[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Synthesis of *sym*-Diaminotetrazine[1a,1b]

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An unequivocal synthesis of 3,6-diamino-1,2,4,5-tetrazine (VIIa) is reported in which 1,2,4,5-tetrazine-3,6-dicarbonyl azide is degraded to VIIa by means of a Curtius rearrangement. Visible absorption spectra confirm the fact that the 1,2,4,5-tetrazine ring is preserved during the sequence of reactions leading to the diamine VIIa. It is further demonstrated that VIIa may be obtained as a result of the action of nitrous acid on diaminoguanidine or from the action of dilute sodium hydroxide on *s*-methylthiosemicarbazide. The physical properties of VIIa are qualitatively consistent with the properties of known 1,2,4,5-tetrazines.

In 1913, Ponzio and Gastaldi isolated a reddish-violet solid as a result of the action of potassium hydroxide on aminoguanidine hydrochloride[3] and, on the basis of questionable analytical data together with loosely interpreted degradative observations, assigned the structure 3,6-diamino-1,2,4,5-tetrazine (VIIa) to their product.[4]

When the preparation of the Ponzio product was repeated in this Laboratory and the resulting product subjected to a meticulous procedure of purification, the analytical values were in no better agreement with the proposed structure than those presented by the original workers.[5]

In view of the doubt cast upon the work of Ponzio and Gastaldi by our preliminary investigation, it was decided to undertake the synthesis of VIIa by unequivocal methods in order to establish the true identity of the diamine in question.

The unsuccessful attempt to degrade 1,2,4,5-tetrazine-3,6-dicarbonyl azide (VI) to the corresponding diamine VIIa was recorded[6] even before the appearance of the observations of Ponzio and Gastaldi. Nevertheless, the Curtius rearrangement[7] still appeared to be a most attractive approach to the solution of this problem. Accordingly, 3,6-dicarboxy-1,2-dihydro-1,2,4,5-tetrazine (II) was prepared from ethyl diazoacetate (I) in the manner described by Curtius and Lang.[8] However, the esterification of II with excess diazomethane produced 1-methyl-3,6-dicarboxy-1,2-dihydro-1,2,4,5-tetrazine (IV) in addition to the expected ester III. The structure assigned to IV is based on a similar reaction reported for the action of diazomethane on 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxamide.[9]

The hydrazinolysis of III had been reported to yield an impure yellow solid for which the original workers were unable to obtain a satisfactory elementary analysis.[6] The same analytical difficulties were encountered when the original procedure was repeated in this Laboratory. However, the simple expedient of reversing the mode of addition of reactants afforded pure 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarbonyl hydrazide (V) in 90% yield. Curtius and Rimeli reported the isolation of a red-violet, explosive solid[6] on treatment of their impure dihydrazide V with excess, aqueous nitrous acid in which the usual transformation of hydrazide to azide is accompanied by the oxidation of the dihydrotetrazine ring.[10] All attempts to duplicate this procedure met with failure. However, when a mixture of benzene and glacial acetic acid was substituted for the aqueous medium, an amorphous, red-violet solid separated which exploded on heating in a flame.

An attempt to convert 3-carbethoxy-1,2,4,5-tetrazine-6-carbonyl azide to the corresponding ethylurethan was described in which these same workers observed the complete disintegration of the tetrazine ring.[6] All attempts to rearrange VI in ethanol in this laboratory led to the formation of ill-defined products, again suggesting the breakdown of the tetrazine ring.

In view of the apparent sensitivity of these compounds to water and alcohol, it seemed advisable to seek a solvent in which the transformation of azide VI to amine VIIa could be directly effected, thus circumventing the intermediate formation of the corresponding urethan. When glacial acetic acid was used, a slow stream of gas bubbles appeared to be evolved as the mixture was warmed, with the subsequent isolation of a red solid whose elementary analysis conformed to the requirements of 3,6-diamino-1,2,4,5-tetrazine. Furthermore, the presence of two amino groups was established through the formation of both a diacetyl VIIb and a ditosyl derivative VIIc.

It has been demonstrated that a number of 1,2-dihydro-1,2,4,5-tetrazines undergo facile ring contraction to the corresponding N^4-amino-1,2,4-triazole.[11] That such a ring contraction did not occur during our experiments is supported by the absorption spectrum of the product VIIa.

Müller and Herrdegen had measured the visible absorption spectra of a number of 1,2,4,5-tetrazines and noted that these compounds exhibit characteristic absorption maxima between 500 and 600 mμ.[12] It is evident from Table I that, in non-polar solvents, the majority of 1,2,4,5-tetrazines employed in this study manifest at least a single prominent maximum in the region 520–530 mμ. Further, log

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[1] (a) Abstracted in part from a dissertation submitted by Chao-Han Lin to the Graduate School of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This work was supported by the U. S. NOTS, Inyokern, China Lake, Calif., Research Contract N123S-61517, Task Order 3.

[2] Requests for reprints should be addressed to this author.

[3] G. Ponzio and C. Gastaldi, *Gazz. chim. ital.*, **43**, 2, 129 (1913).

[4] (a) G. Ponzio and C. Gastaldi, *ibid.*, **44** [1], 257 (1914); (b) **44** [1], 277 (1914); (c) **45** [1], 181 (1915).

[5] C. H. Lin, J. P. Horwitz and E. Lieber, unpublished work.

[6] T. Curtius and E. Rimeli, *Ber.*, **41**, 3108 (1908).

[7] P. A. S. Smith, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1946, Chap. 9.

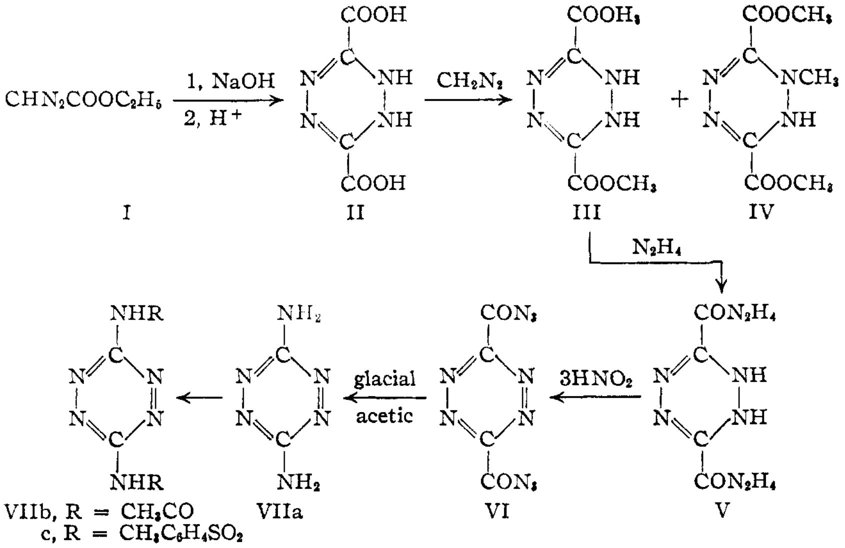
[8] T. Curtius and C. Lang, *J. prakt. Chem.*, **38**, 532 (1888).

[9] T. Curtius, A. Darapsky and E. Müller, *Ber.*, **42**, 3284 (1909).

[10] A. Pinner, *ibid.*, **26**, 2133 (1893).

[11] C. Bülow and F. Weber, *ibid.*, **42**, 1992 (1909).

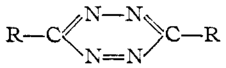
[12] E. Müller and L. Herrdegen, *J. prakt. Chem.*, **102**, 113 (1921).



ϵ_{max} for these same compounds varies only slightly from values of 2.70–2.75.

TABLE I

VISIBLE ABSORPTION MAXIMA OF 1,2,4,5-TETRAZINES



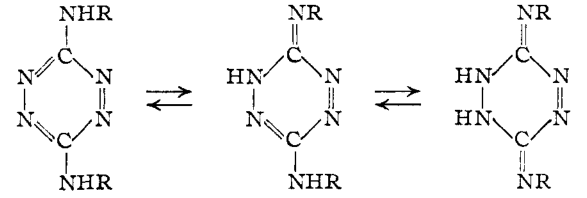
R	Solvent	λ_{max}, mμ	ϵ_{max}	log ϵ_{max}
H[a]	Ether	557	430	2.63
		536	660	2.82
		516	550	2.74
		498	330	2.52
CO$_2$H	Water	513	180	2.26
	Dioxane	521	460	2.66
CO$_2$CH$_3$[b]	Ether	526	580	2.76
C$_6$H$_5$[b]	Ether	554	480	2.76
NH$_2$	Water	428	1340	3.12
	Dioxane	428	1980	3.30
		528	590	2.77
CH$_3$CONH	Ether	363	1800	3.26
		525	520	2.72
p-CH$_3$C$_6$H$_4$SO$_2$NH	Ether	363	1860	3.27
		527	560	2.75

[a] T. Curtius, A. Darapsky and E. Müller, *Ber.*, 40, 85 (1907). [b] Prepared by Dr. A. Ravve of this Laboratory.

Recently, the resonance energy of 1,2,4,5-tetrazine was calculated from visible absorption data in which the principal maximum in the gas phase was observed at 520 mμ.[13] This maximum led to a value of 20 kcal. for the resonance energy of 1,2,4,5-tetrazine. It is apparent from Table I that the carboxyl and carbomethoxy groups exert only a minor influence on the resonance energy of the 1,2,4,5-tetrazine ring. In contrast to the small effects induced by these groups, a relatively large bathochromic displacement is observed in the case of 3,6-diphenyl-1,2,4,5-tetrazine. The magnitude of this displacement is presumably the result of the conjugation of two benzene resonators to a ring which is already stabilized tc the extent of 20 kcal.

The product of the Curtius rearrangement VIIa exhibits, in anhydrous dioxane, absorption maxima at both 428 and 528 mμ. However, in water the latter maximum is no longer discernible. From the preceding discussion, it would seem fairly well established that the maximum at 528 mμ is indicative of the presence of a 1,2,4,5-tetrazine ring. On the other hand, the appearance of a strong maximum at 428 mμ for this same compound both in anhydrous dioxane and water, together with an extinction coefficient which, in anhydrous dioxane, is approximately four times as large as that observed for the majority of 1,2,4,5-tetrazines, strongly suggests some change in structure of the red solid in solution.

In view of these observations it seems reasonable to conclude that a tautomeric change is responsible for the observed hypsochromic displacement, since it is apparent that VIIa is more highly stabilized through resonance than either of its tautomers (VIIIa or IXa).



VIIa, R = H VIIIa,b,c IXa,b,c
b, R = CH$_3$CO
c, R = CH$_3$C$_6$H$_4$SO$_2$

The same phenomenon appears to be operative in both 3,6-diacetamido- and 3,6-ditosylamido-1,2,4,5-tetrazine (VIIb and VIIc), as manifested in the appearance of maxima at 363 and 525 mμ for the acetylated compound and maxima of 363 and 527 mμ for the ditosyl derivative (Table I). The data appear consistent with the assumption that the imino structure should be enhanced as a result of exocyclic conjugations with either carbonyl or sulfonyl oxygen. Furthermore, the fact that the displacement toward shorter wave length is more pronounced in the derivatives of 3,6-diamino-1,2,4,5-tetrazine suggests a transfer of two protons as compared to a single proton transfer in the case of the free base.

From the preceding discussion it is evident that visible absorption spectra confirm the fact that the 1,2,4,5-tetrazine ring has been preserved during the sequence of reactions involved in the Curtius rearrangement and thereby the structure of 3,6-diamino-1,2,4,5-tetrazine has been unequivocally established.

The reactions involved in the Curtius sequence described above afford the red base in relatively low over-all yield (11%). Consequently a more direct synthesis was undertaken in order to expedite the complete study of this interesting diamine.

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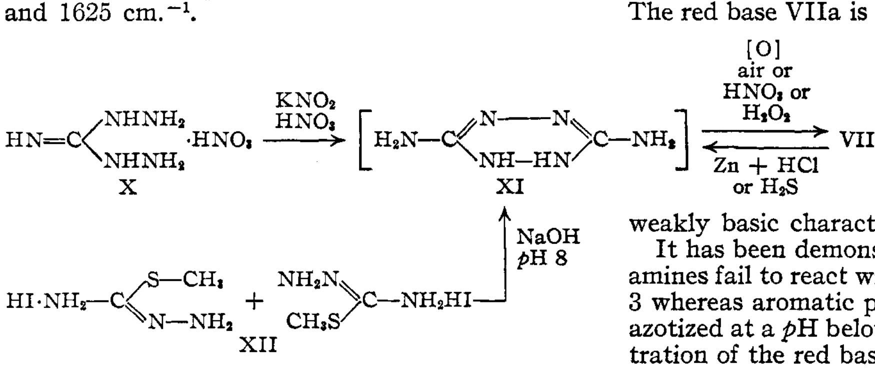
(13) A. Maccol, *J. Chem. Soc.*, 670 (1946).

An earlier investigation[14] concerned with the reaction of nitrous acid with diaminoguanidine (X) in nitric acid medium led to the isolation of an unidentified red solid whose color suggested the chromophoric arrangement in the 1,2,4,5-tetrazine system. A sample obtained by repetition of this work gave an analysis agreeing with VIIa and an identical infrared spectrum with principal maxima occurring in each case at 928, 1060, 1480 and 1625 cm.$^{-1}$.



Although the oxidation of the dihydro compound XI to VIIa may be accomplished by employing a large excess of nitric acid in the original reaction mixture, or by simply evaporating the mixture in a stream of air, it was found that oxidation with hydrogen peroxide afforded a purer product.[15]

In the preparation of diaminoguanidine nitrate from S-methylthiosemicarbazide (XII), it was observed that the mother liquor possessed a red color reminiscent of what had already been noted in the preparation of the red powder described above. Thus, it appeared that XII offered still another route to the diamine.[16] Accordingly, an aqueous solution was adjusted to the *p*H of 8 with dilute sodium hydroxide and almost immediately the odor of mercaptan was perceptible with the simultaneous development of an orange-red coloration in the reaction mixture. Evaporation of this solution in a stream of air resulted in the deposition of a red solid which proved to be identical with the products obtained from both diaminoguanidine and the Curtius rearrangement of 1,2,4,5-tetrazine-3,6-dicarbonyl azide. The infrared spectra of the diamine prepared in the three different ways were essentially superimposable.

While the preparation of VIIa from either diaminoguanidine or S-methylthiosemicarbazide represents an improvement over the tedious operations involved in the unequivocal procedure, the yields failed to surpass those obtainable by the Curtius rearrangement.

Properties of 3,6-Diamino-1,2,4,5-tetrazine.—The red base VIIa is only slightly soluble in water. However, it readily dissolves in concentrated mineral acid from which it may be reprecipitated unchanged on dilution with water. These observations are indicative of the weakly basic character of the diamine.

It has been demonstrated that primary aliphatic amines fail to react with nitrous acid at a *p*H below 3 whereas aromatic primary amines are readily diazotized at a *p*H below 1.[17] The potentiometric titration of the red base against 0.5 *N* sodium nitrite in strong acid (Fig. 1) reveals the fact that two equivalents of nitrous acid are consumed in this reaction. In a somewhat less quantitative fashion it was observed that tetrazotization of VIIa followed by coupling with β-naphthol produced the vivid color characteristic of aromatic amines. These observations lend further support to the evidence already accumulated in favor of the aromatic character of the 1,2,4,5-tetrazine system.[13]

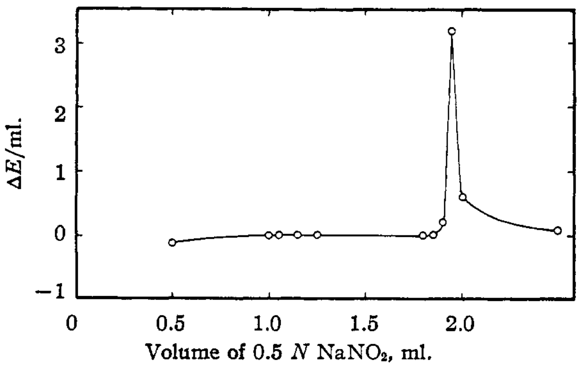


Fig. 1.—Potentiometric titration of IV in 6 *N* HCl *vs.* 0.5 *N* $NaNO_2$.

Though the red solid does not melt up to 300°, it does sublime in the region of 200–240°, depending on the rate of heating, and this property provided an additional means of purification.

Reduction with either hydrogen sulfide or a mixture of zinc and acetic acid results in complete discharge of the red color originally imparted to the solution. However, the color may be regenerated on oxidation with either nitric acid or bromine water or by simply directing a stream of air over the surface of a solution of the reduced product. This qualitative observation is in complete agreement with the properties of compounds possessing the 1,2,4,5-tetrazine ring.[18] Several attempts were made to isolate the reduced form of the red base XI by treat-

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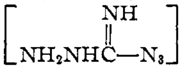
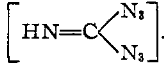
[14] E. Lieber and D. R. Levering, unpublished work.

[15] It is the opinion of J. P. H. that the formation of VIIa from diaminoguanidine does involve the transient existence of either aminoguanyl azide,



$$\left[NH_2NH\overset{\overset{NH}{\|}}{C}—N_3\right]$$

or carbonimidyl diazide



$$\left[HN{=}C(N_3)_2\right]$$

. Thus, the self-condensation of aminoguanyl azide would lead to the dihydro compound XI. Similarly, the reaction of carbonimidyl diazide with unchanged diaminoguanidine would yield the same product XI. Both intermediates require the elimination of two moles of hydrogen azide.

These same intermediates explain the formation of tetrazolyl azide from the interaction of diaminoguanidine with two molar proportions of nitrous acid in acetic acid media; *cf.* E. Lieber and D. R. Levering, THIS JOURNAL, **73**, 1313 (1951).

[16] While this work was in progress, F. L. Scott and J. Reilly, *Chemistry & Industry*, 908 (1952) announced, the preparation of *sym*-diaminotetrazine from the action of heterocyclic amines on S-methylthiosemicarbazide (XII). This prior publication offered no proof for the assigned structure other than a statement to the effect that acceptable elemental analyses had been obtained for the free base and two salts (picrate and sulfate). However, the results of the present investigation appear to lend credence to their conjecture.

[17] N. Kornblum and C. Iffland, THIS JOURNAL, **71**, 2137 (1949).

[18] A. Pinner, *Ber.*, **26**, 2133 (1893).

ing VIIa with excess hydrogen sulfide. However, the rapidity of the reverse reaction thwarted all efforts to isolate the dihydro compound XI in a pure form.

In conclusion, it is pertinent to mention that the properties manifested by VIIa are distinctly different from those originally attributed to this structure by Ponzio and Gastaldi.[4] The structure of the Ponzio product will be the subject of a future communication.

Experimental[19]

Reaction of 3,6-Dicarboxy-1,2-dihydro-1,2,4,5-tetrazine (II) with Diazomethane.—To an ice-cold ethereal solution of diazomethane (0.4 mole) was added portionwise 2.4 g. of 3,6 - dicarboxy - 1,2 - dihydro - 1,2,4,5 - tetrazine (II)[8] (0.14 mole). The mixture was then warmed on a steam-bath for a few minutes, filtered and dried. The rust-colored material weighed 1.2 g. (43%), m.p. 167–168°. Two recrystallizations from water provided 3,6-dicarbomethoxy-1,2-dihydro-1,2,4,5-tetrazine (III) in the form of orange prismatic needles, m.p. 168–170° (lit.[6] 167°).

The ether filtrate was evaporated to dryness leaving 1.5 g. (50%) of a yellow solid, m.p. 112–113°. Two recrystallizations from water afforded 1-methyl-3,6-dicarbomethoxy-1,2-dihydro-1,2,4,5-tetrazine (IV) in the form of a mat of yellow needles, m.p. 114–115°.

Anal. Calcd. for $C_7H_{10}N_4O_4$: C, 39.29; H, 4.70; N, 26.16. Found: C, 39.90; H, 4.75; N, 26.31.

1,2-Dihydro-1,2,4,5-tetrazine-3,6-dicarbonyl Hydrazide (V).—To a solution of 5 g. of 96% hydrazine (150 millimoles) in 20 cc. of absolute ethanol under gentle reflux was added, dropwise with mechanical stirring, a solution of 0.1 g. of III (0.5 millimole) in 30 cc. of warm absolute ethanol. The mixture was refluxed for 16 hours, during which time fine yellow needles were deposited. The product was collected, washed with alcohol and dried. The yellow solid weighed 0.09 g. (90%), m.p. 287–288° dec. (lit.[6] 265–275°).

Anal. Calcd. for $C_4H_8N_8H_2$: C, 24.01; H, 4.03; N, 55.99. Found: C, 23.94; H, 4.07; N, 55.71.

3,6-Diamino-1,2,4,5-tetrazine (**VIIa**).—A suspension of 0.5 g. of V (2.5 millimoles) in a mixture of 50 cc. of glacial acetic acid and 25 cc. of benzene was treated at ice-bath temperature first with 1.0 cc. of concentrated hydrochloric acid and then with 1.25 cc. of a 6.7 *M* aqueous solution of potassium nitrite (8.3 millimoles). Almost immediately the suspended material took on a deep red color, and the solid (VI) (0.25 g.) was collected, washed with a few cc. of glacial acetic acid and used directly in the rearrangement.

A suspension of 0.25 g. of the crude 1,2,4,5-tetrazine-3,6-dicarbonyl azide in 125 cc. of glacial acetic acid was heated on a steam-bath for two hours. A small amount of a white residue remained at the end of this period which was removed by filtration. The filtrate was evaporated to dryness in a stream of air on a steam-bath. The red residue was loosened with a few cc. of water, and collected to give 0.1 g. (36% based on V) of impure 3,6-diamino-1,2,4,5-tetrazine. This material failed to melt below 300°, though it did sublime in the region 200–240°, depending on the rate of heating. One recrystallization from dioxane and three from water provided an analytical sample of the orange-red, micro-crystalline product.

Anal. Calcd. for $C_2H_4N_6$: C, 21.42; H, 3.57; N, 75.00. Found: C, 21.45; H, 3.55; N, 75.02.

VIIa from Diaminoguanidine Nitrate (X).—To a solution of 6.08 g. of diaminoguanidine nitrate[14] (0.038 mole) in 50 cc. of 1 *N* nitric acid, was added dropwise with mechanical stirring a solution of 6.8 g. of potassium nitrite (0.08 mole) in 50 cc. of water over a period of 6.5 hours. Usually the red material began to deposit at the end of this period. If only a small amount of product appeared, the mixture was placed in the refrigerator overnight. The impure solid was then collected, washed with water and dried to give 0.25 g. (11% yield) of the crude product IV. The latter was dissolved in 20 cc. of 3% hydrogen peroxide and the solution evaporated in a vacuum desiccator over sulfuric acid. The dry residue was finally triturated with 10 cc. of water and filtered to give 75 mg. of the diamine IV. A sample of IV for both elementary analysis and spectroscopic study (Fig. 1) was prepared by sublimation at 200–220° and 1 mm.

Anal. Calcd. for $C_2H_4N_6$: C, 21.42; H, 3.57; N, 75.00. Found: C, 21.56; H, 3.44; N, 75.34.

It was found that the diamine may be recrystallized from either water or dioxane; the shade of color of the purified product appears to depend on the solvent. The red amorphous solid is only slightly soluble in water, alcohol, acetone and ethyl acetate while it is virtually insoluble in ether. It readily dissolves in concentrated nitric or sulfuric acid and may be reprecipitated without change by diluting the solution with water. On the other hand, dilution of a concentrated hydrochloric acid solution of the red solid fails to precipitate the free base, though the latter may be recovered on evaporation of the acid. Any conclusion regarding the significance of this difference is at the present date unapparent.

VIIa from S-Methylthiosemicarbazide Hydroiodide (XII).—A solution of 9.2 g. of S-methylthiosemicarbazide hydroiodide[20] (0.04 mole) in 30 cc. of water was adjusted to a *p*H of approximately 8 (pHydrion Paper) with 12 cc. of a 10% solution of sodium hydroxide. An additional 8 cc. of water was then introduced and a stream of air was directed across the surface of the mixture for several hours, during which time the red solid was deposited. The product was collected, washed with water and dried; yield 0.29 g. (13%). An analytical sample was prepared by sublimation at 200–220° and 1 mm.

Anal. Calcd. for $C_2H_4N_6$: C, 21.42; H, 3.57; N, 75.00. Found: C, 21.62; H, 3.38; N, 75.10.

3,6-Diacetamido-1,2,4,5-tetrazine (**VIIb**).—A mixture of 0.1 g. of VIIa (0.9 millimole) and 20 cc. of acetic anhydride was refluxed for 30 minutes. The excess acetic anhydride was removed *in vacuo* and the residue taken up in 30 cc. of ethyl acetate. On cooling, 10 mg. of solid deposited, m.p. 272–274°. This material has not yet been identified but appears to be the monoacetyl derivative of VII. The ethyl acetate filtrate was next evaporated to dryness *in vacuo* and the residue taken up in 10 cc. of cold ethanol. Slow evaporation of the solvent gave 50 mg. of an orange, micro-crystalline solid, m.p. 156–158°.

Anal. Calcd. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.63; H, 4.14; N, 42.50.

3,6-Di-(*p*-toluenesulfonamido)-1,2,4,5-tetrazine (**VIIc**).—A mixture of 0.1 g. of VIIa (0.9 millimole) and 0.7 g. of *p*-toluenesulfonyl chloride (3.7 millimoles) in 10 cc. of pyridine was refluxed for one hour, after which the red solution was taken to dryness *in vacuo*. The addition of 10 cc. of 50% ethanol caused the deposition of an orange-yellow solid which was collected and washed with cold 50% ethanol. This material amounted to 90 mg., m.p. 224–227°. A second recrystallization from 95% alcohol yielded the ditosyl derivative in the form of orange, prismatic needles, m.p. 227–228°.

Anal. Calcd. for $C_{16}H_{16}N_6S_2O_4$: C, 45.70; H, 3.84; N, 19.99; S, 15.21. Found: C, 46.26; H, 4.25; N, 20.00; S, 15.04.

CHICAGO, ILLINOIS

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[19] All melting points are uncorrected. Analyses are by the Micro-Tech Laboratories, Skokie, Ill. The visible absorption spectra were measured in a Cary Recording Spectrophotometer, Model 11 PM. Infrared absorption measurements were obtained with a Perkin–Elmer recording spectrophotometer, model 21.

[20] M. Freund and T. Paradies, *Ber.*, **34**, 3114 (1901).