TABLE IV

OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF 1,1,3,3-TETRAMETHYLGUANIDINE IN DIFFERENT ACIDS AT 138.5°

Acid	H_0[a]	Log a_{H_2O}[b]	$10^6 k_1$, sec^{-1}
3.5 *M* $HClO_4$	−1.47	−0.106	0.0289
4 *M* HCl	−1.40	−0.107	0.118
3.5 *M* H_2SO_4	−1.62	−0.111	0.211

[a] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956 (1961).

to 6 *M* sulfuric acid suggesting that the transition state for acid hydrolysis consists of a proton, water, and the substrate which is $TMGH^+$ ($pK_a = 13.6$). In solutions more concentrated than 7.5 *M* H_2SO_4, the observed second-order rate constants decreased and the occurrence of a side reaction of undetermined nature was indicated by the nmr spectra of the reaction solutions.

Solvent Isotope Effect.—In 4 *M* sulfuric acid the solvent isotope effects, $k_{H_2SO_4}/k_{D_2SO_4}$, of 0.78 and 0.83 at 108.1 and 138.5°, respectively, are consistent with fast preequilibrium protonation of the substrate as indicated in eq 1. For the hydrolysis of lysidine in 4 *M* sulfuric acid at 90°, $k_{H_2SO_4}/_{D_2SO_4}$ is 0.71.[2]

Entropies of Activation.—From the rates of hydrolysis of TMG in 4 *M* sulfuric acid at 108.1 and 138.5°, activation parameters of $\Delta S = -25$ eu and $\Delta H = 27$ kcal/mol may be calculated for the second-order rate constant $k_1/[H_2SO_4]$. The entropy of activation is very similar to that observed for the acid hydrolysis of lysidine, −26 eu, and other A2 reactions.[2]

Acid Effect.—It has been observed that A2 reactions are faster in sulfuric and hydrochloric acids than in perchloric acid solutions of comparable acidity and water activity.[3] The ratio of hydrolysis rates of TMG in perchloric, hydrochloric, and sulfuric acids of 1:4:7 (Table IV) is consequently consistent with the A2 mechanism of eq 1. The relative order observed for the hydrolysis of lysidine of 1:3.1:2.7 is slightly different.[2]

Thus our experimental results are consistent with the proposal that guanidines hydrolyze by an A2 mechanism as outlined in eq 1 and support the proposition that compounds, such as amidines and guanidines, which form highly resonance-stabilized conjugate acids undergo acid hydrolysis by nucleophilic attack by water on the diprotonated compounds.[1] The present experimental data are not considered sufficient to justify our speculating on whether the nucleophilic attack by water on the diprotonated guanidine consists of nucleophilic addition of water to form a tetrahedral intermediate (as favored for the amidine hydrolysis[2]) or a direct displacement (SN2) reaction analogous to the mechanism proposed for the acid hydrolysis of carbamates.[8a]

Experimental Section

Nmr spectra were determined on a Varian T-60 spectrometer. Acid solutions were standardized as previously described.[1]

Dimethylurea was synthesized from dimethylamine and potassium cyanate[9a] and recrystallized from ethanol, mp 182–183° (lit.[9b] mp 182–183°). Aldrich 1,1,3,3-tetramethylurea was purified by distillation, bp 174–175° (lit.[10] bp 174–177°). Aldrich 1,1,3,3-tetramethylguanidine was purified by distillation, bp 164° [lit.[11] bp 159.5° (745 mm)]. The nmr spectra of the compounds were consistent with their structures.

In the acid solutions employed for the rate determinations, the ureas and 1,1,3,3-tetramethylguanidine absorbed at the same chemical shift and on hydrolysis gave rise to an upfield triplet which was confirmed to be due to dimethylammonium ion. For example, in 4 *M* H_2SO_4 the ureas and the tetramethylguanidine gave singlets at 3.3 ppm upfield from the solvent signal and dimethylammonium ion gave a triplet of 3.5 ppm upfield from the solvent signal. The rates of hydrolysis were determined from plots of ln $A_R/(A_R + A_P)$ *vs.* time, where A_R is the area of the reactant (urea or guanidine) singlet and A_P equals the area of the product dimethylammonium ion triplet. Linear plots consisting of four to five points and covering approximately 2 half-lives were obtained. The nmr determination of the protonation of tetramethylguanidinium ion was performed as previously described.[1,5]

Registry No.—1,1-Dimethylurea, 598-94-7; 1,1,3,3-tetramethylurea, 632-22-4; sulfuric acid, 7664-93-9; 1,1,3,3-tetramethylguanidine, 80-70-6.

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(8) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969); (b) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *ibid.*, 1099 (1968); (c) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

(9) (a) F. Arndt, *Org. Syn.*, **15**, 48 (1935); (b) F. Kurzer, *ibid.*, **32**, 61 (1952).

(10) H. Z. Lecler and K. Gubernator, *J. Amer. Chem. Soc.*, **75**, 1087 (1953).

(11) M. L. Anderson and R. N. Hammer, *J. Chem. Eng. Data*, **12**, 442 (1967).

Formation of 2-Alkyl-5-phenyltetrazoles from 1-Alkyl-5-phenyltetrazoles

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It is generally recognized that the reaction of a 1,5-disubstituted tetrazole with alkyl halide or alkyl benzenesulfonate gives a 1,4,5-trisubstituted tetrazolium salt.[2-9] We have found, however, that treatment of 1-alkyl-5-phenyltetrazole with alkyl iodide at 130° gave no tetrazolium salt but rather 2-alkyl-5-phenyltetrazole. To elucidate this novel isomerization process, some experiments were carried out at lower temperatures.

On heating 1-methyl-5-phenyltetrazole (**1**) with methyl iodide at 130° for 10 hr, 2-methyl-5-phenyltetrazole (**2**) was obtained in a quantitative yield. The presence of methyl iodide was essential to this reaction, since there was no conversion without methyl iodide.

Treatment of the 1-methyl isomer **1** with methyl iodide at 70° for 20 hr gave the 2-methyl isomer **2** together with the usual product, 1,4-dimethyl-5-phenyl-

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(1) (a) To whom correspondence should be addressed: Department of Industrial Chemistry. (b) College of Liberal Arts and Sciences. (c) Department of Industrial Chemistry.

(2) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964).

(3) A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.*, 3377 (1969).

(4) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Amer. Chem. Soc.*, **73**, 4457 (1951).

(5) G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind.* (*London*), 1355 (1955).

(6) H. R. J. Waddington, G. F. Duffin, and J. D. Kendall, British Patent 785,334 (1957); *Chem. Abstr.*, **52**, 6030*i* (1958).

(7) S. Hünig and K.-H. Oette, *Justus Liebigs Ann. Chem.*, **641**, 94 (1961).

(8) E. K. Harville, C. W. Roberts, and R. M. Herbst, *J. Org. Chem.*, **15**, 58 (1950).

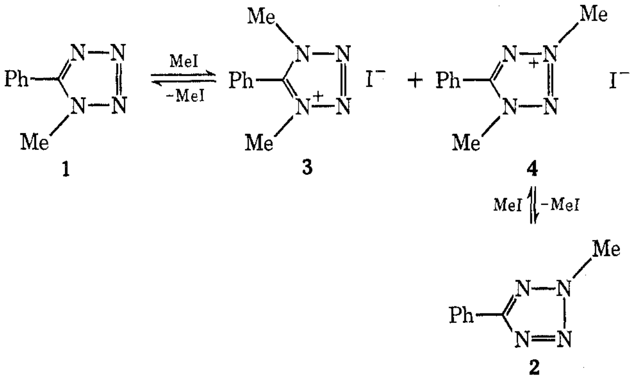
(9) R. Stolle, F. Pollecoff, and Fr. Henke-Stark, *Chem. Ber.*, **63**, 965 (1930).

tetrazolium iodide (**3**), in 27 and 35% yields, respectively. The structure of **3** was determined by the nmr spectrum, which had a singlet at δ 4.30 ppm indicating the equivalence of the two *N*-methyl protons. Thermal treatment of the 1,4-dimethyl salt **3** at 140° gave **1** in a quantitative yield.

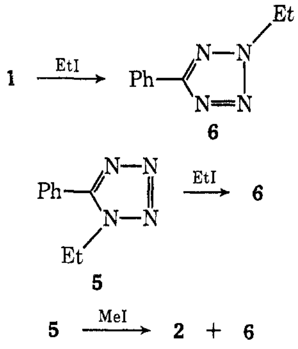
When a solution of the 1-methyl isomer **1** in methyl iodide was kept at room temperature for 90 days, there was obtained a small amount of the 2-methyl isomer **2** (6%) as well as a mixture (37%) of 1,4-dimethyl- (**3**) and 1,3-dimethyl-5-phenyltetrazolium iodide (**4**); 55% of **1** was recovered. Attempted separation of **4** from **3** was unsuccessful because of the thermal unstability of **4**. The nmr spectrum of the salts mixture showed three singlet peaks at δ 4.30, 4.54, and 4.76 ppm (78:11:11). The peak at δ 4.30 ppm was identified as the 1,4-dimethyl protons of **3**, and the other peaks at δ 4.54 and 4.76 ppm could be assigned to the 1-methyl and 3-methyl protons of **4**, respectively.[10-12] The ratio of **3** and **4** in the mixture was determined from the nmr spectrum (**3**:**4** = 78:22). Pyrolysis of the salt mixture (**3** and **4**) in refluxing toluene afforded the 1-methyl isomer **1** and the 2-methyl isomer **2** in a ratio of 76:24. This ratio is in accord with the ratio of **3** and **4** in the starting mixture, indicating the predominant formation of **2** from **4**, since the quantitative yield of **1** from the 1,4-dimethyl salt **3** was established.

These results suggest the following conclusions: (a) 1,3-dimethyl salt **4** is thermally less stable than 1,4-dimethyl salt **3** and decomposes at a temperature below 70°; (b) **4** is an intermediate in the formation of 2-methyl isomer **2** from 1-methyl isomer **1**: (c) on heating **4**, the 1-methyl group is preferentially eliminated to yield **2**.

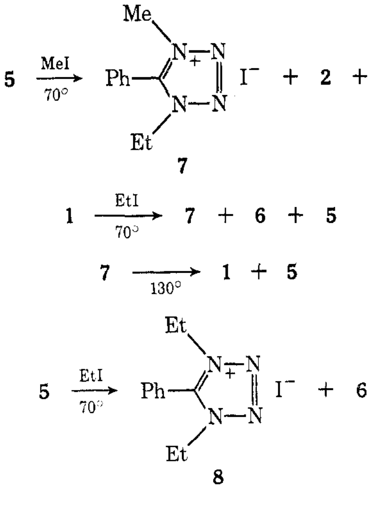
In the reaction of the 1-methyl isomer **1** with methyl iodide at 130°, the formation of **3** is reversible, and the net reaction leads to the 2-methyl isomer **2** by way of the 1,3-dimethyl salt **4**. The reaction of **2** with methyl iodide at 130° gives no **1**.



The same type of conversion was also studied on mixed alkyl systems. Treatment of 1-methyl- (**1**) or 1-ethyl-5-phenyltetrazole (**5**) with a large excess of ethyl iodide at 130° for 10 hr afforded the expected 2-ethyl-5-phenyltetrazole (**6**) quantitatively. Analogous treatment of the 1-ethyl isomer **5** with methyl iodide gave the 2-methyl isomer **2** (94%) together with a small amount of the 2-ethyl isomer **6** (6%).



When the reaction of the 1-ethyl isomer **5** with methyl iodide was carried out at 70° for 22 hr, 1-methyl-4-ethyl-5-phenyltetrazolium iodide (**7**) was obtained in 76% yield together with the 2-methyl isomer **2** (9.8%) and the 1-methyl isomer **1** (1.3%). The structure of **7** was elucidated by nmr and was also supported by the pyrolysis of **7**. On heating at 130°, **7** was decomposed completely within 40 min to give the 1-methyl isomer **1** and the 1-ethyl isomer **5** with a ratio of 16:84. The pyrolysis product contained no 2-alkyl isomer detected by nmr analysis. This indicated that both methyl and ethyl groups of **7** are attached to 1 and 4 nitrogen in the tetrazole ring, and methyl iodide was more easily eliminated than ethyl iodide. This tendency was consistent with the results in the thermal decomposition of pyrazolium[13] and indazolium halides.[14] Treatment of the 1-methyl isomer **1** with ethyl iodide at 70° afforded the 2-ethyl isomer **6** (52%) and the 1-ethyl isomer **5** (12.7%) together with a small amount of 1,4-dialkyl salt **7** (3.7%). The sharp contrast of the yields of 1-methyl-4-ethyl salt **7** in the above alkylations of 1-alkyl-5-phenyltetrazole might be attributed to the different formation ratios of 1,4- *vs.* 1,3-dialkyl-5-phenyltetrazolium iodides. In the reaction of ethyl iodide with the 1-methyl isomer **1** or the 1-ethyl isomer **5**, the 1,3-diakyl salts might be formed in considerable yields and were decomposed to the 2-ethyl isomer **6**.



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[10] The nmr assignments in the 1,3-dimethyl salt **4** are in accordance with those of the 1,3-dimethyltetrazolium salt[11] in which chemical shifts of 1- and 3-methyl protons were assigned to δ 4.60 and 4.80 ppm, respectively. As for the structure of the dimethyl salt assigned to **4**, a possibility of 1,2-dimethyl-5-phenyltetrazolium iodide could be excluded, since Henry, Finnegan, and Lieber reported no formation of 1,2-disubstituted derivative in the alkylation of 1- or 2-alkyl-5-aminotetrazole.[12]

[11] W. P. Norris and R. A. Henry, *Tetrahedron Lett.*, 1213 (1965).

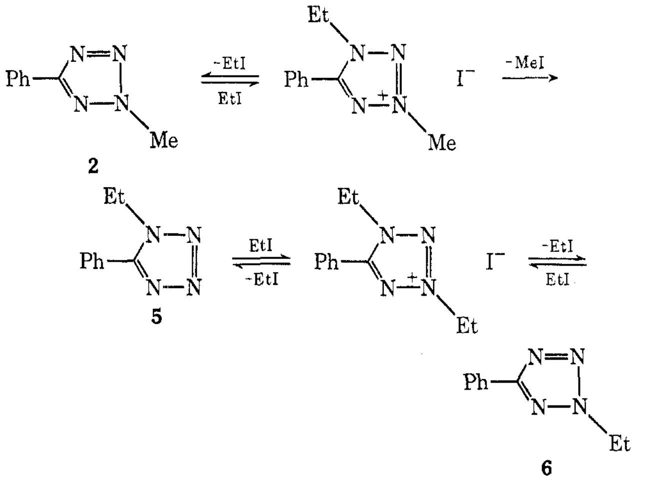
[12] R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76**, 2894 (1954).

[13] I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.*, **30**, 2942 (1960); *Chem. Abstr.*, **55**, 16519*e* (1961).

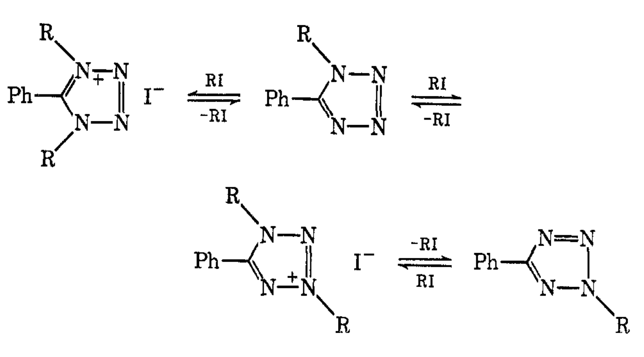
[14] K. V. Auwers and W. Pfuhl, *Chem. Ber.*, **58**, 1360 (1925); K. V. Auwers, H. Düsterdick, and H. Kleiner, *ibid.*, **61**, 100 (1928).

By contrast, in the reaction of **1** or **5** with methyl iodide at 70°, the 1,4-diakyl salt was formed in a greater proportion than the 1,3-dialkyl salt, which was suggested by the poorer yield of the 2-methyl isomer **2** and higher yield of the 1,4-dialkyl salt **3** or **7**.

Treatment of the 2-methyl isomer **2** with a large excess of ethyl iodide at 130° for 22 hr afforded the 2-ethyl isomer **6** in 16.8% yield. The converse reaction of **6** with methyl iodide at 130° for 13 hr gave **2** in 4.8% yield. These results suggest that 1,3-dialkyl-5-phenyltetrazolium iodide formed from the 2-alkyl isomer[11,12] decomposed under the reaction conditions to give a small amount of the 1-alkyl isomer as well as the 2-alkyl isomer, although thermal elimination of methyl iodide from 1,3-dimethyl-5-phenyltetrazolium iodide gives predominantly the 2-methyl isomer **2**. The 1-alkyl isomer formed *in situ* could be converted into another 2-alkyl isomer.



The overall isomerization processes from the 1-alkyl isomer into the 2-alkyl isomer have been shown to be reversible under the experimental condition at 130°, and the equilibria have favored the 2,5-disubstituted tetrazoles which are thermodynamically more stable than the 1,5 isomers.[15]



Experimental Section

Conversion of 1-Methyl-5-phenyltetrazole (1) into 2-Methyl-5-phenyltetrazole (2).—A solution of **1**[16,17] (1.60 g) in methyl iodide (15 ml) was heated in a sealed glass tube at 130° for 10 hr. Evaporation of excess methyl iodide gave 1.59 g (100%) of crystalline **2**, mp 48.5° (lit.[18] mp 48–50°), identified by the nmr and mass spectra.[17]

Reaction of 1 with Methyl Iodide at 70°.—A solution of **1** (0.203 g) in methyl iodide (2 ml) was heated at 70° for 20 hr. The resultant mixture separated into two layers. The upper oily layer was washed with benzene and kept *in vacuo* to give 0.133 g (35%) of crystalline 1,4-dimethyl-5-phenyltetrazolium iodide (**3**): sintered at 128°, bubbled at 134°, and completely melted at 142°; nmr ($CDCl_3$) δ 4.30 (s, 6 H, 2 Me), 7.80 (m, 3 H, meta and para protons), 8.25 ppm (m, 2 H, ortho protons).

Anal. Calcd for $C_9H_{11}N_4I$: C, 35.78; H, 3.67; N, 18.54. Found: C, 35.64; H, 3.75; N, 18.23.

The lower layer and the benzene solution used for the washing of the oil were collected, and the solvents were removed *in vacuo* to give 0.115 g (57%) of crystals which consisted of 0.056 g (27%) of **2** and 0.059 g (30%) of **1** recovered. The ratio of **2** and **1** in the crystals was determined by integral ratio of the nmr spectrum at δ 4.38 and 4.18 ppm, respectively.[17]

Thermal Decomposition of 3.—The crystalline **3** (0.078 g) obtained in the above reaction was heated to reflux in xylene (5 ml). After 2 hr, all crystals of **3** were completely decomposed to be dissolved in xylene. Xylene was evaporated *in vacuo* to give 0.041 g (100%) of pale yellowish crystals identified as pure **1** by nmr spectrum.

Reaction of 1 with Methyl Iodide at Room Temperature.—A solution of **1** (0.127 g) in methyl iodide (10 ml) was allowed to stand at room temperature. After 90 days, a pale brownish oil was separated from the upper layer. The oil was washed with benzene, and the solvent was removed *in vacuo* at room temperature to give 0.088 g (37%) of crystals, whose nmr spectrum ($CDCl_3$) has three singlets at δ 4.30, 4.54, and 4.76 ppm (78:11:11). The distribution of **3** and **4** in the crystals was determined as 78:22. The upper layer and the benzene solution used for the washing of the oily product were collected, and the solvents were evaporated off *in vacuo* to give 0.077 g (61%) of crystals containing 0.008 g (6%) of **2** and 0.069 g (55%) of **1** recovered.

Thermal Decompositon of the Mixture of 3 and 4.—The mixture of **3** and **4** (0.100 g) obtained in the above reaction was heated in toluene for 18 hr. Insoluble solids, **3** and **4**, were completely decomposed to be dissolved in toluene. Evaporation of toluene *in vacuo* gave 0.053 g (100%) of pale yellowish crystals. The nmr spectrum showed that the product consisted of **1** and **2** in a ratio of 76:24.

Reaction of 1-Ethyl-5-phenyltetrazole (5) with Ethyl Iodide.—A solution of **5**[16,19] (0.2178 g) in ethyl iodide (3 ml) was heated at 130° for 10 hr. Evaporation of ethyl iodide gave 0.2316 g of brownish oil. To a methylene chloride solution of the product was added 0.001 g of charcoal. After filtration, methylene chloride was evaporated to give 0.2160 g (99%) of colorless liquid identified as 2-ethyl-5-phenyltetrazole (**6**). There was no detection of the starting ingredient **5** in the product by nmr analysis: bp 123° (5 mm); $n^{22}\mathrm{D}$ 1.5536; nmr ($CDCl_3$) δ 1.68 (t, 3 H), 4.67 (q, 2 H), 7.50 (m, 3 H, meta and para protons), 8.15 ppm (m, 2 H, ortho protons); uv (EtOH) λ_{max} 239 nm (ϵ_{max} 15,800).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17. Found: C, 62.10; H, 5.66; N, 32.44.

Reaction of 5 with Ethyl Iodide at 70°.—A solution of **5** (0.0985 g) in ethyl iodide (3 ml) was heated at 70° for 24 hr. Evaporation of ethyl iodide gave 0.1043 g of crystals which were dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted and the residual colorless crystals (0.0146 g, 8.1%) were identified as 1,4-diethyl-5-phenyltetrazolium iodide (**8**): mp 154–155° (160° dec); nmr ($CDCl_3$) δ 1.73 (t, 6 H), 4.56 (q, 4 H), 7.76 (m, 3 H, meta and para protons), 8.25 ppm (m, 2 H ortho protons).

Anal. Calcd for $C_{11}H_{15}N_4I$: C, 40.02; H, 4.58; N, 16.97. Found: C, 40.20; H, 4.62; N, 17.14.

The ethereal solution was evaporated off to give 0.0898 g of pale yellowish crystals containing 0.0808 g (82.1%) of the starting ingredient **5** and 0.0090 g (9.1%) of isomerized **6**.

Reaction of 5 with Methyl Iodide.—A solution of **5** (0.1238 g) in methyl iodide (2 ml) was heated at 130° for 10 hr. Evaporation of methyl iodide gave 0.1172 g of long needles containing no ether-insoluble tetrazolium iodide. By nmr analysis, the composition of the product was found to be **2** (94%) and **6** (6%).

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(15) W. S. McEwan and M. W. Rigg, *J. Amer. Chem. Soc.*, **73**, 4725 (1951); M. M. Williams, W. S. McEwan, and R. A. Henry, *J. Phys. Chem.*, **61**, 261 (1957).

(16) E. K. Harville, R. M. Herbst, and F. C. Sheiner, *J. Org. Chem.*, **15**, 662 (1950).

(17) R. R. Frazer and K. F. Haque, *Can. J. Chem.*, **46**, 2855 (1968).

(18) R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961).

(19) Mp 67–68° (lit.[16] mp 70–71°); nmr ($CDCl_3$) δ 1.55 (t, 3 H), 4.46 (q, 2 H), 7.64 and 7.67 ppm (d, 5 H); uv (EtOH) λ_{max} 231 nm (ϵ_{max} 10,900).

Reaction of 5 with Methyl Iodide at 70°.—A solution of 5 (0.1670 g) in methyl iodide (2 ml) was heated at 70°. When the reaction time was 3 hr, there was found a small amount of oily material as an upper layer, the amount of which increased as reaction time extended. After 22 hr of heating, methyl iodide was evaporated *in vacuo* to give an oily product which was dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted and the residual crystals (0.2308 g, 76.3%) were purified by the same additional procedure. The crystals were identified as 1-methyl-4-ethyl-5-phenyltetrazolium iodide (7): mp 118–119° (130° dec); nmr ($CDCl_3$) δ 1.83 (t, 3 H, CH_3CH_2), 4.29 (s, 3 H, CH_3), 4.58 (q, 2 H, CH_3CH_2), 7.70 (m, 3 H, meta and para protons), 8.24 ppm (m, 2 H, ortho protons).

Anal. Calcd for $C_{10}H_{13}N_4I$: C, 37.99; H, 4.15; N, 17.72. Found: C, 37.74; H, 4.07; N, 17.58.

The ethereal solutions were collected, and ether was evaporated off *in vacuo* to give 0.0393 g of liquid whose composition was determined by nmr analysis to be 0.0020 g (1.3%) of 1, 0.0150 g (9.8%) of 2, and 0.0173 g (10.3%) of 5.

Thermal Decomposition of 7.—To 3 ml of benzene was added 0.0514 g of 7, and the mixture in a sealed glass tube was kept at 130°. Upon heating for 40 min, the insoluble, molten 7 was decomposed completely to be dissolved in benzene. Evaporation of benzene gave 0.0277 g of liquid consisting of 0.0235 g (83%) of 5 and 0.0042 g (16%) of 1.

Reaction of 1 with Ethyl Iodide.—A solution of 1 (0.0478 g) in ethyl iodide (2 ml) was heated at 130° for 10 hr. Evaporation of ethyl iodide gave 0.0520 g (100%) of pure 6. Even a trace of 2 was not detected by nmr analysis.

Reaction of 1 with Ethyl Iodide at 70°.—A solution of 1 (0.1093 g) in ethyl iodide (2 ml) was heated in a sealed glass tube at 70°. Upon heating for 72 hr, a small amount of oily material was found in the reaction mixture. Evaporation of ethyl iodide gave 0.1201 g of yellowish liquid, which was dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted from the residual crystals (0.0079 g, 3.7%) which were identified as 7 by comparing the ir and nmr spectra with those of the authentic 7 prepared by the reaction of 5 with methyl iodide. The ethereal solution was evaporated *in vacuo* to give 0.1122 g of liquid which crystallized on standing. By nmr analysis, 0.0612 g (51.5%) of 6, 0.0151 g (12.7%) of 5, and 0.0359 g (30.5%) of 1 were found in the ether-soluble fraction.

Reaction of 2 with Ethyl Iodide.—A solution of 2 (0.1014 g) in ethyl iodide (2 ml) was heated at 130° for 22 hr. Evaporation of the solvent gave 0.1028 g of liquid containing 0.0834 g (83.1%) of 2 recovered and 0.0185 g (16.8%) of 6.

Reaction of 6 with Methyl Iodide.—A solution of 6 (0.1080 g) in methyl iodide (2 ml) was heated at 130° for 13 hr. Evaporation of the solvent *in vacuo* gave 0.1101 g of liquid whose component was determined by nmr analysis to be 6 (95.2%) and 2 (4.8%).

Registry No.—1, 20743-50-4; 3, 31818-92-5; 5, 24433-71-4; 6, 31818-94-7; 7, 31818-95-8; 8, 31818-96-9; methyl iodide, 74-88-4; ethyl iodide, 75-03-6.

Lactam Formation from the Condensation of Stilbenediamine with Glyoxal

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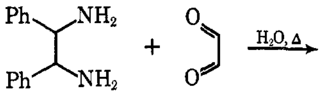
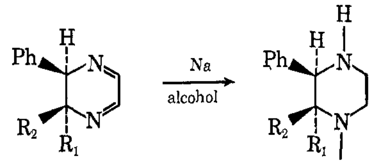
Received April 27, 1971

In 1941 Hayashi reported[1] that condensation of *dl*-stilbenediamine (1) with glyoxal yielded *trans*-2,3-diphenyl-2,3-dihydropyrazine (2) which on subsequent reduction with sodium and alcohol afforded *trans*-2,3-diphenylpiperazine (3). In a similar fashion *meso*-stilbenediamine (4) gave *cis*-2,3-diphenyl-2,3-dihydropyrazine (5) which in turn was readily reduced to *cis*-2,3-diphenylpiperazine (6).



1, *dl*
4, meso

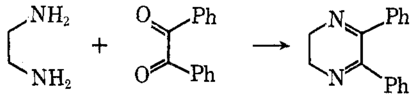


2, R_1 = Ph; R_2 = H
5, R_1 = H; R_2 = Ph

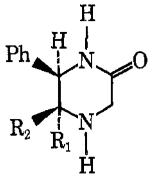
3, R_1 = Ph; R_2 = H
6, R_1 = H; R_2 = Ph

We now offer conclusive evidence that the original structural assignments for the condensation products 2 and 5 were incorrect and propose a plausible explanation for the formation of the observed products.

It has long been believed that 2,3-dihydropyrazines could be obtained by condensing α diketones with α,β-diamines;[2] for example, Mason[3] reported that heating benzil with ethylenediamine in alcoholic solution yielded 5,6-diphenyl-2,3-dihydropyrazine (7). Our experimental results confirmed the structure of this condensation product (7) as proposed by Mason. It was, therefore, of considerable interest to us to find that the product of the condensation of 1 with glyoxal di(sodium bisulfite) was *trans*-5,6-diphenylpiperazin-2-one (8) instead of the reported product 2.



7



8, R_1 = Ph; R_2 = H
9, R_1 = H; R_2 = Ph

The presence of a lactam group in 8 was demonstrated by the ir spectrum, which displayed absorption bands at 1665 (C=O), 3180 (amide NH), and 3300 cm^{-1} (amine NH). The mass spectrum[4] showed a molecular ion at *m/e* 252 (rel intensity 30), indicating addition of glyoxal to stilbenediamine with the resulting loss of only 1 equiv mol of water. Fragment ions present at *m/e* (rel intensity) 147 (8), 146 (6), 118 (45), 106 (100), 104

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[1] T. Hayashi, *Sci. Pap. Inst. Phys. Chem. Res.*, **38**, 455 (1941); *Chem. Abstr.*, **41**, 5886 (1947).

[2] Y. T. Pratt, *Heterocycl. Compounds*, **6**, 412 (1957).

[3] A. T. Mason, *J. Chem. Soc.*, **55**, 97 (1889).

[4] Numbers following *m/e* values in the text refer to per cent relative abundance normalized to *m/e* 106 = 100%.