max} 2.71. Additional confirmation is derived from the characteristic facile interconversion of IIIa and its 1,2-dihydro derivative IVa through oxidation–reduction. The position of the bromine substituent is established on the basis of the ease of reductive debromination with $NaBH_4$ and the ready displacement of the halogen by nucleophilic reagents. The synthesis is extended to include the preparation of other 3-bromo-6-substituted phenyl-1,2,4,5-tetrazines (Ib and e). The corresponding *p*-nitro- (Ic) and *m*-nitrophenylformazans (Id) gave red solids, λ_{max} 527–529 mμ (anisole), which failed to afford analyses consistent with 3-bromo-6-*p*-nitro- (IIIc) and *m*-nitrophenyl-1,2,4,5-tetrazine, respectively. However, the solids were readily converted to 3-diethylamino-6-*p*- and *m*-nitrophenyl-1,2,4,5-tetrazine on treatment with excess diethylamine. A number of 3-mono- and disubstituted amino derivatives of III are reported together with their principal absorption maxima.

Wedekind observed that the oxidation of C,N′-diaryl-N-guanylformazans (guanazyls) with nitric acid gave 2,5-diaryltetrazoles.[3] Recently, Scott, O'Sullivan and Reilly applied this reaction to the synthesis of 2,5-diaryltetrazoles from bisguanazyls which lose the guanidine carbon atom on treatment with a variety of oxidizing agents.[4] The possible application of this reaction to the preparation of 2-(5-tetrazolyl)-5-aryltetrazoles (II) prompted the present investigation. However, it was found that oxidation of C-phenyl-N-guanyl-N′-5-tetrazolylformazan[5] (Ia) with concentrated nitric acid[6] failed to yield a tetrazole. In fact, the complete degradation of I appeared to occur, as indicated by a copious evolution of gas and the failure to detect a nitrogenous product. A similar phenomenon was observed with amyl nitrite.

The desired oxidative ring closure was ultimately effected in 70% yield with aqueous alkaline potassium permanganate at room temperature. The reaction was extended to include the preparation of 2-(5′-tetrazolyl)-5-*p*-chloro-(IIb) and *p*-nitrophenyltetrazole (IIc) in comparable yields from the corresponding formazan (Ib and c).

In the course of a search for a suitable reagent to accomplish the desired transformation (I → II), it was observed that treatment of Ia with bromine in glacial acetic acid at 40–60° gave a red crystalline solid with properties considered inconsistent with those anticipated of II. Thus, the product IIIa afforded an analysis corresponding to the molecular formula $C_8H_5N_4Br$ and exhibited a sharp absorption maximum in the visible range, λ_{max} (ethanol) 530 mμ, log ϵ 2.71.

Treatment of IIIa with zinc dust in glacial acetic acid resulted in a rapid discharge of the red color and the formation of a light yellow solid, $C_8H_7N_4Br$ (IVa). The latter readily could be reoxidized to the original red solid by the action of bromine in acetic acid. Reduction of IIIa with excess sodium borohydride in aqueous tetrahydrofuran, followed by oxidation with nitrous acid, gave a new red solid, $C_8H_6N_4$ (Va), λ_{max} (ethanol) 540 mμ (log ϵ 2.75).

The facile interconversion of IIIa and IVa through oxidation–reduction together with the spectral evidence are characteristic of the 1,2,4,5-tetrazine ring.[7a,b] Furthermore, the ready reductive debromination suggested attachment to the heterocycle rather than benzene. On the basis of this interpretation, the structure 3-bromo-6-phenyl-1,2,4,5-tetrazine was assigned to IIIa and Va must then be 3-phenyl-1,2,4,5-tetrazine. It follows, then, that the product of reduction, IVa, with zinc and acetic acid is 3-bromo-6-phenyl-1,2-dihydro-1,2,4,5-tetrazine.[8]

Further confirmation for the assignment of the bromine to the "3-" position of the tetrazine ring was obtained from the reactions of the red solid with nucleophilic reagents. Thus, treatment of IIIa with ethanolic potassium hydroxide gave, on acidification, 3-hydroxy-6-phenyltetrazine (VIa) in 95% yield. The same transformation may be effected, though in low yield, with aqueous ammonia.

Attempts to convert IIIa into an alkoxy derivative with both sodium ethoxide and methoxide were unsuccessful. Instead, the reaction mixtures afforded the hydroxy derivative VIa in high yield.

A quantitative yield of 3-amino-6-phenyltetrazine (VIIa) was obtained by bubbling anhydrous ammonia through a benzene solution of IIIa. A comparable yield of 3-diethylamino-6-phenyltetrazine (VIIIa) was obtained by the addition of IIIa to an excess of diethylamine without the use of a

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(2) (a) Detroit Institute of Cancer Research, 4811 John R Street, Detroit 1, Mich. (b) To whom all requests for reprints and additional information should be directed.

(3) E. Wedekind, *Ber.*, **31**, 473 (1898).

(4) F. L. Scott, D. A. O'Sullivan and J. Reilly, THIS JOURNAL, **75**, 5309 (1953).

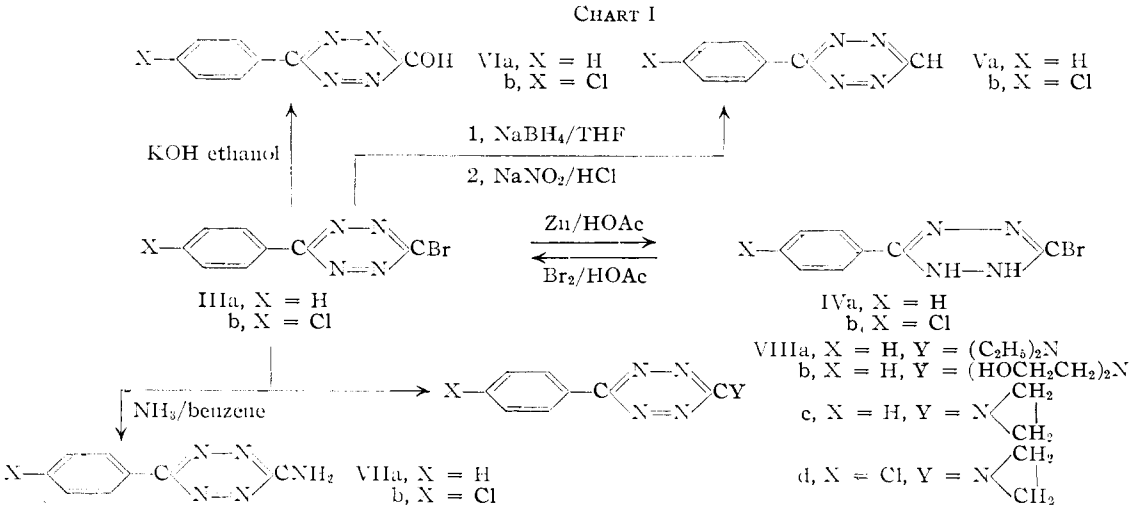
(5) K. A. Hofmann and H. Hock, *Ber.*, **44**, 2951 (1911).

(6) The oxidation of this same compound with 5% nitric acid yields a white solid, $C_9H_{10}N_4$, which has not yet been identified; see ref. 4.

(7) (a) E. Muller and L. Herrdegen, *J. prakt. Chem.*, **102**, 113 (1921); (b) C. H. Lin, E. Lieber and J. P. Horwitz, THIS JOURNAL, **76**, 427 (1954).

(8) Hereafter, the numbering directly preceding the tetrazine ring will be omitted.

CHART I



solvent. By contrast, the reaction of IIIa with diethanolamine proceeded more rapidly to the 3-bis-(2-hydroxyethyl)-amino- derivative VIIIb in tetrahydrofuran, while the 6-aziridinyl-derivative VIIIc was obtained in benzene using equimolecular quantities of ethyleniminc and triethylamine.

The literature contains only a few isolated examples of 3,6-unsymmetrically disubstituted tetrazines. This situation prevails as a result of an inherent limitation in the two general preparative methods for this ring system. These consist of (1) the conversion of a nitrile, an imino ester or a thiocarboxamide to a symmetrically disubstituted dihydrotetrazine by the action of hydrazine and (2) the alkaline dimerization of diazoacetic ester to 3,6-dicarboxydihydrotetrazine.[9]

The unexpected transformation of a guanazyl (Ia) to a 3,6-unsymmetrically substituted tetrazine (IIIa) prompted an investigation of the scope and limitations of a method potentially capable of affording an entirely new class of tetrazines. Accordingly, it was found that C-*p*-chlorophenyl[4]- (Ib) and C-*p*-methoxyphenyl-N-guanyl-N′-5-tetrazolylformazan[4] (Ie) readily could be converted to the corresponding tetrazine derivative III in yields of 49 and 25%, respectively. Furthermore, the series of reactions conducted with IIIa (*cf.* Chart I) were repeated successfully with 3-bromo-6-*p*-chlorophenyltetrazine (IIIb). In addition, a number of 3-mono- and disubstituted amino derivatives of IIIb were prepared by methods already described. The effect of these derivatives on tumor-bearing animals is now under study and the results will be reported elsewhere.

The reaction of C-*p*-nitro-(Ic) and *m*-nitrophenyl-N-guanyl-N′-5-tetrazolyl-formazan (Id) with bromine gave red solids, λ_{max} 527–529 mμ which appeared to be 3-bromo-6-*p*-nitro-(IIIc) and *m*-nitrophenyltetrazine (IIId), respectively. However, all attempts to obtain satisfactory elementary analyses for these products proved unsuccessful. On the other hand, the red solids were readily converted, in nearly quantitative yield, to 3-diethylamino-6-*p*-nitro- and *m*-nitrophenyltetrazine on warming with excess diethylamine. Apparently the desired bromo compounds IIIc and d were obtained, but the products still retain a small amount of impurity which is not readily removed by repeated fractional crystallization, vacuum sublimation or chromatography over silica gel.

Attempts to convert C-3-pyridyl- and C-2-thienyl-N-guanyl-N′-5-tetrazolylformazan to the corresponding tetrazines were unsuccessful. Instead, yellow explosive solids were obtained which have not yet been identified. It seems pertinent to mention that significant quantities of apparently similar yellow solids were detected in the successful preparations of III. The sensitivity of these compounds toward heat has, to date, precluded the procurement of satisfactory elementary analyses.

The visible absorption spectra of some of the tetrazines prepared in the present study have been measured and the principal maxima are summarized in Table II. In accord with previous observations,[7a,b] the maxima occur in the region 520–545 mλ, although in some cases these maxima appear to be somewhat broader than usual.

Experimental[10]

C-*m*-Nitrophenyl-N-guanyl-N′-5-tetrazolylformazan (Id).—The intermediates C-phenyl-5 (143–147° dec.), C-*p*-chlorophenyl-[4] (142–146° dec.) and C-*p*-methoxyphenyl-N-guanyl-N′-5-tetrazolylformazan[4] (149–155° dec.) were prepared according to previously described methods. The preparation of the analogous C-3-thienyl and C-3-pyridyl-formazans, which failed to afford a tetrazine, will be reported subsequently as part of a related investigation.

Melting points, as determined on a Fisher–Johns block, generally are not sharp, which is in accord with previous observations.[4] Furthermore, all of the formazans prepared in the present study explode in a capillary tube and the explosion point appears to vary with the rate of heating. This property precluded the possibility of obtaining satisfactory elementary analyses.

Attempts to purify these compounds by crystallization from organic solvents appeared to effect decomposition. On the other hand, all formazans bearing a tetrazolyl substituent are readily soluble in dilute alkali, from which they may be reprecipitated in an apparently purified form.

The preparation of Id, which has not previously been described, is presented as a typical example of the general technique of formazan formation.

(a) **Diazotization.**—To a solution of 2.58 g. of 5-aminotetrazole hydrate (0.025 mole) in 6 ml. of concentrated

(9) P. F. Wiley in A. Weissberger, "The Chemistry of Heterocyclic Compounds," Vol. X, Interscience Publishers, Inc., New York, N. Y., 1956, pp. 179–181.

(10) All melting points are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

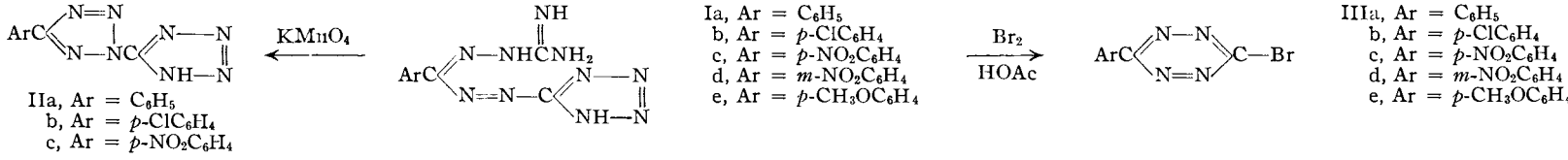


TABLE I

SOME 3,6-DISUBSTITUTED 1,2,4,5-TETRAZINES RC(N=N)=NCR'

R	R'	M.p., °C.	Crystalline form	Solvent of recrystn.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	X, % Calcd.	X, % Found
C_6H_5	Br	131–132	Red plates	Ether–petr. eth.	$C_8H_5N_4Br$	40.52	40.65	2.13	2.23	23.64	23.87	33.71	33.49
p-ClC_6H_4	Br	176–177	Red needles	Petr. eth.	$C_8H_4N_4BrCl$	35.29	35.60	1.48	1.65	20.64	20.59	42.49	42.36
p-$CH_3OC_6H_4$	Br	159–160	Orange ndls.	Ether–EtAcO	$C_9H_7N_4BrO$	40.47	40.99	2.64	2.70	20.98	21.39	29.92	29.02
C_6H_5	OH	184–185 d.	Red plates	Abs. EtOH	$C_8H_6N_4O$	55.17	55.10	3.47	3.68	32.17	32.10	...	...
p-ClC_6H_4	OH	175 dec.	Orange plates	Abs. EtOH	$C_8H_5N_4OCl$	46.05	46.40	2.42	2.44	26.86	26.82	...	...
C_6H_5	NH_2	226–227	Red needles	Abs. EtOH	$C_8H_7N_5$	55.48	55.39	4.07	4.22	40.45	40.45	...	...
p-ClC_6H_4	NH_2	243–244	Red plates	Abs. EtOH	$C_8H_6N_5Cl$	46.28	46.59	2.91	3.15	33.73	33.73	...	...
C_6H_5	H	125–126	Red plates	MeOH	$C_8H_6N_4$	60.75	60.87	3.83	3.85	35.43	35.14	...	...
p-ClC_6H_4	H	166–167	Red plates	Ether–petr. eth.	$C_8H_5N_4Cl$	49.88	50.09	2.62	2.81	29.09	28.82	18.41	18.64
C_6H_5	$N(CH_2)_2$	121–122	Red plates	Petr. eth.	$C_{10}H_9N_5$	60.29	60.67	4.55	5.10	35.17	34.49	...	...
C_6H_5	$N(CH_2CH_2OH)_2$	118.5–119.5	Red needles	Benzene	$C_{12}H_{15}N_5O_2$	55.16	55.25	5.79	5.72	26.81	26.57	...	...
C_6H_5	$N(CH_2CH_2SO_3CH_3)_2$	116–117 d.	Orange plates	Aq. acetone	$C_{14}H_{19}N_5S_2O_6$	40.28	40.48	4.59	4.63	16.78	16.80	...	...
C_6H_5	$NHCH_2COOH$	219–220	Orange plates	HOAc	$C_{11}H_{11}N_5O_2$	53.87	53.39	4.52	4.60	28.56	27.83	...	...
C_6H_5	$N(C_2H_6)_2$	60	Red plates	Aq. EtOH	$C_{12}H_{15}N_5$	62.86	63.23	6.59	6.75	30.55	30.29	...	...
p-ClC_6H_4	$N(CH_2)_2$	154–156	Red needles	EtOH	$C_{10}H_8N_5Cl$	51.40	51.41	3.45	3.62	29.98	29.69	...	...
p-ClC_6H_4	NHC_2H_5	189–190	Orange-red plates	Abs. EtOH	$C_{10}H_{10}N_5Cl$	50.96	51.28	4.27	4.41	29.72	29.80	...	...
p-ClC_6H_4	$N(C_2H_4OH)_2$	179–180	Red needles	EtOAc	$C_{12}H_{14}N_5O_2Cl$	48.73	48.95	4.77	4.89	23.68	23.88	12.00	12.06
p-ClC_6H_4	$N(CH_2)_5$	134–135	Red plates	Abs. EtOH	$C_{13}H_{14}N_5Cl$	56.62	56.91	5.12	5.44	25.40	25.17	...	...
p-ClC_6H_4	NHC_6H_5	244–245	Red-violet plates	Abs. EtOH	$C_{14}H_{10}N_5Cl$	59.26	59.42	3.55	3.51	24.69	24.89	...	...
p-ClC_6H_4	$NHNH_2$	200–201 d.	Red needles	Abs. EtOH	$C_8H_7N_6Cl$	43.16	43.42	3.17	3.44	37.75	38.60	...	...
p-ClC_6H_4	$NHNCHC_6H_5$	237–238 d.	Yellow-orange plates	Acetone–EtOH	$C_{15}H_{11}N_6Cl$	57.97	58.24	3.57	3.81	27.05	27.21	...	...
p-ClC_6H_4	$NHNHCSNH_2$	227.5–228.5	Orange-red needles	Benzene–EtOH	$C_9H_8N_7ClS$	38.37	38.61	2.86	3.12	34.81	35.38	12.58	11.88
p-ClC_6H_4	$NHNHC_6H_5$	198–199 d.	Red plates	Abs. EtOH	$C_{14}H_{11}N_6Cl$	56.28	56.39	3.71	3.75	28.14	28.30	...	...
p-$CH_3OC_6H_4$	$N(C_2H_5)_2$	91–92	Red needles	EtOH	$C_{13}H_{17}N_5O$	60.20	59.80	6.60	6.56	27.01	27.64	...	...
p-$NO_2C_6H_4$	$N(C_2H_5)_2$	215–216	Red needles	Acetone	$C_{12}H_{14}N_6O_2$	52.54	52.76	5.14	5.31	30.64	30.78	...	...
m-$NO_2C_6H_4$	$N(C_2H_5)_2$	118–119	Red needles	EtOH	$C_{12}H_{14}N_6O_2$	52.54	52.70	5.14	5.13	30.64	30.92	...	...

TABLE II

VISIBILE ABSORPTION MAXIMA OF SOME 1,2,4,5-TETRAZINES[a] RC(N—N)(N=N)CR′

R	R′	λmax, mμ	log εmax
C_6H_5	Br	530	2.71
p-ClC_6H_4	Br	530	2.71
p-$CH_3OC_6H_4$	Br	525–530	2.70
C_6H_5	NH_2	530–535	2.71
p-ClC_6H_4	NH_2	530–535	2.71
C_6H_5	OH	545	2.50
p-ClC_6H_4	OH	545	2.49
C_6H_5	H	540	2.75
p-ClC_6H_4	H	540	2.72
p-ClC_6H_4	NHC_2H_5	535	2.66
p-ClC_6H_4	NHC_6H_5	530–535	2.72
p-$NO_2C_6H_4$	$N(C_2H_5)_2$	530–537	2.64
m-$NO_2C_6H_4$	$N(C_2H_5)_2$	534–537	2.64

[a] The visible absorption spectra were measured in 95% ethanol using a Beckman model DU spectrophotometer.

hydrochloric acid and 100 ml. of water, cooled to 0°, was added dropwise with stirring a solution of 1.75 g. of sodium nitrite (0.025 mole) in 20 ml. of water. The temperature of the reaction mixture was maintained between 0–4° during the course of addition and then held at 0° for 20 minutes after all of the sodium nitrite solution had been introduced.

(b) **Coupling.**—To a solution of 5.18 g. of *m*-nitrobenzalguanylhydrazone (0.025 mole), m.p. 210° (lit.[11] 210°) in 200 ml. of pyridine, cooled to −10°, was added, all at once with stirring, the cold (0°) diazonium solution. An orange solid appeared almost immediately. An additional 100 ml. of cold pyridine was added followed by dilution with 500 ml. of water. The solid was then dissolved by the addition of 50 ml. of 10% aqueous sodium hydroxide. Crushed ice was then added and the clear solution acidified with 6 *N* hydrochloric acid. The product was collected and washed successively with water, methanol and ether, wt. 7.0 g. (92% yield), m.p. 155–157° dec. Application of this procedure to coupling of *p*-nitrobenzalguanylhydrazone gave Ic in 80% yield, m.p. 168–170° dec.

2-(5′-Tetrazolyl)-5-phenyltetrazole (IIa).—The preparation of the tetrazole derivatives IIa, b and c was accomplished in all cases at room temperature with a saturated solution of potassium permanganate. The preparation of IIa is presented as a typical example.

To a solution of 1.3 g. of Ia (5 mmoles) in 50 ml. of 5% sodium hydroxide was added dropwise with stirring a saturated solution of potassium permanganate (6.4 g./100 ml. water) until the permanganate-color began to persist (*ca.* 18 ml.). The excess oxidizing agent was destroyed by the addition of a few drops of methanol and the inorganic material was removed by filtration. Acidification of the filtrate with excess, concentrated hydrochloric acid gave a cream-colored solid which was collected and sucked dry, wt. 0.75 g. (70% yield), m.p. 124–125° dec. Recrystallization from an ethyl acetate–petroleum ether mixture gave an off-white amorphous solid, m.p. 125–126° dec.

Anal. Calcd. for $C_8H_6N_8$: C, 44.86; H, 2.82; N, 52.32; neut. equiv., 214. Found: C, 45.01; H, 3.06; N, 52.38; neut. equiv., 215.

2-(5′-Tetrazolyl)-5-*p*-chlorophenyltetrazole (IIb) was obtained in 75% yield and crystallized from aqueous ethanol in the form of yellow microscopic needles, m.p. 137.5–138.5° dec.

Anal.[12] Calcd. for $C_8H_5N_8Cl$: C, 38.64; H, 2.03; N, 45.07; Cl, 14.26; neut. equiv., 249. Found: C, 38.87; H, 2.26; Cl, 13.96; neut. equiv., 250.

2-(5′-Tetrazolyl)-5-*p*-nitrophenyltetrazole (IIc) was obtained in 77% yield and crystallized from aqueous ethanol as light-yellow microscopic needles, m.p. 142° dec.

Anal.[12] Calcd. for $C_8H_5N_9O$: C, 37.07; H, 1.94; N, 48.64; neut. equiv., 259. Found: C, 37.37; H, 2.49; neut. equiv., 260.

3-Bromo-6-*p*-chlorophenyl-1,2,4,5-tetrazine (IIIb).—The 3-bromo-6-aryltetrazines[13] were obtained by the portionwise addition of the corresponding formazan to two molar equivalents of bromine in acetic acid at 53–65°. The preparation of IIIb is presented as a typical example and the individual differences in the purification technique are discussed below.

To a solution of 16.0 g. of bromine (0.1 mole) in 250 ml. of glacial acetic acid at 55° was added portionwise, with continuous stirring, 14.6 g. of Ib (0.05 mole). The rate of this addition was such as to maintain a temperature of 53–58° (30 minutes). A small amount of yellow solid remained following the completion of addition which was removed by filtration. The filtrate was poured onto ice and the resulting red solid collected, wt. 6.5 g., m.p. 156–170°. The crude product was then triturated with 200 ml. of hot benzene and additional yellow, insoluble material removed by filtration, wt. 1.5 g., m.p. 152–162°. Similar yellow solids are obtained in all of the formazan–tetrazine reactions, but have not yet been identified.

The benzene extract was evaporated to dryness *in vacuo* and the bright red residue, wt. 5.0 g. (37% yield), m.p. 169–173°, crystallized from a mixture of ether–petroleum ether (65–110°) to give red needles, m.p. 175–177°.

3-Bromo-6-phenyl-1,2,4,5-tetrazine (IIIa) was separated from the accompanying yellow solid by trituration with warm ether, filtration and concentration of the ether extract. The residue crystallized from a mixture of ether–petroleum ether (30–60°) to give red plates (35% yield), m.p. 131–132°.

3-Bromo-6-*p*-methoxyphenyl-1,2,4,5-tetrazine (IIIe) was separated from the yellow contaminant by digesting the mixture with five 100-ml. portions of ether. The product crystallized from a mixture of ether and ethyl acetate as orange-red needles (27% yield), m.p. 159–160°.

3-Bromo-6-*m*-nitrophenyl-1,2,4,5-tetrazine (IIId).—To a solution of 24 g. of bromine (0.15 mole) in 300 ml. of glacial acetic, warmed to 55°, was added, portionwise with stirring, 22.0 g. of formazan (Id) (0.07 mole). Again, the rate of addition of Id was such as to maintain a temperature of 55–60°. Following the completion of addition, the reaction mixture was stirred for an additional 0.5 hour at 60°. A small amount of yellow solid was removed by filtration and the filtrate was then poured into ice. The red solid was collected, washed with generous amounts of water and sucked dry, wt. 7.1 g., m.p. 178–186° dec. The red product was next triturated with 300 ml. of hot benzene and the extract filtered from the yellow insoluble material. Concentration of the benzene solution gave several crops of product which crystallized in the form of red needles, wt. 5.0 g., m.p. 197–198° dec., λ_{max} (anisole) 527–529 mμ, log ε 3.26.

3-Bromo-6-*p*-nitrophenyl-1,2,4,5-tetrazine (IIIc).—The conversion of Ic to IIIc was carried out in essentially the same manner. The product was purified by digestion with hot anisole and crystallized from this solvent in the form of red prisms, m.p. 276–278° dec., λ_{max} (anisole) 527–529 mμ, log ε 3.08.

3-Bromo-6-phenyl-1,2-dihydro-1,2,4,5-tetrazine (IVa).—To a solution of 1.5 g. of IIIa (6 mmoles) in 80 ml. of glacial acetic acid was added, portionwise, 5 g. of zinc dust. The deep red color of the original solution was discharged within a few minutes and the mixture was filtered. The yellow solution was poured onto ice and the solid collected, wt. 1.3 g., m.p. 185–201°. Recrystallization from absolute ethanol gave yellow plates, m.p. 186–204°.[14]

Anal. Calcd. for $C_8H_7N_4Br$: C, 40.19; H, 2.95; N, 23.44. Found: C, 40.29; H, 2.63; N, 23.51.

A solution of 0.5 g. of the IVa (2 mmoles) in 30 ml. of glacial acetic acid was treated with a few drops of bromine at 50°. The red solution was cooled to room temperature and then diluted with water. The red solid was collected, washed with water and sucked dry, wt. 0.35 g., m.p. 124–126°. A single recrystallization from absolute ethanol gave

(11) J. Thiele and R. Bihan, *Ann.*, **302**, 305 (1898).

(12) Several attempts to obtain a satisfactory nitrogen analysis proved unsuccessful.

(13) Elementary analyses are given in Table I.

(14) There is some indication that the product is undergoing a thermal rearrangement over this range. The possibility of ring contraction to a triazole has been considered (see ref. 9).

shiny red plates, m.p. 129–131°, alone or when admixed with an authentic sample of IIIa.

These same oxidation–reduction studies were carried out with 3-bromo-6-*p*-chlorophenyl-1,2,4,5-tetrazine (IIIb). The corresponding dihydro derivative IVb, yellow needles, also exhibited a broad melting point range,[9] 190–210°.

Anal. Calcd. for $C_8H_6N_4BrCl$: C, 35.13; H, 2.21; N, 20.49. Found: C, 35.51; H, 2.53; N, 20.72.

3-Phenyl-1,2,4,5-tetrazine (Va).—A solution of 0.48 g. of IIIa (2 mmoles) in 10 ml. of tetrahydrofuran was added portionwise to a solution of 0.5 g. of sodium borohydride (13 mmoles) in a mixture of 10 ml. of methanol and 3 ml. of water. The red color was discharged almost immediately in this mildly exothermic reaction. After the evolution of hydrogen had subsided, the mixture was warmed to 50° and then allowed to stand for 1.5 hours. The solution containing the reduced product was cooled to 0° and treated with excess acetic acid (*ca.* 25 ml.). To this cold acidified solution was added, all at once, 1.0 g. of $NaNO_2$ whereupon the original red color was regenerated. After 45 minutes, the solution was extracted with three 100-ml. portions of ether, the extract washed successively with saturated solutions of sodium bicarbonate and sodium chloride and finally dried over magnesium sulfate. The filtered, ether extract was concentrated to approximately 50 ml., diluted to about 100 ml. with petroleum ether (30–60°) and the resulting solution concentrated to a small volume (*ca.* 5 ml.). A red solid was deposited on cooling which was collected and sucked dry, wt. 0.160 g. (50% yield), m.p. 117–119°. Recrystallization from an ether–petroleum ether (30–60°) mixture provided an analytical sample, red prisms, m.p. 125–126°.

3-*p*-Chlorophenyl-1,2,4,5-tetrazine (Vb).—Using the above procedure, a 60% yield of Vb was obtained in the form of red plates, m.p. 166–167°.

3-Hydroxy-6-phenyl-1,2,4,5-tetrazine (VIa).—To a solution of 1.2 g. of potassium hydroxide (0.021 mole) in 50 ml. of ethanol was added 2.0 g. of IIIa (8.5 mmoles) and the deep red solution warmed on a steam-bath for a few minutes. On dilution with water (*ca.* 200 ml.), followed by acidification with dilute hydrochloric acid, the product separated and was collected, wt. 14 g. (95% yield), m.p. 183–185°. Recrystallization from absolute ethanol provided an analytical sample.

3-Hydroxy-6-*p*-chlorophenyl-1,2,4,5-tetrazine (VIb), m.p. 175° dec., was obtained in 91% yield from IIIb by this same procedure.

3-Amino-6-phenyl-1,2,4,5-tetrazine (VIIa).—A rapid stream of anhydrous ammonia was passed through a solution of 4.0 g. of IIIa (0.017 mole) in 100 ml. of dry benzene. The clear solution became turbid almost immediately, followed by the deposition of a mixture of the product and ammonium bromide. The solvent was evaporated on a steam-bath with the aid of a stream of air and the residue suspended in 100 ml. of water. The product was collected, washed with generous amounts of water and sucked dry, wt. 2.9 g. (100% yield), m.p. 220–224°. Recrystallization from absolute alcohol gave thick red needles, m.p. 226–227°.

3-Amino-6-*p*-chlorophenyl-1,2,4,5-tetrazine (VIIb), red plates, m.p. 243–244°, was obtained in 88% by this same procedure.

3-Diethylamino-6-phenyl-1,2,4,5-tetrazine (VIIIa).—To 7.0 g. of diethylamine (0.1 mole) was added, portionwise with stirring, 1.0 g. of IIIa (4 mmoles). The reaction was then diluted with *ca.* 200 ml. of water and the sticky solid collected, washed with water and sucked dry, wt. 0.95 g. (100% yield), m.p. 55–59°. A single recrystallization from aqueous ethanol provided an analytical sample, m.p. 60°.

The majority of 3-mono- and disubstituted amino derivatives of II contained in Table I were prepared by the above procedure. Therefore, only the exceptions to this method will be presented.

3-Diethylamino-6-*p*-nitrophenyl-1,2,4,5-tetrazine.—To a solution of 5 ml. of diethylamine in 10 ml. of pyridine was added, all at once, 0.56 g. of IIIc (1.5 mmoles). The mixture was heated to 70° and held at this temperature for 0.5 hour. The dark solution was then poured onto a mixture of ice and hydrochloric acid, the product collected and recrystallized from acetone to give 0.3 g. (95% yield) of product, m.p. 205–210°. A second recrystallization from acetone provided an analytical sample, red needles, m.p. 215–216°.

The preparation of 3-diethylamino-6-*m*-nitrophenyl-1,2,-4,5-tetrazine was accomplished in nearly quantitative yield in the usual manner from IIId and an excess of diethylamine. The diethylamino derivative crystallized from ethanol in the form of red needles, m.p. 118–119°.

3-(Bis-2-hydroxyethylamino)-6-phenyl-1,2,4,5-tetrazine (VIIIb).—A solution of 2.0 g. of IIIa (8.4 mmoles) in 10 ml. of tetrahydrofuran containing an excess (10.5 g.) of diethanolamine was warmed to 60° and then stirred for 30 minutes. The solution was concentrated to a small volume on a steam-bath in a stream of air and then poured into 200 ml. of water. The orange product was collected, washed with generous amounts of water and sucked dry, wt. 1.9 g. (90% yield), m.p. 113–115°. The analytical sample was obtained by recrystallization from benzene; red needles, m.p. 118.5–119.5°.

To a solution of 1.9 g. of VIIIb (m.p. 113–115°) (7.5 mmoles) in 15 ml. of dry pyridine at 0° was added dropwise 6.0 g. of methanesulfonyl chloride (52 mmoles), maintaining a temperature of 0–5°. The mixture was held at 0° for one hour, then poured on ice and the product collected. The crude material crystallized from aqueous acetone in the form of orange plates to give 2.0 g. (64% yield) of 3-(bis-2-mesyloxyethylamino)-6-phenyl-1,2,4,5-tetrazine, m.p. 116–117° dec.

3-(1-Aziridinyl)-6-phenyltetrazine (VIIIc).—To a solution of 0.65 g. of ethylenimine (0.015 mole) and 1.5 g. of triethylamine (0.015 mole) in 100 ml. of dry benzene was added, dropwise, at room temperature with stirring a solution of 3.4 g. of IIIa (0.014 mole) in 50 cc. of benzene. The red solution was then washed with three portions of water and the organic extract dried over magnesium sulfate. The filtered benzene solution was evaporated to dryness *in vacuo* and the residue crystallized from 95% ethanol, wt. 2.3 g. (85% yield) of a red solid, m.p. 112–117°. Two recrystallizations from petroleum ether (65–100°) gave small red plates, m.p. 121–122°.

3-(1-Aziridinyl)-6-*p*-chlorophenyl-1,2,4,5-tetrazine (VIIId) was obtained in 43% yield by essentially the same procedure, red needles, m.p. 154–156°. The lower solubility of IIIb in benzene required a larger volume of this solvent to perform the addition and may be a factor in the lower yield in this case as a result of mechanical loss.

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