CHAPTER III

The 1,2,3,4-Tetrazines

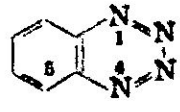
Introduction

In the older literature, monocyclic or uncondensed 1,2,3,4-tetrazines (I) are called osotetrazines, the prefix *oso-* denoting their derivation from the oxidation of the osazones of α,β-diketones.[50] Osotetrazine implies the 2,3-dihydro derivatives. Von Pechmann, their discoverer, had originally named them *osotetrazones*, but he used this term for only a short time.[48] *Chemical Abstracts* has indexed 1,2,3,4-tetrazines variously under *Osotetrazine* or *v-Tetrazine*. From 1928 to 1938 they were indexed at *v-Tetrazine* with no cross reference to *Osotetrazine*. From 1938 to the present *Osotetrazine* has been preferred, undoubtedly because the 1,2,3,4-tetrazine structure assigned certain compounds is questionable.* *The Ring Index* prefers the name *v-tetrazine* (*R.I.* 133).[36]

As in the nomenclature of the triazines, the prefixes *v*, *as-*, and *s-* may be used to advantage in designating the isomeric 1,2,3,4-, 1,2,3,5-, and 1,2,4,5-tetrazines, respectively. In this chapter *v-tetrazine* is used to name specific 1,2,3,4- or "vicinal" tetrazines when the structure appears to be correct. When the structure is not certain, as in the case of the 2,3-diaryl compounds, the osotetrazine nomenclature is used.

(I)

v-Tetrazine
1,2,3,4-Tetrazine
Osotetrazine (2,3-dihydro)



(II)

Benzotetrazine
1,2,3,4-Benzotetrazine

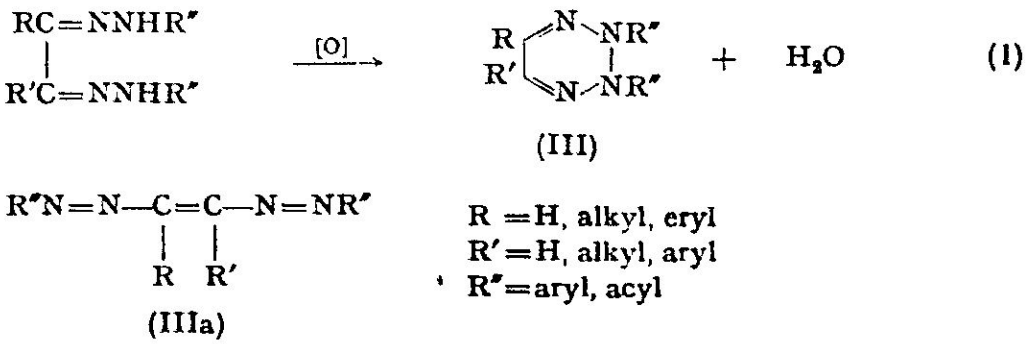
* "Osotriazoles," triazoles derived from osotetrazines or osazones, are in *Chemical Abstracts* at 1,2,3-, 1,2,5-, or 2,1,3-Triazole, less frequently as- or Osotriazole.

The most important of the condensed *v*-tetrazines are those which contain the *benzotetrazine* or *1,2,3,4-benzotetrazine* nucleus (II). Both *Chemical Abstracts* and *The Ring Index* (*R.I.* 910) prefer the former name. Neither the *v*- nor the 1,2,3,4-locants are necessary because no ambiguity exists.

Neither the syntheses nor the reactions of compounds containing the 1,2,3,4-tetrazine ring have been studied very extensively. About forty individual compounds have been prepared and described, although the tetrazine structures proposed for most of them are doubtful. No naturally occurring derivative of 1,2,3,4-tetrazine has been reported. A single reference to the practical application of a 1,2,3,4-tetrazine is disclosed in the broad claims of a U.S. Patent on corrosion inhibitors for lubricating oils.[35] There are no sulfonamide type antibiotics derived from 1,2,3,4-tetrazine rings listed in the compilation of Northey.[33]

Almost all of the published literature on the 1,2,3,4-tetrazines deals with their preparation. Relatively little study has been made of the reactivity of this heterocyclic ring aside from that incidental to its preparation. More than half of the papers published on this class of compounds predate World War I, and only a few important ones have appeared since 1940.

The principal reaction employed for the synthesis of the 1,2,3,4-tetrazine ring is the oxidation of the dihydrazones (or osazones) of α,β-diketones, a reaction first described in 1888 by H. von Pechmann.[48] Most of the uncondensed tetrazines have been prepared by some modification of this reaction, the usual variation being in the choice of



oxidizing agent. Recent spectral evidence indicates that, when R″ = aryl, the products are not dihydro-*v*-tetrazines (III) but rather have

the isomeric bis(phenylazo)ethylene structure (IIIa).[7,16,54] This possibility was already recognized by Bucherer and Stickel[9] and advanced by Stollé[43] in the middle 1920's.

The oxidation of osazones has been limited to those containing simple alkyl, aryl, and acyl groups, and their positions on the tetrazine nucleus are predetermined. The 5-and 6-positions are occupied by radicals from the original α,β-diketone, and the 2- and 3- positions hold radicals from the original hydrazine molecules. The tetrazines produced are the 2,3-dihydro derivatives, generally of the form IIIa in equation 1.

Benzotetrazine and naphthotetrazine systems have been prepared most commonly by the diazotization of *o*-aminoarylhydrazines followed by reduction[59] or neutralization with alkali.[21]

Other reactions which have been used to prepare 1,2,3,4-tetrazines are more specialized and diversified, and are not conveniently grouped together. They will be discussed under the specific compounds for which they were employed.

Aside from oxidation, reduction, and the hydrolysis of substituents, the reaction of 1,2,3,4-tetrazines that has been investigated most extensively is their rather easy conversion into 1,2,3-triazoles by the action of acids, bases, and heat.[45,48,50] This important transformation is discussed in greater detail as part of the historical development of the monocyclic 1,2,3,4-tetrazines.

Substitution reactions on the 1,2,3,4-tetrazine ring have been limited to acylations; bromination of phenyl-*v*-tetrazines introduces a bromo group on the aromatic nucleus, rather than the heterocyclic ring. Of the substituted 1,2,3,4-tetrazines reported in the literature, the substituents resulting from ring closure or introduced as an integral part of the reactants have been acyl, carbethoxy, cyano, and keto groups.

1. UNCONDENSED 1,2,3,4-TETRAZINES

A. 1,2,3,4-Tetrazine

1,2,3,4-Tetrazine itself has not been described in the literature. H. von Pechmann and his students at Tübingen considered the possibility of its synthesis and embarked on a rather extensive but

successful program to secure it.[3,5,33] The intermediates they prepared during this work are of greater importance in other connections, and the results of these experiments are discussed elsewhere in this chapter. The only recent reference to 1,2,3,4-tetrazine concerns its hypothetical structure. By means of the valence-bond method, Maccoll[30] predicted the first absorption maximum of 1,2,3,4-tetrazine to be 5300 A., and its resonance energy 10 kilocalories per mole. Of the two possible nonequivalent Kekulé structures that can be drawn for this substance, the one containing the =N–N=N–N= sequence is considered to be more stable than the other, which has the –N=N–N=N– arrangement of double bonds.

B. Dihydro-1,2,3,4-Tetrazines

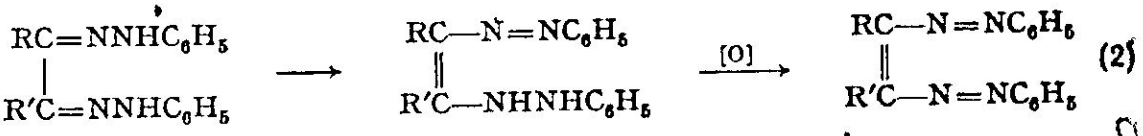
Completely unsaturated 1,2,3,4-tetrazines also have never been prepared; practically all of the compounds that have been reported are the dihydro derivatives. The apparent nonexistence of true tetrazines is doubtless associated with the rather easy rearrangement of the 2,3-dihydro derivatives into aminotriazoles.

The chemistry of the 1,2,3,4-tetrazines may be more clearly presented by grouping certain of the specific compounds into two genera: (1) those substituted in the 2- and 3- positions with phenyl groups and (2) those substituted in the 2- and 3- positions with benzoyl groups. The former are derived from the bis(phenylhydrazones) of α,β-diketones and the latter from the bis(benzoylhydrazones) of α,β-diketones. The two types have strikingly different properties.

All of the dihydro-*v*-tetrazines of the first type are colored, some of them intensely; those of the second type are white or colorless. Compounds of the first may be reduced to the original osazone with phenylhydrazine or alcoholic hydrogen sulfide; those of the second type are stable toward these reagents.

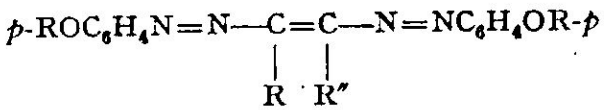
Using these two experimental facts as his basis, Stollé[43] suggested that the 2,3-diaryl-2,3-dihydro-*v*-tetrazines may not be tetrazines at all, but may exist in an open-chain azo structure (IIIa). On the other hand, the lack of color and the stability toward reducing agents of the benzoyl compounds prompted Stollé to accept them as derivatives of *v*-tetrazine.

Recent studies of visible and ultraviolet spectra by Bodforss[7] and Grammaticakis[16] offer additional evidence for the linear structure of the osotetrazines. Grammaticakis suggested that the oxidation of osazones may take the course shown in reaction 2, and proposed the intermediate formation of a tautomer of the osazone.

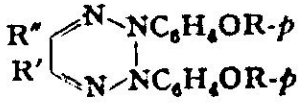


(2)

The ingenious experiments of Vorländer and co-workers[54] lend considerable support to Stollé's contention that the highly colored 2,3-diaryl derivatives, obtained by the oxidation of osazones, are indeed azo compounds. They investigated the liquid crystal properties of a series of osazones and their oxidation products, the osotetrazines. Osotetrazines might be expected to form liquid crystals on melting if they exist in the linear azo form (IV), but not if they have the cyclic tetrazine structure (IVa). The oxidation products obtained were actually found to pass into a liquid crystal state and characteristically exhibited two melting points. Accordingly Vorländer concluded that structure IV is the correct one.



(IV)



(IVa)

$R = CH_3, C_2H_5$
$R' = H, CH_3$
$R'' = H, CH_3$

The evidence in favor of the azo structure for the oxidati products of the osazones is steadily mounting. However, in the a of more rigorous structure proof, the osotetrazines are still treated heterocyclic compounds in this chapter. The potential importance extensive spectroscopic study and the application of other ph techniques to structure proofs in this field is quite apparent.

(1) Substituted in the 2- and 3-Positions with Aryl Groups

A discussion of the individual 1,2,3,4-tetrazines might best with those substituted in the 2- and 3-positions by Structurally simpler species are known, but the 2,3-diaryl

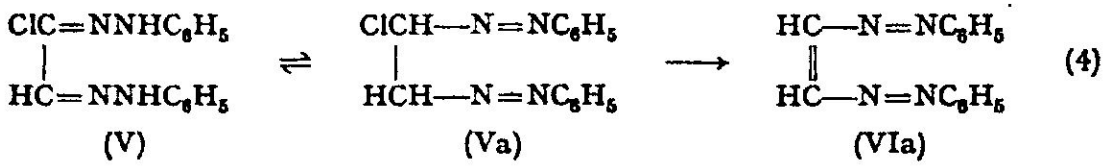
offer a better introduction to the subject from the standpoints of chronology of development and simplicity of presentation.

In his earliest researches, von Pechmann treated the phenylosazones of glyoxal, pyruvaldehyde, and biacetyl with potassium dichromate in dilute acetic acid, and got neutral, colored products. They contained two hydrogen atoms less than the original osazone. Because of this, and since osazones without hydrogens on their secondary nitrogen atoms do not readily oxidize, von Pechmann concluded that the products isolated were cyclic compounds. He regarded them as diphenyl-2,3-dihydro-s-tetrazines and called them osotetrazines[50] (originally osotetrazones[48]), to differentiate them from the 1,2,4,5- or s-tetrazines, which were already known and called "tetrazines."

2,3-Diphenylosotetrazine (VI), prepared by the oxidation of glyoxal phenylosazone, is described as dark red plates of m.p. 152° (dec.) from alcohol, but no experimental details are given for its preparation. A second preparation by the same method is reported[49]; however, again the experimental part in this paper is sketchy, but a satisfactory analysis is included. Dieckmann and Platz[13] obtained VI in 70% yield by treating the phenylosazone of glyoxylyl chloride (V) with potassium hydroxide in alcohol (eq. 3). In this novel reaction, the result was

(V) (VI) (3)

accomplished by dehydrochlorination rather than oxidation. By this process the formation of the linear azo compound (VIa) is more readily conceivable, especially if the glyoxylyl chloride phenylosazone is considered in the form of the tautomer (Va).



(V) (Va) (VIa) (4)

Experimental details are presented by von Pechmann for the preparation of 5,6-dimethyl-2,3-diphenylosotetrazine by the oxidation of biacetyl phenylosazone with potassium dichromate in dilute acetic

acid solution.[48] Oxidation of biacetyl phenylosazone may be performed with either alkaline or acidic oxidizing agents. The reaction is reported to be quantitative in the absence of strong acid.

5,6-Dimethyl-2,3-diphenylosotetrazine, recrystallized from hot acetone and then alcohol, forms dark red needles of m.p. 169° (dec.). It is soluble in chloroform, benzene, and ether, slightly soluble in acetone and alcohol, and insoluble in water and acetic acid. Solutions of it are reddish-brown, and a brown color develops when it is dissolved in concentrated sulfuric acid. On warming with phenylhydrazine, it is reduced to the original osazone of m.p. 245°.

5-Methyl-2,3-diphenylosotetrazine, likewise obtained by the dichromate oxidation of pyruvaldehyde phenylosazone, melts at 106–7° and decomposes at 124°. Its reactions with sulfuric acid and phenylhydrazine are similar to those of the dimethyl homolog.[48]

Other 2,3-diarylosotetrazines described in the literature are included in Table III-1 and discussed in greater detail in the following paragraphs.

TABLE III-1. 2,3-Dihydro-*v*-tetrazines

Substituents	Color, crystal habit	M.p., °C.	Ref.
2-Benzoyl-5,6-dimethyl[a]	White crystals	95	50
2-Benzoyl-5,6-diphenyl[a]	Colorless fine needles	248	46
5,6-Bis(carbethoxy)-2,3-diphenyl[b]	Violet black needles or flat red prisms	143 (dec. pt.)	2, 43
2,3-Bis(2,4-dichlorophenyl)5,6-diphenyl[b,c]	Lemon yellow needles	217	10
2,3-Bis(4-ethoxyphenyl)-5-methyl[b]	Red needles	116	3, 50, 54
5,6-Bis(2-indolyl)-2,3-diphenyl[b]	Colored solution only		40
5,6-Bis(2-methoxyphenyl)[a]	Colorless needles	138	56
2,3-Bis(2-nitrophenyl)-5,6-diphenyl[a]	White powder	200 (dec.)	17

TABLE III-1 *(continued)*

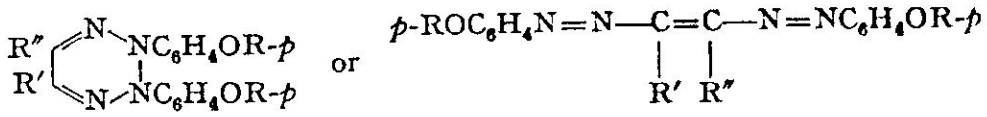
Substituents	Color, crystal habit	M.p., °C.	Ref.
5-Cyano-2,3-diphenyl[b]	Reddish-brown needles	137 (dec. pt.)	53
2,3-Dibenzoyl-5,6-dimethyl	White needles	140	45, 50, 51
2,3-Dibenzoyl-5,6-diphenyl	White voluminous powder	189	32, 44, 45, 46
5,6-Dibenzoyl-2,3-diphenyl[b]	Small red-brown needles	200–201	29
2,3-Dibenzoyl-5-methyl	Small white needles	124	43
5,6-Dimethyl[a]	Colorless plates	95	50
5,6-Dimethyl-2,3-diphenyl[b]	Dark red needles	169 (dec.)	48
2,3-Diphenyl[b]	Dark red plates	152	7, 13, 48, 49
5,6-Diphenyl[a]	Colorless stout needles	135	8, 29, 31, 44, 46
2,3-Diphenyl-5-methyl[b]	(Not described)	106–107 124 (dec. pt.)	48

[a] May be an aminotriazole.
[b] May have linear structure; called osotetrazines in text.
[c] 1,2,3,4-Tetrahydro derivative.

In the course of his work on the synthesis of *v*-tetrazine, Auden prepared 5-methyl-2,3-bis(*p*-ethoxyphenyl)osotetrazine, as red needles of m.p. 116°, by oxidizing the corresponding osazone.[3,50] It could not be reconverted to the osazone, presumably by phenylhydrazine reduction. This osotetrazine was also prepared by Vorländer, Zeh, and Enderlein[54] (Compound IVa, R″ = H, R′ = CH_3, and R = C_2H_5) for their study of the liquid crystal properties of osazone oxidation products. They report that the lower melting point, 116° in this case, is not the true melting point but rather the transition temperature at which the substance passes into the liquid crystal phase. The true melting point is actually about 210° (dec.). In Table III-2 are listed the osotetrazines studied by Vorländer and co-workers. The lower melting points (transition temperatures) are those observed by the ordinary capillary

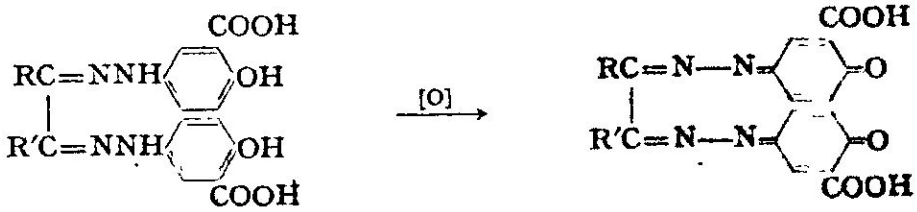
tube method. The higher melting points were determined by the Seger cone method. Between these two temperatures the substances are birefringent.

TABLE III-2. Osazone Oxidation Products (Osotetrazines) of Vorländer, Zeh, and Enderlein[54]



R	R′	R″	Color	Melting point, °C. Lower	Upper
CH_3	H	H	Garnet red	158	*ca.* 200
C_2H_5	H	H	Garnet red	167	*ca.* 220
CH_3	CH_3	H	Yellow-red	123	*ca.* 200
C_2H_5	CH_3	H	Red-violet	115	*ca.* 210
CH_3	CH_3	CH_3	Red-violet	171.5	*ca.* 188
C_2H_5	CH_3	CH_3	Brown-violet	170	*ca.* 187

Auden[3] produced the osazones (VII) and (VIII) by reacting 5-hydrazinosalicylic acid with pyruvaldehyde and 2,3-pentanedione, respectively. Neither of these could be oxidized to the corresponding osotetrazine in the usual manner. Stollé[43] attributed this failure to the formation of quinoneimines, perhaps of the type illustrated by compound IX, which could not cyclize to the desired tetrazine (eq. 5).



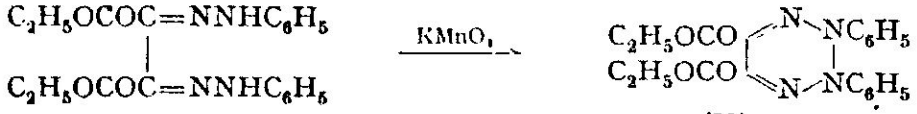
(VII) R=CH_3, R′=H
(VIII) R=CH_3, R′=C_2H_5

(IX) (5)

Benzil bis(*o*-nitrophenylhydrazone) forms a white powder of m. 200° (dec.) on exposure to air. This osazone is apparently oxidized by air, and Guha and De[17] tentatively assigned the *v*-tetrazine structure to the product. The white color of the product consistent with the *v*-tetrazine structure, but the possibility of being an aminotriazole ought not to be excluded.

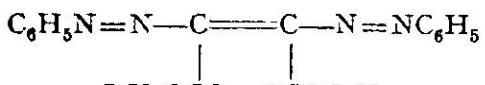
Oxidation of the phenylosazone of cyanoglyoxal[52] with ferric chloride or potassium dichromate in dilute acetic acid gives 5-cyano-2,3-diphenylosotetrazine,[53] reddish brown needles, m.p. 137° (dec.). This compound forms 4-cyano-2-phenyl-1,2,3-triazole (colorless needles) on heating with hydrochloric acid.

Anschütz and Pauly[2] obtained three isomeric phenylosazones from diethyl dioxosuccinate and phenylhydrazine: α-, m.p. 120–1°; β-, m.p. 136–7°; and γ-, m.p. 173–5°. Only the α-isomer could be oxidized to the corresponding osotetrazine (X) with potassium per-



(6)

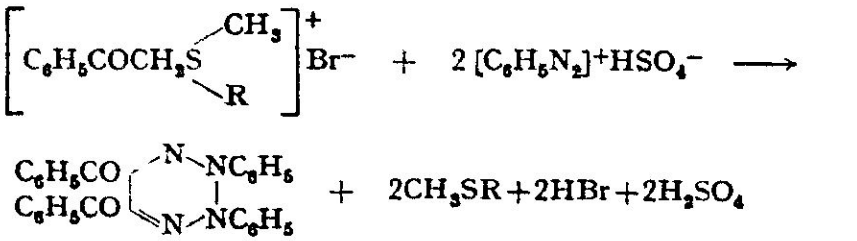
(X)



(Xa)

manganate and hydrochloric acid in ether solution (eq. 6). The product is dimorphic, occurring as violet black needles, or flat red prisms. Both forms melt at 143° with decomposition. This is another of the tetrazines that Stollé[43] suggested as possibly existing in the linear azo form. Accordingly he felt the compound could be the isomeric α,β-bis-(phenylazo)maleic ester (Xa).

A unique reaction that apparently produced an osotetrazine analogous to X is reported by Krollpfeiffer and Hartmann.[39] They obtained 5,6-dibenzoyl-2,3-diphenylosotetrazine by the reaction of benzenediazonium salts with certain phenacylsulfonium salts according to equation 6a. The primary coupling product is not stable and elim-



(6a)

$R = CH_3, C_3H_5, C_6H_5CH_2$

inates the sulfide and hydrogen bromide. The osotetrazine apparently arises by the dimerization of the diazophenacyl intermediate. When R

is methyl, allyl or benzyl, the reaction proceeds as shown in equation 6a, but, when R is phenyl, the tetrazine does not form; only methyl phenyl sulfide is eliminated and ω-phenyl-azo-ω-bromoacetophenone is obtained in good yield.

In a typical experiment dimethylphenacylsulfonium bromide is reacted with benzenediazonium sulfate in a solution buffered with sodium acetate. After standing overnight the crude product is isolated and purified by being boiled with methanol and recrystallized from acetic acid. 5,6-Dibenzoyl-2,3-diphenylosotetrazine occurs as small needles that possess the typical red-brown color of the osotetrazines, m.p. 200–201°.

Sanna[40] reported a typical osazone-osotetrazine transformation in the oxidation of α,α- or β,β-biindoxyl bis(phenylhydrazone) with ferric chloride in alcohol or ether. However, in neither case did he isolate the product. He merely reported the formation of the "red color" characteristic of osotetrazines.

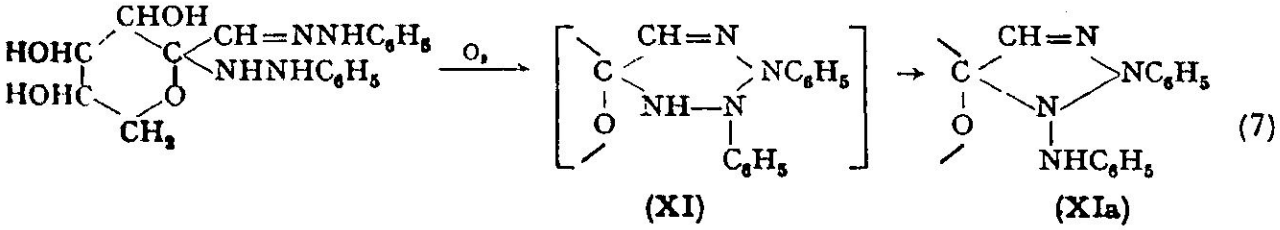
The production of the intense osotetrazine color is useful for the qualitative detection of phenylosazones.[48] The osazone is moistened with alcohol, gently warmed with ferric chloride solution, and shaken with ether. The formation of the red to brown-red color of the resulting osotetrazine is indicative of an osazone. According to von Pechmann, only the osazones of simple aliphatic diketones, or those containing only one aromatic radical, respond to this test; tartrazine, and the osazones of benzil, acetylglyoxylic acid, dioxosuccinic acid, and glucose do not give the reaction.

Recent studies have disclosed that the osazones of sugars are nevertheless affected by mild oxidizing reagents, although the final products are not osotetrazines. A brief discussion of this phase of the chemistry of osazones in not out of order, because of its close relationship to the chemistry of the 1,2,3,4-tetrazines.

Diels and co-workers[14,15] have oxidized (dehydrogenated) osazones of several sugars, especially glucose, to compounds similar to the original osazones but containing two hydrogen atoms less. oxidation is readily accomplished by bubbling air through a solution of the osazone in alcoholic potassium hydroxide. They contended their "dehydroösazones" were not osotetrazines because the

could not be regenerated by mild reduction. The possibility that the dehydrogenation has occurred elsewhere in the sugar molecule is excluded on the basis that osazones prepared from 1-methyl-1-phenylhydrazine are not dehydrogenated.

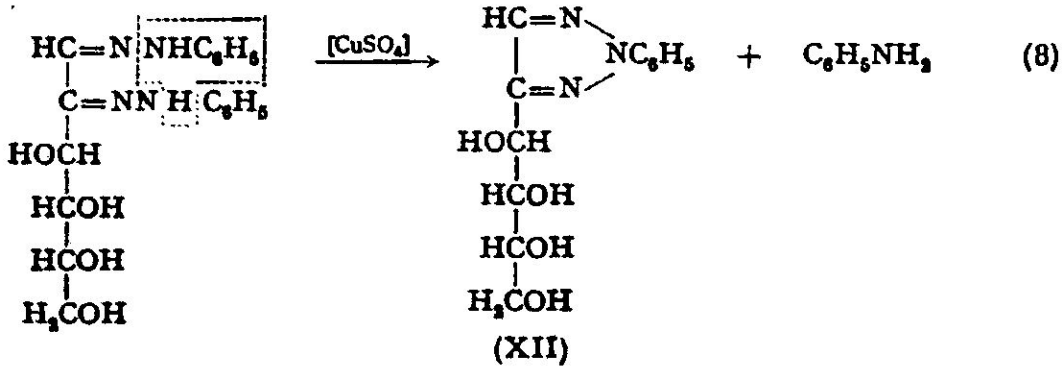
Diels suggests that the "dehydroösazones" are aminotriazoles of the type XIa and that the reaction proceeds with the intermediate formation of a dihydroösotetrazine (XI) as in reaction 7.



(7)

(XI) (XIa)

More recently C.S. Hudson and his collaborators[18] have discovered that the treatment of sugar osazones with aqueous copper sulfate produces 1,2,3,2H-triazoles with the elimination of aniline (eq. 8). The role of the copper sulfate is not understood; however, it is not primarily an oxidizing agent. The reaction is a general one, and the products, called osotriazoles (for example, phenyl-*D*-glucosotriazole, XII), have become very popular derivatives for the characterization of sugars.[19,20,39] Experiments by Weygand, Grisebach, and Schmeiser, using glucosė-*p*-bromophenylosazone, made from *p*-bromophenylhydrazine tagged with Br,[82] show that the aniline molecule eliminated is the one from the phenylhydrazono group attached to the first carbon atom as indicated in equation 8.[55]

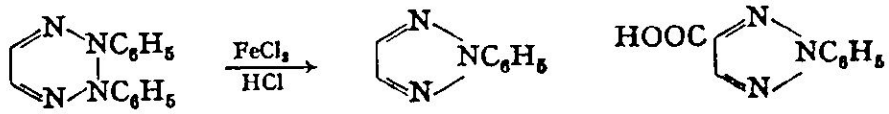


(8)

(XII)

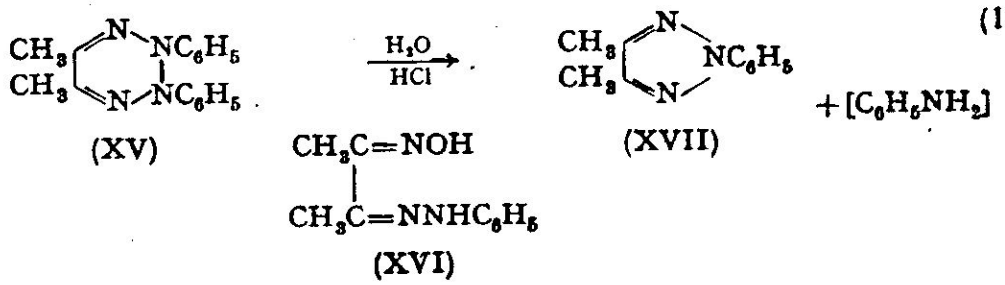
Under the influence of moderately strong mineral acids, osotetrazines likewise form osotriazoles. They are oily, neutral substances that von Pechmann described as non-volatile and very stable.[48] He

identified them as triazoles and proved their structures by alternative syntheses. For example, the reaction of 2,3-diphenylosotetrazine (VI) with hot ferric chloride and hydrochloric acid solution (eq. 9) yielded 2-phenyl-1,2,3-triazole (XIII), which was identified with a sample prepared by the decarboxylation of the silver salt of 2-phenyl-1,2,3-triazole-4-carboxylic acid (XIV).[23]



(VI) (XIII) (XIV) (9)

Furthermore, the product obtained by treating 5,6-dimethyl-2,3-diphenylosotetrazine (XV) with hydrochloric acid (eq. 10) was shown to be identical with that resulting from the action of phosphorus pentachloride on the phenylhydrazone oxime of biacetyl (XVI), *viz.*, 5,6-dimethyl-2-phenyl-1,2,3-triazole (XVII).[48]



(XV) (XVI) (XVII) (10)

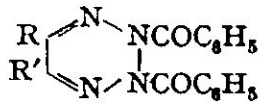
It is difficult to conceive how aniline, reported to be a product of the reaction, could arise in equation 10; reducing conditons are absent and only the elements of C_6H_5N are lost in the over-all reaction. Because compound XVII was obtained in only 20% yield and considerable tar formation had occurred, the course of the reaction appears to be quite complex and the mode of elimination of the aniline is obscure. The subject of osotriazoles, their formation and reactions, is discussed more thoroughly by von Pechmann in a later paper.[47]

It should be mentioned, in order to be complete, that osazones may be converted directly to osotriazoles by heating in alcohol at 200°.[6]

(2) Substituted in the 2- and 3-Positions with Benzoyl Groups

The second important class of uncondensed *v*-tetrazines comprises the 2,3-dibenzoyl-2,3-dihydro-*v*-tetrazines (XVIII), usually by the oxidation of the bis(benzoylhydrazones) of *α*

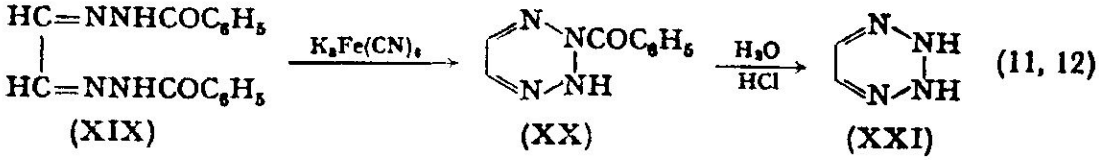
differ markedly from osotetrazines in that they are colorless, cannot be reduced to the original osazone, and rearrange to aminotriazoles upon heating or treatment with strong acids. Stollé [3] maintains that compounds of type XVIII actually contain the 1,2,3,4-tetrazine ring.



(XVIII)

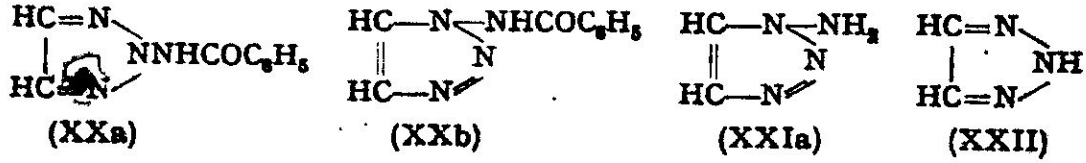
R and R′=H, alkyl, or aryl

In an early attempt to obtain dihydro-*v*-tetrazine (XXI), Bauer[5] followed the general procedure for the production of osotetrazines[48,50] and oxidized the bis(benzoylhydrazone) of glyoxal (XIX) with alkaline potassium ferricyanide (eq. 11). He obtained a crystalline compound of m.p. 151°, and assumed that it was 2-benzoyl-2,3-dihydro-*v*-tetrazine (XX). It is surprising that one of the benzoyl groups should have been eliminated in the reaction, particularly if it simply involved the oxidation to the tetrazine. Acid hydrolysis (eq. 12) gave a debenzoylated product, at first reported to be the desired tetrazine (XXI). It was obtained as a very hygroscopic, colorless, crystalline mass of m.p. 51°, which upon treatment with nitrogen trioxide gave 1,2,3-triazole (XXII).



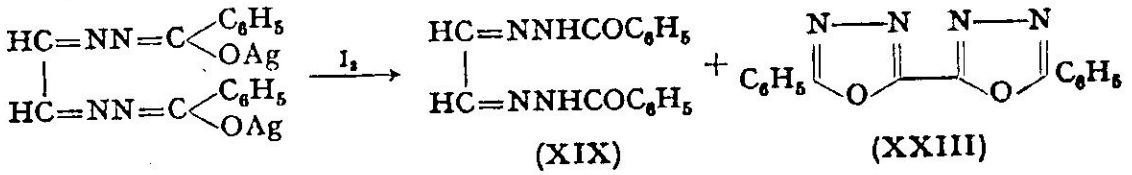
(XIX) (XX) (XXI) (11, 12)

Subsequently von Pechmann and Bauer[51] recognized compound XX to be a triazole and assigned to it structure XXa. According to Stollé's later findings,[43] however, the correct structure is XXb, and therefore the supposed dihydro-*v*-tetrazine is actually 1-amino-1,2,3-triazole (XXIa). Compound XXIa should be expected to give 1,2,3-triazole with nitrogen trioxide. Stollé claimed priority over von Pechmann and Bauer in suggesting that certain 2,3-dihydro-*v*-tetrazines are in reality aminotriazoles.[42]



(XXa) (XXb) (XXIa) (XXII)

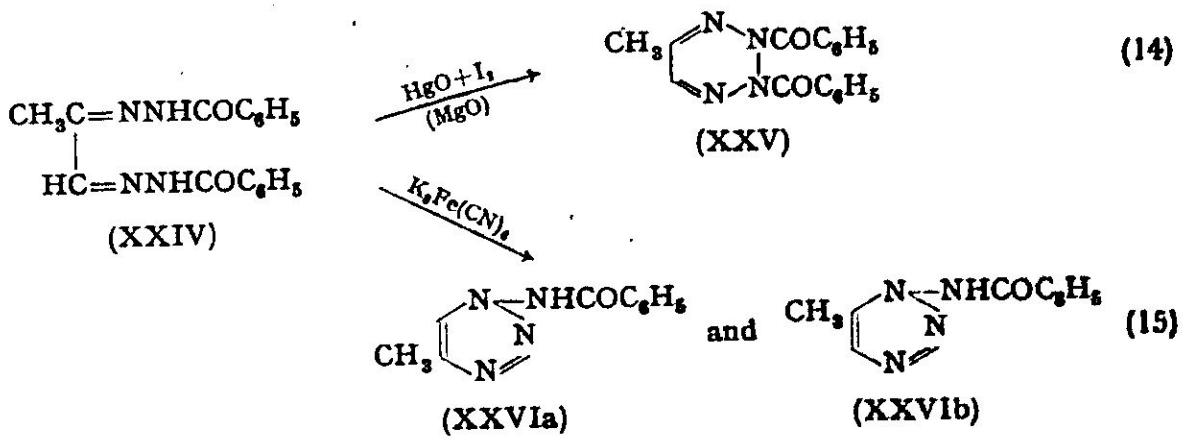
Münch[32] attempted to procure 2,3-dibenzoyl-2,3-dihydro-*v*-tetrazine by oxidizing the silver salt of glyoxal bis(benzoylhydrazone) with iodine (eq. 13). Instead, the free osazone (XIX) was regenerated and 5,5′-diphenyl-2,2′-bi-1,3,4-oxadiazole (XXIII) resulted as a side product.



(13)

(XIX) (XXIII)

Stollé oxidized the bis(benzoylhydrazone) of pyruvaldehyde (XXIV) with mercuric oxide and iodine in the presence of magnesium oxide in dry ether (eq. 14).[43] The product of this reaction appears to be the desired 2,3-dibenzoyl-5-methyl-2,3-dihydro-*v*-tetrazine (XXV). However, oxidation of XXIV with alkaline potassium ferricyanide



(14)

(XXIV) (XXV)

(15)

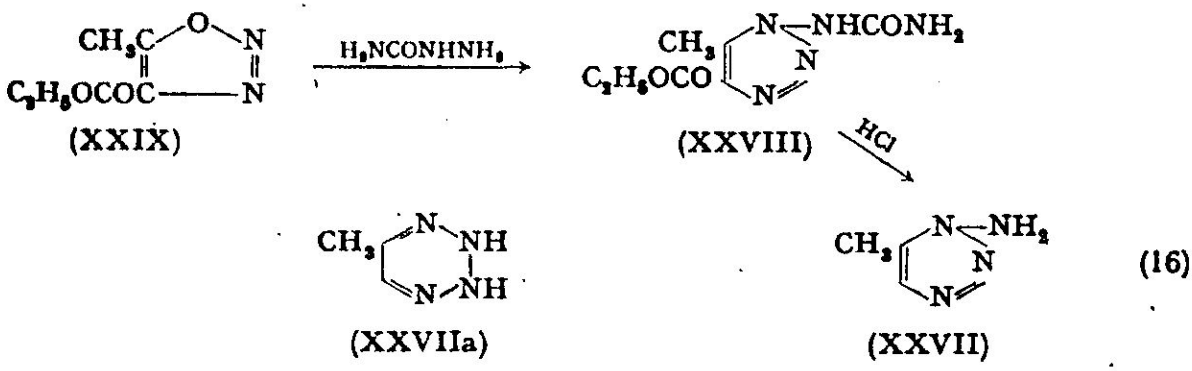
(XXVIa) (XXVIb)

does not give rise to the dihydro-*v*-tetrazine (XXV), but gives a mixture of 1-benzamido-4-methyl- and 1-benzamido-5-methyl-1,2,3-triazoles (XXVIa) and (XXVIb).[43] The result obtained in reaction 15 is identical with the experience of von Pechmann and Bauer shown in reaction 11. Choosing the proper oxidizing agent appears to be a critical factor in preparing dihydro-*v*-tetrazines of type XVIII, particularly where R or R and R′ are hydrogen.

2,3-Dibenzoyl-5-methyl-2,3-dihydro-*v*-tetrazine (XXV) lizes from ethanol in small white needles, m.p. 124°. It is water and alkalis, and moderately soluble in ether. It is in hot, but not in cold, ethanol. When finely divided, it is slowly

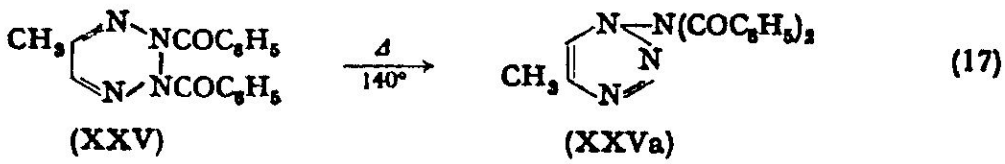
by hot aqueous sodium carbonate. This behavior is strange in view of the absence of an acidic hydrogen atom in XXV.

When XXV is refluxed for twenty-four hours with ethanolic hydrochloric acid, it is debenzoylated with the formation of 1-amino-5-methyl-1,2,3-triazole (XXVII), m.p. 135° (dec.), and not 5-methyl-2,3-dihydro-*v*-tetrazine (XXVIIa). The triazole (XXVII) is identical with a sample prepared by the method of Wolff and Hall[57] from compound XXVIII, the reaction product of semicarbazide and the diazoanhydride of ethyl acetoacetate (XXIX). Although the oxadiazole structure of ethyl acetoacetate diazoanhydride (XXIX) is considered to be improbable,[41] the structure of XXVIII is nevertheless reasonable, and XXVII is probably correct.



(16)

Heating tetrazine XXV, m.p. 124°, for two hours at 140° results in its rearrangement exclusively to 1-dibenzoylamino-4-methyl-1,2,3-triazole (XXVa), m.p. 152° (eq. 17). Compound XXVa is identical with the product obtained by benzoylating 1-amino-4-methyl-1,2,3-triazole with benzoyl chloride and calcined sodium carbonate in benzene. The other isomer in this series, 1-dibenzoylamino-5-methyl-1,2,3-triazole, melts at 202°



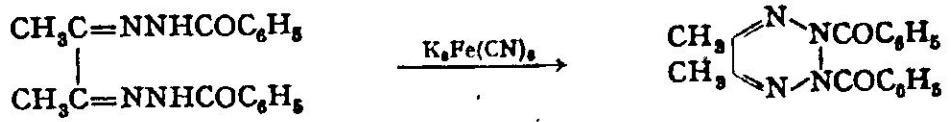
(17)

Stollé offered the foregoing reactions as partial proof that 1-amino-1,2,3-triazoles and not 2-amino-1,2,3-triazoles are the products resulting from both the acid catalyzed and thermal isomerizations of 2,3-dibenzoyl-2,3-dihydro-*v*-tetrazines.

In the course of his attempts to obtain *v*-tetrazine, Auden[3] tried to prepare 5-methyl-2,3-dihydro-*v*-tetrazine (XXVIIa). 5-Methyl-2,3-bis(*p*-ethoxyphenyl)osotetrazine (XXX), prepared by the mild oxidation of the corresponding osazone, was further oxidized by an undisclosed means (eq. 18) in an attempt to eliminate the 2,3-aryl substituents and thus obtain XXVIIa. This approach, however, was reported as unsuccessful.[50]

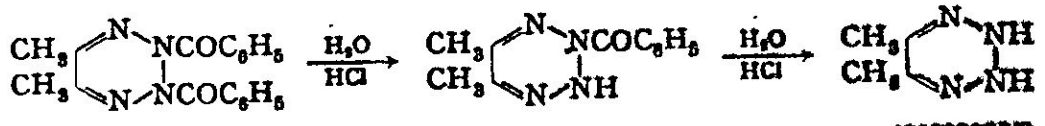
(XXX) (XXVIIa) (18)

von Pechmann and Bauer[50] prepared 2,3-dibenzoyl-5,6-dimethyl-2,3-dihydro-*v*-tetrazine (XXXI) by oxidizing the bis(benzoylhydrazone) of biacetyl with potassium ferricyanide (eq. 19). Compound XXXI cannot be reduced to the original hydrazone with phenylhydrazine. This reagent merely acts as a base and cleaves off one of the benzoyl groups.



(XXXI) (19)

Stepwise hydrolysis of the benzoyl groups of XXXI with dilute hydrochloric acid (eq. 20) gives first the monobenzoyl compound (XXXII), m.p. 140°, and finally 5,6-dimethyl-2,3-dihydro-*v*-tetrazine (XXXIII), m.p. 95°. Treatment of XXXII or XXXIII with benzoyl chloride and sodium hydroxide regenerates the dibenzoyl derivative (XXXI). The beautifully crystalline hydrochloride of XXXIII can be readily converted to the free base with silver oxide.

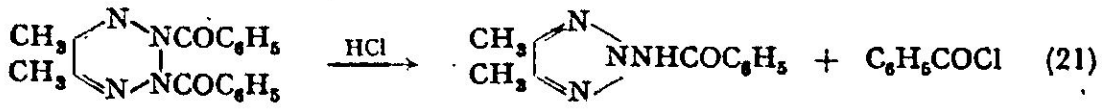


(XXXI) (XXXII) (XXXIII)

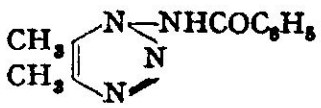
5,6-Dimethyl-2,3-dihydro-*v*-tetrazine (XXXIII) is soluble in ordinary organic solvents, and it forms neutral aqueous solutions. In contrast to the osotetrazines, it is very stable toward dilute

acids. With mercuric chloride, XXXIII forms a white precipitate, which crystallizes from hot water in needles of m.p. 146–7°. Silver nitrate slowly produces a precipitate and ferric chloride gives a red-yellow solution with XXXIII. It reduces Fehling's and alkaline silver solutions, and is vigorously oxidized by potassium dichromate and sulfuric acid in the cold. However, none of the fully aromatic tetrazine is obtained with any of these reagents. Rapid heating leads to an explosion and the formation of a weakly alkaline vapor.

In a subsequent paper von Pechmann and Bauer[51] reported the treatment of 2,3-dibenzoyl-5,6-dimethyl-2,3-dihydro-*v*-tetrazine with one equivalent of concentrated hydrochloric acid (eq. 21). They obtained a product in 90% yield which they thought was 2-benzamido-4,5-dimethyl-1,2,3-triazole (XXXIV). Benzoyl chloride was isolated as a side product. Stollé's work discussed elsewhere in this chapter, indicates that XXXIVa, the 1-benzamido isomer, is the compound actually obtained.



(XXXI) (XXXIV) (21)

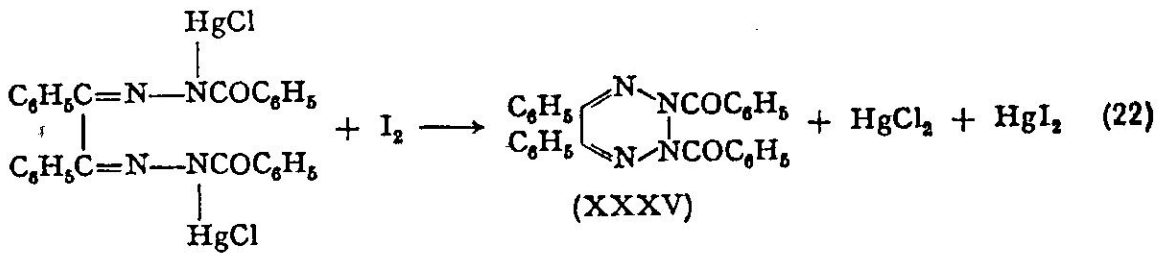


(XXXIVa)

Heating 2,3-dibenzoyl-5,6-dimethyl-2,3-dihydro-*v*-tetrazine, m.p. 140°, at 150° isomerizes it to 1-(*N*,*N*-dibenzoylamino)-4,5-dimethyl-1,2,3-triazole, m.p. 114°. This thermal rearrangement appears to be generally characteristic of 2,3-diacyl-*v*-tetrazines.[43]

Stollé, Münch, and Kind[46] prepared 2,3-dibenzoyl-5,6-diphenyl-2,3-dihydro-*v*-tetrazine (XXXV) in 75% yield by suspending the chloromercuric derivative of benzil bis(benzoylhydrazone) in ether and shaking it with the calculated amount of iodine until the color disappeared (eq. 22). The reaction mixture was treated with aqueous potassium iodide to remove the mercury salts, and the residue of

practically pure dihydrotetrazine was recrystallized from ethanol giving a white voluminous powder, m.p. 189°.



(22)

(XXXV)

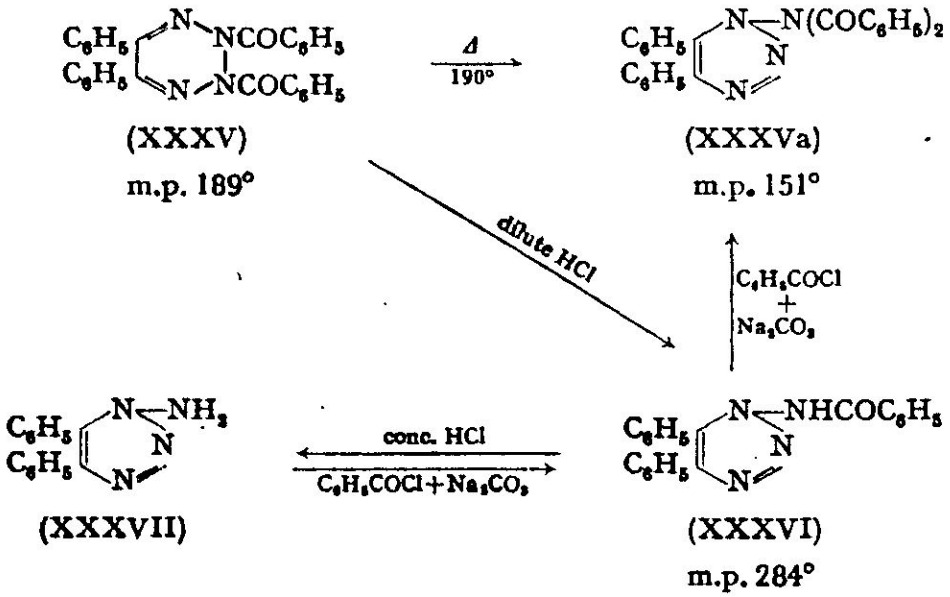
A less satifactory method for preparing XXXV is from the monosilver salt of benzil bis(benzoylhydrazone) and iodine in carbon tetrachloride solution. Small yields of XXXV may also be obtained by oxidizing the bis(benzoylhydrazone) with potassium ferricyanide in aqueous sodium hydroxide solution.

2,3-Dibenzoyl-5,6-diphenyl-2,3-dihydro-*v*-tetrazine (XXXV) is soluble in ethanol and carbon tetrachloride, sparingly soluble in ether, and insoluble in water. When recrystallized from carbon tetrachloride, the product contains one molecule of carbon tetrachloride of crystallization that is lost on heating at 100°.

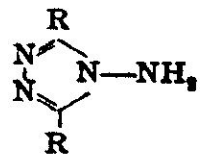
Treatment of XXXV with boiling dilute hydrochloric acid in alcohol for one and one-half days produces a monobenzoyl derivative in good yield but many days' refluxing with concentrated hydrochlo acid in alcohol is necessary to remove the second benzoyl group.[44] The monobenzoyl derivative occurs as fine colorless needles w melt at 248°. This product is apparently no longer a *v*-tetrazine ho ever but rather 1-benzamido-4,5-diphenyl-1,2,3-triazole (XXXVI) Treatment of XXXVI with benzoyl chloride and sodium carbo produces a dibenzoyl derivative (XXXVa) of m.p. 151°, and not original 2,3-dibenzoyl isomer (XXXV) of m.p. 189°.[45]

The completely debenzoylated product although reported to 5,6-diphenyl-2,3-dihydro-*v*-tetrazine, is undoubtedly 1-amino-4,5-phenyl-1,2,3-triazole (XXXVII). It crystallizes as stout needles ethanol, m.p. 135°.[46] It is stable to dilute hydrochloric acid, even sealed tube at 125°, and attempts to decompose it with hot acids only yielded small amounts of hydrazine. Compound XXXVII benzaldehyde condensation product, m.p. 184°, and, with nitrogen in cold ether, 4,5-diphenyl-1,2,3-triazole is produced.

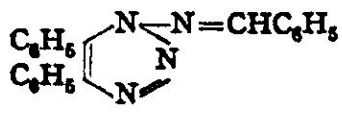
Heating 2,3-dibenzoyl-5,6-diphenyl-2,3-dihydro-*v*-tetrazine at 190° also produces the isomer which melts at 151°.[45] It is identical with the dibenzoyl derivative that forms when the monobenzoyl derivative, from the acid hydrolysis of XXXV, is rebenzoylated with benzoyl chloride and sodium carbonate. Without presenting any experimental details, Stollé stated that the following reactions occurred. (The triazole products are written as 1-amino-1,2,3-triazole derivatives in accordance with Stollé's revised version.[43])



By this scheme, Stollé advanced an explanation for the difference in stability towards hydrolysis of the first and second benzoyl groups of XXXV. In addition, he pointed out that the reactions of the end product, 1-amino-4,5-diphenyl-1,2,3-triazole (XXXVII), are in complete agreement with those of the 4-amino-1,2,4-triazoles (XXXVIII, *R.I.* 78). Neither class reduces Fehling's or ammoniacal silver solutions;



(XXXVIII)



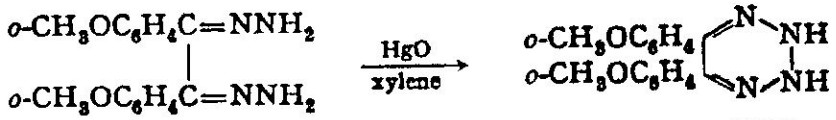
(XXXIX)

both yield stable aldehyde condensation products (*e.g.*, XXXIX), and are deaminated by nitrous acid. The formation of the benzaldehyde condensation products lends support to the contention that the final

hydrolysis products of 2,3-diacyl-2,3-dihydro-*v*-tetrazines are actually 1-amino-1,2,3-triazoles.

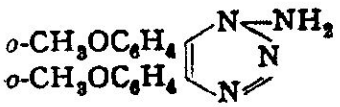
Although the investigations of Stollé discussed in the preceding paragraphs have established that the existence of 2,3-dihydro-*v*-tetrazines unsubstituted in the 2- and 3-positions is unlikely, a few reactions involving such compounds have been reported since that time. They are of little value as synthetic methods, but are included to make the discussion complete.

Weygand and Siebenmark[56] attempted to prepare bis(2-methoxyphenyl)acetylene by treating the dihydrazone of 2,2′-dimethoxybenzil with mercuric oxide in refluxing xylene (eq. 23), a reaction that was successful on the dihydrazones of benzil and 4,4′-dimethoxybenzil. Their main product, however, was not the desired acetylene, but a compound that had two hydrogen atoms less than the starting material. It occurs as colorless needles of m.p. 138°. These authors suggest that the product is 5,6-bis(2-methoxyphenyl)-2,3-dihydro-*v*-tetrazine (XL) on the basis of its analysis and a reference to Stollé's 1926 paper.[43] If structure XL is indeed the correct one, reaction 23 is the only recorded instance of a dihydro-*v*-tetrazine having been formed directly by the oxidation of a dihydrazone. It seems more likely that Weygand and Siebenmark's product is the aminotriazole (XLa).



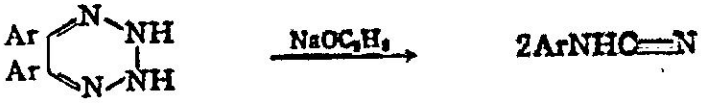
(23)

(XL)



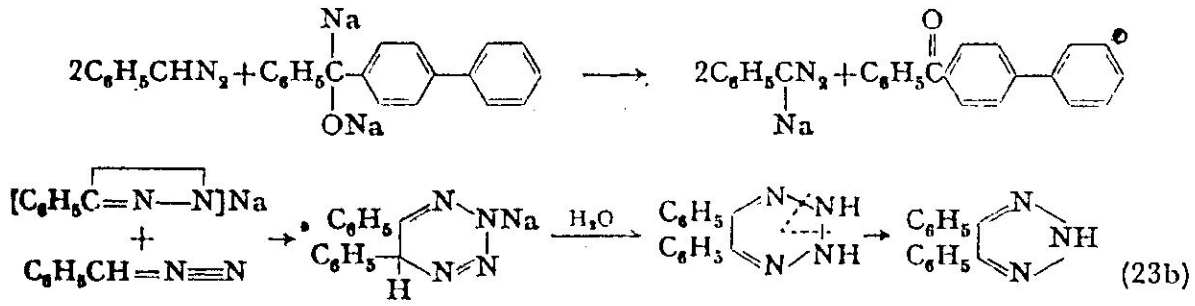
(XLa)

In a footnote to Krollpfeiffer and Hartmann's paper on phenacylsulfonium salts,[29] it was disclosed that treatment of 5,6-diaryl-2,3-dihydro-*v*-tetrazines with sodium ethylate solution transforms them smoothly into arylcyanamides (eq. 23a).[8]



(23a)

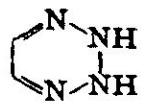
Müller and Disselhoff[31] obtained 4,5-diphenylosotriazole from the reaction of phenyldiazomethane with the disodium derivative of 4-phenylbenzophenone. Its formation is explained by postulating a dihydro-*v*-tetrazine intermediate (eq. 23b).



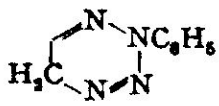
(23b)

(3) 1,2- and 2,5-Dihydro-1,2,3,4-Tetrazines

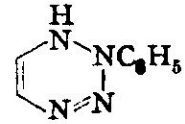
Perusal of this chapter discloses that practically all of the *v*-tetrazines described in the literature have been derivatives of 2,3-dihydro-*v*-tetrazine (XXI). Kleinfeller and Bönig[24,25] have reported some derivatives of 2-phenyl-2,5-dihydro-*v*-tetrazine (XLI) and 2-phenyl-1,2-dihydro-*v*-tetrazine (XLII). They are obtained by the reaction of acetylene bis(magnesium bromide) with phenylazides.



(XXI)



(XLI)

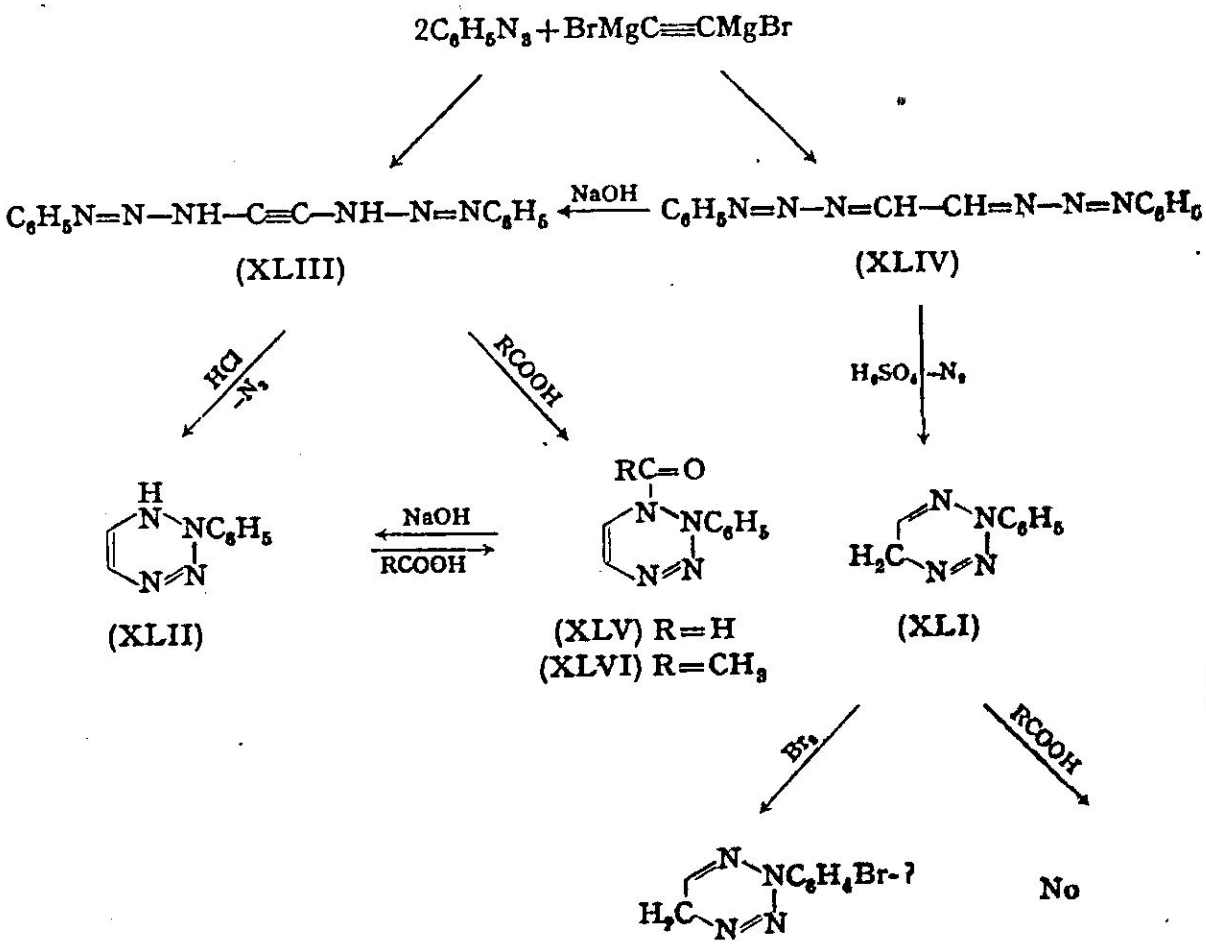


(XLII)

In the mixture produced by reacting two moles of phenylazide with acetylene bis(magnesium bromide) relatively large amounts of aniline, phenol, and biphenyl are found along with small quantities of bis(phenyltriaza)acetylene (XLIII), an isomer of the latter thought to have the structure XLIV, and 2-phenyl-2,5-dihydro-*v*-tetrazine (XLI). Compound XLI may also be obtained by the action of cold sulfuric acid on compound XLIV. Treatment of the latter with alkali isomerizes it to the acetylene (XLIII).

The 2,5-dihydro structure was assigned to XLI because in contrast to the 1,2-isomer to be described later, it could not be acylated with acetic or formic acids, indicating the absence of an –NH– grouping in the ring. In addition it is not identical with the known isomeric phenylamino-1,2,3-triazoles.

2-Phenyl-2,5-dihydro-*v*-tetrazine (XLI) occurs as pearly white platelets m.p. 172°. It forms a very easily hydrolyzed hydrochloride. Bromination of XLI in chloroform produces a 2-(bromophenyl)-2,5-dihydro-*v*-tetrazine, m.p. 150° (dec.) of undetermined orientation, although other brominations in this paper indicate that it is the *o*-bromophenyl isomer.



Derivatives of 2-phenyl-1,2-dihydro-*v*-tetrazine (XLII) are o tained in two ways from bis(phenyltriaza)acetylene (XLIII): trea with hydrochloric acid produces XLII directly, whereas cleavage XLIII by organic acids gives XLII *via* the 1-acyl derivatives (XLV XLVI). Nitrosation of XLII with nitrogen oxides (As + yields 1-nitroso-2-phenyl-1,2-dihydro-*v*-tetrazine, which on trea with sodium hydroxide forms a sodium derivative, $C_8H_8N_5O_2Na$. latter crystallizes from water as small violet needles which at 175°. The yellow nitroso compound can be regenerated by of acid on the sodium derivative. It explodes at *ca.* 120°.

No direct proof of structure is offered for this series of compounds by Kleinfeller and Bönig, and it is not clear why the 1,2-dihydro structure is preferred to the equally reasonable 2,3-dihydro form.

Kleinfeller and Bönig also reacted acetylene bis(magnesium bromide) with *p*-bromophenylazide. The products obtained included 1,2-bis(4-bromophenyltriaza)acetylene (XLVII) but not 2-(4-bromophenyl)-2,5-dihydro-*v*-tetrazine or the isomer of XLVII corresponding to compound XLIV of the unbrominated series described above.

The behavior of 1,2-bis(4-bromophenyltriaza)acetylene (XLVII) towards acetic anhydride is normal; it gives 1-acetyl-2-(4-bromophenyl)-1,2-dihydro-*v*-tetrazine (XLVIII), m.p. 265°. The isomer, 1-acetyl-2-(2-bromophenyl)-1,2-dihydro-*v*-tetrazine (XLIX), m.p. 148°, is obtained by brominating 2-phenyl-1,2-dihydro-*v*-tetrazine (XLII) with bromine in chloroform, followed by acetylation. The acetylene (XLVII) rca be debrominated to XLIII with hydrogen and a palladium-calcium canbonate catalyst by the method of Busch and Stöve.[12] A sample of XLIII obtained this way, when acetylated and brominated with bromine in dilute sulfuric acid, yields the *o*-bromo isomer (XLIX). The inter-relation of these products is outlined in the following scheme.

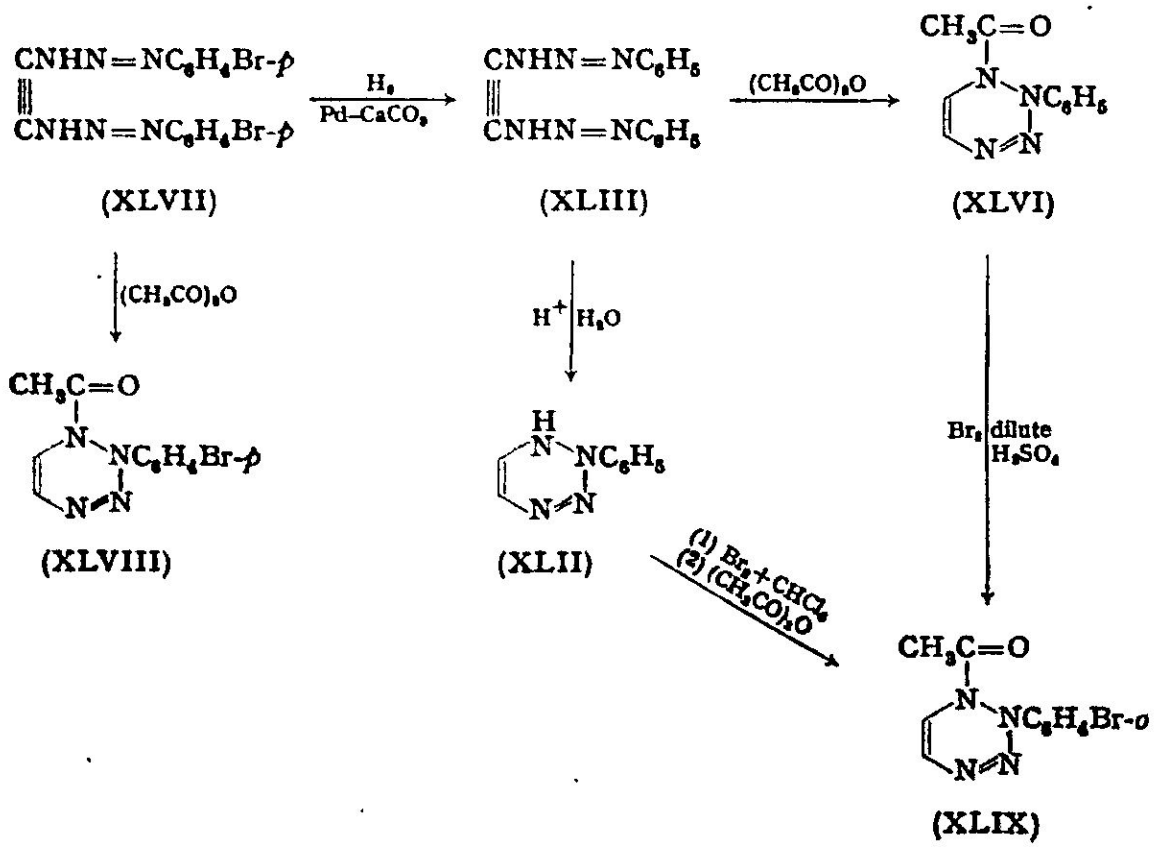
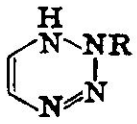
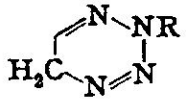


TABLE III-3. Dihydro-*v*-tetrazines of Kleinfeller and Bönig[25]

R	Parent	Melting point, °C. 1-Acetyl deriv.	1-Promyl deriv.	Hydrochloride
	1,2-Dihydro-*v*-tetrazine			
2-(2-Bromophenyl)-	185[a]	148[b]		
2-(4-Bromophenyl)-		265 (dec.)		
1-Nitroso-phenyl-[e]	*ca.* 120 (expl.)[d]			
2-Phenyl-	107	219[f]	172[g]	185[h]
	2,5-Dihydro-*v*-tetrazine			
2-(2-Bromophenyl)-	150 (dec.)			
2-Phenyl-	172	(Did not form)	(Did not form)	(Stable conc. HCl)

[a] Colorless quadratic leaflets.
[b] White needles.
[c] Small golden-yellow rods.
[d] Yellow-colored crystalline mass.
[e] Sodium derivative, small violet needles, dec. 175°
[f] Ivory-colored leaflets.
[g] Cream-colored tetragonal rods.
[h] Square leaflets.

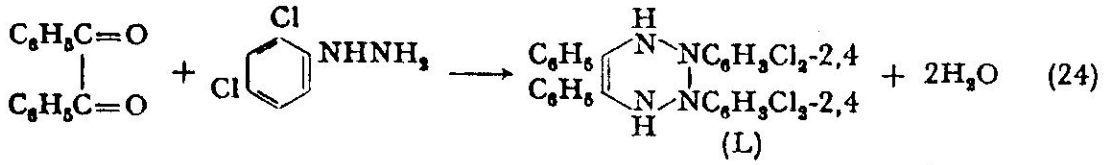
The properties of the dihydro-*v*-tetrazines of Kleinfeller Bönig are summarized in Table III-3.

C. Tetrahydro-1,2,3,4-Tetrazines

A single compound reported to be a tetrahydro-*v*-tetrazine been reported in the literature. It was obtained by Bülow and while studying the chlorination of phenylhydrazones.

The treatment of phenylhydrazones with chlorine in cold decomposes them with the formation of a diazonium salt the phenylhydrazine moiety. In fact, Bülow and Hüss

nonformation of a diazonium salt is strong presumptive evidence that a compound is not a phenylhydrazone. For example, they found that, with 2,4-dichlorophenylhydrazine, benzil gave a compound that was indifferent to chlorine (eq. 24). Analysis showed that it had the same composition as the expected osazone, and they concluded that it was probably 2,3-bis(2,4-dichlorophenyl)-5,6-diphenyl-1,2,3,4-tetrahydro-*v*-tetrazine (L). In addition it was not deeply colored like the osotetrazines, so they excluded that possibility.

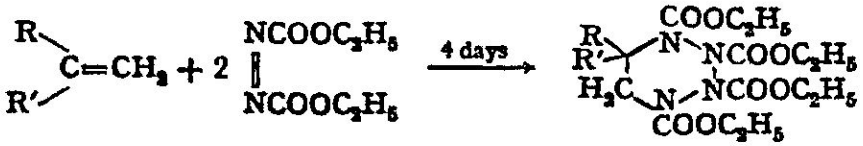


(L) (24)

Compound L forms pale lemon yellow needles, m.p. 217°, when crystallized from ligroin or alcohol and benzene. It is easily soluble in hot pyridine, benzene, and chloroform, soluble with difficulty in ethyl acetate, still less soluble in ether, acetone, ethanol, and cold acetic acid, and insoluble in ligroin. Cold concentrated sulfuric acid decomposes it.

D. Hexahydro-1,2,3,4-Tetrazines

Two hexahydro-*v*-tetrazines have been described by Ingold and Weaver.[22] They are produced by a unique synthesis, which may be pictured as a "cotrimerization" of two unsaturated species. Equimolar quantities of 1,1-diphenylethylene and diethyl azodiformate are mixed and allowed to stand at room temperature for four days (eq. 25). The color of the azo compound is discharged and the solution becomes viscous. Trituration with ether yields a solid which crystallizes from a chloroform-ligroin solution in colorless prisms, m.p. 164–166°. Ingold and Weaver assigned the structure, tetraethyl 5,5-diphenyl-1...-6-hexahydro-*v*-tetrazine-1,2,3,4-tetracarboxylate (LI), to their product. The ester is not attacked by cold potassium permanganate or boiling



(25)

(LI) R=R'=C6H5
(LII) R=C6H5, R'=H

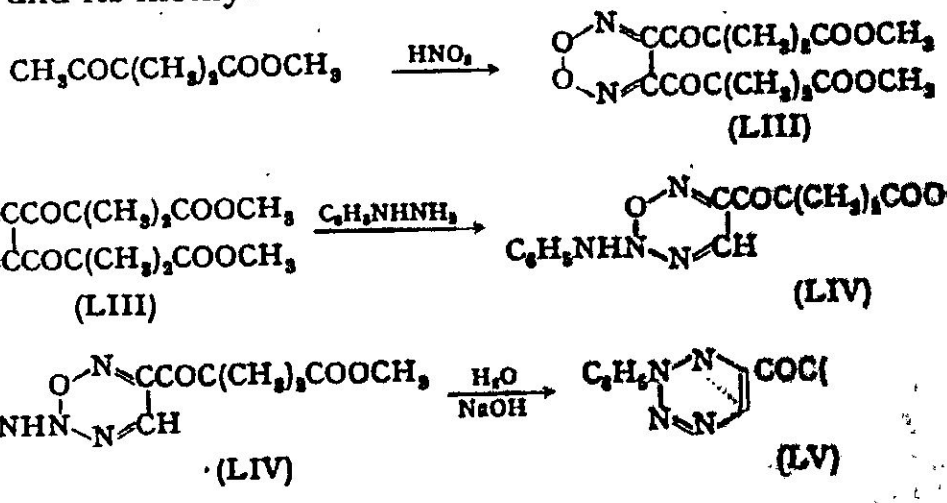
acetyl chloride. It could not be successfully hydrolyzed to the free acid; complete decomposition occurred.

By the same procedure tetraethyl 5-phenyl-1...6-hexahydro-*v*-tetrazine-1,2,3,4-tetracarboxylate (LII) was prepared from diethyl azodiformate and styrene. The colorless prisms of m.p. 133–134° (from chloroform and ligroin) had properties similar to those described for the diphenyl compound (LI).

E. 1,2,3,4-Tetrazines with Valence Bridges

The existence of 1,2,3,4-tetrazines that contain valence bridges is very doubtful. Only one such uncondensed *v*-tetrazine has been reported in the literature. It is the final product of a series of not-well-understood reactions carried out by W. H. Perkin.[38] He suggested a valence bridge structure for his product only because it agreed well with the empirical formula determined by analysis.

Oxidation of methyl dimethylacetoacetate with concentrated nitric acid (eq. 26) gives a product called a "glyoximeperoxide" (1,2,3,6-dioxadiazine, *R.I.* 127) but referred to by the author as compound $C_{14}H_{18}O_8N_2$ (LIII). The structure of LIII was assumed by Perkin to be correct on the basis of earlier work on glyoximeperoxi by Beckh[6] and others. On treating compound LIII with phenyl-hydrazine (eq. 27) an intensely red 1,2,3,6-oxatriazine (LIV, *R.I.* 1 results. Hydrolysis of this oxatriazine with alkali (eq. 28) gi rise to the questionable product, reported to be 3-(3-phenyl tetrazinyl)-2,2-dimethyl-3-oxopropionic acid (LV). The acid (LV) at 164° and its methyl ester at 89°.

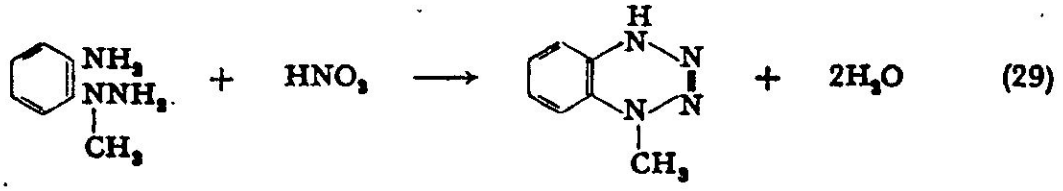


Satisfactory analyses were obtained on the barium and calcium salts and on the methyl ester, but other than that no further proof of structure is offered. Perkin himself was not entirely satisfied with the proposed structure of LV. He remarked: "It has been found very difficult to construct a satisfactory formula for this remarkable acid owing to the very small proportion of hydrogen which it contains, but it is thought that the configuration [LV] is probably correct."

2. 1,2,3,4-TETRAZINE RINGS CONDENSED WITH CARBOCYCLES

A. Condensed with a Benzene Ring

Although benzotetrazines were first prepared by Zincke and Lawson,[59] the simplest compound of this type on record has been reported by Hempel.[21] 1-Methyl-1,4-dihydrobenzotetrazine (LVI, *R.I.* 910) was obtained by treating a dilute hydrochloric acid solution of 1-methyl-1-(2-aminophenyl)hydrazine with sodium nitrite followed by neutralization with sodium carbonate (eq. 29). The product was isolated as an oil which partially solidified in a freezing mixture to a red crystalline mass. It was pressed on a gypsum plate and dried over sulfuric



(29)

(LVI)

acid giving colorless, mother-of-pearl-like plates, m.p. 62°. Compound LVI is soluble in ether, benzene, warm alcohol, and petroleum ether. The tetrazine also dissolves in mineral acids with the formation of a beautiful red color; alkalis cause the precipitation of yellow flocs from the acid solution. Hot concentrated sodium hydroxide dissolves large amounts of the tetrazine giving the same yellow flocs on cooling. If, on the other hand, the hot alkaline solution is diluted, extremely fine, colorless needles of unknown composition precipitate.

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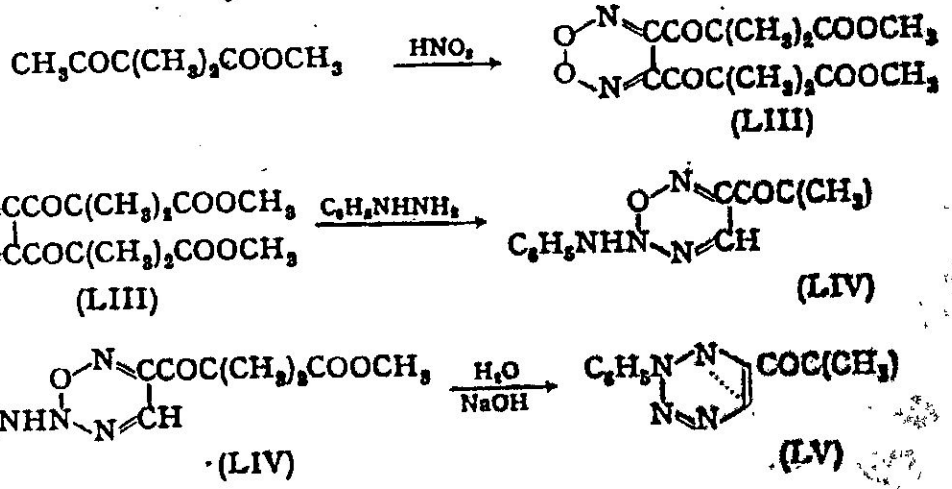

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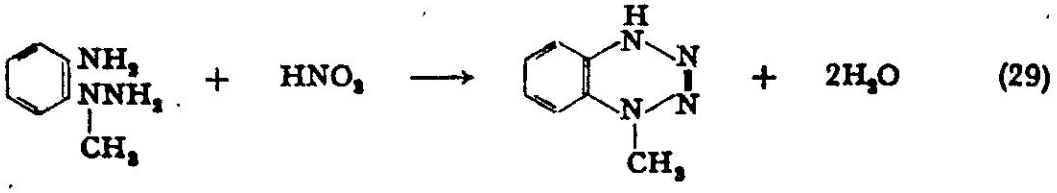

(29)

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As in the case of most *v*-tetrazines encountered in the literature,

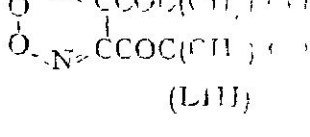
acetyl chloride ... lyz...
acid; complete... 1
By the ... 6-h
tetrazine-1,2,3,4-... ...d
azodiformate and ... 133–
chloroform ... descri
the diphenyl ...

... gen

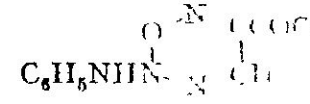
The existence of ... dence bridges
very doubtful, and ... has been
ported in the literature ... ies of not-
understood reactions ... He
valence bridge ... it agreed
with the ...

Oxidation ... ith
nitric acid (eq. ... oxi
(1,2,3,6-... the a
pound $C_{14}H_{12}O_4$ ... was
Perkin to be ... lyo
by Beckh ... III
hydrazine (eq. 27) ... zine (LIV)
results. Hydrol... kali (eq.
rise to the question ... 3-(
tetrazinyl)-2,2-... the acid
at 164° and it, ...

$CH_3COC(CH_3)_2$ ... $(CH_3)_2$ ...
... (CH_3) colorl
(LIII) le in



(LIII) ... CCOC also
... CH colo



... C_6H_5N

valence-bridge structure, the 1,2-dihydro structure corresponding to LIXb will be used in this section to describe the compounds prepared by Zincke and his co-workers.

The general method used to synthesize this series of benzotetrazines is illustrated by reaction 30, the preparation of 7-methyl-2-(4-methylphenyl)-1,2-dihydrobenzotetrazine (LIXb) *via* LVIII. *p*-Toluidine is diazotized and coupled with a second molecule of *p*-toluidine. A second diazotization yields the diazonium chloride (LVIII), which can be isolated. The diazonium salt is then reduced to the benzotetrazine (LIXb) with sulfur dioxide, sodium bisulfite, or best with stannous chloride.

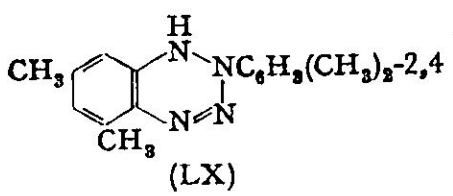
The properties of this class of compounds are exemplified by those of LIXb. It is not basic and may be recrystallized from hot concentrated hydrochloric acid without change. It is insoluble in water, soluble with difficulty in ether and chloroform, soluble in benzene and acetic acid, and very soluble in hot alcohol.

An important characteristic reaction of these heterocycles is their instantaneous and quantitative formation of perbromides on treatment with bromine in alcohol or acetic acid, for example, $C_7H_6N_4Br_3C_7H_7$. The same perbromide may also be obtained by brominating the diazonium salt (LVIII). Ammonia converts the perbromide to an "imide," $C_7H_6N_5C_7H_7$, which loses nitrogen on heating with the formation of a so-called "azimide" whose empirical formula is $C_7H_6N_3C_7H_7$.

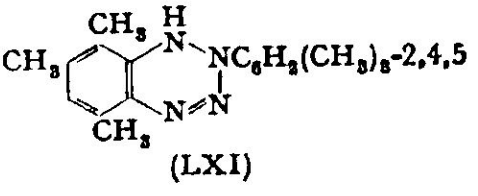
The 2-aryl-1,2-dihydrobenzotetrazines of this series do not give definite products with amyl nitrite, benzaldehyde, ethyl chlorocarbonate, or methyl iodide. Compound LIXb forms an acetyl derivative that occurs as shiny, white leaflets, m.p. 132–134°. Reducing agents such as stannous chloride or hydrogen iodide are without effect on LIXb, but it is energetically attacked by oxidizing agents, yielding nitrogen-free products or resins. Moreover, the action of silver oxide produces a substance having the empirical formula $C_7H_7N_2C_7H_7$, which appears to be a *m,p*-azotoluene. The same material may be obtained by reducing the diazonium salt (LVIII) with zinc (and acid).

Employing the same series of reactions, Zincke and Jaenke[58] prepared 5,7-dimethyl-2-(2,4-dimethylphenyl)-1,2-dihydrobenzotetra-

zine (LX), m.p. 136–137°, and 5,7,8-trimethyl-2-(2,4,5-trimethylphenyl)-1,2-dihydrobenzotetrazine (LXI), m.p. 151–153°, from 2,4-dimethylaniline and 2,4,5-trimethylaniline, respectively. Their chemical properties are similar to those described for LIXb.

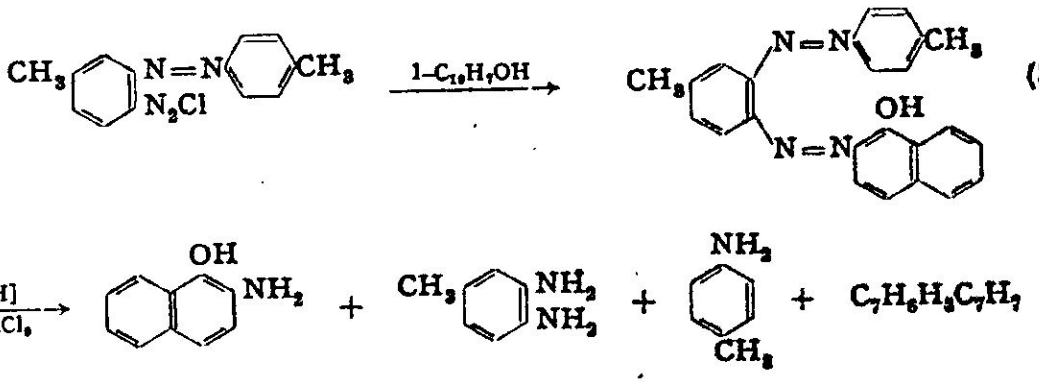


(LX)



(LXI)

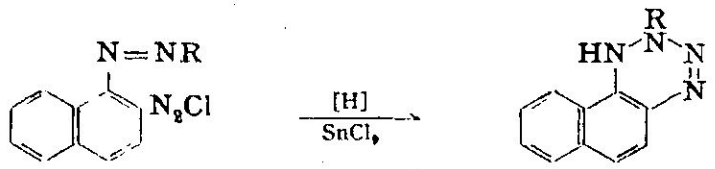
When *o*-(*p*-tolylazo)-*p*-toluenediazonium chloride (LVIII) is coupled with 1-naphthol and the intermediate coupling product is reduced with stannous chloride (eq. 31), the benzotetrazine is not formed, but rather the same "azimide," $C_7H_6N_3C_7H_7$, mentioned above, along with 2-amino-1-naphthol, toluylene-3,4-diamine and *p*-toluidine.[60] Substitution of 2-naphthol or 2-naphthylamine for 1-naphthol as coupling agent, or *o*-toluidine as the starting amine, gives similar results.



B. Condensed with a Naphthalene Ring

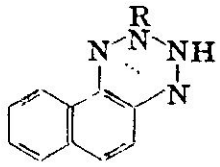
Coupling of 2-naphthylamine with benzenediazonium chloride, diazotization of the product, followed by reduction of the resulting diazonium salt with sulfur dioxide, sodium bisulfite or chloride (eq. 32) gave 2-phenyl-1,2-dihydronaphtho[1,2] (LXII, *R.I.* 1801) as colorless, shiny needles, m.p. 204–205°. and Lawson[61] also referred to the product of reaction 32 as a " hydride" and gave it the structure LXIIa, although the formula LXII might be the more probable. The properties of LXII are similar.

those of the toluene derivative described above, and it can be acetylated to a monoacetyl derivative, m.p. 137–139°.



(32)

(LXII) R=C_6H_5
(LXIII) R=2-$C_{10}H_7$

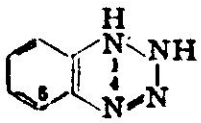


(LXIIa)

1-(2-Naphthylazo)-2-naphthylamine, diazotized and reduced with stannous chloride, likewise forms 2-(2-naphthyl)-1,2-dihydronaphtho-[1,2]-*v*-tetrazine (LXIII). Unlike the corresponding phenyl derivative (LXII), LXIII did not form an acetyl derivative with acetyl chloride on the steam bath; increasing the temperature to 110° resulted in resinification.

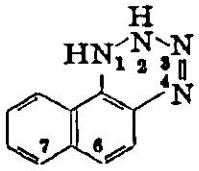
Table III-4 summarizes the properties of the benzo- and naphthotetrazines that are described in the literature.

TABLE III-4.

Substituents	Color, crystal habit	M.p., °C.	Ref.
	1,2-Dihydrobenzotetrazines		
5,7-Dimethyl-2-(2,4-dimethylphenyl)	Dirty yellow monoclinic prisms	136–7	58
1-Methyl[a]	Mother-of-pearl-like plates	62	21
7-Methyl-2-(4-methylphenyl)	Colorless or weak yellow needles	168 (Acetate 132–4)	59
5,7,8-Trimethyl-2-(2,4,5-trimethylphenyl)	Thick monoclinic crystals or small almost colorless 6-sided tables	151–3	58

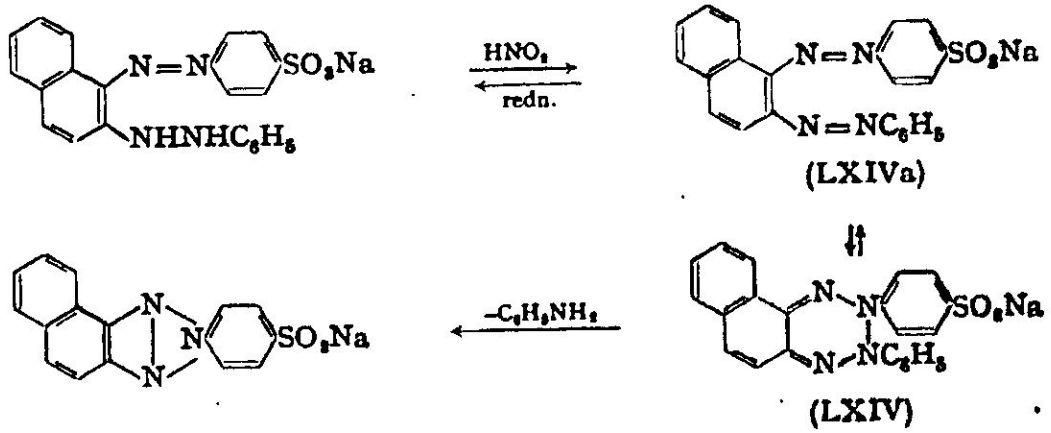
(Table continued)

TABLE III-4. *(continued)*

Substituents	Color, crystal habit	M.p., °C.	Ref.
	1,2-Dihydronaphtho[1,2]-*v*-tetrazines		
2-(2-Naphthyl)	White needles	202–4	61
2-Phenyl	Colorless needles	204–5	61
3-Phenyl-2-(4-sulfophenyl)[b]	Red solution only		9

[a] 1,4-Dihydro derivative.
[b] 2,3-Dihydro derivative, sodium salt.

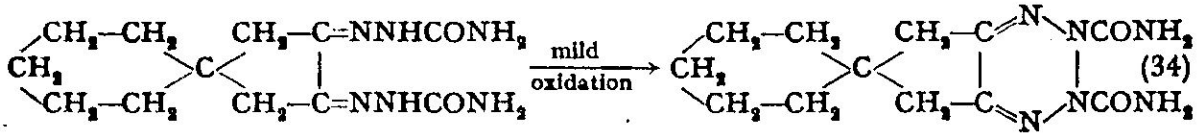
Bucherer and Stickel[9] merely postulate that the sodium salt of 3-phenyl-2-(4-sulfophenyl)-2,3-dihydronaphtho[1,2]-*v*-tetrazine (LXIV) may exist as an isomeric intermediate when sodium 4-(2-phenylhydrazino-1-naphthylazo)benzenesulfonate is oxidized with nitrous acid and excess hydrochloric acid.



It is of historical interest that these authors were the first recognize the possibility that the osotetrazines of von P might exist in the bis(phenylazo)ethylene forms, similar to

It should be of interest to investigate the oxidation (eq. 34) the bis(semicarbazone) of spiro[4,5]decane-2,3-dione (*R.I.* 878) pared by Kon.[28] A 2,3-dihydro-*v*-tetrazine substituted with groups has never been reported. Furthermore, there is a whether the resulting product would have the properties

of the osotetrazines or the 2,3-diacyl-2,3-dihydro-*v*-tetrazines. One might speculate that the carbonyl function of the carbamyl group would influence the formation of products of the latter type.



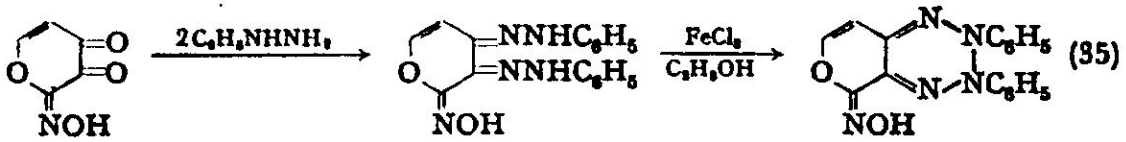
(34)

3. 1,2,3,4-TETRAZINE RINGS CONDENSED WITH HETEROCYCLES

A. Condensed through Two Carbon Atoms

(1) Condensed with 1,4-Pyrone

Peratoner[37] demonstrated that an unidentified compound, $C_{10}H_7NO_7$, obtained by Ost,[34] from the reaction of 3-hydroxy-1,4-pyrone and nitrogen trioxide, had the structure LXV. Upon reacting LXV with phenylhydrazine, two apparently stereoisomeric bis-(phenylhydrazono) derivatives (LXVI) occurred. Both isomers were oxidized by alcoholic ferric chloride to the same product, 2,3-diphenyl-5-oximino-2,3-dihydro-2-pyrano[3,4]-*v*-tetrazine (LXVII, *R.I.* 909), m.p. 137–8°. Compound LXVII exhibits the typical deep red color of the osotetrazines in transmitted light, and appears black with a metallic luster in incident light.



(35)

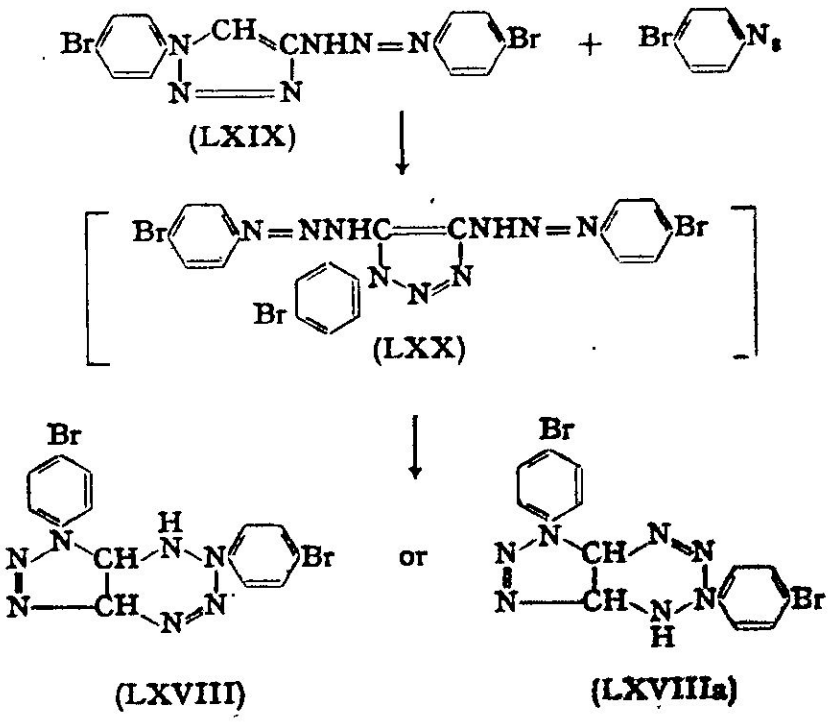
(LXV) (LXVI) (LXVII)

(2) Condensed with 1,2,3-Triazole

Among the products formed in the reaction of *p*-bromophenylazide and acetylene bis(magnesium bromide), Kleinfeller and Bönig[25] isolated 1,6-bis(4-bromophenyl)-6,7,8,9-tetrahydro-1-triazolo[*e*]-*v*-tetrazine (LXVIII, *R.I.* 699), or its isomer (LXVIIIa), and 1-(4-bromophenyl)-4-(4-bromophenyltriazeno)-1,2,3-triazole (LXIX). The structure assigned to LXVIII or LXVIIIa suggests that it was formed by the

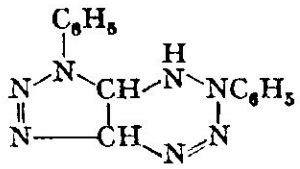
interaction of the 1,2,3-triazole (LXIX) with a second molecule of *p*-bromophenylazide *via* the intermediate LXX.

The reactions of LXVIII are similar to those already described for the mononuclear tetrazines of this series discussed earlier in this chapter. It is completely stable towards organic or mineral acids. Acetylation with acetic anhydride gives an acetyl derivative of m.p. 149° (dec.), and it forms a nitroso derivative of m.p. 103° (dec.) (nitroso nitrate, m.p. 162°, dec.). Compound LXVIII can be debrominated catalytically to 1,6-diphenyl-6,7,8,9-tetrahydro-1-triazolo[*e*]-*v*-tetrazine (LXXI or isomer), m.p. 176° (dec.). The latter likewise is stable toward acids and forms an acetyl derivative of m.p. 148° (dec.). It is interesting that the triazolo-*v*-tetrazine (LXXI) was not found among the products from the reaction of acetylene bis(magnesium bromide) and phenylazide. This is an additional point of difference between the brominated and unbrominated series.

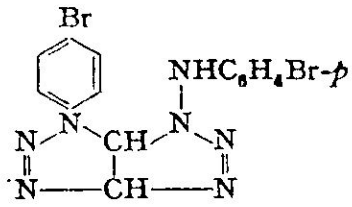


Kleinfeller and Bönig do not present any direct proof that
does contain the 1,2,3,4-tetrazine ring. They contend that the
of the nitroso derivative of LXVIII, which demonstrates the
of a secondary amino group, is evidence for the te
structure because the possibility of LXVIII being an

excluded. However, they fail to consider the phenylaminotriazole structure (LXVIIIb or isomer), which is a logical alternative.



(LXXI) or isomer

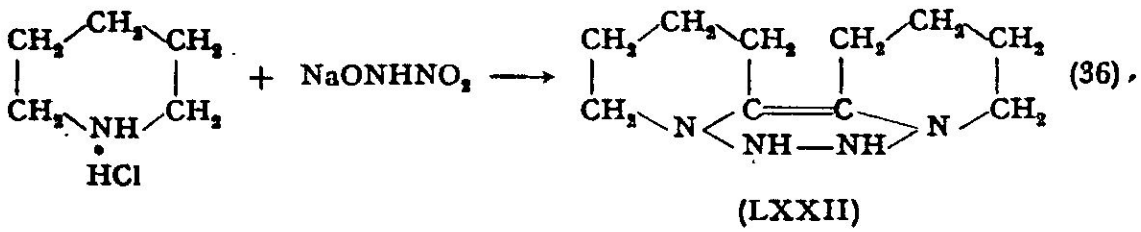


(LXVIIIb) or isomer

B. Condensed through a Carbon Atom and a Nitrogen Atom

(1) Condensed with Piperidine

Among the products formed by heating equimolar amounts of piperidine hydrochloride and sodium nitrohydroxamate in concentrated aqueous solution (eq. 36), Angeli and Castellana[1] isolated a product having the empirical formula $C_{10}H_{18}N_4$. They suggested the tetrahydro-*v*-tetrazine structure, LXXII. Compound LXXII crystallized from light petroleum as large colorless crystals, m.p. 154°. It can be obtained in a purer state by oxidizing the orignal reaction mixture with mercuric oxide. Compound LXXII reduces Fehling's solution, forms a benzoyl derivative, and gives a picrate, $C_{10}H_{18}N_4 \cdot 2C_6H_3O_7N_3$, m.p. 174°.

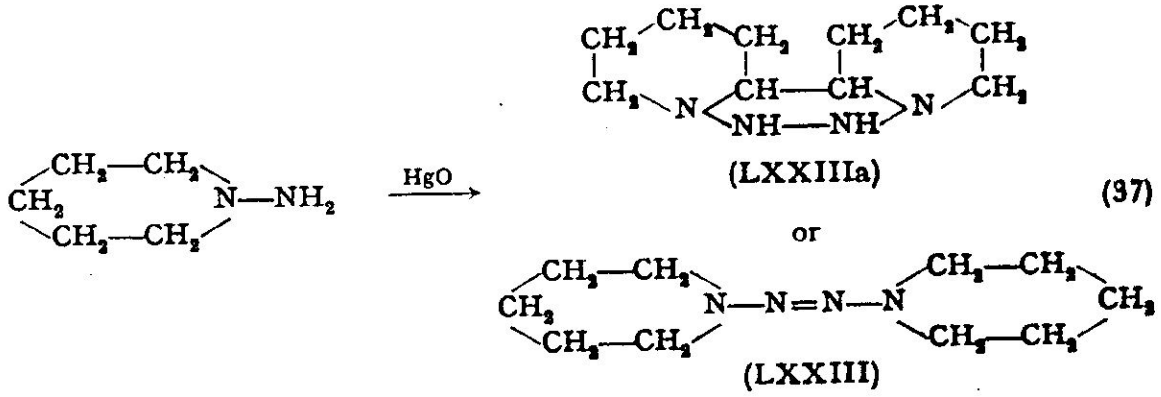


(LXXII)

Another product of this reaction is the "piperyltetrazone" of Knorr,[26,27] originally obtained by the oxidation of *N*-aminopiperidine with mercuric oxide. Knorr proposed the linear structure LXXIII (his experiments were reported in 1882–4, before von Pechmann or Lawson had discovered the *v*-tetrazine ring), but the isomeric hexahydro-*v*-tetrazine formula, LXXIIIa, is also a possibility.

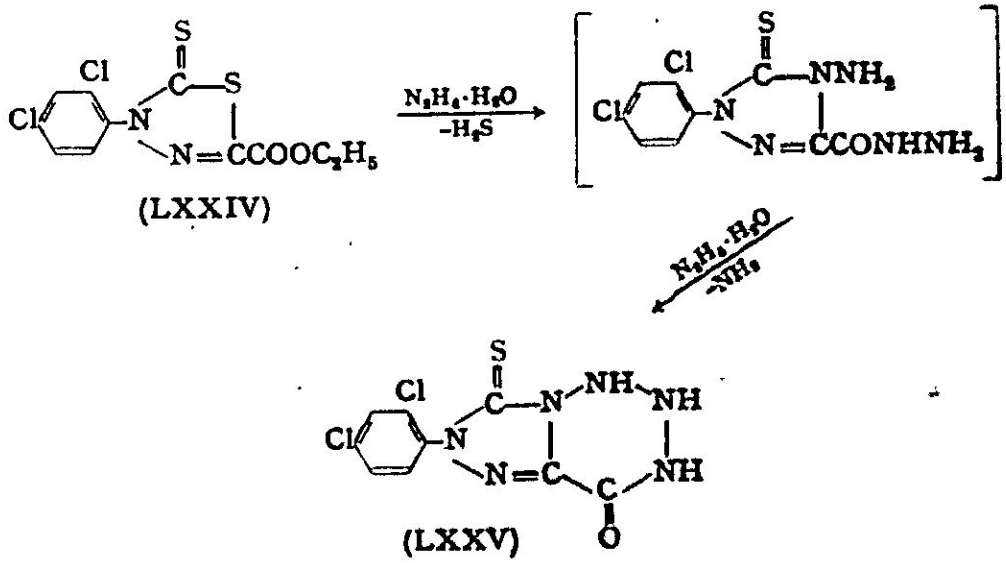
The "tetrazone" melts at 45° and is insoluble in water but soluble in acids. It is very unstable in hot acid solutions and decomposes with

the evolution of half its nitrogen and the formation of piperidine. The hydrochloride is a heavy oil, and the chloroplatinate, $(C_{10}H_{20}N_4)_2 \cdot H_2PtCl_6$ is an amorphous powder which detonates at 70°.



(2) Condensed with 1,2,4-Triazole

Bülow and Seidel[11] reacted ethyl 4-(2,4-dichlorophenyl)-5-thioxo-2-thiadiazolecarboxylate (LXXIV) with excess hydrazine hydrate and obtained a product which they thought was 6-(2,4-dichlorophenyl)-4-oxo-7-thioxo-1,2,3,4-tetrahydro-5-triazolo[4,3-*d*]-*v*-tetrazine (LXXV, *R.I.*700). Their basis for this conclusion was a satisfactory analysis for LXXV and the elimination of ammonia, which, however, was only demonstrated qualitatively. To accomplish this cyclization the hydrazine must be, in effect, an oxidizing agent.



The final product (LXXV) is obtained as white needles decompose with gas evolution at 196–197°, after sintering at 1

The color of LXXV changes to red-violet after 2 days' exposure to light in a nonevacuated desiccator, possibly because of oxidation to a dehydro form. Compound LXXV is soluble in alcohol, acetic acid, and 10% sodium hydroxide, slightly soluble in acetone and sodium carbonate solution, and insoluble in ether, ligroin, benzene, and concentrated hydrochloric acid.

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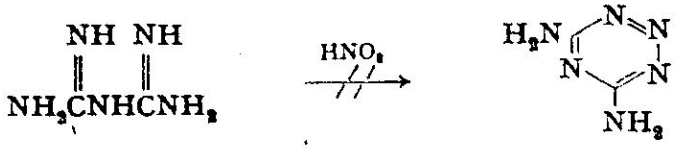
CHAPTER IV

The 1,2,3,5-Tetrazines

No one has yet described a compound containing the *1,2,3,5-* or *as*-tetrazine ring. There are doubtless several types of reactions that might give rise to such compounds. One of these is the reaction of nitrous acid with biurets, guanylureas, or biguanides. Thus, with biguanide, one would expect 4,6-diamino-*as*-tetrazine (eq. 1). Several



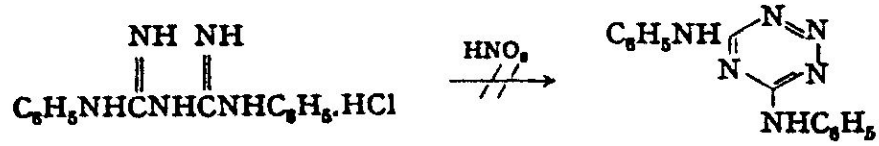
(1)

studies of this sort have been made. Pellizzari[2] reported that the reaction of nitrous acid with biguanide yields dicyandiamide and, presumably, nitrogen and water (eq. 2). Rosenthaler[4] has also studied this reaction.

(2)

His results indicate that the Van Slyke reaction gives less than half a mole of nitrogen per mole of biguanide sulfate. He made no attempt to isolate any reaction products other than nitrogen. It is possible that an *as*-tetrazine is formed in this reaction; this would account for the low yield of nitrogen.

Wystrach[5] attempted to prepare 4,6-dianilino-*as*-tetrazine by the reaction of nitrous acid with 1,5-diphenylbiguanide hydrochloride



(3)

(eq. 3). He used two moles of nitrous acid at 25°; one mole of nitrogen was evolved per mole of diphenylbiguanide. The solid product from

this reaction was identified as 1,5-diphenylguanylurea. Similarly, Pellizzari[3] obtained phenylguanylurea from 1-phenylbiguanide and nitrous acid.

Maccoll[1] has calculated the resonance energy (20 kilocalories per mole) and long wave length electronic absorption band 5200 A.) of *as*-tetrazine.

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CHAPTER V

The 1,2,4,5-Tetrazines

Introduction

The fundamental compound in this series is 1,2,4,5-tetrazine (I), which is No. 134 in *The Ring Index*. The preferred *Ring Index* and *Chemical Abstracts* name is *s*-tetrazine. This compound is usually

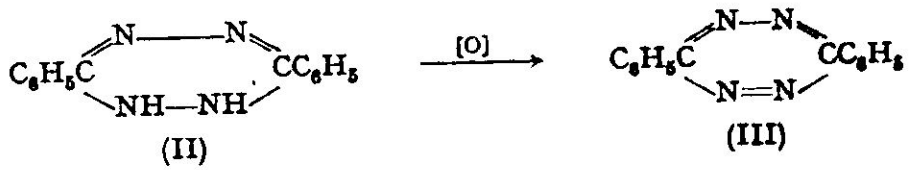
(I)

referred to in the literature as simply tetrazine. The dihydro-, tetrahydro-, and most of the hexahydro-*s*-tetrazines are named as substituted tetrazines, *s*-tetrazines, or 1,2,4,5-tetrazines. In the older literature trivial names are frequently encountered, but they will be used infrequently in this chapter. The tetrahydro-3,6-*s*-tetrazinediones are usually referred to in the literature as urazines or *p*-urazines with tetrahydro-3,6-*s*-tetrazinedione being called *p*-urazine. This compound and its derivatives are listed under *p*-urazine in *Chemical Abstracts*, but they are also called tetrahydro-3,6-*s*-tetrazinediones. The urazine and *p*-urazine nomenclature will not be used in this chapter because of the confusion as to whether or not they are actually *s*-tetrazines. In this discussion, where the position of the nitrogen atoms in tetrazines is not specified, 1,2,4,5-tetrazines are the compounds intended.

In addition to *s*-tetrazines, dihydro-, tetrahydro-, and hexahydro-*s*-tetrazines are known. Of these the dihydro series is much more extensive than is any of the others including the completely unsaturated *s*-tetrazines. Very few tetrahydro derivatives and only a small number of hexahydro derivatives are known. There are four possible isomeric dihydro-*s*-tetrazines. These are 1,2-, 1,4-, 1,6- and 3,6-, of which the

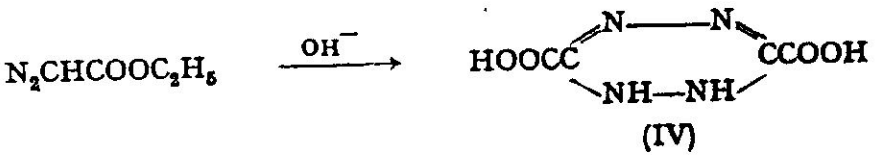
1,2-dihydro-*s*-tetrazines are best known. Only two isomeric tetrahydro-*s*-tetrazines (1,2,3,4- and 1,2,3,6-tetrahydro-) are possible and both are known.

The principal preparative method for *s*-tetrazines is oxidation of dihydro-*s*-tetrazines by mild oxidizing agents such as amyl nitrite, bromine, air, ferric chloride, hydrogen peroxide, chromic oxide, etc. (eq. 1).

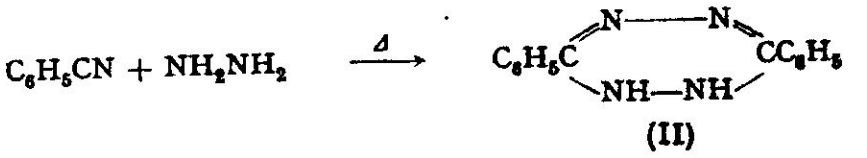


(II) (III) (1)

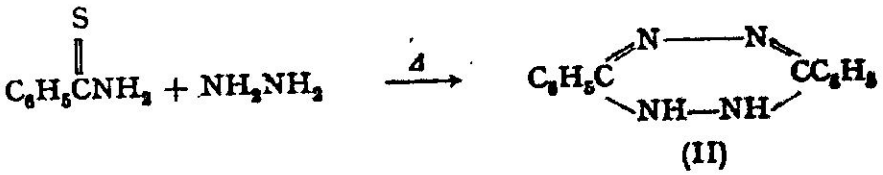
There are several methods for preparing dihydro-*s*-tetrazines. Reactions illustrative of the chief methods of preparation are shown in



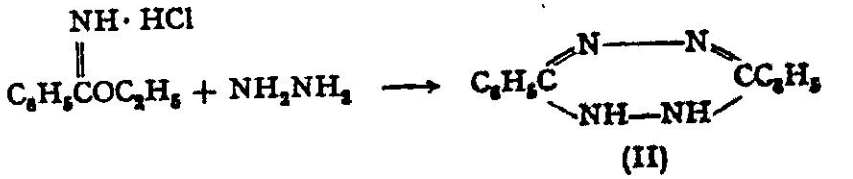
(IV) (2)



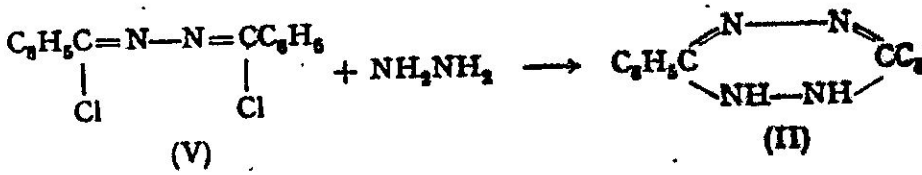
(II) (3)



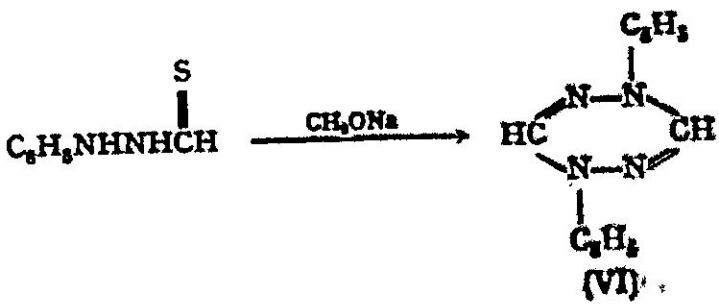
(II) (4)



(II) (5)



(V) (II) (6)

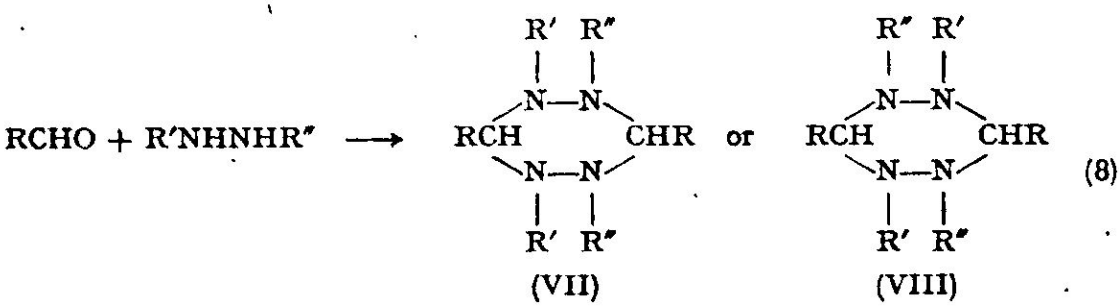


(VI)

equations 2 to 7. A number of modifications of the above procedures have been used as well as a number of special procedures. Although most of the above series of reactions have been shown as applying only to aromatic compounds, the methods of equations 3 and 5 can be used to prepare 3,6-dialkyl-1,2-dihydro-*s*-tetrazines. The only examples of *N*-alkyldihydro-*s*-tetrazines have not been prepared by direct cyclization but by action of diazoalkanes on 1,6-dihydro-*s*-tetrazines (eq. 41, p. 204). In general, the reactions used to prepare dihydro-*s*-tetrazines give low yields and other compounds are frequently the principal products.

So few tetrahydro-*s*-tetrazines have been prepared that methods of preparation will be discussed in the sections dealing only with them.

The hexahydro-*s*-tetrazines are prepared by the reaction of aliphatic aldehydes, usually formaldehyde, with hydrazines (eq. 8).



(VII) (VIII) (8)

Only aliphatic aldehydes have been used in this method, but the hydrazines have been substituted with either aliphatic or aromatic groups or with both. If R′ and R″ in eq. 8 are the same, VII and VIII are identical and the structure of the product is known, but there are two isomeric possibilities if R′ and R″ are different. In these cases only one product is obtained but which isomeric form it may be has not been determined in any reported case.

Tetrahydro-3,6-*s*-tetrazinedione and similar compounds such as tetrahydro-3,6-*s*-tetrazinedithione and tetrahydro-3,6-*s*-tetrazinediimine have been prepared in a variety of ways and there is no good general method of preparation. The methods that are used will be discussed as the classes of compounds are considered.

s-Tetrazines are very weakly basic compounds. They are deeply colored, being deep red, bluish-red, or violet-red. The dihydro derivatives are usually white or yellow solids and are not basic; in some cases they

are actually acidic. The tetrahydro and hexahydro-*s*-tetrazines are white solids, and are usually basic. *s*-Tetrazines and dihydro-*s*-tetrazines can be decomposed easily with heat, the latter class usually giving 1,2,4,4*H*-triazoles. Hydrolysis of *s*-tetrazines and dihydro-*s*-tetrazines in basic or acidic solutions to give hydrazine, nitrogen, and acids is very easy.

1,2-Dihydro-*s*-tetrazines can be converted to 1,2,4,4*H*-triazoles by heating at temperatures of about 100° or higher. Many reported preparations of dihydro-*s*-tetrazines have involved use of temperatures in this range. In these cases the products claimed to be dihydro-*s*-tetrazines are very likely 1,2,4,4*H*-triazoles. This has led to considerable confusion and it is well to keep in mind that many compounds claimed to be hydro-*s*-tetrazines are triazoles. This last statement also applies to *p*-urazines.

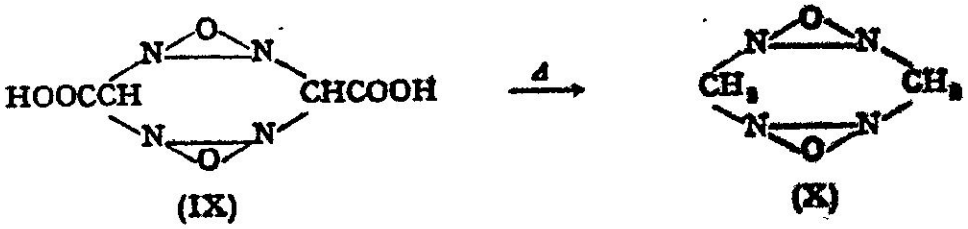
No *s*-tetrazines or hydro-*s*-tetrazines have been found in nature. Several patents[65–67,142] have been issued covering *s*-tetrazines or hydro-*s*-tetrazines and mentioning such uses as ingredients in the preparation of resins, as desensitizing agents in photographic emulsions, and as drugs. However, it is doubtful that any are being used commercially.

1. UNCONDENSED *s*-TETRAZINES

A. Mononuclear *s*-Tetrazines

(1) *s*-Tetrazine and Hydro Derivatives

s-Tetrazine (I) was first prepared by Hantzsch and Lehmann[73] 1900 by thermal decarboxylation of 3,6-*s*-tetrazinedicarboxylic These authors erroneously reported the product to be X obtained decarboxylation of IX. These were called *bisazoxymethane* and

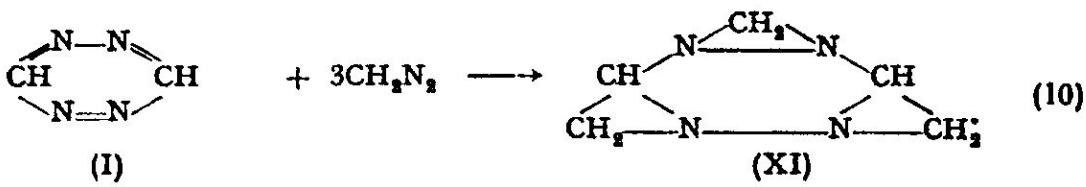


(IX) (X)

acetic acid, respectively. The yield was only 1–2% and the point of 75° was much lower than that of 99° which was later

be correct for *s*-tetrazine. Their incorrectly formulated structure was probably a result of analytical work on very impure material. A few years later Curtius, Darapsky, and Müller[45] prepared *s*-tetrazine in the same way and obtained a product melting at 99° and crystallizing in purplish-red rods. The yield was 14%. In a later paper[50] it was stated that purification by sublimation with barium oxide caused a severe explosion. Wood and Bergstrom[167] also prepared *s*-tetrazine by decarboxylation of 3,6-*s*-tetrazinedicarboxylic acid in 17% yield. These authors as well as Müller and Herrdegen[95] have prepared *s*-tetrazine by oxidation of 1,2-dihydro-*s*-tetrazine with air or nitrous acid.

s-Tetrazine is readily decomposed by air and can be stored only in a sealed tube under its own vapor. Mild alkaline treatment does not change *s*-tetrazine but in stronger alkaline solution it turns brown. Mester[91] has proposed to determine *s*-tetrazine quantitatively by hydrolysis with 33% sodium hydroxide solution in the presence of Devarda alloy. The ammonia so formed would then be distilled and titrated. Extremely mild acid treatment such as dilute hydrochloric acid gives hydrazine hydrochloride, nitrogen, and formic acid.[47] It has been stated by Müller[94] that *s*-tetrazine reacts with diazomethane to give a saturated *s*-tetrazine (XI). Mild reducing agents such as hydrogen



(I) (XI) (10)

sulfide or zinc dust in acid reduce *s*-tetrazine to 1,2-dihydro-*s*-tetrazine. *s*-Tetrazine is soluble in water and most organic solvents.

The absorption spectrum of *s*-tetrazine in the visible region has been studied by Müller and Herrdegen,[95] Koenigsberger and Vogt,[83] and Maccoll.[89] The principal absorption is at 520 mμ with bands at 543 and 553–568 mμ. Maccoll has calculated that *s*-tetrazine has a resonance energy of 20 kilocalories per mole.

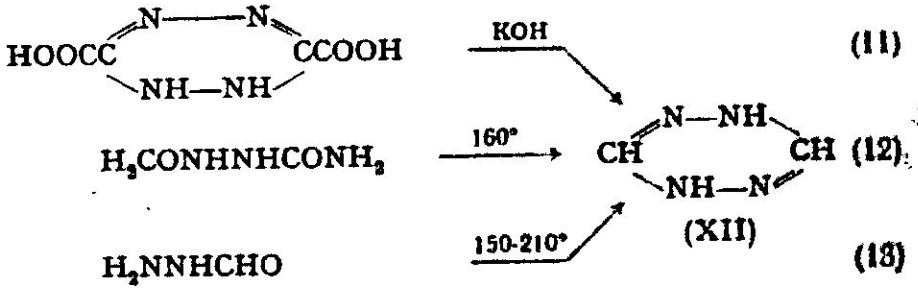
Although *s*-tetrazine is neutral to litmus, potassium amide in liquid ammonia forms a salt of approximate composition $K_2C_2N_4$.[167] This salt decomposes rapidly when it is warmed. Wood and Bergstrom[167] state that *s*-tetrazine reacts with aqueous solutions of silver nitrate,

mercuric chloride, auric chloride, and chloroplatinic acid, but compounds of definite composition are not formed although Curtius, Darapsky, and Müller[45] have reported that reaction of *s*-tetrazine with silver nitrate forms a green crystalline salt. An addition complex is formed with methyl magnesium bromide.

Of the four possible dihydro-*s*-tetrazines all but 1,6-dihydro-*s*-tetrazine have been reported and derivatives of 1,6-dihydro-*s*-tetrazine have been claimed. However, 1,2-dihydro-*s*-tetrazine is the only well authenticated isomer. This has been prepared by the action of hydrazine on hydrogen cyanide (eq. 3, C_6H_5 is H)[95], from ethyl formimidate (eq. 5, C_6H_5 is H),[167] and by reduction of *s*-tetrazine with hydrogen sulfide.[46] The yields were either not stated or were given as being very poor.

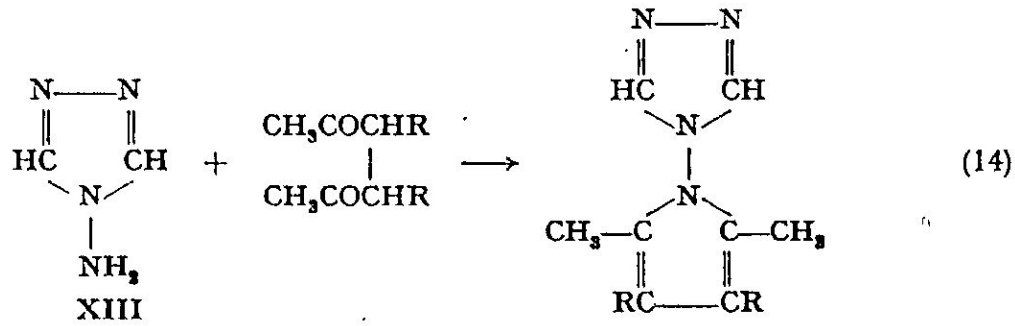
1,2-Dihydro-*s*-tetrazine crystallizes in yellow prisms. Two melting points, 117–119° and 125–126°, have been recorded. The compound is easily oxidized with nitric acid to *s*-tetrazine. Acid hydrolysis gives hydrazine and formic acid.[46]

A compound once believed to be 1,4-dihydro-*s*-tetrazine (XII) was first reported by Curtius and Lang[58] under the name *trimethinetriazimide*. Hantzsch and Silberrad[75] obtained the same compound and first called it *isobisdiazomethane* and later *N-dihydrotetrazine*. In both cases the product was obtained by the action of hot potassium hydroxide on 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid (eq. 11). The same product



was reported by Pellizzari[99] from the thermal condensation of (eq. 12) and by Ruhemann and Stapleton[138] from heating formh (eq. 13). The reaction of ethyl orthoformate with hydrazine[148] also ga this compound. In most cases the hydrochloride, m.p. 151°, was The free base melted at 70° according to one report[58] and according to another.[138]

It was shown by Bülow[18,19] that the supposed 1,4-dihydro-*s*-tetrazine reacted with 1,4-diketones to give bicyclic compounds (eq. 14). It had previously been shown that this was characteristic of a primary

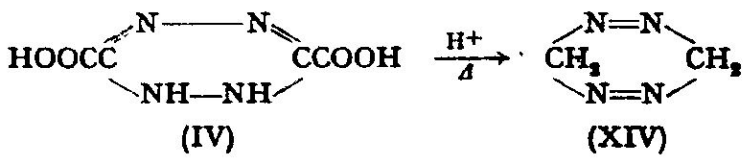


(14)

XIII

amino group so the structure 4-amino-1,2,4,4H-triazole (XIII) was proposed. In later papers Curtius and co-workers[46,48,50] agreed with Bülow and showed that 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid was isomerized by heat or hot potassium hydroxide solution to 4-amino-1,2,4,4*H*-triazole-3,5-dicarboxylic acid which readily decarboxylates to 4-amino-1,2,4,4*H*-triazole.

Curtius and Lang[58] isolated an acid from the prolonged action of hot potassium hydroxide solution on 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid (IV). Vigorous heating of the acid product gave a compound melting at 145° that was reported to have the formula $C_3H_6N_6$. Hantzsch and Silberrad[75] obtained the 145° compound by heating 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid in acid. These workers found that the formula was $C_2H_4N_4$ and reported a melting point of 155°. They proposed the name *bisdiazomethane* and the structure XIV (3,6-dihydro-*s*-tetrazine). This same compound was also



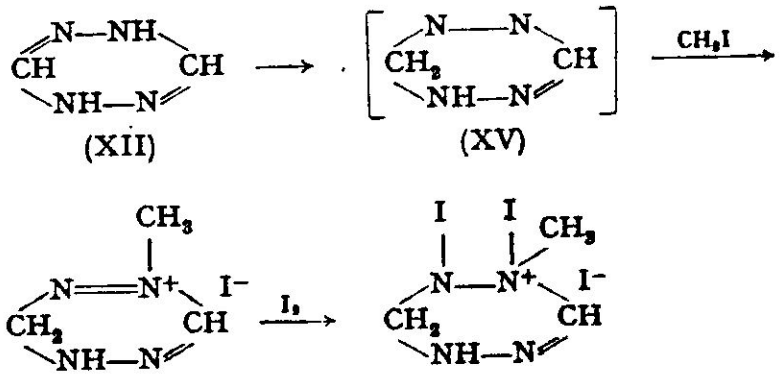
(15)

(IV) (XIV)

prepared by Ruhemann.[133] After Bülow's criticism of the structures of various tetrazines Curtius, Darapsky, and Müller[46] reinvestigated the series of reactions leading to *bisdiazomethane*. They found that the acid isolated from prolonged action of potassium hydroxide on IV was the already known 3-amino-1,2,4-triazole-5-carboxylic acid, which then decarboxylated to form 3-amino-1,2,4-triazole. This triazole was

identical with the so-called bisdiazomethane. In attempting to repeat the dimerization of diazomethane under the influence of sunlight to 3,6-dihydro-*s*-tetrazine, which was reported by Hantzsch and Lehmann,[74] it was found that the reaction gave only ethylene and nitrogen.

Ruhemann and Merriman[133,136,137] have studied a compound which they called *tetrazoline* and which they believed to be 1,4-dihydro-*s*-tetrazine but is in reality 4-amino-1,2,4,4*H*-triazole. They proposed that tetrazoline could be converted into an isomer by recrystallization or by reaction with methyl iodide. This was based on the finding that before recrystallization of tetrazoline hydrochloride it formed with platinum chloride a salt of the composition $(C_2H_4N_4)_2PtCl_4$ but after recrystallization the salt formed was $(C_2H_4N_4)_2H_2PtCl_6$. Also reaction with methyl iodide gave a salt with the formula $C_3H_7N_4I$ which added iodine. Furthermore it was found that tetrazoline gave aldehyde derivatives. These reactions were accounted for by isomerization of tetrazoline (believed to have structure XII) to 1,6-dihydro-*s*-tetrazine (XV), which then formed a different salt with platinum chloride,



(16)

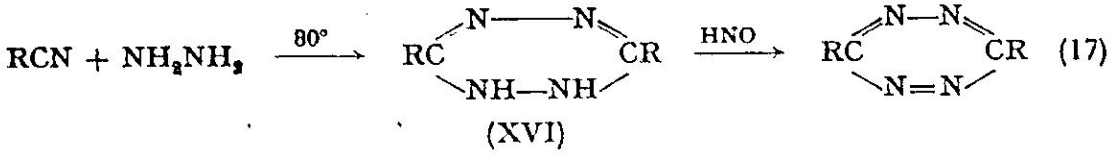
reacted with methyl iodide and iodine as shown (eq. 16), and reacted with aldehydes at the methylene group. It appears that Ruhemann's proposals are completely erroneous and all of these compounds are derivatives of 4-amino-1,2,4,4*H*-triazole.

Neither of the theoretically possible tetrahydro-*s*-tetrazines is known nor is hexahydro-*s*-tetrazine.

(2) Substituted *s*-Tetrazines and Hydro Derivatives

Alkyl Derivatives. Only two simple alkyl-*s*-tetrazines are known. These are 3,6-dimethyl-*s*-tetrazine crystallizing in red needles, m.p. 74°[51] and

3,6-diethyl-*s*-tetrazine which has been obtained only in solution.[95] These were prepared by oxidation of the corresponding dihydro-



(XVI)

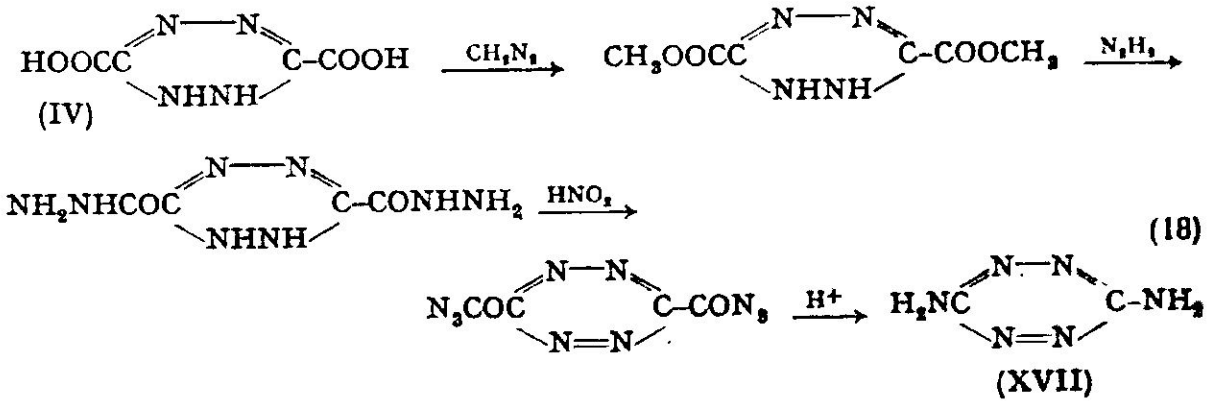
$R = CH_3$ or C_2H_5

tetrazines with nitrous acid (eq. 17). Acid hydrolysis of 3,6-dimethyl-*s*-tetrazine gives acetaldehyde, acetic acid, hydrazine, and nitrogen.

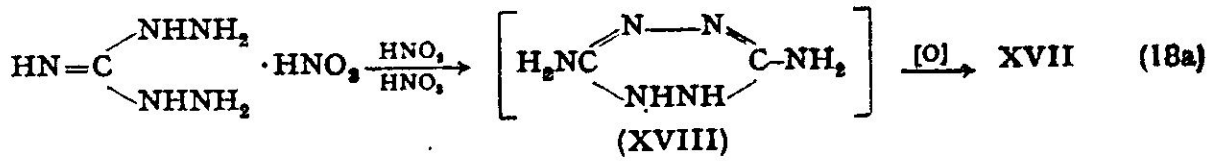
3,6-Dimethyl-1,2-dihydro-*s*-tetrazine, m.p. 180°, has been prepared (eq. 17) using acetonitrile and anhydrous hydrazine.[52] The reaction required several days heating in boiling alcohol and gave only 5% yield of the dihydro compound. Müller and Herrdegen[95] have prepared the diethyl derivative (XVI, $R = C_2H_5$) in the same manner. The principal product was 3,5-diethyl-4-amino-1,2,4,4*H*-triazole. The reaction failed to yield a dihydro-*s*-tetrazine when propionitrile was used. 3,6-Dimethyl-1,2-dihydro-*s*-tetrazine isomerizes at its melting point to 3,5-dimethyl-4-amino-1,2,4,4*H*-triazole. Mild acid hydrolysis of 3,6-diethyl-1,2-dihydro-*s*-tetrazine gives *sym*-diproprionylhydrazine but more vigorous hydrolysis forms propionic acid, hydrazine, and nitrogen.

Pellizzari[99] reported the preparation of 3,6-dimethyl-1,4-dihydro-*s*-tetrazine by heating acethydrazide at 180–190°. In a later paper[100] he agrees with Bülow that the supposed 1,4-dihydro-*s*-tetrazines are triazoles and reports the structure of his compound as 3,5-dimethyl-4-amino-1,2,4,4*H*-triazole. In view of the easy thermal isomerization of dihydrotetrazines to triazoles it is likely that Pellizzari is correct in his revised view. Ruhemann and Merrimann[136] have also prepared the triazole in the same way and erroneously called it a 1,4-dihydro-*s*-tetrazine. Heating diacetylaniline with hydrazine hydrate at 260° was reported by Silberrad[143] to give 3,6-dimethyl-1,4-dihydro-*s*-tetrazine but this too is the same 3,5-dimethyl-4-amino-1,2,4,4*H*-triazole. Stollé[148] has claimed the preparation of 3,6-dipropyl- and 3,6-diundecyl-1,4-dihydro-*s*-tetrazine by heating *n*-butyrylhydrazide and undecylhydrazide, respectively, at 180°. Since it has been shown that condensations of this type produce triazoles it is likely that these compounds are also triazoles.

Amino Derivatives. 3,6-Diamino-*s*-tetrazine (XVII) was prepared by Lin, Lieber, and Horowitz[170] from 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid by way of the dimethyl ester, the dihydrazide, and 3,6-*s*-tetrazinedicarboxylic acid diazide. The same product was obtained by oxidation of diaminoguanidine nitrate (eq. 18a), and by the self-



(18)



(18a)

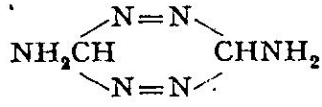
condensation of *S*-methylthiosemicarbazide hydroiodide presumably through 3,6-diamino-1,2-dihydro-*s*-tetrazine (XVIII).

Crystallization of 3,6-diamino-*s*-tetrazine from water gave a microcrystalline orange-red powder melting above 300°. This compound gives the characteristic *s*-tetrazine absorption[95] at 528 mμ, log ϵ_{max} 2.77. The synthesis of XVII has been reported by Ponzio and Gastaldi.[116] However, their compound, m.p. (dec.) 204–205°, was obviously different from that reported by Lin and co-workers[170] and so was not 3,6-diamino-*s*-tetrazine.

A French patent[65] has suggested the use of 3,6-diamino-*s*-tet and its N^3,N^6-tetraalkyl derivatives as photographic emulsion sensitizers.

The synthesis of 3,6-diamino-1,2-dihydro-*s*-tetrazine (XVIII) been reported by Lin, Lieber, and Horowitz[170] as an intermediate the corresponding tetrazine synthesis and also from reduction of tetrazine. However, the dihydrotetrazine was not isolated. Ponzio Gastaldi[116, 117, 119] have also reported XVIII as an intermediate in thesizing XVII, so this report also must be erroneous.

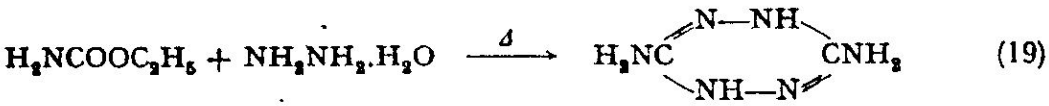
3,6-Diamino-3,6-dihydro-*s*-tetrazine (XIX) has been reported by Seiberlich[142] in a patent. Neither the method of preparation nor the physical properties were mentioned, and there was no discussion of any proof of structure. It would be of considerable interest to find a 3,6-



(XIX)

dihydro-*s*-tetrazine that had a hydrogen atom in both the 3- and 6-positions, as no well authenticated cases are known. However, until further proof appears this structure must be questioned. The compound was said to react with formaldehyde giving useful resinous materials.

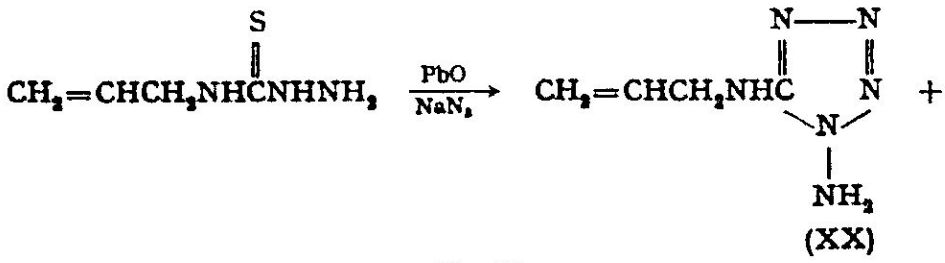
Walter[163] has recently reported the preparation of 3,6-diamino-1,4-dihydro-*s*-tetrazine by the reaction of urethans with hydrazine hydrate under pressure at temperatures of 120–175° (eq. 19). It was



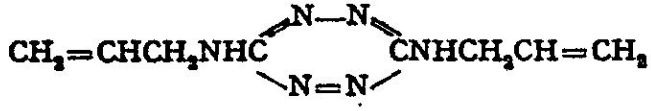
(19)

necessary to use excess urethan in order to prevent replacement of amino groups by hydrazino groups. The product was a white solid which was recrystallized from water. No other physical properties and no proof of structure were given. Here again acceptance of such an unusual structure as this, a 1,4-dihydro-*s*-tetrazine in which the 1,4-positions are unsubstituted, must await more proof.

Stollé and Gaertner[154] have isolated two products from the action of lead monoxide and sodium azide on 4-allylthiosemicarbazide. The principal product was shown to be 1-amino-5-allylaminotetrazole (XX). A second product formed in small yields was 3,6-bis(allylamino)-*s*-



(XX)



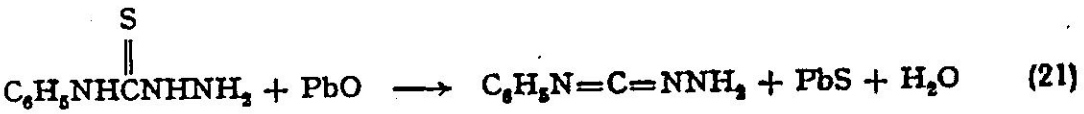
(20)

(XXI)

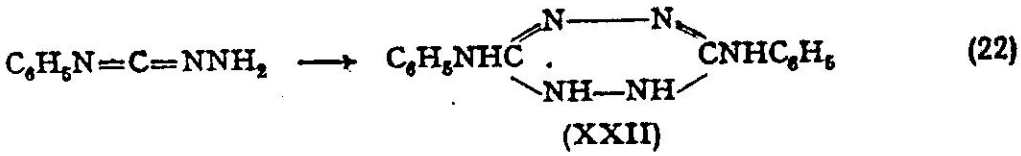
tetrazine (XXI) (red flakes from water, m.p. 118°). A solution of this compound is readily decolorized by sodium hydrosulfite.

The synthesis of 3,6-bis(hydroxymethylamino)-3,6-dihydro-*s*-tetrazine has been claimed by Seiberlich.[142] This compound was purportedly prepared by the action of formaldehyde on 3,6-diamino-3,6-dihydro-*s*-tetrazine. No physical properties and no proof of structure were given.

3,6-Dianilino-1,2-dihydro-*s*-tetrazine[154] was prepared by reaction of 4-phenylthiosemicarbazide with lead monoxide and sodium azide or with lead monoxide at 80°. The reaction was pictured as proceeding as shown in equations 21 and 22. The principal product in this reaction



(21)

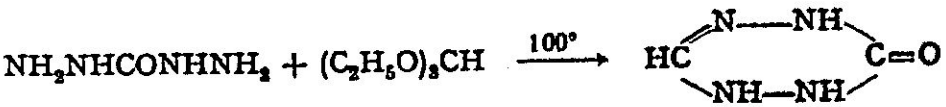


(22)

(XXII)

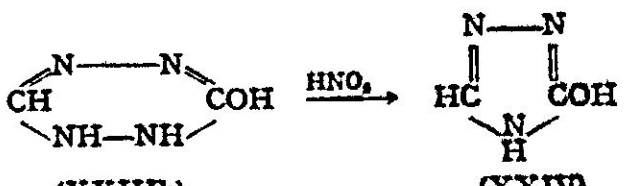
was the anilino tetrazole corresponding to XX while the dihydro-*s*-tetrazine (XXII) was formed in very small yields. The compound XXII crystallizes in white needles melting with decomposition at 275°.

Oxo and Polyoxo Derivatives. Curtius and Heidenreich[64,65] have reported that the reaction of carbohydrazide with ethyl orthoformate at 100° gives 1,2,3,4-tetrahydro-3-*s*-tetrazinone (XXIIIa). It is a mono



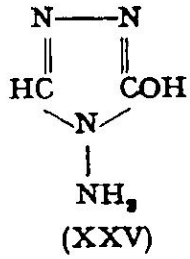
(XXIIIa)

acid forming a monosilver salt so it may actually exist as the 3-h 1,2-dihydro-*s*-tetrazine (XXIIIb). Busch also reported this and stated that nitrous acid converted it to 3-hydroxy-1,4,4*H* (XXIV). However, Stollé,[152] as a result of his own studies and those



(XXIIIb) (XXIV)

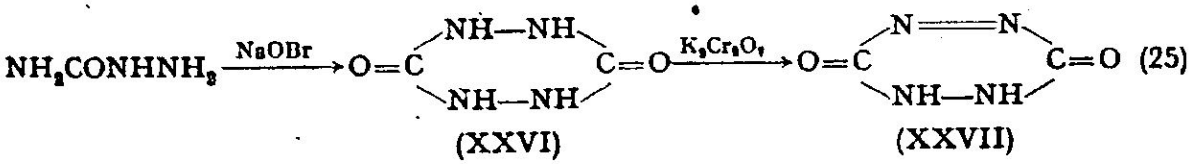
Busch and Bülow on the relationship of *s*-tetrazine to triazoles (this will be discussed in later sections), concluded that the probable structure for the product of the reaction shown in equation 23 was that of the triazole XXV. Evidence cited for this was the formation of a



(XXV)

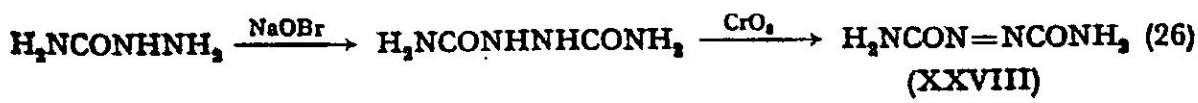
benzylidene derivative by reaction with benzaldehyde and analogy to *p*-urazine which was also believed to be a triazole.

1,2-Dihydro-3,6-*s*-tetrazinedione (XXVII) has been claimed by Linch[87] to be a product of the action of potassium dichromate in



(XXVI) (XXVII) (25)

sulfuric acid on *p*-urazine (25). The *p*-urazine was obtained by the action of sodium hypobromite on semicarbazide hydrochloride. The product (XXVII) crystallizes in small orange needles which have no definite melting point. Stannous chloride reversed the dichromate oxidation to give *p*-urazine which was believed to have the structure XXVI. Once more Stollé[153] entered the controversy and declared that Linch's interpretation of these reactions was incorrect. He reported that the product of the reaction of the hypobromite with semicarbazide was biurea, which Linch had mistaken for *p*-urazine. The biurea was then oxidized to azodicarbonamide (XXVIII). In support of these statements

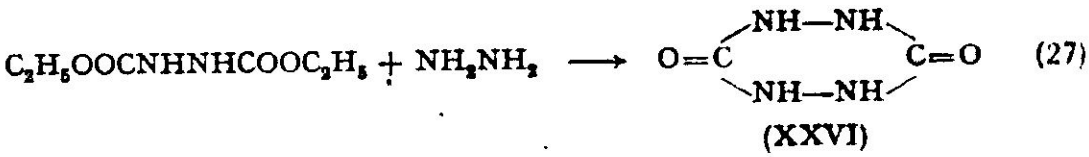


(XXVIII) (26)

Stollé claimed that *p*-urazine is unstable to chromic acid and heat and that the azo compound actually obtained by oxidizing *p*-urazine is 4-amino-1,2,4,4*H*-triazole-3,5-dione, which explodes at 72° and is decomposed by cold water. Linch's compound was quite stable to

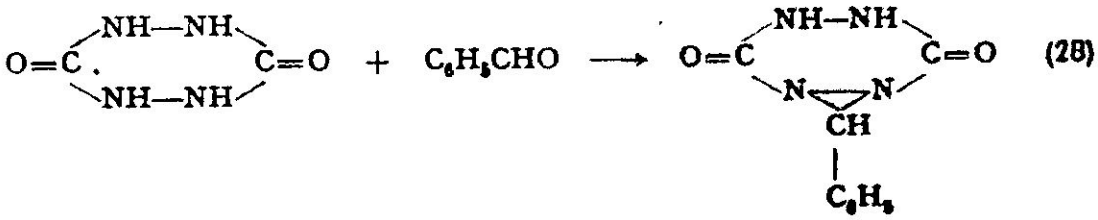
water. Stollé gave no experimental results to support his contentions. However, further investigation[156] of the reaction of sodium hypobromite with semicarbazide hydrochloride has shown that biurea is obtained using the conditions that Linch used. Linch reports that his compound (supposedly XXVII) does not react with aldehydes while *p*-urazine does. This result casts doubt on his conclusions as it seems likely that a product obtained by removal of only two ring hydrogen atoms should still react with aldehydes. Also, the fact that semicarbazide does not give *p*-urazine by reaction with sodium hypobromite is additional evidence that Linch did not have XXVII.

p-Urazine (believed to be tetrahydro-3,6-*s*-tetrazinedione) was first reported by Curtius and Heidenreich[54,55] as a product of the reaction of diethyl bicarbamate with hydrazine (eq. 27.) The product was



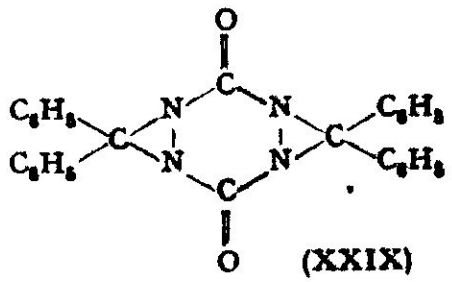
(XXVI) (27)

obtained as its hydrazine salt which, when treated with acid, gave *p*-urazine crystallizing from water in white prisms melting at 270°. This product was a monoacidic base forming silver, ammonium and barium salts. It reacted readily with aldehydes in a mole to mole ratio to give products formulated as shown in eq. 28. *p*-Urazine was later prepared by



(28)

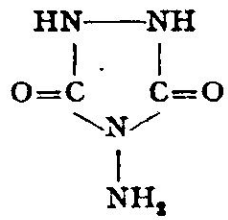
Purgotti[122–124] by heating biurea with hydrazine sulfate at 210°. Shortly thereafter Purgotti and Vigano[125] reported that *p*-urazine formed a dimethiodide, m.p. 200°. These workers prepared both the diacetyl



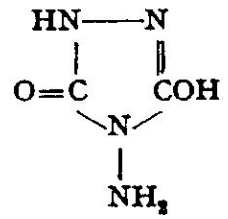
(XXIX)

derivative, which was a syrup, and a crystalline monoacetate, m.p. 235°, by the action of boiling acetic anhydride on *p*-urazine. They prepared a series of ketone derivatives thought to be of the type of XXIX. Chattaway[34] obtained *p*-urazine in 20% yield by the reaction of *N,N'*-dichlorourea with ammonia. The claimed preparation of *p*-urazine by the action of sodium hypobromite on semicarbazide or biurea has already been mentioned. *p*-Urazine has also been prepared by Guha and De[70] by the reaction of urea with carbohydrazide at 120°. Recently the reaction of carbon dioxide and hydrazine at 100–300 atmospheres pressure has been used to prepare *p*-urazine.[17]

The chief reasons for proposing tetrahydro-3,6-*s*-tetrazinedione as the structure for *p*-urazine were analyses and methods of synthesis. Busch and Grohmann,[24] Stollé,[152] and Diels[62] have contended that the true structure of the compound usually called *p*-urazine is 4-amino-1,2,4,1*H*-triazole-3,5(2*H*,4*H*)-dione (XXXa) or its tautomer XXXb.



(XXXa)



(XXXb)

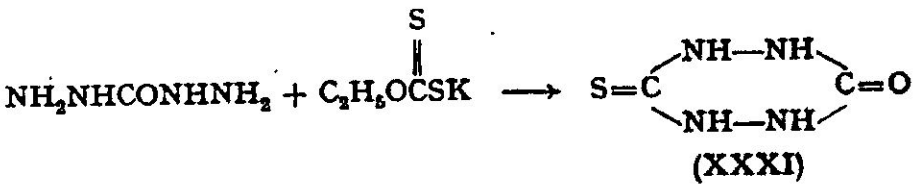
Busch and Grohmann[25,27] have shown that a number of aryl substituted *p*-urazines are actually triazoles. This will be discussed in detail in a later section. Stollé has carried this work further and concluded that in analogy *p*-urazine must have either structure XXXa or XXXb, preferably the latter, as *p*-urazine is a monobasic acid. In addition, since *p*-urazine gives a benzal and other aldehyde and ketone derivatives it must have a primary amino group and react in a straightforward fashion to give normal Schiff bases. Stollé found that the compounds reported by Purgotti and Vigano as arising from the combination of two molecules of ketone with one of *p*-urazine were identical with the azines prepared from the same ketone and hydrazine. This must occur by decomposition of the triazolidine to hydrazine followed by reaction with the ketone.

Guha and De[70] have synthesized tetrahydro-3,6-*s*-tetrazinedithione and find that it does not react with aldehydes, using this as evidence

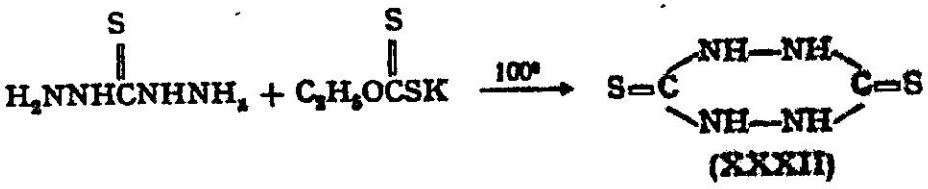
for the proposed *s*-tetrazine structure. Rather surprisingly they report the synthesis of *p*-urazine with no comment on the fact that in analogy to their thiono compound, the accepted tetrahydro-3,6-*s*-tetrazinedione structure for *p*-urazine would not permit aldehyde condensation. The evidence indicates that the compound usually called *p*-urazine in the literature has structure XXXa or XXXb rather than XXVI.

In summary it would appear that the structure of all reported unsubstituted and alkyl substituted tetrahydro-3,6-*s*-tetrazinediones should be considered as not fully established and that triazole structures are the most probable ones.

Thiol and Thiono Derivatives. 6-Thionotetrahydro-3-*s*-tetrazinone (XXXI) has been prepared by Guha and De[70] by two methods: (1) the reaction of carbohydrazide with potassium ethyl xanthate, and (2) the reaction of thiocarbohydrazide with urea at 130°. It is a white compound melting at 238°. Purgotti and Vigano[125] reported the preparation



of tetrahydro-3,6-*s*-tetrazinedithione (XXXII), m.p. 198–199°, by reaction of dithiobiurea with hydrazine hydrate. Later Guha and prepared this compound in nearly quantitative yield by heating disulfide and hydrazine hydrate at 130–140° for several hours. preparations by the same authors were from thiocarbohydrazide potassium ethyl xanthate (eq. 31) and from carbon disulfide hydrazine in alkali.[71] Beckett and Dyson[13] prepared XXXII by



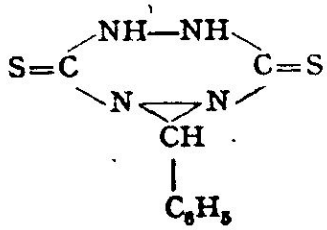
reaction of *s*-dithiocarbimidothiourea (XXXIII) with aniline or toluidine in alcohol (33). In addition the corresponding

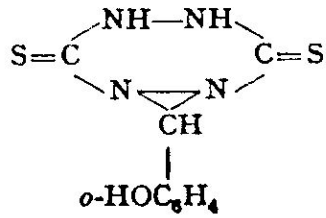
was obtained. The product obtained by Guha and De melted at 203–204° in good agreement with the melting point of Beckett and Dyson and in

$$Cl_2C{=}S + NH_2NH_2.H_2SO_4 \longrightarrow S{=}C(NHN{=}C{=}S)_2 \quad (32)$$
(XXXIII)

$$S{=}C(NHN{=}C{=}S)_2 + ArNH_2 \longrightarrow S{=}C\begin{matrix}NH{-}NH\\ \diagdown\quad\diagup\\ NH{-}NH\end{matrix}C{=}S + ArNHC(=S)NHAr \quad (33)$$
(XXXII)

fair agreement with the melting point reported by Purgotti. However, Guha and De state that their product did not react with aldehydes, whereas Purgotti and Vigano reported that their product gave benzaldehyde and salicylaldehyde derivatives believed to have structures XXXIV and XXXV. The products prepared by both groups crystallized

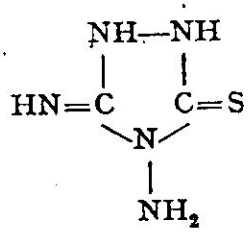

(XXXIV)

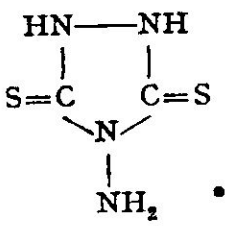

(XXXV)

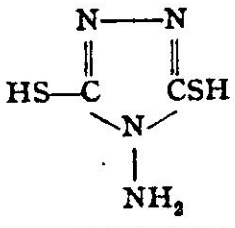
in white platelets. Guha and De oxidized tetrahydro-3,6-*s*-tetrazinedithione to a disulfide, m.p. 218° (dec.) and converted it to a dibenzyl derivative, m.p. 142°. They reported a disilver salt while Purgotti and Vigano reported a monosilver salt. Both compounds were soluble in water but insoluble in organic solvents.

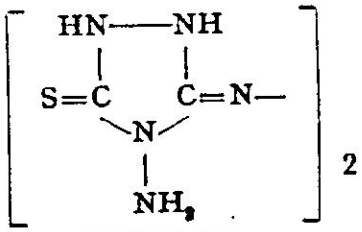
In view of the methods and conditions used by Guha and De and Beckett and Dyson, it appears certain that their product actually is tetrahydro-3,6-*s*-tetrazinedithione or more likely 1,2-dihydro-3,6-*s*-tetrazinedithiol. In accordance with their findings such a compound would not be expected to react with aldehydes. The compound prepared by Purgotti and Vigano, in spite of its similarity in melting point, is probably different. Arndt and Bielich[3] attempted to repeat the Purgotti experiments exactly. Three products (XXXVI, XXXVII and XXXVIII) were obtained, and none was identical with that of Purgotti and Vigano. This refuted Stollé's[152] suggestion that the compound of Purgotti and Vigano was the triazolidine XXXVII a or its isomer

XXXVIIb. About the same time Fromm and co-workers[69] also repeated this reaction. They isolated a compound they thought was

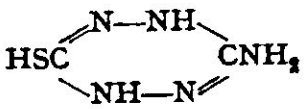

(XXXVI)

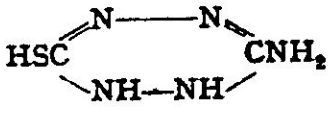

(XXXVIIa)


(XXXVIIb)


(XXXVIII)

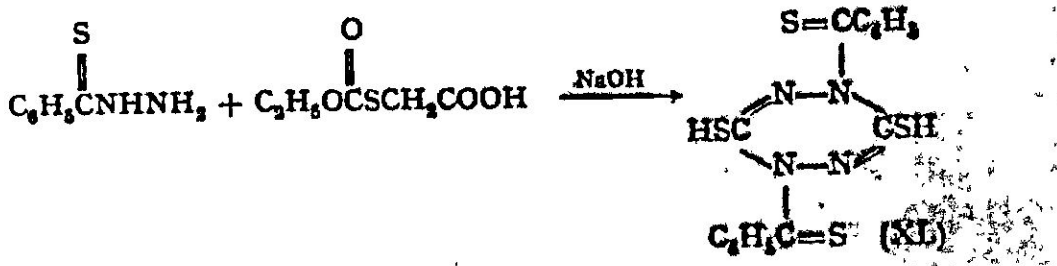
3,4-diamino-1,2,4,4*H*-triazole-5-thiol (a tautomer of XXXVI) but also considered it might be 3-amino-1,4-dihydro-6-*s*-tetrazinethiol (XXXIXa). It crystallizes from water in yellow needles, m.p. 217°. It


(XXXIXa)

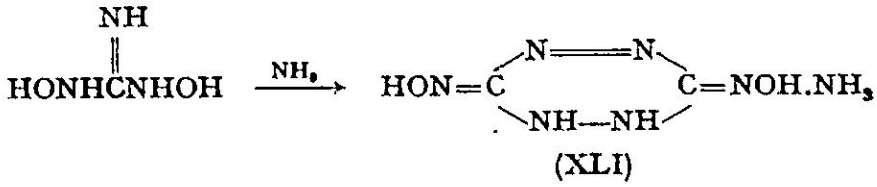

(XXXIXb)

gives a benzylidene derivative, m.p. 270°, and a monoacetyl derivative, m.p. 265°. The benzylidene derivative can be oxidized to a disulfide which is a yellow powder, m.p. 265°. It forms a *S*-benzyl derivative, m.p. 220°, which then gives a crystalline benzoyl derivative, m.p. 198°, and an amorphous acetyl derivative melting at the same place. If this compound is indeed an *s*-tetrazine the structure XXXIXb would be much more likely than XXXIXa.

Holmberg[79] has prepared 1,4-bis(thiobenzoyl)-1,4-dihydro-3,6-*s*-tetrazinedithiol (XL) in very small yields by the reaction shown in equation 34. This is a colorless solid melting at 211–213°.



Amino-Oximino Derivatives. Dihydroxyguanidine in ammonia solution reacts to give the monoammonium salt of 1,2-dihydro-3,6-*s*-tetrazinedione dioxime (XLI)[164] crystallizing in feathery red crystals

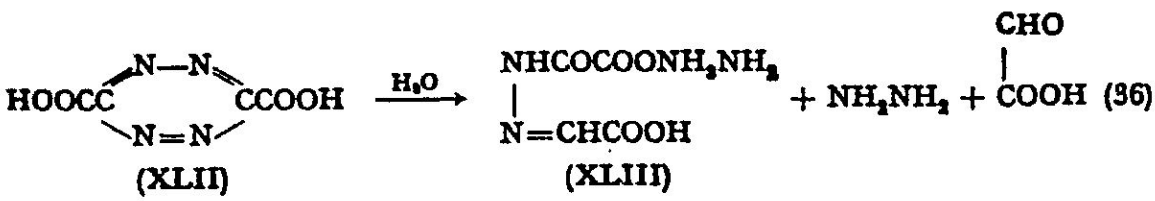


(35)

(XLI)

that explode at 158°. Treatment of dihydroxyguanidine hydrobromide with sodium hydroxide[165] was reported to give 3-amino-1,6-dihydro-6-*s*-tetrazinone oxime, an orange powder melting above 350°.

s-Tetrazinecarboxylic Acids and Derivatives. 3,6-*s*-Tetrazinedicarboxylic acid was first reported in 1900 as bisazoxyacetic acid (IX) by Hantzsch and Lehmann.[73] The correct structure (XLII) was assigned to this compound by Curtius, Darapsky, and Müller.[43] The usual method of preparation has been oxidation of 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid using nitrous acid or nitrogen trioxide although several other mild oxidizing agents such as chlorine, bromine, and ferric chloride have been used. This oxidation usually occurs in yields of 90% or better. The oxidation is easily reversible. For example hydrogen sulfide reduces the *s*-tetrazine to 1,2-dihydro-*s*-tetrazinedicarboxylic acid. Reduction of 3,6-*s*-tetrazinedicarboxylic acid in ammonia using sodium amalgam has been reported to give hydrazinoacetic acid. Very mild aqueous hydrolysis forms the monohydrazide of oxalic acid. Using more vigorous hydrolysing conditions such as dilute sulfuric acid, glyoxylic acid, hydrazine, and the glyoxylic acid derivative (XLIII) of the monohydrazide of oxalic acid (36) are obtained. 3,6-*s*-Tetrazinedicarboxylic acid decarboxylates readily on heating to give *s*-tetrazine.



(36)

(XLII) (XLIII)

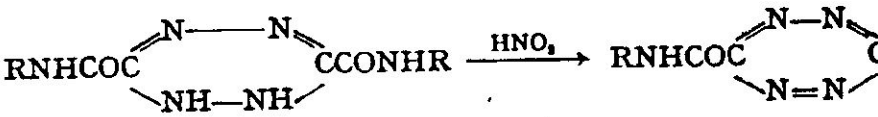
The acid is somewhat soluble in water and alcohol but insoluble in most organic solvents. This acid and its carboxyl derivatives are listed in Table V-1.

TABLE V-1. 3,6-*s*-Tetrazinedicarboxylic Acid Derivatives ROCC(N=N)(N=N)CCOR

R	M.p.,°C.	Color and crystal form	Ref.
HO[a]	148 (dec.)	Carmine red, purple-red or blue-violet needles	43, 50, 73, 92, 167
C_2H_5O	135–136	Purplish	92
NH_2	210–280 (dec.)	Bluish-red	43
CH_3NH	237	Carmine red platelets	93
C_2H_5NH	195	Carmine red platelets	93
	196 (dec.)	Red platelets	93

[a] Forms monohydrazino salt crystallizing in yellow needles, m.p. 185° (dec.).

Derivatives of 3,6-*s*-tetrazinedicarboxylic acid have been obtained by oxidation of dihydro-*s*-tetrazines with nitrous acid. In the case of the diethyl ester the 1,2-dihydro ester was used. The diamides listed in Table V-1 were prepared by oxidation of 1,2-dihydro-3,6-*s*-tetrazine-



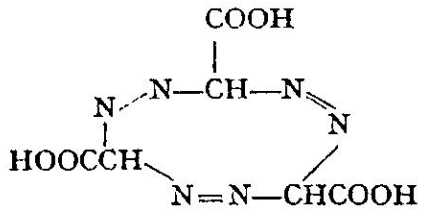
(37)

dicarboxamides (eq. 37).[93] These compounds are insoluble in ether, somewhat more soluble in water, and moderately soluble in alcohol.

Although 1,6-dihydro-3,6-*s*-tetrazinecarboxylic acid (XLV) has been obtained only in solution, its potassium salt can be obtained by the action of potassium hydroxide on ethyl diazoacetate. If the ester is treated for a short time at room temperature or lower with concentrated aqueous or alcoholic potassium hydroxide solutions the potassium salt of the 1,6-dihydroacid is obtained. 1,2-Dihydro-3,6-*s*-tetrazinedicarboxylic acid (IV) can also be prepared by the action of base, either sodium or potassium hydroxide, on ethyl diazoacetate (eq. 2). The potassium salt of the 1,6-dihydro acid is converted to the salt of the 1,2-dihydro acid by warming for a short time with potassium or sodium hydroxide solution. If the heating is continued too long,
occurs and a triazole is formed. The salt of 1,2-dihydro-3,6-*s*-
dicarboxylic acid can be obtained directly by adding ethyl

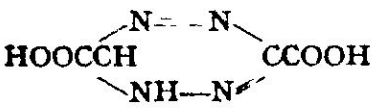
to a solution of sodium hydroxide at 100°. The reaction is extremely vigorous. The two other theoretically possible dihydro-3,6-*s*-tetrazinedicarboxylic acids are unknown.

Curtius[39] was the first to report that the action of either potassium hydroxide or sodium hydroxide on ethyl diazoacetate gives an acid. It was his belief[58] that the acid was a trimer of diazoacetic acid and he called it *triazoacetic acid*. This acid was obtained at steam bath temperature and was the 1,2-dihydro acid. The yield of sodium salt was nearly quantitative. The free acid crystallized as a dihydrate, m.p. 152° (dec.). The formula XLIV was proposed.[40] Hantzsch and Silberrad[75]

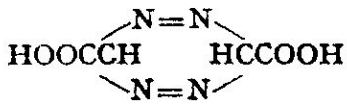


(XLIV)

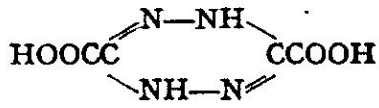
found that the compound called *triazoacetic* acid was a dimer of diazoacetic acid so they proposed the structure 3,6-dihydro-3,6-*s*-tetrazinedicarboxylic acid (XLVI) and called it *bisdiazoacetic acid*. They reported



(XLV)

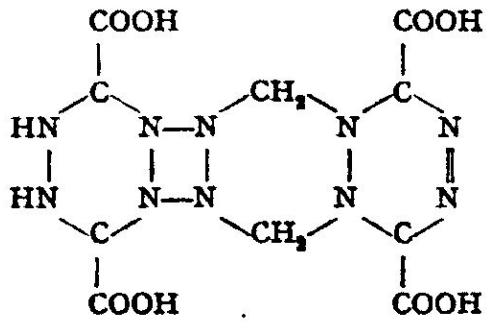


(XLVI)



(XLVII)

a melting point of 180° for the anhydrous compound. These authors reported that a second acid could be obtained by long action of hot potassium hydroxide on "bisdiazoacetic acid." The second acid forms colorless needles, m.p. 287°. The structure proposed was 1,4-dihydro-3,6-*s*-tetrazinedicarboxylic acid (XLVII). Still a third acid is obtained

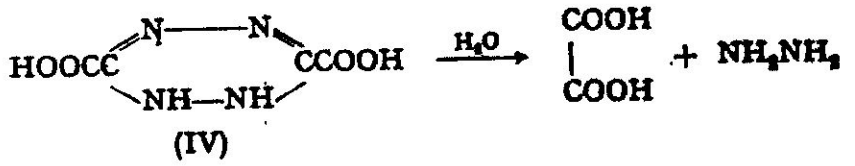


(XLVIII)

from the reaction mixture that yields the second acid. The structure proposed for this was XLVIII and it was called *trisbisdiazomethanetetracarboxylic acid.* A fourth acid was obtained by Müller[92] as its potassium salt and was called *pseudodiazoacetic acid.* Derivatives of this acid had been prepared earlier[38,43] and the structure proposed was 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid (IV).

It was discovered that the acid, m.p. 287°, obtained by Hantzsch and which he believed was the 1,4-dihydro acid could be decarboxylated to a compound believed to be 1,4-dihydro-*s*-tetrazine. As mentioned previously, Bülow found that this supposed 1,4-dihydro-*s*-tetrazine was 4-amino-1,2,4,4*H*-triazole. Bülow proposed that the acid precursor was 4-amino-1,2,4,4*H*-triazole-3,5-dicarboxylic acid. Curtius and coworkers,[50] as a result of Bülow's work, investigated further the action of potassium hydroxide on ethyl diazoacetate. The acid called *trisbisdiazomethanetetracarboxylic acid* by Hantzsch was shown to be identical with the already known 3-amino-1,2,4-triazole-5-carboxylic acid hemihydrate melting at 182°. The acid that Hantzsch had described as 1,4-dihydro-3,6-*s*-tetrazinedicarboxylic acid, m.p. 287°, was found to be the monopotassium salt of 4-amino-1,2,4,4*H*-triazole-3,5-dicarboxylic acid readily converted by treatment with mineral acid to the free acid, m.p. 77°. This was easily decarboxylated to 4-amino-1,2,4,4*H*-triazole.

Curtius, Darapsky, and Müller[44] revised their opinions as to the structure of *bisdiazoacetic acid* and *pseudodiazoacetic* on the basis of hydrolysis studies. Hydrolysis of *bisdiazoacetic* acid gave oxalic acid and hydrazine and this was believed to indicate the 1,2-dihydro struc-

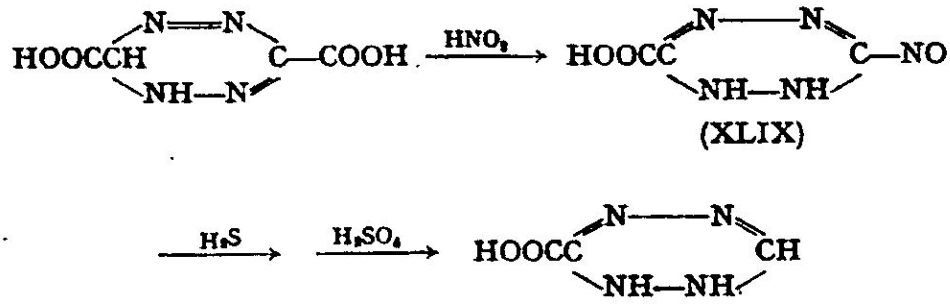


(IV) (38)

ture IV for this acid. It was thought that the grouping –N–N– gave rise to hydrazine while the grouping –N=N– gave rise to nitrogen. no nitrogen was formed, the –N=N– structure could not be present in *bisdiazoacetic acid. Pseudodiazoacetic* acid has been obtained only solution and has been isolated in the form of salts. It forms a tripotassium salt[92] while 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid forms a dipotassium salt. For purposes of structure determination the

of the "pseudo" acid has been used. Hydrolysis of this amide gave glyoxylic acid amide, nitrogen, and hydrazine. From this fact the 3,6-dihydro structure (XLVI) was inferred for the acid. However, since both *bisdiazoacetic acid* and *pseudodiazoacetic* can be oxidized to 3,6-*s*-tetrazinedicarboxylic acid, the conclusion was reached that the hydrogen atoms must be adjacent in both. This indicates that *pseudodiazoacetic acid* must be 1,6-dihydro-3,6-*s*-tetrazinedicarboxylic acid (XLV). This would also be in better agreement with the fact that both hydrazine and nitrogen were obtained from hydrolysis of *pseudodiazoacetamide.* Although the arguments presented by workers in this field are not conclusive, their final structural assignments are undoubtedly correct. The "pseudo" acid and its derivatives have a ring hydrogen which is acidic. Only in the 1,6-dihydro series is there nonequivalence of the hydrogen atoms. Consequently, the "pseudo" series is the 1,6-dihydro one (XLV). The "bis" acid must be the 1,2-dihydro acid (IV) since the bonds in the ring would certainly be conjugated rather than isolated.

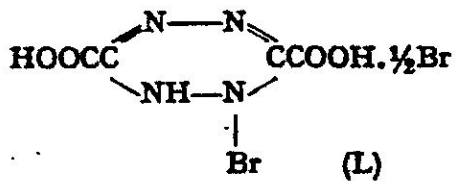
The reaction of the dipotassium salt of 1,6-dihydro-3,6-*s*-tetrazinedicarboxylic acid with nitrous acid has given the potassium salt of 6-nitroso-1,2-dihydro-3-*s*-tetrazinecarboxylic acid (XLIX), a yellow solid melting at 170°.[92] Treatment of an aqueous solution of the



(39)

potassium salt of the nitroso compound with hydrogen sulfide followed by sulfuric acid (eq. 39) gives 1,2-dihydro-3-*s*-tetrazinecarboxylic acid. This compound was obtained as the monohydrate melting at 93–105° (dec.).

Potassium salts of either 1,6-dihydro-3,6-*s*-tetrazinedicarboxylic

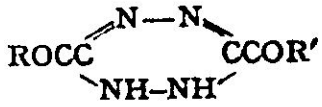


(L)

acid or 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid have been reported[92] to react with bromine to yield a bromo-1,2-dihydrotetrazine (L). Treatment of this compound with potassium acetate gives the dipotassium salt of 3,6-*s*-tetrazinedicarboxylic acid.

Only three esters of 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid are known. These are the dimethyl, diethyl and diisopropyl (Table V-2). These esters have been prepared from the silver or potassium salts of

TABLE V-2. Carboxyl Derivative of 1,2-Dihydro-3,6-*s*-tetrazinedicarboxylic Acids

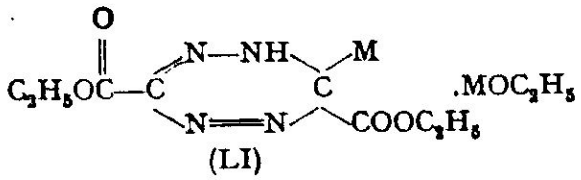


R	R′	M.p., °C.	Color and crystal form	Ref.
HO[a]	HO	185	Yellow rods	47, 58
HO	NH_4O	192	Orange-red crystals	59
NH_4O	NH_4O	217, 222		58, 59
NH_2NH_3O	NH_2NH_3O	183–188	Yellow needles	59
$C_2H_5NH_2O$	$C_2H_5NH_3O$	179–180	Orange-yellow	93
CH_3O	CH_3O	167–168	Red biaxial platelets	58
C_2H_5O	C_2H_5O	113	Yellow-red prisms	58, 59
$(CH_3)_2CHO$	$(CH_3)_2CHO$			58
CH_3O	NH_2NH	211		59
C_2H_5O	NH_2NH	228–231	Yellow needles	59
C_2H_5O	$NH_2NH.HCl$	212	Yellow needles	59
C_2H_5O	$C_6H_5CH=NNH$	233	Yellow powder	59
C_2H_5O	p-$CH_3C_6H_5CH=NNH$	237	Yellow needles	59
C_2H_5O	$(CH_3)_2C=NNH$	115	Yellow needles	59
C_2H_5O	$C_6H_5C(CH_3)=NNH$	182–185	Yellow needles	59
C_2H_5O	$CH_3CONHNH$	166	Yellow powder	59
C_2H_5O	N_3	decomposes	Violet-red needles	59
NH_2	NH_2	>300	Golden leaflets	58
CH_3NH	NH_2	234 (dec.)	Rectangular leaflets	51
CH_3NH	CH_3NH	295 (dec.)	Prisms	93
C_2H_5NH	C_2H_5NH	287 (dec.)	Yellow needles	93
n-$C_7H_{15}NH$	n-$C_7H_{15}NH$	240	Yellow leaflets	93
$(CH_3)_2N$	$(CH_3)_2N$	225	Yellow prisms	93
$C_5H_{10}N$	$C_5H_{10}N$	266	Yellow needles	93
NH_2NH	NH_2NH	265–275		59
$C_6H_5CH=NNH$	$C_6H_5CH=NNH$	290	Yellow powder	59

[a] Forms dihydrate crystallizing in yellow needles, m.p. 152° (dec.).

the acid and the appropriate alkyl halide.[58,75] In addition the methyl and ethyl esters have been synthesized from the acid and diazomethane and diazoethane,[59] respectively. The diethyl ester of 3,6-dihydro-3,6-*s*-tetrazinedicarboxylic acid has been reported but it was actually the ester of the 1,2-dihydro acid. Silberrad[144] claimed to have prepared dimethyl 1,4-dihydro-3,6-*s*-tetrazinedicarboxylate, but the acid he used was later shown[50] to be 4-amino-1,2,4,4*H*-triazole-3,5-dicarboxylic acid and thus the ester must have been a derivative of this acid.

The reaction of sodium or potassium ethoxide with ethyl diazoacetate in ether or alcohol gives an ester which according to Curtius and co-workers[49] has the formula LI although in view of later knowledge the M must be on the nitrogen. Their conclusion was derived from the



(LI)

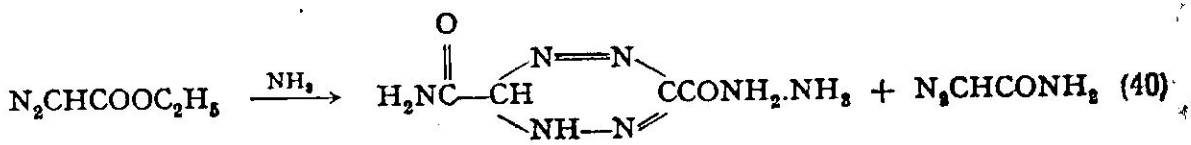
M = K or Na

facts that acid hydrolysis yields hydrazine and ethyl glyoxylate and treatment with 50% potassium hydroxide at 30° gives the potassium salt of 1,6-dihydro-3,6-*s*-tetrazinedicarboxylic acid and at 100° the potassium salt of 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid. Curtius and co-workers stated that this is the same compound that Hantzsch and Lehmann[74] had believed was a salt of ethyl isodiazoacetate. These latter authors obtained a noncrystalline ester by treatment of their product with acid. This ester might be diethyl 1,6-dihydro-3,6-*s*-tetrazinedicarboxylate.

The diamide of 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid (Table V-2) has been obtained by the reaction of alcoholic ammonia with ethyl diazoacetate at 100°, from the ethyl ester of the 1,2-dihydro-*s*-tetrazine acid and ammonia at room temperature and by treatment of the isomeric 1,6-dihydro amide with warm concentrated alkali solution.[43,58] It has a melting point of above 300° and is somewhat brighter yellow than the isomeric 1,6-dihydro amide. The 1,2-dihydro amide is usually referred to in the literature as *bisdiazoacetamide.*

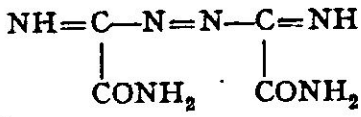
If aqueous ammonia is allowed to react with ethyl diazoacetate in

the cold, there are formed diazoacetamide and the ammonia salt o 1,6-dihydro-3,6-*s*-tetrazinedicarboxamide[38,43] (eq. 40). Treatment o



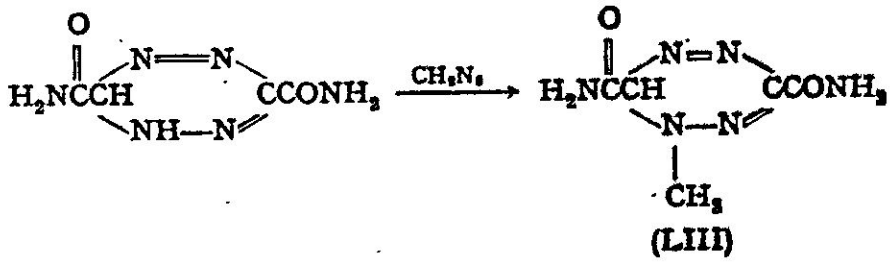
(40)

the ammonium salt with acetic acid gives a yellow solid that is 1,6-dihydro-3,6-*s*-tetrazinedicarboxamide (also called pseudodiazoacetamide). This amide has been reported to melt at 170° when air dried but to explode at 133° when dried *in vacuo*. The same product can be obtained in 80–85% yield by the reaction of liquid ammonia with ethy diazoacetate at room temperature followed by treatment of the ammonium salt with acetic acid. Silberrad[144] first prepared this amide and called it *iminoazoacetamide*. The structure proposed was LII. Careful acid



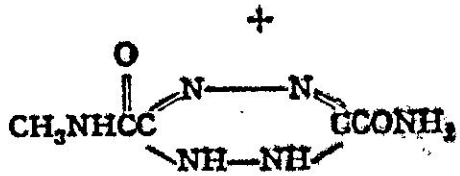
(LII)

hydrolysis of 1,6-dihydro-3,6-*s*-tetrazinedicarboxamide gives nitro hydrazine, and glyoxylamide in the ratio of one-half mole of hydraz to one mole of each of the other products. Nitrous acid oxidizes amide to 3,6-*s*-tetrazinedicarboxamide.[43] Treatment of 1,6-dihy 3,6-*s*-tetrazinedicarboxamide with diazomethane gives a 1-methyl de ative LIII as well as N^3-methyl-1,2-dihydro-3,6-*s*-tetrazinedi amide (LIV). The compound LIII is a yellow powder, m.p. 118° (dec.),



(LIII)

+

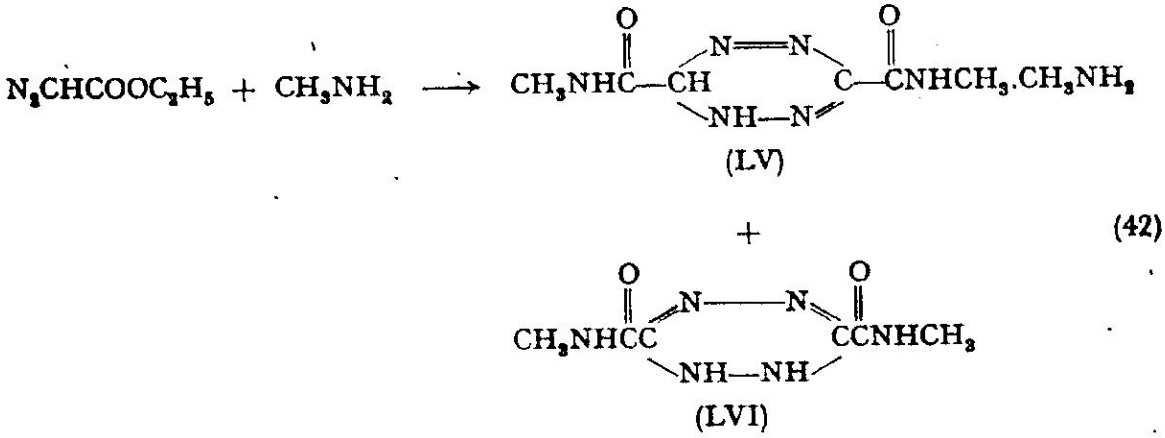


(LIV)

The 1-ethyl-dihydro-*s*-tetrazine corresponding to LIII can be obtained using diazoethane. The structure of the 1-alkyl-1,6-dihydro-3,6-*s*-tetrazinedicarboxamides has been shown by hydrolysis of LIII to give methylhydrazine. Methylation of 1,6-dihydro-3,6-*s*-tetrazinedicarboxamide in the 1-position using diazomethane indicates that the acid ring hydrogen in the 1,6-dihydro-*s*-tetrazine series is on the nitrogen rather than on the carbon atom. This follows from the fact that diazoalkanes react at the site of more acidic hydrogen atoms.

Silberrad[144] has reported 1,4-dihydro-3,6-*s*-tetrazinedicarboxamide, but it is now believed that the compound he obtained was a triazole.

Ethyl diazoacetate reacts with methylamine to give the methylamine salt of N^3,N^6-dimethyl-1,6-dihydro-3,6-*s*-tetrazinedicarboxamide (LV), a yellow solid melting at 115° (dec.), and N^3,N^6-dimethyl-

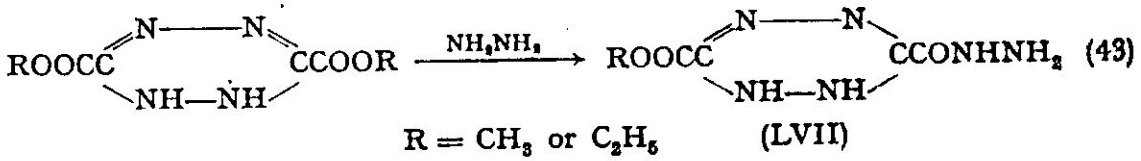


(42)

1,2-dihydro-3,6-*s*-tetrazinedicarboxamide (LVI).[93] Similar products are obtained with ethylamine. The reaction requires several days and gives very poor yields. *n*-Heptylamine, dimethylamine, and piperidine give, after several weeks, diamides of the 1,2-dihydro acid (Table V-2). Diethylamine and aniline did not give amides. Gentle warming of the 1,6-dihydro amides with the corresponding amines converted them to 1,2-dihydro amides. Acid hydrolysis of the 1,6-dihydro amides gives nitrogen, hydrazine, glyoxylic acid, and amines. The 1,2-dihydro amides with acid give hydrazine, oxalic acid, and amines.

Either dimethyl or diethyl 1,2-dihydro-3,6-*s*-tetrazinedicarboxylate react with hydrazine in boiling alcohol to give the dihydrazide.[59] This reacts readily with benzaldehyde to give a dibenzylidene derivative. At room temperature, hydrazine and the esters mentioned above react

to form ester hydrazides (eq. 43) The ester hydrazides can be acetylated on the amino group of the hydrazide and react readily with aldehydes



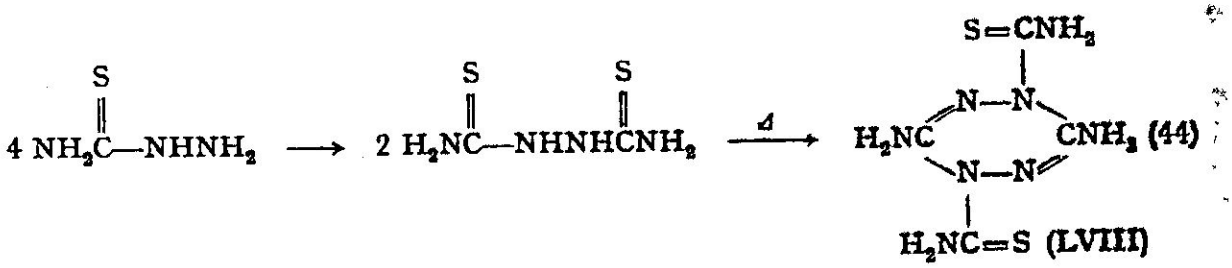
(43)

and ketones to give alkylidene derivatives These hydrazides and their derivatives are listed in Table V-2.

Reaction of the dihydrazide of 1,2-dihydro-3,6-*s*-tetrazinedicarboxylic acid with nitrous acid gives a very unstable product that is believed to be the diazide. The ester hydrazide LVII ($R = C_2H_6$) reacts with nitrous acid to give a very unstable ester azide.[59]

Ruhemann and Stapleton[139] have reported that 1,4-dihydro-*s*-tetrazine reacts with phenyl isothiocyanate to give a thiocarbamide derivative. Actually this product is a derivative of 4-amino-1,2,4,4*H*-triazole.

Mazourewitch[90] has claimed that the thermal condensation of thiosemicarbazide or dithiobiurea with aromatic amines gives 1,4-dihydro-*s*-tetrazines. The reaction was believed to proceed as shown in eqs. 44 and 45 with three possible types of structures proposed for the



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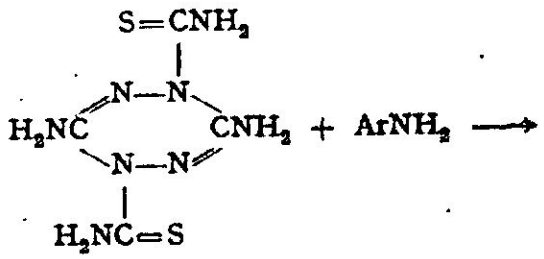
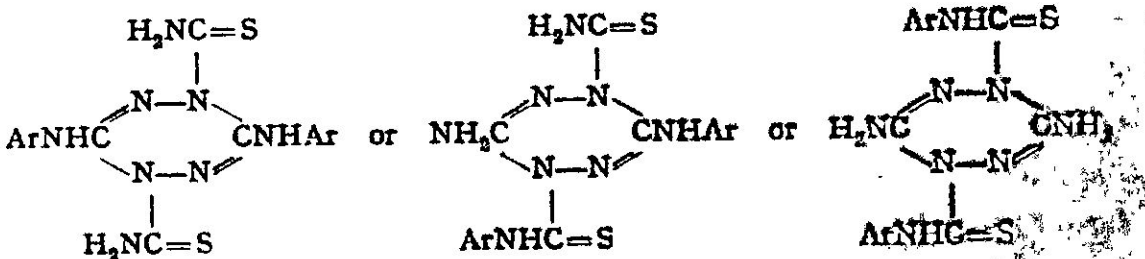


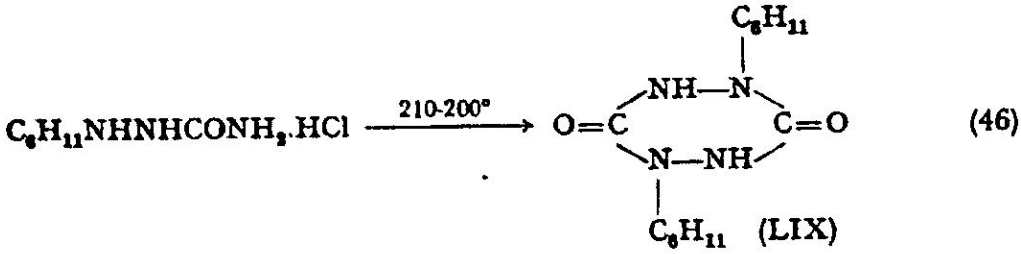


products. However, the author was unable to decide which was the correct one. Using aniline as the arylamine, a yellow solid, m.p. 260–261° (dec.) was obtained. The same product was obtained from 1-phenyldithiobiurea and aniline. *o*-Toluidine also gives a yellow solid, but it melts at 228–229°. The use of *o*-toluidine and 1-phenyldithiobiurea gives a product containing both a phenyl and an *o*-tolyl group. It is a white powder, m.p. 219–220°. Both thiosemicarbazide and dithiobiurea give with *m*-toluidine a di-*m*-tolyltetrazine, m.p. 259–260°. In the same reactions *p*-toluidine gives a colorless crystalline solid, m.p. 272–273°, containing two *p*-tolyl groups. In each of these reactions a high melting white solid is obtained, m.p. 297–300° (dec.), which proved to be LVIII. All of these compounds are weak dibasic acids, soluble in water but not very soluble in organic solvents. In view of the fact that these reactions were carried out at 185° the possibility that these compounds are triazoles rather than dihydro-*s*-tetrazines must be kept in mind.

B. Polynuclear Uncondensed *s*-Tetrazines

(1) Aliphatic Carbocyclic Rings Coupled Directly to *s*-Tetrazines

Only one example of this type of structure has been reported. Poth and Bailey[121] heated 1-cyclohexylsemicarbazide hydrochloride at 200–210° and obtained in 70% yield a product to which was assigned the structure 1,4-dicyclohexyltetrahydro-3,6-*s*-tetrazinedione (LIX).



(46)

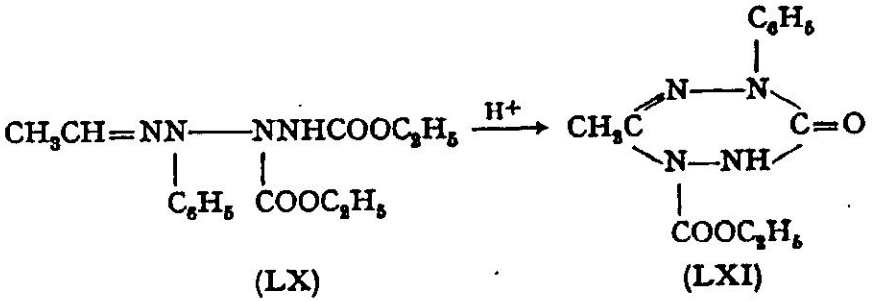
(LIX)

The product is a white solid crystallizing in prisms, m.p. 197°, and soluble in water, chloroform, alcohol, and benzene. It reduces Fehling's solution readily and gives no color with ferric chloride. There was no rigorous proof of structure. Since high temperatures were used and this is known to isomerize hydro-*s*-tetrazines to triazoles, the proposed structure should be viewed with some doubt.

(2) Aromatic Carbocyclic Rings Coupled Directly to *s*-Tetrazines

Aryl and Alkyl Derivatives. Busch, Müller, and Schwarz[80] have prepared ethyl 6-methyl-3-oxo-4-phenyl-1,2,3,4-tetrahydro-1-*s*-tetrazinecarboxylate (LXI) by rearrangement and cyclization of 1-ethylidene-2-phenyl-3,4-dicarbethoxytetrazane (LX). The product may exist as the

$$CH_3CH{=}NNHC_6H_5 + H_5C_2OOCN{=}NCOOC_2H_5 \longrightarrow$$

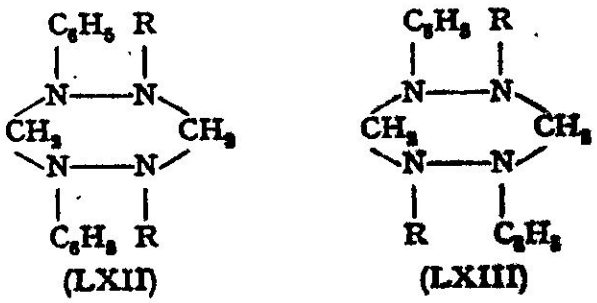


(47)

(LX) (LXI)

enolic form since it is soluble in dilute alkali. It crystallizes from alcohol in white needles, m.p. 112°.

Hexahydro-*s*-tetrazines having alkyl and phenyl groups on the nitrogen atoms have been synthesized by reaction of formaldehyde with substituted hydrazines in aqueous solution at room temperat (eq. 8).[69,82] The yields of water insoluble products were almost quantita tive. The structures of the products were not definitely asce because they could in each case be one of two isomers, since uns metrical hydrazines were used; for example LXII or LXIII (R = CH_3) The product LXII or LXIII (R = CH_3) crystallizes from alcohol white leaflets, m.p. 148°. The ethyl substituted compound was crystallized from the same solvent to give similar crystals, m.p. 1



(LXII) (LXIII)

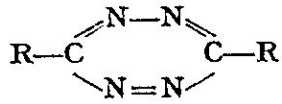
R = CH_3, C_2H_5 or $(CH_3)_2CH$

The product containing isopropyl groups, LXII or LXIII (R $(CH_3)_2CH$) forms white needles, m.p. 163°.

Rassow and Baumann[126,127] have refluxed several aldehydes with hydrazobenzene in alcohol in an attempt to prepare hexahydro-*s*-tetrazines. Propionaldehyde gave 3,6-diethyl-1,2,4,5-tetraphenylhexahydro-*s*-tetrazine, a light yellow compound melting at 193°, and *n*-heptaldehyde gave the corresponding 3,6-di-*n*-hexyl compound forming white crystals, m.p. 133°. Chloral reacted with hydrazobenzene but did not form a hexahydro-*s*-tetrazine while isobutyraldehyde and valeraldehyde did not react at all. The lack of reactivity of valeraldehyde is rather difficult to explain.

Polyphenyl Derivatives with No Substituents on the Tetrazine Ring. The 3,6-diaryl-*s*-tetrazines in which aryl is phenyl or substituted phenyl are listed in Table V-3. These compounds have usually been prepared by oxidation of the corresponding 1,2-dihydro-*s*-tetrazine (eq. 1) using

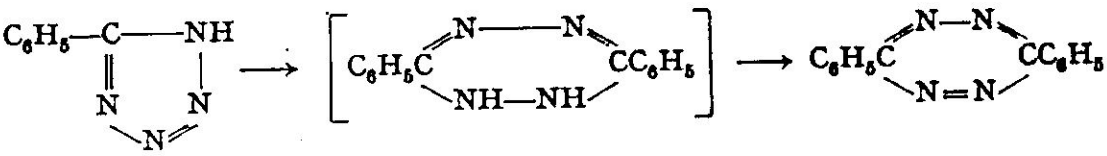
TABLE V-3. Polyraryl-*s*-tetrazines



R	M.p., °C.	Color and crystal form	Ref.
C_6H_5	193, 195	Bluish-red prisms	31, 77, 80, 88, 95 107, 111, 168
p-$CH_3C_6H_4$	233, 235	Bluish-red prisms	95, 111, 113, 168
m-$CH_3C_6H_4$	150	Red needles	95
p-$(CH_3)_2CHC_6H_4$	156	Red plates	36
p-ClC_6H_4			160
p-BrC_6H_4	dec. >280	Bluish-red leaflets	160
p-$NO_2C_6H_4$	215	Red needles	113
m-$NH_2C_6H_4$	266	Red needles	81
m-$CH_3CONHC_6H_4$	295	Violet needles	81
m-$HOOCC_6H_4$	270–280 (dec.)		56
Acid hydrazine salt	>277	Yellow	56
Dipyridinium salt	300–310 (dec.)	Scarlet rhombs	56

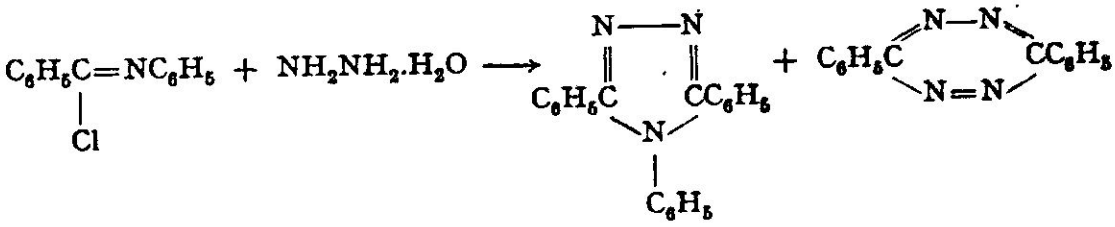
a mild oxidizing agent such as ferric chloride, air, oxygen, amyl nitrite, or nitrous acid.[77,80,88,95,107,111,168] The yields are usually quite good, being 80% or better. A number of other syntheses have been reported, some of which probably proceed through a dihydro-*s*-tetrazine intermediate, which is not isolated. Lossen and Statius[88] reported that phenyltetrazole heated to 218° decomposes to give a small amount of

3,6-diphenyl-*s*-tetrazine (eq. 48) and other products. The reaction was thought to proceed through 3,6-diphenyl-1,2-dihydro-*s*-tetrazine as



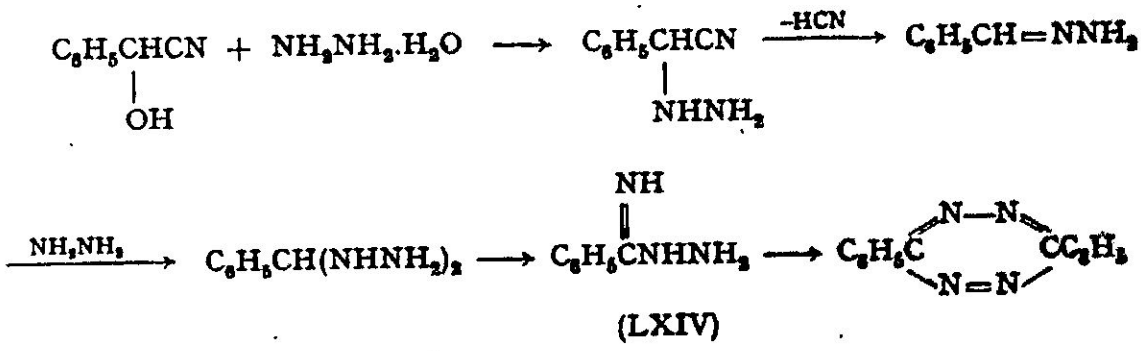
(48)

intermediate. Busch and Schneider[31] have found that *N*-phenylbenzimidyl chloride and hydrazine react in the cold to form a very small amount of 3,6-diphenyl-*s*-tetrazine as well as the main product, 3,4,5-triphenyl-1,2,4,4*H*-triazole (eq. 49). In an attempt to prepare 3,6-bis(α-hydroxybenzyl)-1,2-dihydro-*s*-tetrazine from mandelonitrile and



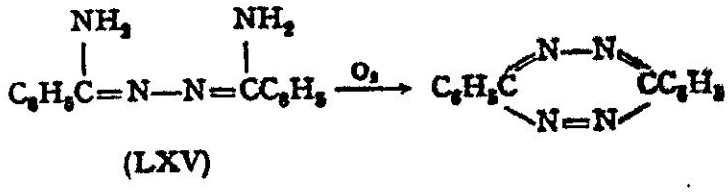
(49)

hydrazine, Darapsky and Adamczewski[60] isolated a compound indefinite composition that formed 3,6-diphenyl-*s*-tetrazine by oxidation with amyl nitrite. It was proposed that this occurred t benzimide hydrazide (LXIV) as shown in eq. 50. Wuyts and Lacourt



(LXIV)

have found that the oxidation of arylamideazines in ethanolic with air gives 3,6-diaryl-*s*-tetrazine (eq. 51). The preparation of



(LXV)

amideazines will be discussed later (eq. 59). 3, 3,6-di(*p*-tolyl)-*s*-tetrazine were prepared in this way.

Stollé and Helwerth[155] have obtained 3,6-diphenyl-*s*-tetrazine from benzaldehyde benzoyl chloride azine (LXVI) by allowing it to stand in the presence of ammonia, ethyl amine or phenylhydrazine. This was believed to proceed by reaction of LXVI with base to form benzoyl chloride hydrazone (LXVII) which then reacted as in equation 53.

$$\underset{\text{(LXVI)}}{C_6H_5C(Cl)=N-N=CHC_6H_5} + RNH_2 \longrightarrow \underset{\text{(LXVII)}}{C_6H_5C(Cl)=NNH_2} + RN=CHC_6H_5 \quad (52)$$

$$C_6H_5C(Cl)=NNH_2 \longrightarrow C_6H_5C\overset{N-NH}{\underset{NH-N}{\diagup\diagdown}}CC_6H_5 \longrightarrow C_6H_5C\overset{N-N}{\underset{N=N}{\diagup\diagdown}}CC_6H_5 \quad (53)$$

These 3,6-diaryl-*s*-tetrazines are deeply colored, being red, bluish-red or violet-red. They are not basic and are therefore insoluble in dilute acid. They are unaffected by cold sulfuric acid or nitric acid. They are insoluble in water, slightly soluble in alcohol, and soluble in benzene and acetone. Hydrolysis with hot sulfuric acid forms a carboxylic acid, hydrazine, and nitrogen (eq. 54).[54,95] Treatment of 3,6-

$$ArC\overset{N-N}{\underset{N=N}{\diagup\diagdown}}CAr \xrightarrow[H_2O]{H_2SO_4} ArCOOH + NH_2NH_2 + N_2 \quad (54)$$

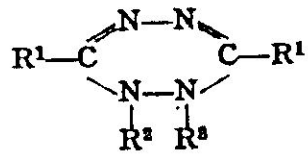
diphenyl-*s*-tetrazine with alcoholic potassium hydroxide gives benzoyl benzaldehyde hydrazone (eq. 55).[108] Functional groups in the benzene

$$C_6H_5C\overset{N-N}{\underset{N=N}{\diagup\diagdown}}CC_6H_5 \xrightarrow[H_2O]{KOH} C_6H_5\overset{O}{\overset{\|}{C}}NHN=CHC_6H_5 \quad (55)$$

rings react normally. 3,6-Bis(*m*-aminophenyl)-*s*-tetrazine[81] forms a dinitrate, a sulfate, a hydrochloride, and a diacetyl derivative. The acid, 3,6-bis(*m*-carboxyphenyl)-*s*-tetrazine, forms salts normally.

The 3,6-diaryl-1,2-dihydro-*s*-tetrazines in which the aryl groups are phenyl or substituted phenyl groups are listed in Table V-4. The first synthesis of compounds of this type was reported by Pinner,[107,108,111] who used imido ester hydrochlorides and hydrazine (eq. 5) to prepare

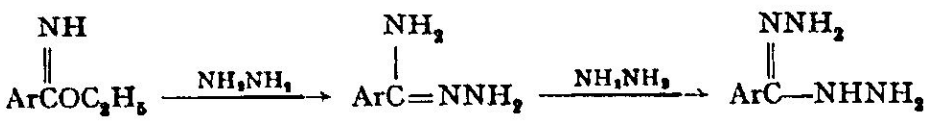
TABLE V-4. Polyphenyl-1,2-dihydro-*s*-tetrazines



R^1	R^2	R^3	M.p., °C.	Color and crystal form	Ref.
C_6H_5	H	H	160	Yellow needles	18, 33, 64, 80, 107, 108, 111, 148, 150, 159, 168
C_6H_5	CH_3CO	CH_3CO	228	White	80, 107
C_6H_5	C_6H_5CO	H	208	Lemon yellow	150
p-$CH_3C_6H_4$	H	H	223, 235	Yellow needles	95, 111, 113, 168
m-$CH_3C_6H_4$	H	H	194	Yellow needles	95
p-ClC_6H_4	H	H	215	Yellow	160
p-BrC_6H_4	H	H	235	Yellow	160
p-BrC_6H_4	C_6H_5CO	C_6H_5CO	248	Yellow	160
p-$NO_2C_6H_4$	H	H	215	Red needles	113
m-$NH_2C_6H_4$	H	H	179–190	Yellow needles	81
m-$HOOCC_6H_4$	H	H	>285	Yellowish-red	56
Dihydrazinium salt			dec. 203	Yellow	56
C_6H_5	C_6H_5	H	126	Orange yellow needles	150, 152, 157
Hydrochloride			180		159
C_6H_5	C_6H_5	CH_3CO	186	White	152
p-BrC_6H_4	C_6H_5	H	167	Yellow needles	150, 160

3,6-diphenyl- and 3,6-di(*p*-tolyl)-1,2-dihydro-*s*-tetrazine. This was carried out by adding the hydrochloride of the imido ester and hydrazine salt to aqueous alcohol containing potassium h The desired product is formed at room temperature or on warming. If the reaction is carried out with exposure to air, a able amount of 3,6-diaryl-*s*-tetrazine is formed by oxidation of dihydro-*s*-tetrazine. Imide hydrazides (LXVIIIa) and amide h (LXVIIIb) are also obtained. Pinner[108,110] suggested the tetrazine is formed through amide hydrazones (eqs. 56 and 57). This was based on the fact that benzamide hydrazone (LXVIIIb, Ar =

reacts with hydrazine to give 3,6-diphenyl-1,2-dihydro-*s*-tetrazine while benzamide azine (LXV) will not. Pinner and Wuyts and Lacourt[168]



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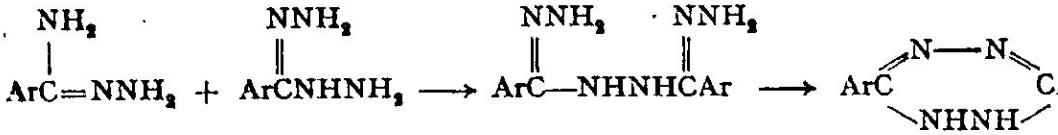


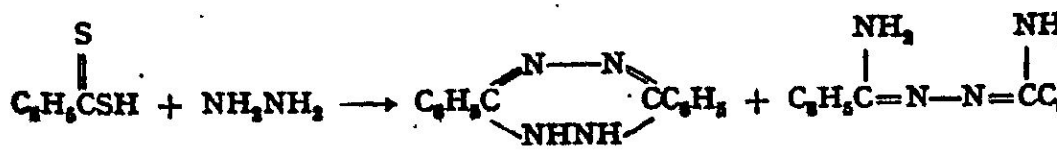
(57)

found that considerable amounts of amide azines were formed in the reaction and it was believed that they occurred by reaction of amide hydrazones with imido esters (eq. 58).

(58)

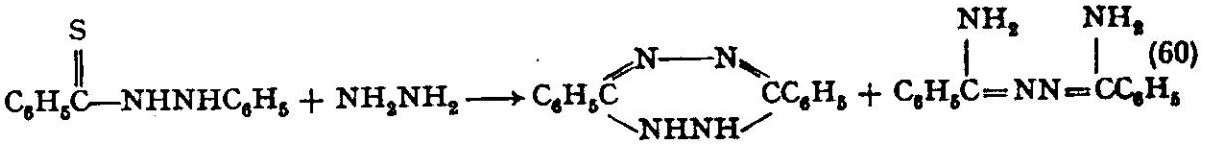
Hofmann and Ehrhardt,[77] Müller and Herrdegen,[95] and Curtius and Hess[56] have synthesized 3,6-diaryl-1,2-dihydro-*s*-tetrazines by the reaction of aromatic nitriles with hydrazine (eq. 3). Benzonitrile, *p*-tolunitrile, *m*-tolunitrile, and *m*-carboxybenzonitrile reacted successfully, but *o*-tolunitrile did not react. The only yields reported were 75% for 3,6-di(*p*-tolyl)-1,2-dihydro-*s*-tetrazine and 22% for the *m*-tolyl compound. Müller and Herrdegen proposed a mechanism for this reaction very similar to that proposed by Pinner for the imido esters. In the case of the nitrile the first step was believed to be reaction with hydrazine to form an imide hydrazide (LXVIIIa), which proceeds as shown in equations 56 and 57 with LXVIIIa substituted for LXVIIIb.

Junghahn[80,81] has found that aromatic thioamides react readily with hydrazine (eq. 4) in boiling aqueous alcohol to give, 3,6-diaryl-1,2-dihydro-*s*-tetrazines. The yield was reported as excellent using thiobenzamide. A somewhat similar method has been used by Wuyts and Lacourt.[168] These workers have treated dithio acids with hydrazine (eq. 59) to obtain 3,6-diaryl-1,2-dihydro-*s*-tetrazines and amide azines.



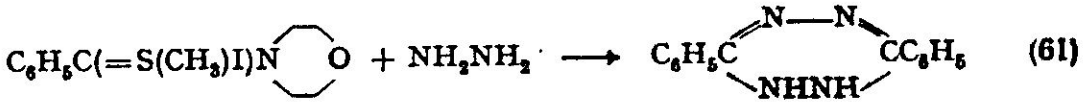
(59)

It was believed that the first step in the reaction was the formation of thiohydrazides. In agreement with this belief is the fact that thiohydrazides react with hydrazine under the same conditions to form 1,2-dihydro-*s*-tetrazines and amide azines (eq. 60). Recently Chabrier and



(60)

Renard[33] have used a variation of the reaction of thiobenzamides with hydrazine. They reported an excellent yield of dihydro-*s*-tetrazines by the reaction of the morpholide (LXIX) with hydrazine (eq. 61). Presumably

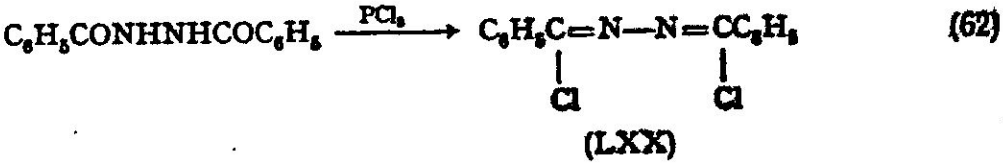


(61)

(LXIX)

LXIX is the *S*-methiodide of thiobenzmorpholide, although the published report does not make this completely clear.

Stollé[148,150,159,160] reported the synthesis of 3,6-diaryl-1,2-dihydro-*s*-tetrazines by the reaction of benzoyl chloride azine (LXX) and substituted aroyl chloride azines with hydrazine (6). The aroyl chloride azines were obtained by treatment of hydrazides with phosphorous pentachloride (eq. 62). Treatment of LXX with hydrazine gave a 28% yield of 3,6-diphenyl-1,2-dihydro-*s*-tetrazine as well as a 28% yield of 3,6-diphenyl-*s*-tetrazine.



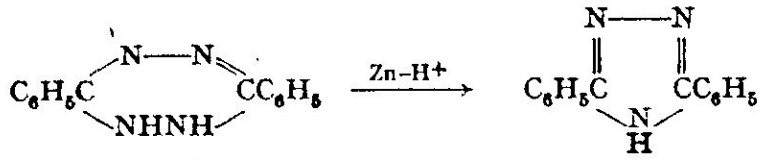
(62)

(LXX)

The melting points reported for the 3,6-diaryl-1,2-dihydro-*s*-tetrazines are very frequently the same as those of the co 3,6-diaryl-*s*-tetrazines. The usual melting point reported for phenyl-1,2-dihydro-*s*-tetrazine is 192°, which is the melting point 3,6-diphenyl-*s*-tetrazine. It was Pinner's opinion that the tetrazines were oxidized to the *s*-tetrazine as they were heated and final melting point was that of the *s*-tetrazine. Franzen and reported a melting point of 160° for 3,6-diphenyl-1,2

and this is probably the correct one. The 3,6-diaryl-1,2-dihydro-*s*-tetrazines are too weakly basic to be soluble in dilute acids. They are soluble in acetone and alcohol but insoluble in benzene and water. 1,2-Dihydro-*s*-tetrazines can frequently be separated from the corresponding *s*-tetrazine by washing away the *s*-tetrazines with benzene.

The characteristic reaction of the 3,6-diaryl-1,2-dihydro-*s*-tetrazines is their easy oxidation to *s*-tetrazines. Heating the 3,6-diaryl-1,2-dihydro-*s*-tetrazines with 25% hydrochloric acid[107,108,111] isomerizes them to what was at first believed to be the 1,4-dihydro-*s*-tetrazines but has since been shown to be 4-amino-3,5-diaryl-1,2,4,4*H*-triazoles. In some cases 3,5-diaryl-1,3,4-oxadiazoles are also obtained. Reducing agents such as zinc in acetic acid also give a triazole but in this case the 4-amino group is removed (eq. 63). 3,6-Diaryl-1,2-dihydro-*s*-tetrazines

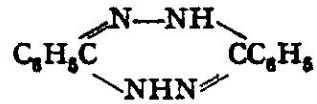


(63)

are readily acylated with acetic anhydride or benzoyl chloride to form both mono and diacyl derivatives. Although 3,6-diphenyl-1,2-dihydro-*s*-tetrazine is very weakly basic, it has been reported[108] to form a dimethiodide melting with decomposition at 128°. 3,6-Di(*m*-tolyl)-1,2-dihydro-*s*-tetrazine has been heated under pressure with hydrochloric acid to give *m*-toluic acid and hydrazine.

Pinner[107] found that in addition to 3,6-diphenyl-1,2-dihydro-*s*-tetrazine several other products could be isolated from the reaction of ethyl benzimidate with hydrazine. Among these was a white crystalline solid, m.p. 258°, for which Pinner proposed the name *benzenylimino-nitrile* and the formula LXXI. Somewhat later the same product[108,111]

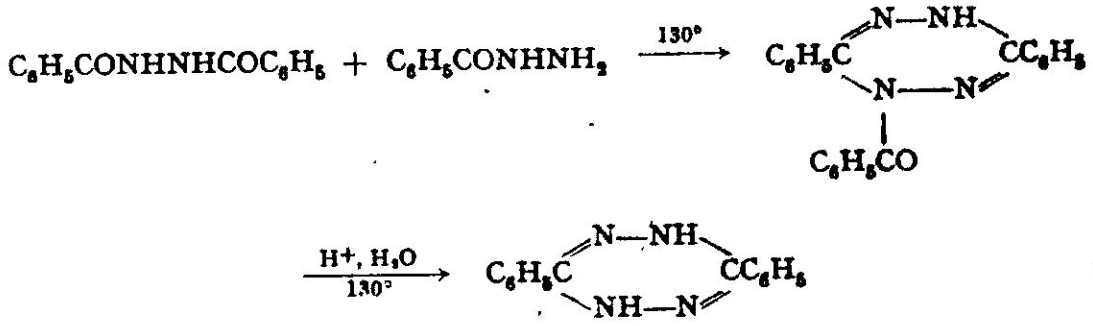
(LXXI)



(LXXII)

was obtained by heating 3,6-diphenyl-1,2-dihydro-*s*-tetrazine with acid. It was realized that it was an isomer of the 1,2-dihydro-*s*-tetrazine; it was therefore called *diphenylisodihydrotetrazine* and the 1,4-dihydro

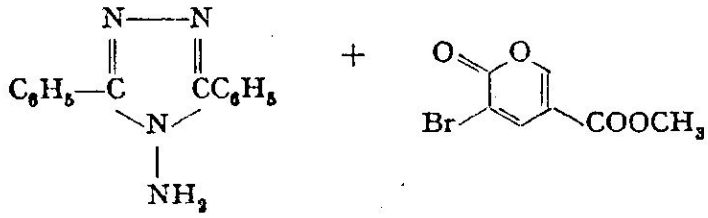
formula LXXII was proposed for it. Curtius[41,53] obtained the same compound by the reaction of benzonitrile with hydrazine hydrate at 150°. It was first called *hydrazicarbamine* by Curtius but this name was soon dropped. Silberrad[143] heated benzhydrazide at 260° and got, in addition to numerous other products, a small amount of *diphenylisodihydrotetrazine*. Heating benzhydrazide with hydrazine at 230° gave very good yields of the same product. Stollé[148–150,159] synthesized *diphenylisodihydrotetrazine* by several methods. One of these was the reaction of benzhydrazide with hydrazine and a second was isomerization of the 1,2-dihydro-*s*-tetrazine with acid. A new method was by condensation of dibenzhydrazide with benzhydrazide to give the benzoyl derivative of *diphenylisodihydrotetrazine* from which the benzoyl group was removed by hydrolysis (eq. 64). Stollé found that 1,2-



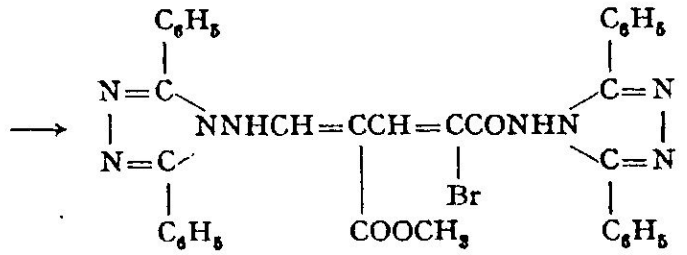
(64)

dihydro-*s*-tetrazines were readily oxidized to *s*-tetrazines, but the 1,4-dihydro-*s*-tetrazines were not. He suggested that what were believed to be 1,4-dihydro-*s*-tetrazines were 4-amino-1,2,4,4*H*-triazoles. This view was supported by the fact that the supposed 3,6-diphenyl-1,4-dihydro-*s*-tetrazines formed a benzaldehyde derivative in contrast to the 1,2-dihydro-*s*-tetrazines, and that the so-called 1,4-dihydro compounds were much more basic than the 1,2-dihydro ones. Pinner[110] had already considered the possibility that 1,4-dihydro-*s*-tetrazines might be triazoles but had rejected it. Stollé apparently did not take his own suggestions to heart since in a later paper[159] he still re the 1,4-dihydro-*s*-tetrazine formulas for what he had previously posed were triazoles. Furthermore he defended the tetrazine structure a polemic[151] attempting to refute Bülow's arguments. However, a time later Bülow and Weber[23] showed the compound believed to have structure LXXII actually was 3,5-diphenyl-4-amino-1,2,4,

(LXXIII). This was done by showing that methyl bromocumalinate (LXXIV) reacted with the supposed 3,6-diphenyl-1,4-dihydro-*s*-



(LXXIII) (LXXIV)

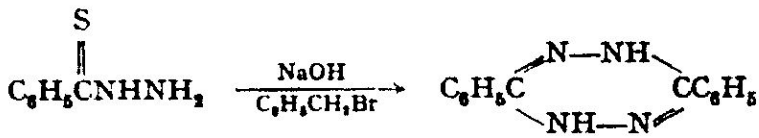


(65)

tetrazine as it had been shown to do with aminotriazoles (eq. 65). The structure LXXIII was accepted by later workers in the field.

The preparation of 3,6-di(*p*-tolyl)-1,4-dihydro-*s*-tetrazine and 3,6-bis(*p*-bromophenyl)-1,4-dihydro-*s*-tetrazine by isomerization of the corresponding 1,2-dihydro-*s*-tetrazines with acid has been reported.[109, 113, 150, 160] In view of the findings concerning the acid isomerization of 3,6-diphenyl-1,2-dihydro-*s*-tetrazine, it is very likely that these compounds also are 3,5-diaryl-4-amino-1,2,4,4*H*-triazoles.

Holmberg[79] has prepared what he believes to be 3,6-diphenyl-1,4-dihydro-*s*-tetrazine in 11% yield from thiobenzhydrazide (eq. 66).

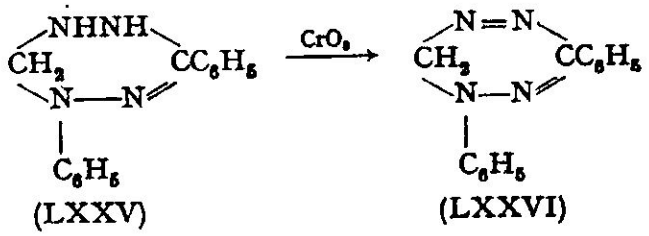


(66)

There was no rigorous proof of structure, and the properties are very similar to those reported in most cases for the 1,2-dihydro isomer. The reaction used for preparation is very similar to that used by Chabrier and Renard (61) for the preparation of 3,6-diphenyl-1,2-dihydro-*s*-tetrazine. Consequently there is a strong possibility that Holmberg may have obtained the 1,2-isomer.

The synthesis of 1,3-diphenyl-1,6-dihydro-*s*-tetrazine (LXXVI) was carried out by Ponzio and Peroglio[120] by chromic oxide oxidation

of 1,3-diphenyl-1,4,5,6-tetrahydro-*s*-tetrazine (LXXV). The compound LXXVI crystallizes in prisms, m.p. 238–239°. 1-Phenyl-3-(*p*-tolyl)1,6-

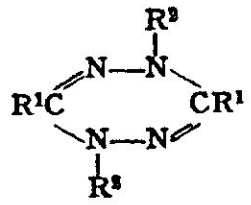


(LXXV) (LXXVI) (67)

dihydro-*s*-tetrazine, m.p. 239°, has been synthesized in the same way starting with the corresponding tetrahydro-*s*-tetrazine.

The 1,4-diaryl-1,4-dihydro-*s*-tetrazines are listed in Table V-5. Ruhemann[130–132, 135] first reported the preparation of 1,4-diaryl-1,4-dihydro-*s*-tetrazines by reaction of aryl hydrazines with potassium

TABLE V-5. Polyphenyl-1,4-dihydro-*s*-tetrazines

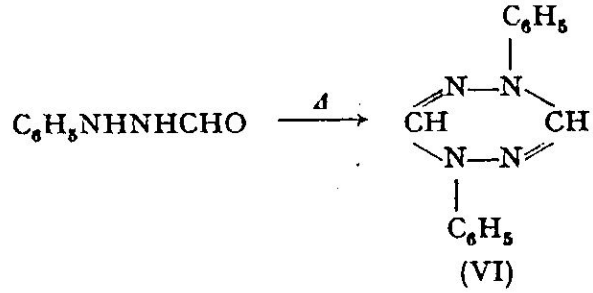


R^1	R^2	M.p., °C.	Color and crystal form	Ref.
C_6H_5	H	190–192	Yellow needles	79
H	C_6H_5	189	Yellow plates	7
H	*p*-$CH_3C_6H_4$	102	Yellow plates	7
H[a]	*o*-$CH_3C_6H_4$	141		132
H[a]	*p*-$(CH_3)_2CHC_6H_4$	234		132
H	*p*-ClC_6H_4	185.5	Yellow plates	7
C_6H_5	C_6H_5	203	Golden yellow needles	9
C_6H_5	*p*-BrC_6H_4	265	Yellow prisms	35
C_6H_5	2,4-$Br_2C_6H_3$	255	Pale yellow leaflets	35
C_6H_5	*p*-$NO_2C_6H_4$	300, 305, 312	Red needles	9, 11, 114, 115
p-$CH_3OC_6H_4$	C_6H_5	173.5	Orange yellow flat prisms	10, 12
p-$CH_3OC_6H_4$	*p*-BrC_6H_4	150		162

[a] It is uncertain as to whether or not these compounds have the structure.

hydroxide and chloroform. The compound later thought to be diphenyl-1,4-dihydro-*s*-tetrazine was called *carbophenylhydrazine*.

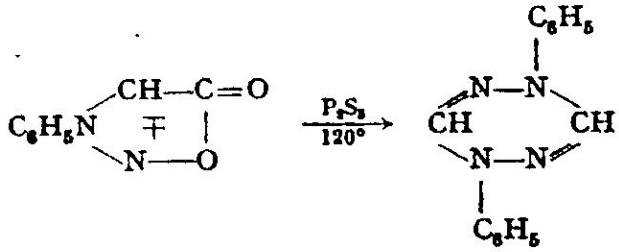
Somewhat later Pellizzari[98] and Bamberger[8] prepared the same compound by heating formylphenylhydrazine and proposed the 1,4-dihydro-*s*-tetrazine formula (VI).



(68)

(VI)

Baker, Ollis, and Poole[7] have prepared 1,4-diphenyl- and 1,4-di(*p*-tolyl)-1,4-dihydro-*s*-tetrazine and found that these compounds were different from those reported by Ruhemann and others to have these structures. Baker and colleagues first prepared 1,4-diphenyl-1,4-dihydro-*s*-tetrazine by treating *N*-phenylsydnone with phosphorous pentasulfide (eq. 69). The yield was 27%. A second method of prepara-

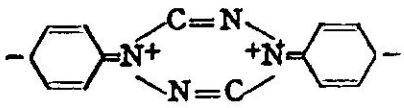


(69)

tion was the action of sodium methoxide in cold methanol on thioformylphenylhydrazine (eq. 7). This reaction gave a 43% yield. Preparation of VI by treatment of formylphenylhydrazine with phosphorous pentasulfide gave only 5% yield. 1,4-Di(*p*-tolyl)- and 1,4-bis(*p*-chlorophenyl)-1,4-dihydro-*s*-tetrazines were prepared by treatment of the appropriate thioformylarylhydrazine with sodium methoxide. The structures of these products were assigned on the basis of the following facts. Hydrolysis of 1,4-diphenyl-1,4-dihydro-*s*-tetrazine with hydrochloric acid gave two molar equivalents of phenylhydrazine and two of formic acid. The 1,4-dihydro-*s*-tetrazines were not basic and formed no acetyl derivatives. Their dipole moments were essentially zero.[63] There was a great similarity in physical properties between these compounds and the 1,3,4,6-tetraaryl-1,4-dihydro-*s*-tetrazines prepared by Bamberger and Grob[9] and Chattaway and Walker.[35]

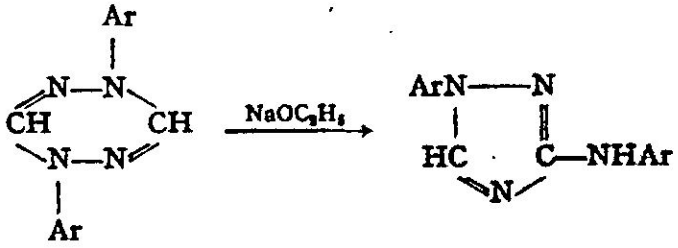
Ruhemann[130, 131] reported, in addition to compounds also prepared by Baker and co-workers the synthesis of 1,4-di(*o*-tolyl)- and 1,4-bis(*p*-isopropylphenyl)-1,4-dihydro-*s*-tetrazine. These compounds are listed in Table V-5, but since Ruhemann's other compounds did not have the structure proposed for them it is probable that these are not 1,4-diaryl-1,4-dihydro-*s*-tetrazines.

The 1,4-diaryl-1,4-dihydro-*s*-tetrazines are characterized by absorption maxima at 290–300 mμ and a bright yellow color. This indicates interaction of the phenyl group with the ring as shown in LXXVII and a planar structure with no *cis-isomerism*. They are soluble in chloroform but insoluble in petroleum ether.



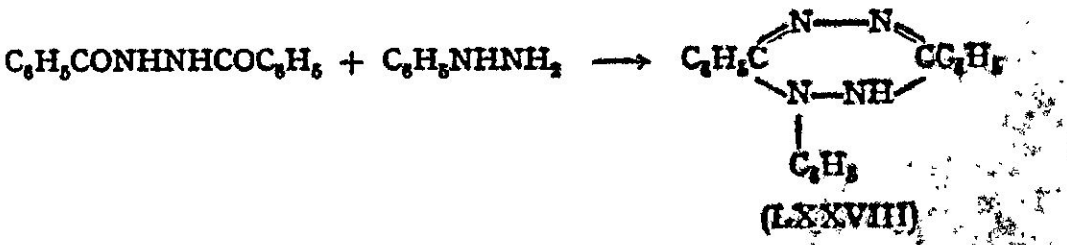
(LXXVII)

Treatment of these 1,4-dihydro-*s*-tetrazines with sodium ethoxide in hot alcohol causes isomerization to 1-aryl-3-arylamino-1,2,4,1*H*-triazoles (eq. 70) with rupture of an N–N bond. This is in contrast to the



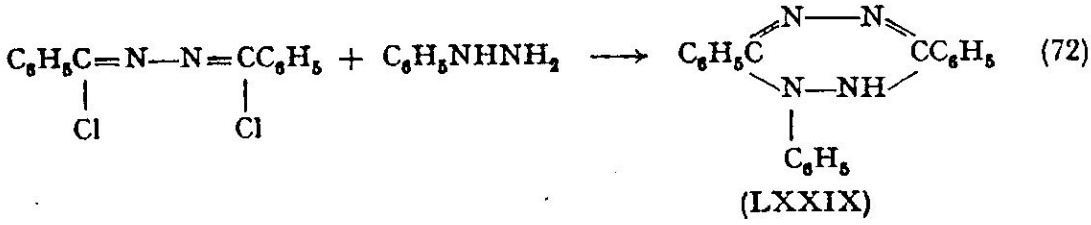
the 3,6-diaryl-1,2-dihydro-*s*-tetrazines, which isomerize to 4,3,5-diaryl-1,2,4*H*-triazoles with rupture of a C–N bond.

Stollé[150, 152, 159, 160] has synthesized 1',3,6-triphenyl-1,2 tetrazine (LXXVIII) by two methods. In one method dibenzh and phenylhydrazine were heated together in boiling alcohol (eq. 7



(LXXVIII)

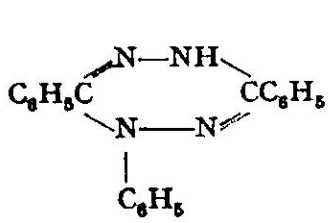
The second method of preparation was the reaction of benzoyl chloride azine (LXX) with phenylhydrazine (eq. 72). In this case LXXIX was



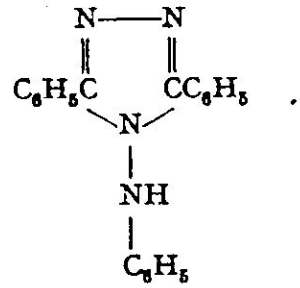
(72)

(LXXIX)

obtained as its hydrochloride, and a considerable amount of an isomeric compound believed to be LXXX was obtained. 1,3,6-Triphenyl-1,2-



(LXXX)



(LXXXI)

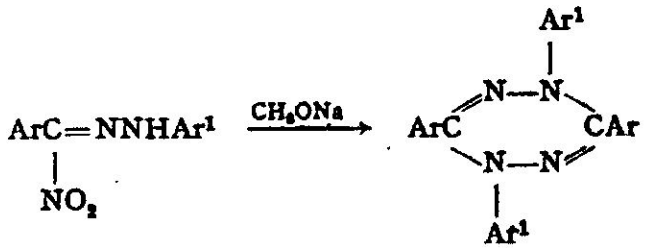
dihydro-*s*-tetrazine crystallizes from alcohol in golden yellow needles. Heating it with mineral acid isomerizes it to a compound identical with the one thought to have structure LXXX. Reaction of LXXIX with nitrous acid gives 2,5-diphenyl-1,3,4-oxadiazole. An acetyl derivative is obtained with acetic anhydride. 1,3,6-Triphenyl-1,2-dihydro-*s*-tetrazine is slightly basic forming a hydrochloride, which is decomposed by boiling water.

Stollé[153] investigated the possibility that the compound thought to have structure LXXIX might actually have a triazole structure LXXXI. He found that the acetyl derivative of LXXIX melted at 186° and the isomeric acetyl derivative of 4-anilino-3,5-diphenyl-1,2,4,4*H*-triazole (LXXXI) melted at 180°. It was Stollé conclusion that the two were identical. However, this is unlikely in view of the following facts. In both of the methods of preparation of 1,3,6-triphenyl-1,2-dihydro-*s*-tetrazine[150, 159] a second product was obtained to which was assigned the structure 1,3,6-triphenyl-1,4-dihydro-*s*-tetrazine (LXXX). This is a white solid melting at 263°. The 1,2-dihydro compound LXXIX is readily isomerized by acid to the same compound. Two characteristic properties of the 1,2-dihydro-*s*-tetrazines are that they are relatively

low melting compounds and readily isomerize with acid to high melting triazoles. These considerations make it probable that the compound thought to have structure LXXX is 4-anilino-3,5-diphenyl-1,2,4,4*H*-triazole (LXXXI). Consequently the other product (LXXXIX) obtained by the reaction of benzoyl chloride azine with phenylhydrazine could not be LXXXI.

Stollé and Weindel[150, 160] have reported the preparation of 3,6-bis(*p*-bromophenyl)-1-phenyl-1,2-dihydro-*s*-tetrazine by both of the methods used for 1,3,6-triphenyl-1,2-dihydro-*s*-tetrazine but using the appropriate *p*-bromophenyl compounds. 3,6-Bis(*p*-bromophenyl)-1-phenyl-1,2-dihydro-*s*-tetrazine is readily isomerized by acid to what was believed to be the corresponding 1,4-dihydro compound but which is undoubtedly 4-anilino-3,5-bis(*p*-bromophenyl)-1,2,4,4*H*-triazole.

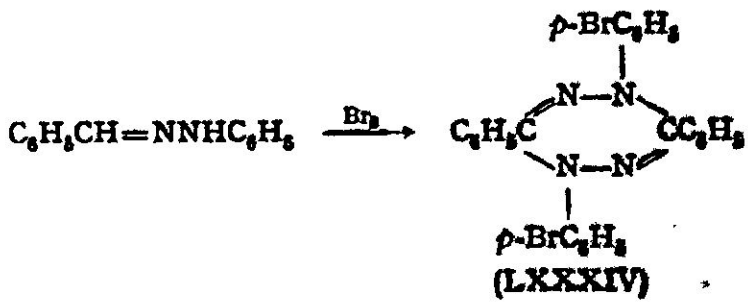
Bamberger and co-workers[9, 10, 12] and Ponzio[114, 115] have synthesized 1,3,4,6-tetraaryl-1,4-dihydro-*s*-tetrazines (Table V-5) by treatment of 1-(α-nitrobenzylidene)-2-phenylhydrazine or analogs (LXXXII) with sodium methoxide in methanol (eq. 73). The nitro compounds (LXXXII)



(73)

(LXXXII) (LXXXIII)

were prepared by nitrosation of the arylhydrazones with nitrous acid amyl nitrite followed by oxidation with nitrogen trioxide. The only yield reported for this method of *s*-tetrazine formation was 10–15 for 1,4-bis(*p*-nitrophenyl)-3,6-diphenyl-1,4-dihydro-*s*-tetrazine.[11] pounds of the type of LXXXIII have been prepared by the action halogens on arylaldehyde arylhydrazones (eq. 74). Bamberger and

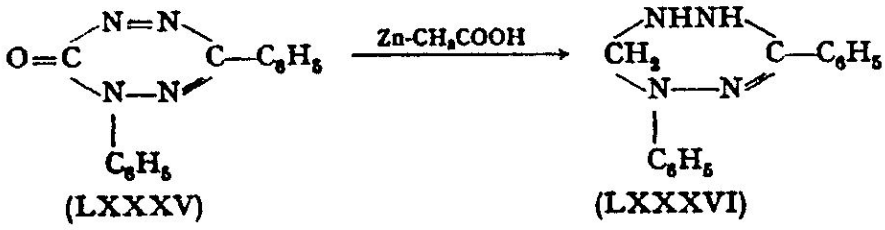


(LXXXIV)

used iodine in this reaction while Chattaway and Walker[35] and Vanghelovitch[162] used bromine. Chattaway and Walker used acetic acid as solvent and obtained a 50% yield. When bromine was used, bromination frequently occurred in the para position of the aromatic ring attached to the nitrogen. With iodine this did not occur. LXXXIV can also be obtained by action of bromine on benzaldehyde *p*-bromophenylhydrazone or on benzoyl chloride phenylhydrazone. Starting with benzaldehyde 2,4-dibromophenylhydrazone, 1,4-bis(2,4-dibromophenyl)-3,6-diphenyl-1,4-dihydro-*s*-tetrazine was obtained. Vanghelovitch found that sunlight was necessary to cause cyclization in this reaction. Bamberger and Grob[9] have nitrated 1,3,4,6-tetraphenyl-1,4-dihydro-*s*-tetrazine to obtain a dinitro derivative of unknown structure. This dinitro compound crystallizes in red needles, m.p. 299°.

1,3,4,6-Tetraaryl-1,4-dihydro-*s*-tetrazines are soluble in benzene, acetone, and chloroform. Reduction of 1,3,4,6-tetraphenyl-1,4-dihydro-*s*-tetrazine by means of zinc dust distillation[9] gave benzonitrile and aniline. The same treatment of 1,4-bis(*p*-bromophenyl)-3,6-diphenyl-1,4-dihydro-*s*-tetrazine[35] also gave benzonitrile while reductions with zinc and hydrochloric acid[35] gave *p*-bromoaniline. These reductions were considered to be adequate proof of structure for compounds of this type.

Ponzio and Perolio[120] have synthesized 1,3-diphenyl-1,4,5,6-tetrahydro-*s*-tetrazine (LXXXVI) by reduction of 1,3-diphenyl-6-*s*-tetrazineone (LXXXV) with zinc and acetic acid (eq. 75). The product



(LXXXV) (LXXXVI) (75)

melts at 86°. The same type of synthesis was used to prepare 1-phenyl-3-(*p*-tolyl)-1,4,5,6-tetrahydro-*s*-tetrazine, m.p. 104°.

Staudinger and Meyer[147] have developed an interesting tetrahydro-*s*-tetrazine synthesis by which they have prepared 3,3,6,6-tetraphenyl-1,2,3,6-tetrahydro-*s*-tetrazine (LXXXVIII). Diazodiphenylmethane and triethylphosphine were allowed to react to give an intermediate

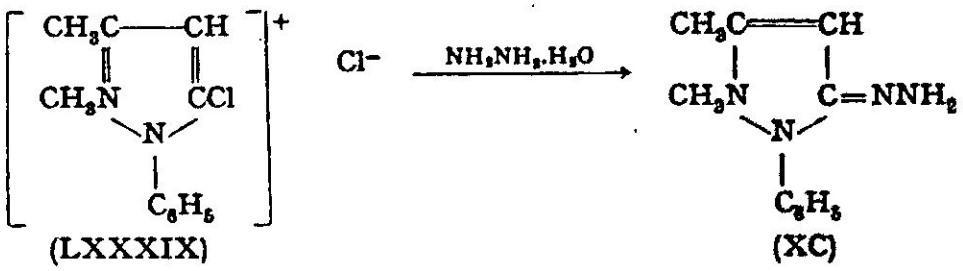
(LXXXVII) which lost triethyl phosphine upon addition of mois benzene or chloroform and formed LXXXVIII (eq. 76). The product is a

$$(C_6H_5)_2CN_2 + (C_2H_5)_3P \longrightarrow (C_6H_5)_2C{=}N{-}N{=}P(C_2H_5)_3$$
(LXXXVII)

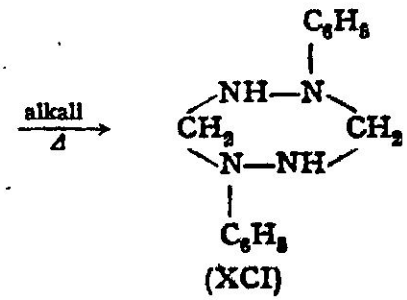
$$\longrightarrow (C_6H_5)_2C\begin{matrix}N{=}N\\ \diagdown\quad\diagup\\ NHNH\end{matrix}C(C_6H_5)_2 \qquad (76)$$
(LXXXVIII)

yellow solid soluble in benzene and chloroform, melting at 204.5–205.5°; above this temperature ammonia is evolved. The only proof of structure was analysis.

The synthesis of 1,4-diphenylhexahydro-*s*-tetrazine (XCI) h been claimed by Thielepape and Spreckelsen[161] by an unusual series reactions shown in equation 77. The methochloride of 5-chloro-methyl-1-phenylpyrazole (LXXXIX) was treated with hydrazine hydrate to give the hydrazone of 1-phenyl-2,3-dimethyl-5-pyrazolone (XC), which then forms the hexahydro-*s*-tetrazine under the influe of heat and alkali. The only proof of structure was analysis. product is a white solid, m.p. 130°. It forms a monopicrate, dec. 195°,



(LXXXIX) (XC)

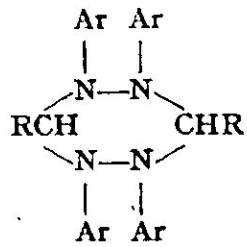


(XCI)

monobenzoyl derivative, m.p. 90°, and a dimethiodide melting at It is neutral to litmus, dissolves in dilute acid, and reduces solution.

1,2,4,5-Tetraphenylhexahydro-*s*-tetrazine has been synthesized by reaction of formaldehyde with diphenylhydrazine[14] (equation 8, R = H, R′ and R″ = C_6H_5). It crystallizes from benzene or ethanol in white plates, m.p. 200°. Reaction with nitrating mixture gives a tetranitroazobenzene.

A series of 1,2,4,5-tetraarylhexahydro-*s*-tetrazines was prepared by Rassow and co-workers[126, 128] by reaction of formaldehyde or acetaldehyde with hydrazobenzenes (eq. 8). The reaction of formaldehyde with *p*-hydrazotoluene, *o*-hydrazotoluene, and *m*-hydrazotoluene gives XCII, R = H, and Ar groups are, respectively: *p*-tolyl, m.p. 213°;

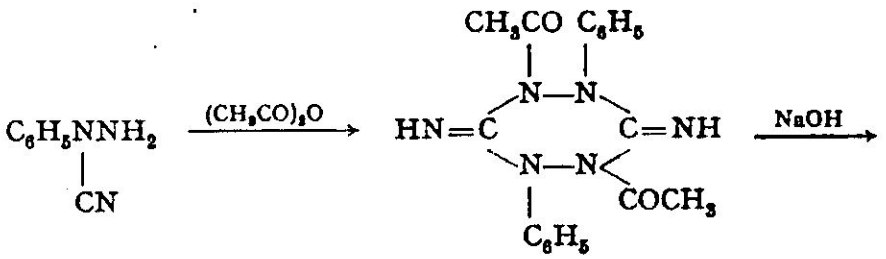


(XCII)

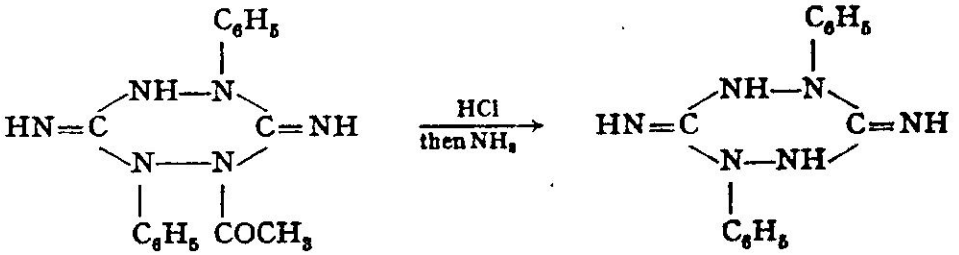
o-tolyl, m.p. 187°; and *m*-tolyl, m.p. 166°. Formaldehyde with phenyl *p*-tolylhydrazine gives a compound, m.p. 191–193°, which might be either 1,4-diphenyl-2,5-di(*p*-tolyl)- or 1,5-diphenyl-2,4-di(*p*-tolyl)-hexahydro-*s*-tetrazine. Acetaldehyde and *p*-hydrazotoluene reacted to give a compound melting at 150° which has structure XCII (R = CH_3, Ar = *p*-tolyl). These reactions were run in alcohol. The yields reported were 30–75%. All the products obtained were white. Attempts to prepare hexahydro-*s*-tetrazines from *p*-dinitrohydrazobenzene and 2,4,6-hexanitrohydrazobenzene were unsuccessful; the hydrazines would not react with formaldehyde.

Aryl and Polyaryl Derivatives with Functional Groups Substituted on the Hydro-s-tetrazine Ring. 1,4-Diphenyltetrahydro-3,6-*s*-tetrazenediimine (XCVIa) or its isomer, 3,6-diamino-1,4-diphenyl-1,4-dihydro-*s*-tetrazine (XCVIb) has been synthesized by Pellizzari.[101] 1-Cyano-1-phenylhydrazine (XCIII) was allowed to stand at room temperature with acetic anhydride, then heated to 100° for a short time. The first product was a diacetyl derivative (XCIV), m.p. 268°. Hydrolysis of this with sodium hydroxide gave a monoacetyl compound (XCV), m.p. 228°. This was heated with dilute hydrochloric acid to form a

hydrochloride, which was converted with ammonia to the free b
XCVIa or XCVIb, m.p. 198°. Either XCVIa or XCVIb reacts wi

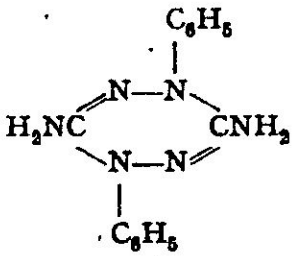


(XCIII) (XCIV)



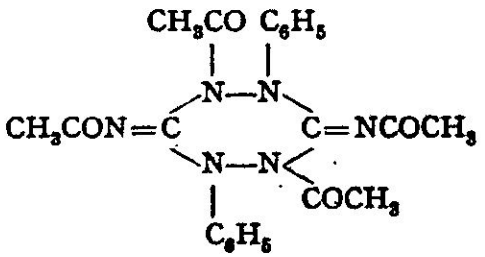
(XCV) (XCVIa)

or

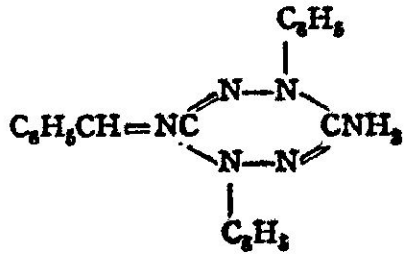


(XCVIb)

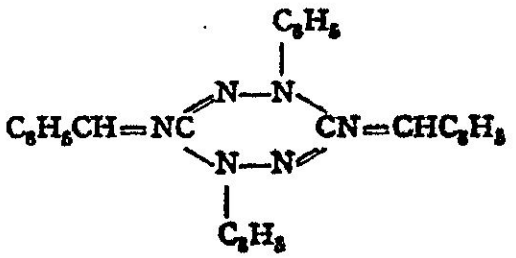
acetic anhydride to give the tetraacetyl derivative XCVII, which
at 188–189°. The compound XCVIb reacts with benzaldehyde to



(XCVII)



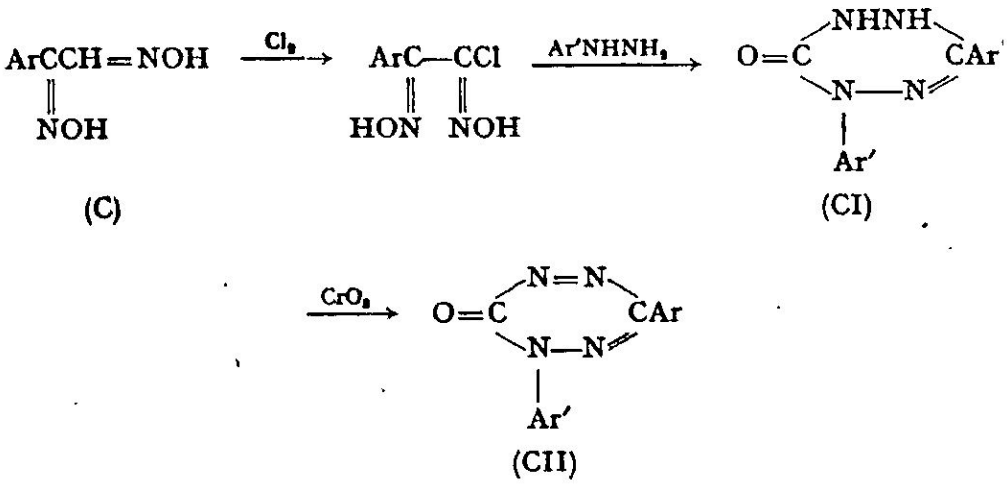
(XCVIII)



(XCIX)

the monobenzylidene derivative XCVIII, m.p. 183°, and the dibenzylidene derivative XCIX, m.p. 150°.

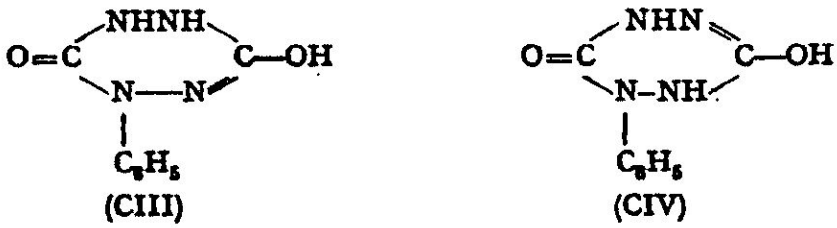
A series of 1,3-diaryl-6-*s*-tetrazinones and dihydro-6-*s*-tetrazinones[120] have been prepared by a rather unusual reaction starting with the dioximes of arylglyoxals (C). The reactions are shown in equation 79. When both Ar and Ar′ are phenyl, the 6-*s*-tetrazinone CII crystallizes in white prisms and melts at 264° while the dihydro-6-*s*-tetrazinone



(79)

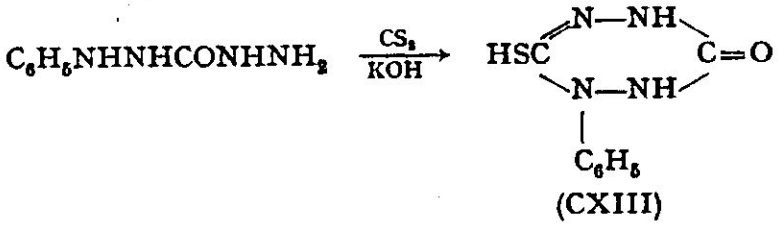
CI melts at 174–175°. The dihydro-6-*s*-tetrazinone forms a monoacetate, m.p. 161°, and a diacetate melting at 174° The products obtained when Ar is *p*-tolyl and Ar′ is phenyl are 1-phenyl-3-(*p*-tolyl)-6-*s*-tetrazinone, m.p. 265°, and 1-phenyl-3-(*p*-tolyl)-4,5-dihydro-6-*s*-tetrazinone, m.p. 190–191°. The latter compound forms a diacetyl derivative, m.p. 170°. Also obtained by this reaction was 1-(*p*-bromophenyl)-3-phenyl-4,5-dihydro-6-*s*-tetrazinone, m.p. 189–190°, and its diacetyl derivatives, m.p. 169–170°. Reduction of compounds of type CII with zinc and acetic acid removes the oxygen and forms tetrahydro-*s*-tetrazines (75).

Phenylurazine was first reported to have been synthesized by Busch and Heinrichs.[28] The structures proposed for it were CIII or



CIV. The triacetyl derivative, a benzylidene derivative and a methyl ether were prepared. Somewhat later Busch showed that phenyl-

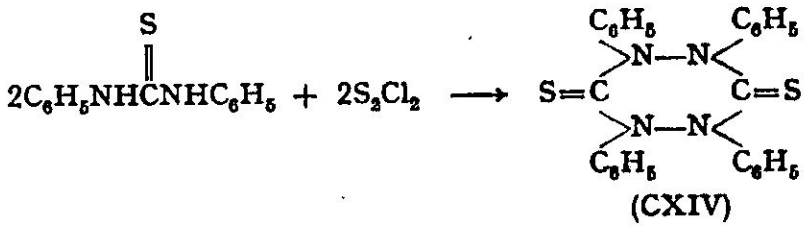
and potassium hydroxide gives 3-oxo-1-phenyl-1,2,3,4-tetrahydro-6-*s*-tetrazinethiol (CXIII) melting at 206°.[72]



(84)

(CXIII)

Naik[96] has reported the synthesis of 1,2,4,5-tetraphenyltetrahydro-3,6-*s*-tetrazinedithione (CXIV) by treatment of *N,N'*-diphenylthiourea with sulfur monochloride (eq. 85) The product crystallizes in prisms melting at 160°. The only proof of structure was by the analyses. These

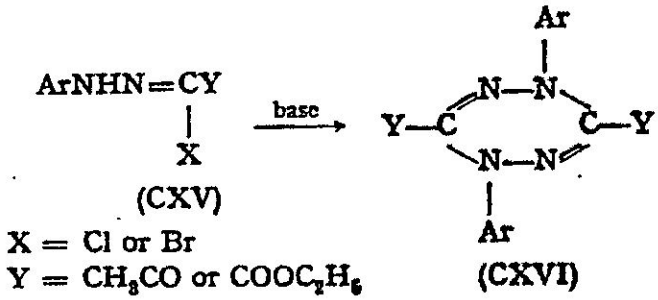


(85)

(CXIV)

were not very good but they were close enough to the theoretical values to make the proposed structure seem likely.

Several compounds believed to be 1,4-diaryl-1,4-dihydrotetrazines have been synthesized by Bowack and Lapworth,[16] Bülo and Neber,[21 22] and Neber and Wörner[97] by treatment of haloglyoxy and pyruvoyl chloride phenylhydrazones of the type CXV with



(CXV)

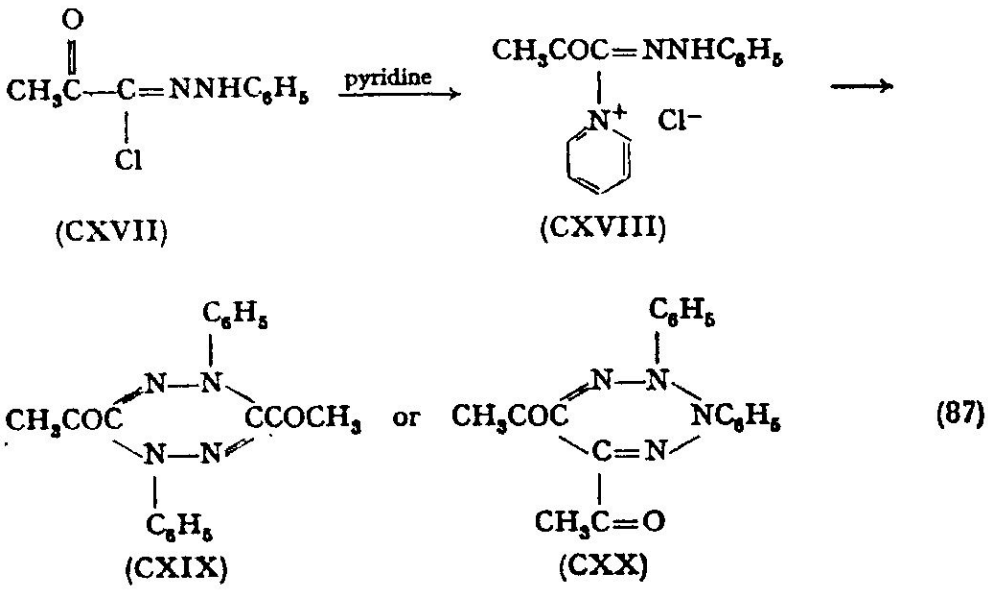
X = Cl or Br

Y = CH_3CO or $COOC_2H_5$

(CXVI)

In the work of Bowack and Lapworth the compounds used of CXV were those in which X = Br, Y = $COOC_2H_5$, and Ar was or *p*-tolyl. The bases used were hydroxides and carbonates of the metals. The structures proposed for the products were diethyl 1 diphenyl and diethyl 1,4-di(*p*-tolyl)-1,4-dihydro-3,6-*s*-tetrazine carboxylate (CXVI, Ar = C_6H_5 or *p*-$CH_3C_6H_4$ and Y =

Both compounds crystallize from ethyl acetate to form deep red crystals. The diphenyl compound melts at 145–146° while the di(*p*-tolyl) compound melts at 158–159°. Hydrolysis of the diphenyl compound in methanolic KOH gives 1,4-diphenyl-1,4-dihydro-3-*s*-tetrazinecarboxylic acid, which is yellow, m.p. 206–207° (dec.). Baker and co-workers report that the two dicarbethoxy compounds have ultraviolet absorption maxima at 375 mμ. They believe that this absorption peak is not consistent with these proposed structures. Bülow and Neber[21,22] have used this same reaction to prepare compounds of structure CXVI, Ar $= 2,4\text{-}Cl_2C_6H_3$ and Y $= COOC_2H_5$. The halogen in their starting material was chlorine. They used potassium ethoxide and potassium cyanide as bases. The product was believed to be diethyl 1,4-bis(2,4-dichlorophenyl)-1,4-dihydro-3,6-*s*-tetrazinedicarboxylate. This compound crystallizes from acetic acid in yellow needles melting at 196°. Since the method of synthesis used for this compound is essentially the same as that used by Bowack and Lapworth, it is likely that, if these latter workers' products are not 1,4-dihydro-*s*-tetrazines, neither is Bülow's product. Neber and Wörner[97] have used an organic base, pyridine, on pyruvoyl chloride phenylhydrazone (CXVII) to prepare what they believed to be 3,6-diacetyl-1,4-diphenyl-1,4-dihydro-*s*-tetrazine (CXIX). The first product obtained was believed to be the

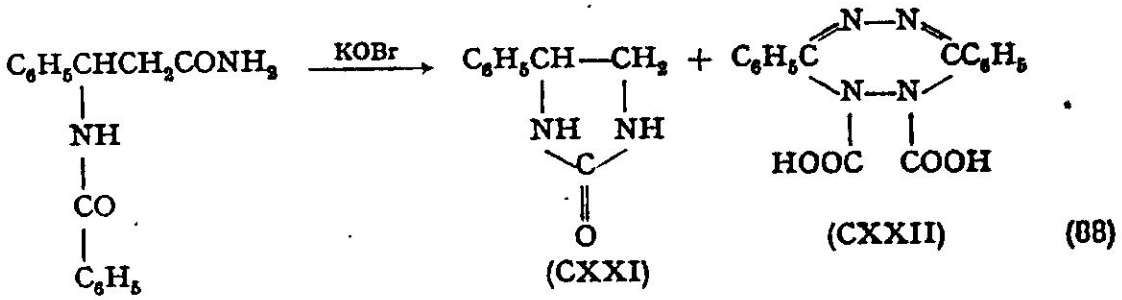


(CXVII) (CXVIII) (CXIX) (CXX) (87)

inner salt CXVIII. This, in boiling alcohol, forms CXIX and pyridine. CXIX crystallizes in deep red leaflets, m.p. 163°, from benzene and

ligroin. The isomeric tetrazine CXX was also considered as a possibility but CXIX was preferred. In view of Baker's objections to the structures proposed by Bowack and Lapworth for their products and the similarity of their products to the others discussed here, it cannot be said with certainty that any of these compounds are 1,4-dihydro-*s*-tetrazines. It may be possible that they are all isomeric tetrazines similar to CXX. However, methods of synthesis would make the CXVI structures appear more likely.

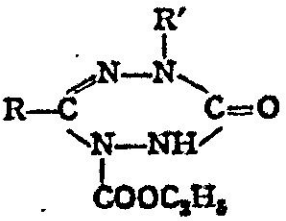
A compound believed to be 3,6-diphenyl-1,2-dihydro-1,2-*s*-tetrazinedicarboxylic acid (CXXII)[129] has been isolated in 29% yield from treatment of β-benzoylaminohydrocinnamide with potassium hypobromite (eq. 88). The principal product was 4-phenyl-2-imidazolidone



(88)

(CXXI). The compound thought to have structure CXXII is acidic with a neutral equivalent of 165. It melts at 137–138°. Other acylaminohydrocinnamides also react with hypobromite to form 2-imidazolidones and CXXII. It is not clear how a compound of structure CXXII would be formed from a β-aminoamide and proof of the structure CXXII was not very extensive. Consequently, the proposed structure must be considered as not fully proved.

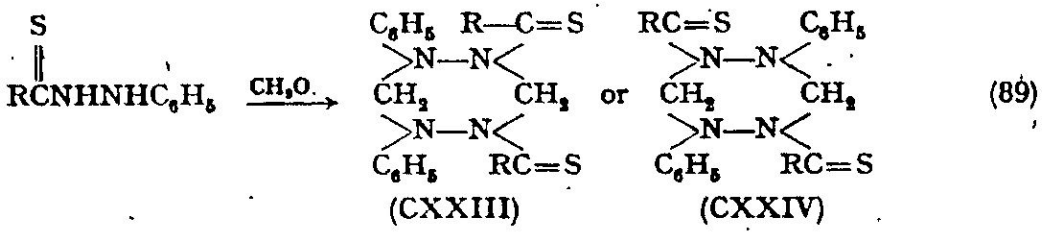
TABLE V-6. Ethyl 4,6-Diaryl-3-oxo-1,2,3,4-tetrahydro-1-*s*-tetrazinecarboxylates



R	R'	M.p., °C.
C_6H_5	C_6H_5	149–150
m-$NO_2C_6H_4$	C_6H_5	179–180
p-HOC_6H_4	C_6H_5	184–185
C_6H_5	*o*-$CH_3C_6H_4$	93–94
o-HOC_6H_4	*o*-$CH_3C_6H_4$	178

A series of ethyl 4,6-diaryl-3-oxo-1,2,3,4-tetrahydro-1-*s*-tetrazinecarboxylates (Table V-6) has been prepared by Busch and co-workers.[30] Arylhydrazones of aromatic aldehydes were allowed to react with diethyl azodicarboxylate to form tetrasubstituted tetrazanes of the type LX (eq. 47). These were then rearranged to the tetrahydro-*s*-tetrazines. These compounds all crystallize in white needles from alcohol. They probably exist in the enolic form as they are soluble in alkali.

Wuyts and Lacourt[169] have synthesized 2,4- or 2,5-bis(thioacyl)-1,4- or 1,5-diphenylhexahydro-*s*-tetrazines (CXXIII or CXXIV) by reaction of thioacyl derivatives of phenylhydrazine with paraformaldehyde (eq. 89). Equimolar amounts of the reagents were heated in alcohol. These structures were assigned on the basis of the known



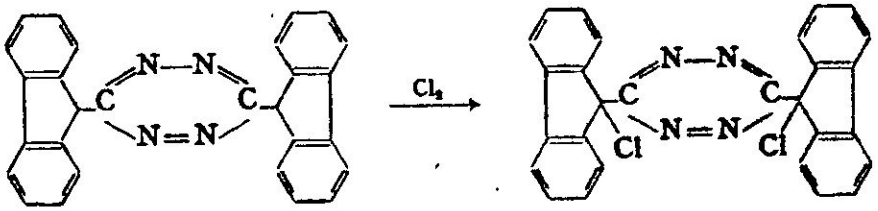
(89)

(CXXIII) (CXXIV)

reaction of formaldehyde with hydrazines to give hexahydro-*s*-tetrazines and from a consideration of molecular weights and analytical data. Structure CXXIII was preferred on the basis that only one active hydrogen was present and the hydrogen atoms in CXXIV would be expected to be equivalent. This argument is not well founded, as the presence of active hydrogen in the product would argue against either of the proposed structures. The compounds obtained were: R = CH_3, m.p. 186°; R = C_6H_5, m.p. 187°; R = *p*-$CH_3C_6H_4$, m.p. 190°; R = $C_6H_5CH_2$, m.p. 172°; R = α-$C_{10}H_7$, m.p. 200°. These compounds are soluble in chloroform. The bis(thiobenzoyl)diphenylhexahydro-*s*-tetrazine reacts with iodine in chloroform to give a blue decaiodo compound melting at 195°. Solution of this compound in acetone and precipitation with ether converted it to a hexaiodo derivative melting at 225°.

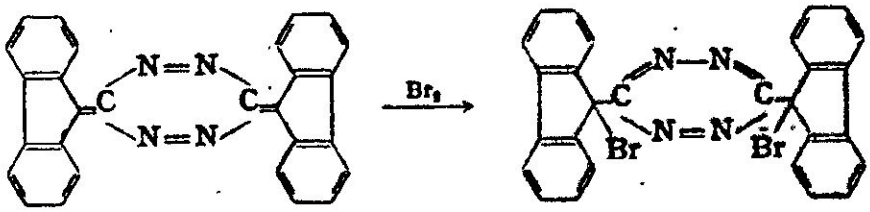
Other Carbocycles. 3,6-Di(β-naphthyl)-*s*-tetrazine has been synthesized by oxidation of the corresponding 1,2-dihydro-*s*-tetrazine (eq. 1, C_6H_5 is β-$C_{10}H_7$) using air, nitric acid, or nitrous acid.[81,95,110,118] The product

forms red needles, m.p. 246°. Wuyts and Lacourt[168] have reported the synthesis of 3,6-di(α-naphthyl)-*s*-tetrazine but they must have obtained the β-naphthyl compound, as 246°, the melting point given, was correct for the β-naphthyl compound. 3,6-Di(α-naphthyl)-*s*-tetrazine, red, m.p. 185°, was prepared by nitric acid oxidation of the product obtained from the reaction of hydrazine with thio-α-naphthamide.[81] It is presumed that the intermediate is 3,6-di(α-naphthyl)-1,2-dihydro-*s*-tetrazine, but this is not necessarily so. Stollé and co-workers[157] have synthesized 3,6-di(9-fluorenyl)-*s*-tetrazine (CXXV), crystallizing in rose-red needles, m.p. 225° (dec.), by oxidation of the corresponding 1,2-dihydro-*s*-tetrazine with amyl nitrite at room temperature. These tetrazines undergo the usual easy reduction to 1,2-dihydro-*s*-tetrazines with such reagents as zinc in acetic acid. 3,6-Di(9-fluorenyl)-*s*-tetrazine can be chlorinated in boiling carbon tetrachloride under ultraviolet light to give 3,6-bis(9-chloro-9-fluorenyl)-*s*-tetrazine (CXXVI). The dichloro compound can then be shaken with mercury to give a 75%



(CXXV) (CXXVI) (90)

yield of 3,6-bis(9-fluorenylidene)-3,6-dihydro-*s*-tetrazine (CXXVII), which then reacts readily with bromine to form 3,6-bis(9-bromo-9-fluorenyl)-*s*-tetrazine (CXXVIII). The chloro compound forms violet

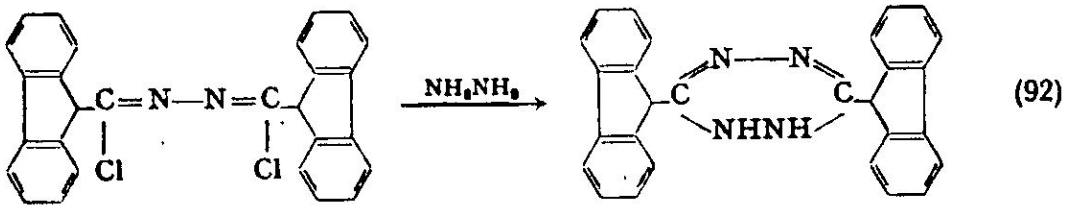


(CXXVII) (CXXVIII) (91)

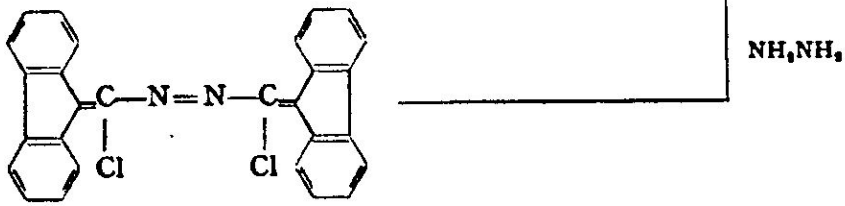
needles, m.p. 206° (dec.). The bromo compound is a red violet powder decomposing at 260°. Attempted replacement of the bromine atoms in CXXVIII with ethoxyl groups by use of sodium ethoxide gave only bifluorene.

3,6-Di(β-naphthyl)-1,2-dihydro-s-tetrazine has been prepared by reaction of hydrazine with thio-β-naphthamide (eq. 4),[81] β-naphthonitrile (3),[95] and ethyl β-naphthimidate (5).[110, 113] The yields in all cases were very small. The compound is reported as crystallizing in yellow needles, and the usual melting point reported was 246° although one report[95] gave 239–240°. This compound was hydrolyzed with acid to β-naphthoic acid and 2,5-bis(β-naphthyl)-1,3,4-furodiazole.[95] Reaction of this dihydro-s-tetrazine with acetic anhydride gives a 1,2-diacetyl derivative melting at 210°.

3,6-Di(9-fluorenyl)-1,2-dihydro-s-tetrazine (CXXX) has been prepared in 50% yield by the action of hydrazine in boiling benzene on 9-diphenyleneacetyl chloride azine (CXXIX).[157] The same product was obtained from 1,1′-dichloro-1,1′-di-9-fluorenylideneazomethane (CXXXI) and hydrazine under the same conditions. Using CXXIX



(CXXIX) (CXXX) (92)

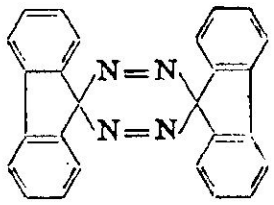


(CXXXI) (93)

there was obtained a 45% yield of 4-amino-3,5-di(9-fluorenyl)-1,2,4,4*H*-triazole in addition to CXXX. The compound CXXX melts at 296°. It can be oxidized with amyl nitrite at room temperature to give 3,6-di(fluorenyl)-s-tetrazine but in boiling benzene with amyl nitrite the product is 3,6-di(9-fluorenylidene-3,6-dihydro-s-tetrazine (CXXVII) obtained in 75% yield. At 240° CXXVII decomposes to α,α′-di(9-fluorenyl)succinonitrile and nitrogen.

Diazofluorene has been used by Staudinger[147] to synthesize 3,6-dibiphenylene-1,2,3,6-tetrahydro-s-tetrazine (CXXXII), as has already

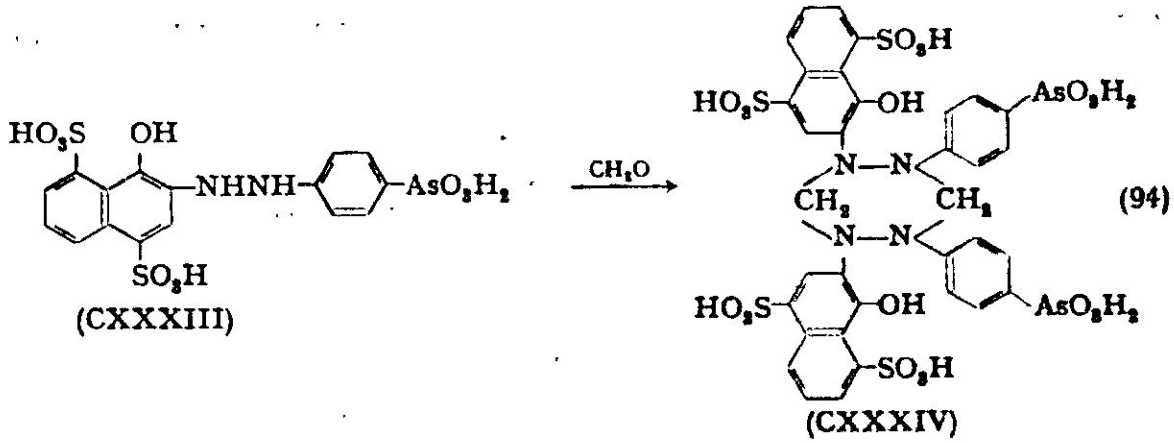
been discussed for 3,3,6,6-tetraphenyl-1,2,3,6-tetrahydro-*s*-tetrazine (eq. 76). Triethylphosphine forms an addition compound with diazo-



(CXXXII)

fluorene that reacts with water to give CXXXII. This product dissolves in sulfuric acid and precipitates out in fine orange needles, m.p. 325°, when water is added. It is insoluble in all organic solvents.

Friedheim has reported the synthesis of CXXXIV from formaldehyde and the hydrazine CXXXIII.[66,67] Neither proof of structure nor

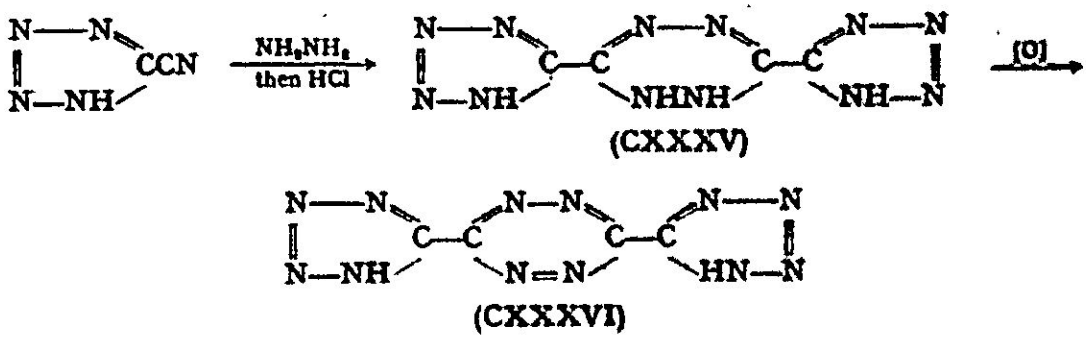


(CXXXIII) (CXXXIV) (94)

analysis was given. The product is claimed to be effective in treatment of certain spirochetal and protozoal diseases.

(3) Heterocyclic Rings Coupled Directly to *s*-Tetrazines

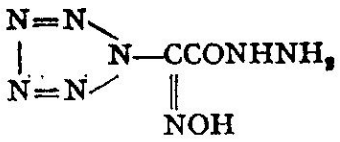
3,6-Di(5-tetrazolyl)-1,2-dihydro-*s*-tetrazine (CXXXV) and 3,6-di(5-tetrazolyl)-*s*-tetrazine (CXXXVI) have been synthesized by Lifschitz[64–66] and Curtius, Darapsky, and Müller[52] by the action of



(CXXXV)

(CXXXVI) (95)

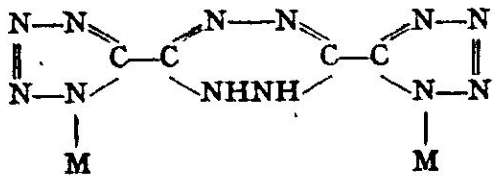
hydrazine on 5-cyanotetrazole (eq. 95). Lifschitz first reported these compounds as being pentazoleacetic acid derivatives. The *s*-tetrazine CXXXVI was called *isonitrosoazidoacetic acid hydrazide* (CXXXVII)



(CXXXVII)

(CXXXVIII)

and the 1,2-dihydro-*s*-tetrazine CXXXV was called *pentazidoacetic acid hydrazide* (CXXXVIII). Curtius and co-workers showed that these compounds were *s*-tetrazines by hydrolyzing CXXXV to 5-tetrazolecarboxylic acid and hydrazine. The reaction of 5-cyanotetrazole with hydrazine hydrate gave first a white dihydrazine salt of CXXXV, m.p. 230°, and a yellow diammonium salt melting above 280°. The total yield of both salts was 54%. These salts could be converted to the 1,2-dihydro-*s*-tetrazine CXXXV by treatment with hydrochloric acid. The 1,2-dihydro-*s*-tetrazine is a yellow solid that decomposes on heating. It is not very soluble in water or organic solvents. Treatment with sodium carbonate or potassium hydroxide gives metal salts believed to be of the type CXXXIX. The salts are neutralized by mineral acids but not

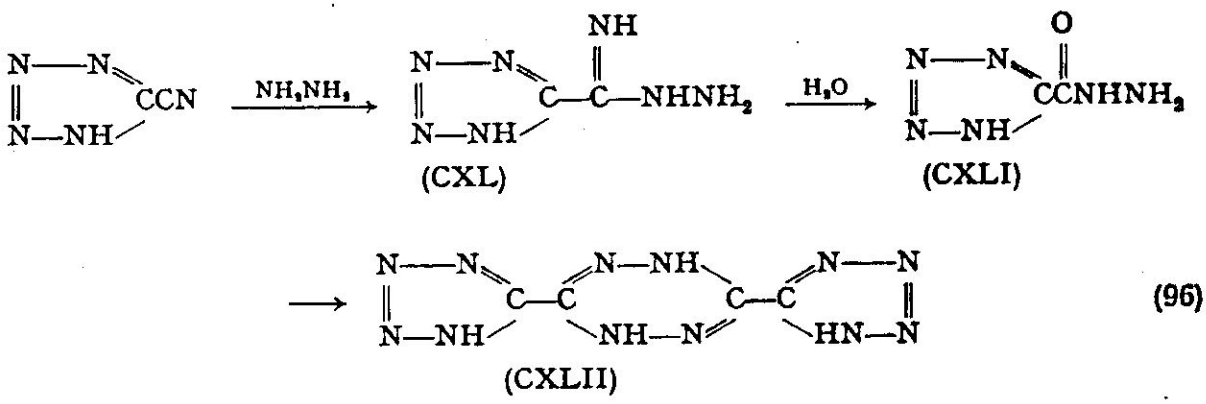


(CXXXIX)

by acetic acid. Oxidation of the 1,2-dihydro-*s*-tetrazine CXXXV with nitrous acid or chromic oxide gives the *s*-tetrazine CXXXVI. This compound crystallizes in crimson needles that decompose upon heating. The *s*-tetrazine forms an ammonium salt melting at 210° as well as two series of potassium and sodium salts. Lifschitz and Donath[86] have suggested that the two series of salts, one yellow and the other violet, are due to isomerism in the tetrazole rings. In one series the salts would be derived from the 1*H*-tetrazole rings and in the other series from the 2*H*-tetrazole rings.

It has been proposed by Lifschitz and Donath[86] that the dihydro-*s*-tetrazine has, instead of structure CXXXV, the structure CXLII,

which would be 3,6-di(5-tetrazolyl)-1,4-dihydro-*s*-tetrazine. It was suggested that the reaction proceeds by formation of the imide hydra-



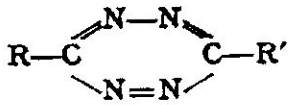
zide CXL, which is hydrolyzed to the hydrazide CXLI. This in turn dimerizes with loss of water to form CXLII. This view of the course of the reaction was mainly based on the fact that the imide hydrazide CXL could be isolated and heated with hydrazine in alcohol to give the dihydro-*s*-tetrazine. It has been found by other workers[99,130,143] that condensation of hydrazides in the manner proposed by Lifschitz and Donath[87] requires rather high temperatures and gives triazoles so it would appear that the proposals of Lifschitz as to structure and mechanism of reaction are incorrect.

Pinner and co-workers[112,113] have synthesized 3,6-di(2-furyl)-1,2-dihydro-*s*-tetrazine by reaction of ethyl furimidate with hydrazine. The product crystallizes from alcohol in yellow needles, m.p. 208°. Reaction of this product with acetic anhydride gives a white diacetate melting at 197°. The 1,2-dihydro-*s*-tetrazine is easily oxidized with air or ferric chloride to 3,6-di(2-furyl)-*s*-tetrazine, which forms red needles, m.p. 195°. Heating the 1,2-dihydro-*s*-tetrazine with 25% hydrochloric acid produces an isomer for which Pinner proposed the structure 3,6-di(2-furyl)-1,4-dihydro-*s*-tetrazine. Later work indicates that the compound is 4-amino-3,5-di(2-furyl)-1,2,4,4*H*-triazole.

(4) Rings Coupled through Carbon Chains to *s*-Tetrazines

A variety of benzyl- and benzhydryl-*s*-tetrazines have been prepared (Table V-7). 3,6-Dibenzyl-*s*-tetrazine, 6-benzhydryl-3-phenyl-*s*-tetrazine, 3,6-dibenzhydryl-*s*-tetrazine, 6-benzhydryl-3-methyl-*s*-tetra-

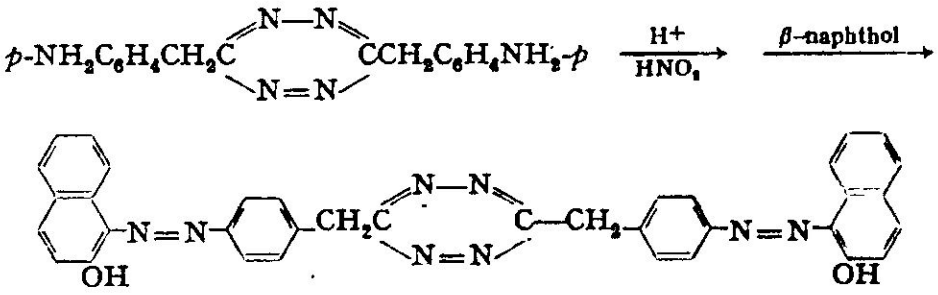
TABLE V-7. *s*-Tetrazines Substituted by Arylmethyl Groups



R	R′	M.p., °C.	Color and crystal form	Ref.
$C_6H_5CH_2$	$C_6H_5CH_2$	74, 76	Red needles, red prisms	80, 110, 113, 167
$(C_6H_5)_2CH$	CH_3	108		6
$(C_6H_5)_2CH$	C_6H_5	136–137	Violet-red	4, 5
$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	172, 174	Violet needles	4, 6, 156
$(C_6H_5)_2C(OH)$	C_6H_5	137		5
$(C_6H_5)_2C(OC_2H_5)$	C_6H_5	161		5
$(C_6H_5)_2C(Br)$	C_6H_5	126		5
$(C_6H_5)_2C(Cl)$	$(C_6H_5)_2C(Cl)$	162 (dec.)	Violet-red	158
$(C_6H_5)_2C(Br)$	$(C_6H_5)_2C(Br)$	162		158
p-$NH_2C_6H_4CH_2$	*p*-$NH_2C_6H_4CH_2$	166	Red platelets	81
p-$CH_3CONHC_6H_4CH_2$	*p*-$CH_3CONHC_6H_4CH_2$	205	Violet needles	81
p-(β-$HOC_{10}H_7N{=}N)C_6H_4CH_2$	*p*-(β-$HOC_{10}H_7N{=}N)C_6H_4CH_2$	200 (dec.)	Red amorphous	81

zine and 3,6-bis(*p*-aminobenzyl)-*s*-tetrazine have been prepared by oxidation of the corresponding 1,2-dihydro-*s*-tetrazine (eq. 1). The yields reported ranged from 10 to 35%.

Aspelund[4-6] and Stollé and Laux[156] have used nitrite in this oxidation. The yields were usually poor and considerable amounts of triazoles isomeric to the desired *s*-tetrazines were obtained. They found that the presence of calcined soda reduced the side reaction. 3,6-Bis(*p*-aminobenzyl)-*s*-tetrazine forms a diacetate and can be diazotized and coupled with β-naphthol to give an azo-*s*-tetrazine CXLIII.[81] Aspelund[5] has reported the synthesis of 3-(α-bromobenzhydryl)-6-phenyl-*s*-tetrazine (CXLV) by bromination of 3-benzhydryl-6-phenyl-*s*-tetrazine



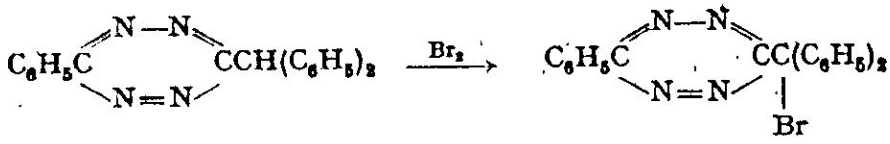
(97)

(CXLIII)

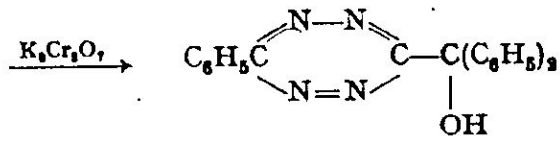
(CXLIV). The bromo-*s*-tetrazine can be hydrolyzed to 3-(α-hydroxybenzhydryl)-6-phenyl-*s*-tetrazine (eq. 101), treated with alcohol and ammonia to give 3-(α-ethoxybenzhydryl)-6-phenyl-*s*-tetrazine (CXLVII), or heated with mercury and oxygen to give the peroxide CXLVIII (eq. 103). The hydroxy-*s*-tetrazine CXLVI can also be synthesized by direct oxidation of CXLIV with potassium dichromate (eq. 99) and by reduction of the peroxide CXLVIII with hydroquinone benzidine (eq. 103). Aspelund has also synthesized CXLVI by c of diphenylacetyl chloride benzoyl chloride azine (CXLIX) to give followed by treatment with mercury to form the peroxide CLI, was converted to 3-(α-hydroxybenzhydryl)-6-phenyl-*s*- (CXLVI) with hydrazine.

3,6-Bis(α-halobenzhydryl)-*s*-tetrazines have been synthesized direct halogenation of 3,6-dibenzhydryl-*s*-tetrazine (CLII) and addition of halogen to 3,6-bis(diphenylmethylene)-3,6-dih zine (CLIII).

This class of *s*-tetrazines is soluble in acetic acid and benzene

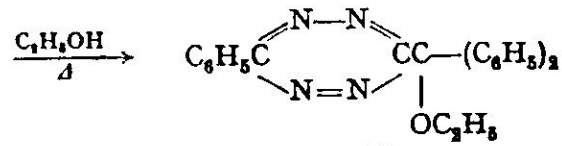


(CXLIV) (CXLV) (98)



CXLIV (99)

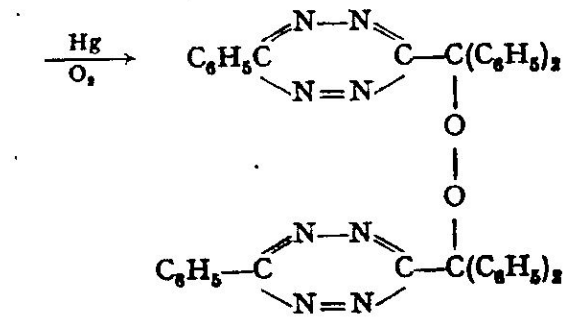
(CXLVI)



CXLV (100)

(CXLVII)

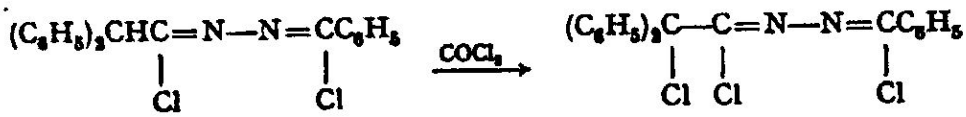
CXLV $\xrightarrow[\Delta]{H_2O}$ CXLVI (101)



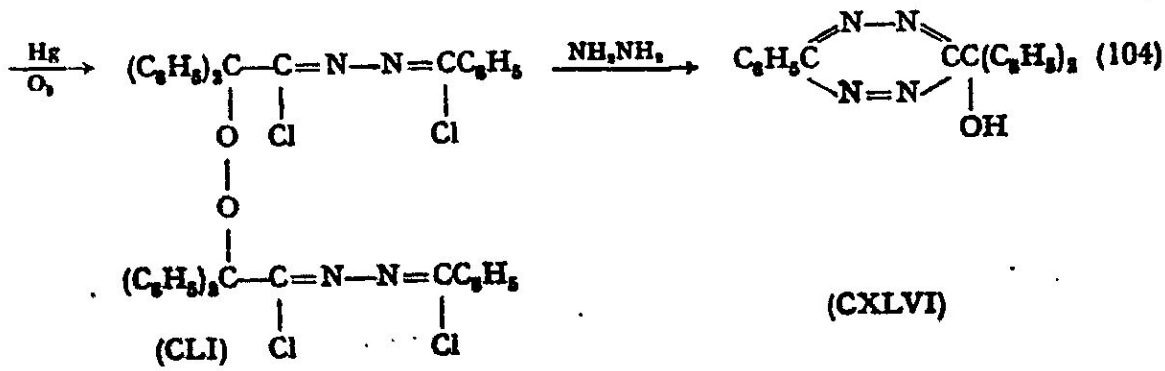
CXLV (102)

(CXLVIII)

CXLVIII $\xrightarrow[\text{or benzidine}]{\text{hydroquinone}}$ CXLVI (103)



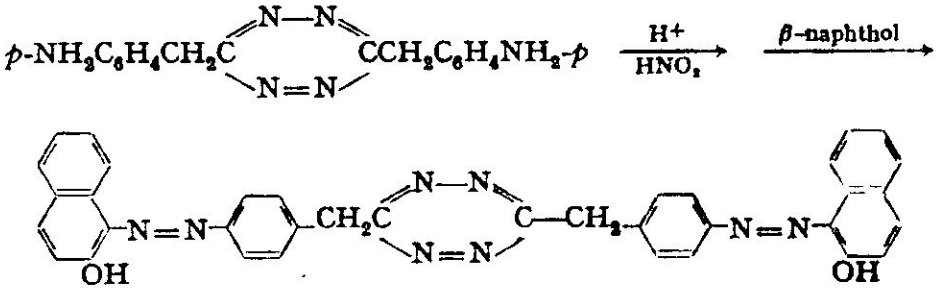
(CXLIX) (CL)



(CLI) (CXLVI) (104)

zine and 3,6-bis(*p*-aminobenzyl)-*s*-tetrazine have been prepared by oxidation of the corresponding 1,2-dihydro-*s*-tetrazine (eq. 1). The yields reported ranged from 10 to 35%.

Aspelund[4-6] and Stollé and Laux[156] have used nitrite in this oxidation. The yields were usually poor and considerable amounts of triazoles isomeric to the desired *s*-tetrazines were obtained. They found that the presence of calcined soda reduced the side reaction. 3,6-Bis(*p*-aminobenzyl)-*s*-tetrazine forms a diacetate and can be diazotized and coupled with β-naphthol to give an azo-*s*-tetrazine CXLIII.[81] Aspelund[6] has reported the synthesis of 3-(α-bromobenzhydryl)-6-phenyl-*s*-tetrazine (CXLV) by bromination of 3-benzhydryl-6-phenyl-*s*-tetrazine

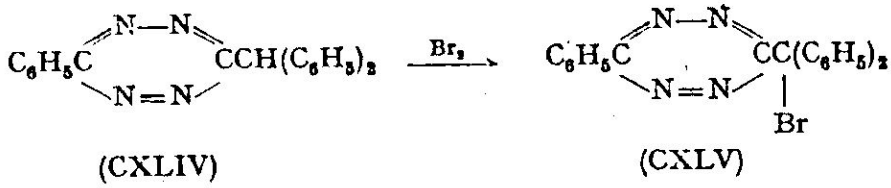


(CXLIII)

(CXLIV). The bromo-*s*-tetrazine can be hydrolyzed to 3-(α-hydroxybenzhydryl)-6-phenyl-*s*-tetrazine (eq. 101), treated with alcohol and ammonia to give 3-(α-ethoxybenzhydryl)-6-phenyl-*s*-tetrazine (CXLVII), or heated with mercury and oxygen to give the peroxide CXLVIII (eq. 103). The hydroxy-*s*-tetrazine CXLVI can also be synthesized by direct oxidation of CXLIV with potassium dichromate (eq. 99) and by reduction of the peroxide CXLVIII with hydroquinone benzidine (eq. 103). Aspelund has also synthesized CXLVI by c of diphenylacetyl chloride benzoyl chloride azine (CXLIX) to give followed by treatment with mercury to form the peroxide CLI, was converted to 3-(α-hydroxybenzhydryl)-6-phenyl-*s*- (CXLVI) with hydrazine.

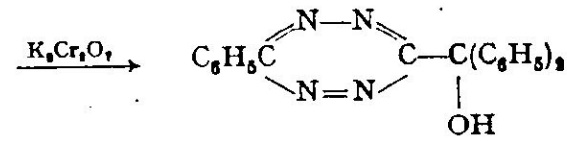
3,6-Bis(α-halobenzhydryl)-*s*-tetrazines have been synthesized direct halogenation of 3,6-dibenzhydryl-*s*-tetrazine (CLII) and addition of halogen to 3,6-bis(diphenylmethylene)-3, zine (CLIII).

This class of *s*-tetrazines is soluble in acetic acid and benzene



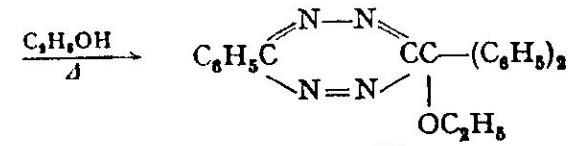
(98)

(CXLIV) (CXLV)



(99)

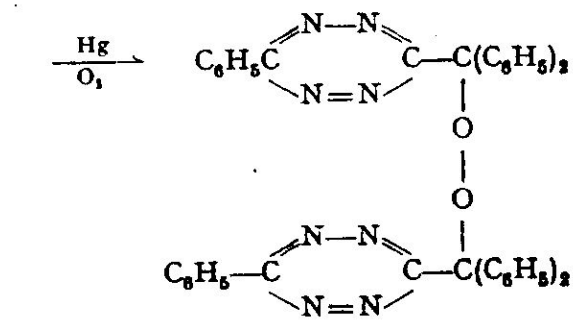
(CXLVI)



(100)

(CXLVII)

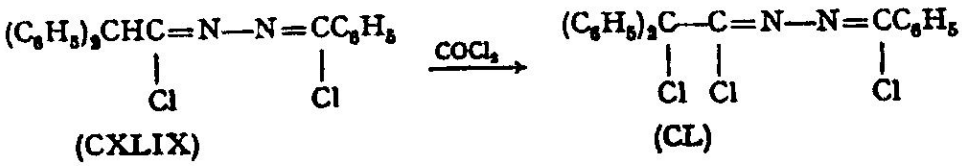
CXLV $\xrightarrow[\Delta]{H_2O}$ CXLVI (101)



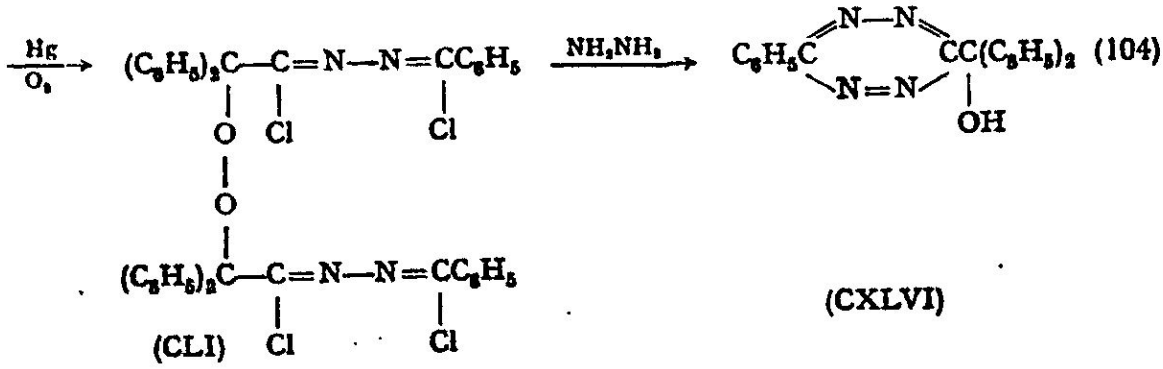
(102)

(CXLVIII)

CXLVIII $\xrightarrow[\text{or benzidine}]{\text{hydroquinone}}$ CXLVI (103)



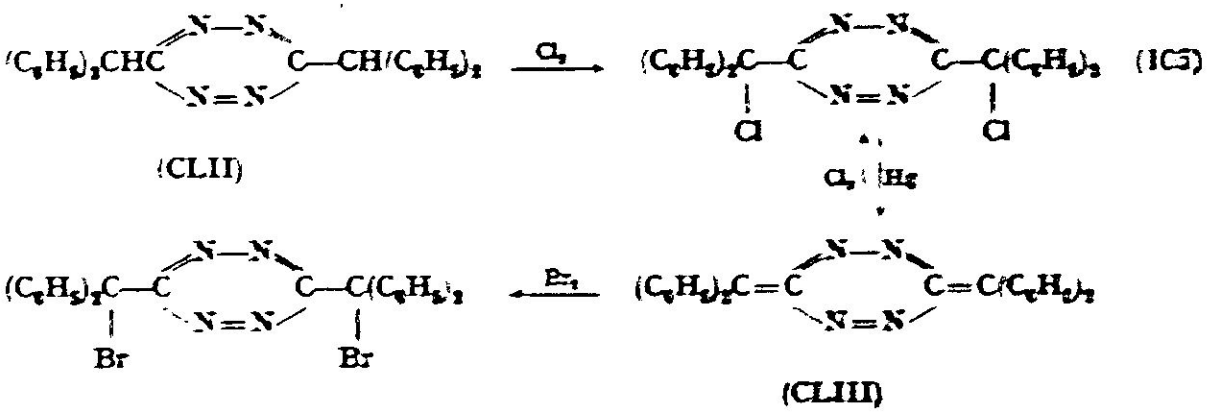
(CXLIX) (CL)



(CLI) (CXLVI)

(104)

usually only slightly soluble in ether and alcohol. They are deep red as are other s-tetrazines, but their melting points are lower than those of



(CLII) (CLIII)

most s-tetrazines. As is usual, they are very easily reduced to the 1,2-dihydro-s-tetrazines.

Benzyl- and benzhydryl-1,2-dihydro-s-tetrazines (Table V-8) have been prepared by the usual methods. 3,6-Dibenzyl- and 3,6-bis(α-

TABLE V-8. 1,2-Dihydro-s-tetrazines Substituted by Arylmethyl Groups

R	R′	M.p., °C.	Color and crystal form	Ref.
$C_6H_5CH_2$	$C_6H_5CH_2$	158	Red needles, white needles	83, 110, 113
$(C_6H_5)_2CH$	CH_3	161–162		6
$(C_6H_5)_2CH$	C_6H_5	216	Yellow needles	4, 5, 6
$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	190	Flocculent	4, 6, 156, 159
p-$NH_2C_6H_4CH_2$	p-$NH_2C_6H_4CH_2$	212	White needles	81
C_6H_5CH | OH	C_6H_5CH | OH	193	Yellow needles	110, 113

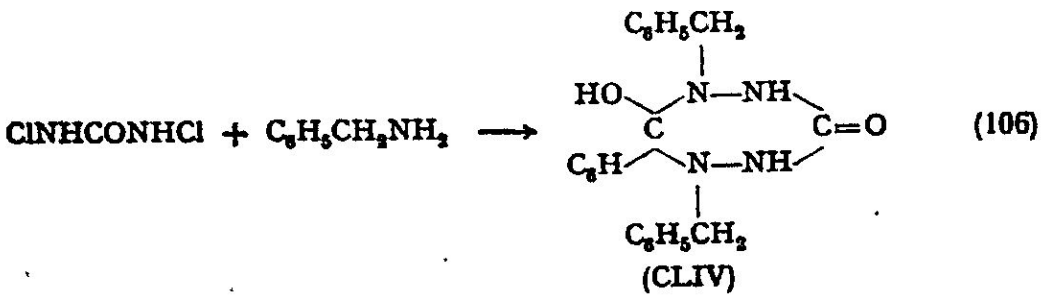
hydroxybenzyl)-1,2-dihydro-s-tetrazine have been synthesized by action of hydrazine on the appropriate imido ester (eq. 5).[80,83] Pinner[110,113] has reported that the dibenzyl compound is red. Junghahn[80] stated that it is white. Since both compounds gave dibenzyl-s-tetrazine they must be identical. It may be that compound was contaminated with some s-tetrazine. Junghahn[80]

used thio-*p*-aminophenylacetamide and hydrazine to prepare 3,6-bis(*p*-aminobenzyl)-1,2-dihydro-*s*-tetrazine in 45% yield (eq. 4). 3,6-Di(benzhydryl)-1,2-dihydro-*s*-tetrazine was prepared by the condensation of diphenylacetyl chloride azine with hydrazine (eq. 6, $(C_6H_5)_2CH$).[156] Aspelund[5,6] has synthesized 3-benzhydryl-6-phenyl- and 3-benzhydryl-6-methyl-1,2-dihydro-*s*-tetrazine using the same method, the former compound being obtained in 20% yield. Oxadiazoles and triazoles were obtained as side products. 3,6-Bis(α-hydroxybenzhydryl)-1,2-dihydro-*s*-tetrazine forms a tetraacetate, m.p. 203°, with acetic anhydride and hydrolyses with acid to benzaldehyde, formic acid, and hydrazine.[113] 3,6-Dibenzhydryl-1,2-dihydro-*s*-tetrazine reacts with diphenylacetyl chloride in pyridine to form 3,6-dibenzhydryl-1-diphenylacetyl-1,2-dihydro-*s*-tetrazine, m.p. 185°.[153] These 1,2-dihydro-*s*-tetrazines are benzene soluble but are not very soluble in alcohol or ether.

It has been reported that 3,6-dibenzyl-1,2-dihydro-*s*-tetrazine isomerizes upon acid treatment to 3,6-dibenzyl-1,4-dihydro-*s*-tetrazine.[110,113] Since Bülow and Weber[23] have shown that such acid treatment of 1,2-dihydro-*s*-tetrazines gives 1,2,4,4*H*-triazoles, it seems likely that the supposed 3,6-dibenzyl-1,4-dihydro-*s*-tetrazine is rather 4-amino-3,5-dibenzyl-1,2,4,4*H*-triazole.

The synthesis and some of the reactions of 3,6-bis(diphenylmethylene)-3,6-dihydro-*s*-tetrazine (CLIII) have already been mentioned (105).[158] This compound forms black prisms that deflagrate at 170°. The products of the decomposition are tetraphenylsuccinonitrile and nitrogen.

Datta and Gupta[61] have found that addition of *N,N'*-dichlorourea to a large excess of a cold solution of benzylamine gives two products (eq. 106). One of these is *p*-urazine, and the structure proposed for the other was 1,5-dibenzyl-6-phenyl-3-oxohexahydro-6-*s*-tetrazinol (CLIV).

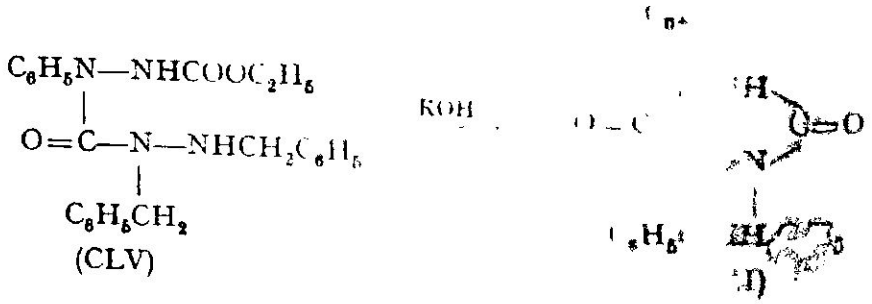


(106)

(CLIV)

This is a white crystalline [illegible] was th
a part of the benzylamin[illegible] N'-dic
This was followed by condensation [illegible] N'-di
one molecule of benzylamm[illegible] nd two
of benzylchloramine to give [illegible] ride.
chloric acid. The structure of th[illegible] cid,
was the only indication that [illegible] osed
this and of the great likelih[illegible] such
suggested would not occur, it [illegible] pread
incorrect.

While showing that phenylura[illegible] nylura
triazoles, Busch[24] synthesized [illegible] trazine
unequivocal methods. The compound [illegible] 1,2-
phenyltetrahydro-3,6-tetrazine-[illegible] is obt
cyclization of 1,2-dibenzyl-1-phenyl[illegible] hydra



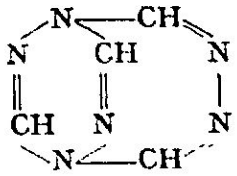
with potassium hydroxide in boiling alcohol. The [illegible]
product crystallizes in white leaflets, m.p. 180°. It [illegible]
to diphenylurazine, which is a monobasic acid. This [illegible]
for the belief that diphenylurazine is not tetrah[illegible]
dione.

2. CONDENSED *o*-TETRAZ[illegible]

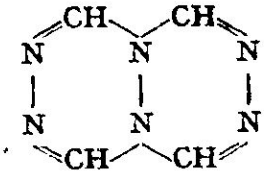
The reported instances of *s*-tetrazines hav[illegible]
systems are very few with the exception of a[illegible]
derivatives of *p*-urazines. Since it is believed that t[illegible]
derivatives of 4-amino-1,2,4,1*H*-triazole-3,5-(2*H*,[illegible]
not be considered in this section.

The thermal condensation of formhydrazid[illegible]

gives 4-amino-1,2,4,4*H*-triazole, formic acid, water, and a compound crystallizing from ethanol in white plates,[100] m.p. 263°. Pellizzari called this compound *diazodimethinetetrazoline* and proposed either CLVII or CLVIII as its structure. Hydrolysis of the compound with hydrochloric



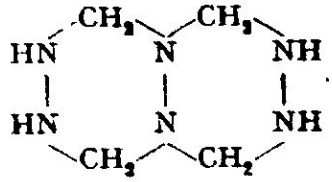
(CLVII)



(CLVIII)

acid gives 4-amino-1,2,4,4*H*-triazole, formic acid, and hydrazine. The structure CLVIII is the more probable one in view of its two fused six-membered rings. If such a structure is present, it could be demonstrated by reduction to CLIX.

Hofmann and Storm[78] prepared the fused ring system CLIX, which they called *tetraformaltrisazine*, by the reaction of formalin with



(CLIX)

hydrazine hydrate. In contrast to the polymer that had been reported previously from this reaction, CLIX crystallizes from water in flat needles as a dihydrate. It has no definite melting point. At about 225° the dihydrate loses water and volatilizes. CLIX is unstable to acids and stable to alkali, and forms precipitates with mercuric chloride and silver nitrate and reduces alkaline solutions of silver, mercuric, and cupric salts.

The preparation of the fused ring compound XI by Müller[194] has already been discussed (eq. 10). In this synthesis *s*-tetrazine reacts with diazomethane in ether to eliminate three equivalents of nitrogen and give a brown precipitate. The proposed structure for the product is shown in formula XI. It was called *trimethylenetetrazine* by Müller. The only products isolated from sulfuric acid hydrolysis were formaldehyde and hydrazine.

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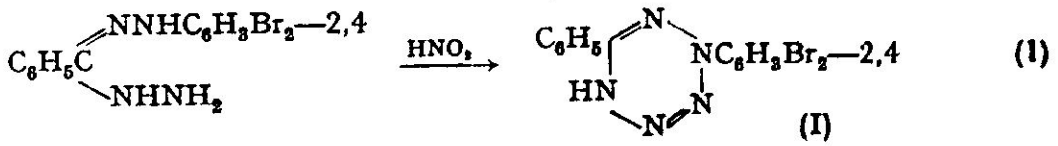
CHAPTER VI

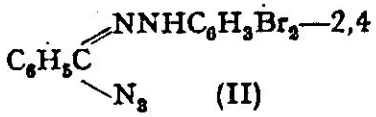
The Pentazines

Only one compound (I) containing the pentazine ring (*R.I.* 123) has been described. Chattaway and Parkes[1] claimed to have prepared it by the reaction of nitrous acid with the 2,4-dibromophenylhydrazone of benzhydrazide (eq. 1). This reaction might conceivably have yielded an



(1)

(I)

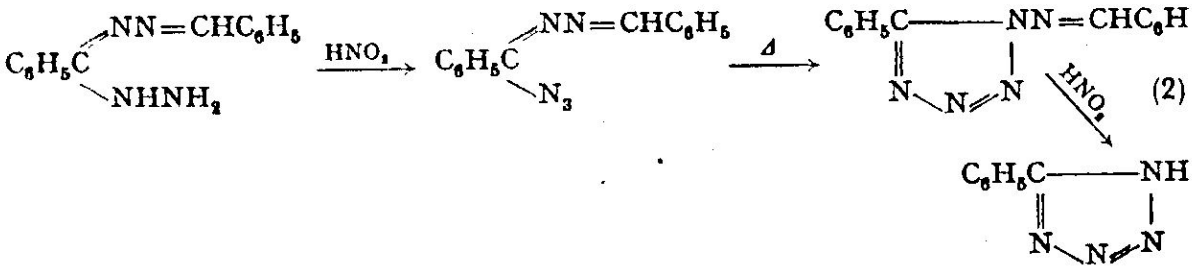


(II)

isomeric azide (II), produced by the action of nitrous acid upon the hydrazide grouping alone. Chattaway and Parkes thought that this possibility could be definitely excluded; they recovered their product unchanged after it had been heated for sixty hours at 100° with a saturated solution of acetylene in acetone. If their material were an azide, it would presumably be converted to a triazole under these conditions.[2] Considering the stability and the good nitrogen and bromine analyses of their compound, they concluded that it actually is 2-(2,4-dibromophenyl)-6-phenyl-2,5-dihydropentazine (I). It was obtained as colorless, odorless, and weakly basic crystals, m.p. 172°, easily soluble in the usual organic solvents. When strongly heated, it decomposes with a puff of black smoke and benzonitrile is formed.

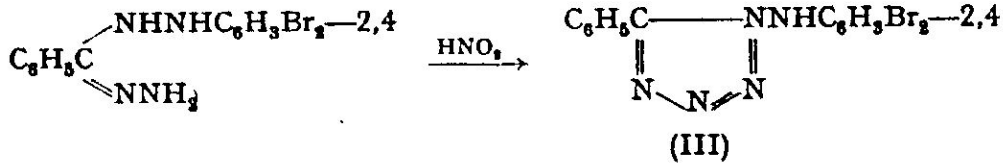
The pentazine structure has been challenged on the basis of done by Stollé and Helwerth,[4] who carried out reactions (eq. 2) similar to that of Chattaway and Parkes. The course taken by these reactions is shown by the isolation of 5-phenyltetrazole. The structure of this compound had previously been established. Stollé felt that

reactions were quite similar to the Chattaway-Parkes reaction-so similar, in fact, as to make it likely that the product of Chattaway and



(2)

Parkes is really a tetrazole derivative (III). We can recognize this possibility by rewriting equation 1, using the tautomeric structure of the starting material (eq. 3).



(3)

(III)

Apparently, we cannot yet say definitely that any pentazines have been synthesized.

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