**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

LASZLO L. DARKO* AND JERROLD KARLINER

*Department of Organic Chemistry and Analytical Research Department, CIBA-GEIGY Corporation, Ardsley, New York 10502*

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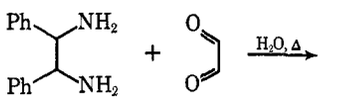
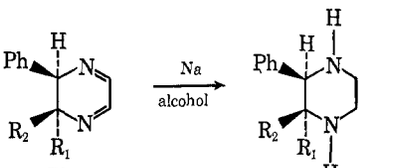
In 1941 Hayashi reported[1] that condensation of *dl*-stilbenediamine (1) with glyoxal yielded *trans*-2,3-diphenyl-2,3-dihydropyrazine (2) which on subsequent reduction with sodium and alcohol afforded *trans*-2,3-diphenylpiperazine (3). In a similar fashion *meso*-stilbenediamine (4) gave *cis*-2,3-diphenyl-2,3-dihydropyrazine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



1, *dl*
4, meso

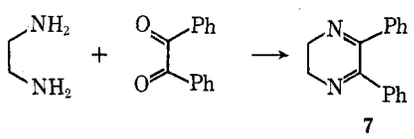


2, $R_1$ = Ph; $R_2$ = H
5, $R_1$ = H; $R_2$ = Ph

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.



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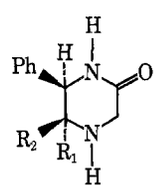


8, $R_1$ = Ph; $R_2$ = H
9, $R_1$ = H; $R_2$ = Ph

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

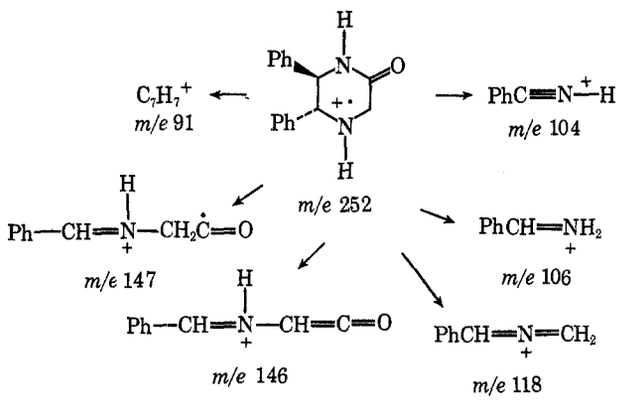
(1) T. Hayashi, *Sci. Pap. Inst. Phys. Chem. Res.*, **38**, 455 (1941); *Chem. Abstr.*, **41**, 5886 (1947).

(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%.

(13), and 91 (14) are compatible with structure **8** as shown in the following scheme.



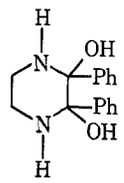

The nmr spectrum further substantiates the assigned structure **8**. The amine and amide protons appeared as broad singlets at 1.84 and 6.24 ppm, respectively, each integrating for one proton. A two-proton singlet at 3.77 ppm was assigned to the methylene group, while one-proton doublets at 3.78 and 4.54 ppm were ascribed to the methine protons adjacent to the amine and amide nitrogen atoms, respectively. The latter exhibited coupling constants of 9 cps, in agreement with axial–axial proton interactions[5] as required by structure **8**. The remaining ten aromatic protons resonate as a complex pattern between 6.8 and 7.4 ppm.

Condensation of **4** with glyoxal took the same unexpected route, yielding *cis*-5,6-diphenylpiperazin-2-one (**9**). Again, compound **9** had the same physical constants that Hayashi reported for *cis*-2,3-diphenyl-2,3-dihydropyrazine (**5**), but the spectral properties exhibited by **9** were similar to those of **8**. In the ir spectrum the lactam carbonyl appeared at 1675 $cm^{-1}$, the amine NH at 3290 $cm^{-1}$, and the amide NH at 3180 $cm^{-1}$. The mass spectral fragmentation pattern was identical with that obtained for **8**. The nmr spectrum displayed resonances at $\delta$ 1.79 (1 H, amine NH), 3.74 (2 H, $HNCH_2$), 4.51 (2 H, center of AB pattern,[6] $J_{ax-eq}$ = 4 cps,[5] HCCH), 6.7–7.3 (10 H, HPh), 7.38 (1 H, amide NH).

(5) M. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.

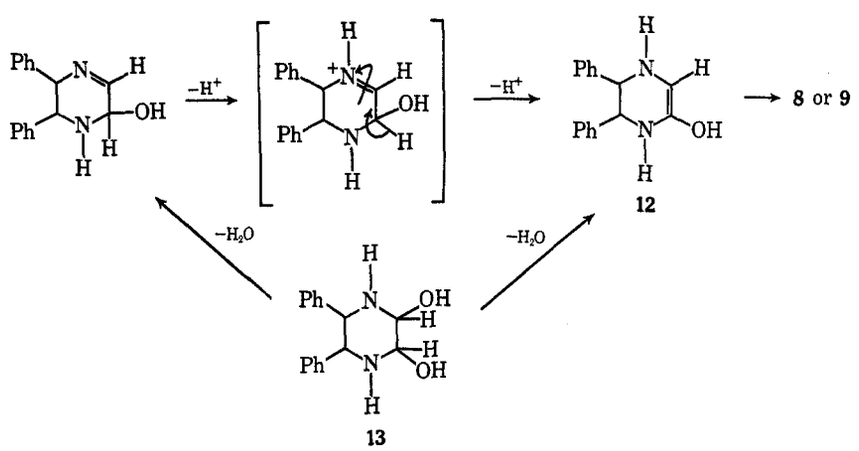
(6) The low-field portion resonates as a triplet before $D_2O$ exchange due to additional coupling ($J$ = 4 cps) to the amide NH proton.

The product obtained (7) from the condensation of ethylenediamine and benzil could be formed either by sequential condensation and dehydration or by condensation to give **10**, followed by elimination of 2 mol of water. In the case of the condensation of **1** or **2**



**10**

with glyoxal, the reaction may proceed through **11**, an imino alcohol intermediate, which by a protonation and deprotonation sequence could form **12**, the tautomeric form of the observed products **8** and **9**. The formation of the imino alcohol **11** could be envisioned by two different pathways. The first mechanism involves the self-condensation of the initially formed imino aldehyde, while the second pathway involves the formation of the dihydroxypiperazine **13** as an intermediate. Experimental data at hand does not exclude the possibility of direct dehydration of the latter to **12** instead of to **11**.




## Experimental Section[7]

*cis*-**5,6-Diphenylpiperazin-2-one**.—To a warm solution of *meso*-stilbenediamine (5.0 g, 0.023 mol) in water (375 ml) was added glyoxal di(sodium bisulfite) (8.5 g, 0.032 mol) and the reaction mixture was kept at 70–80° on a water bath for 3 hr. The orange precipitate which formed was filtered, and the filtrate was treated with charcoal, filtered, and concentrated. The resulting solid was recrystallized from acetone–hexane, yielding 3.2 g (55%) of pure *cis*-5,6-diphenylpiperazin-2-one, mp 163.5–164.5° (reported for *cis*-2,3-diphenyl-2,3-dihydropyrazine, mp 163.5–164.5° [1]).

*trans*-**5,6-Diphenylpiperazin-2-one**.—To a hot solution of *dl*-stilbenediamine dihydrochloride (10.0 g, 0.035 mol) in water (350 ml) was added a hot solution of glyoxal di(sodium bisulfite) (10.0 g, 0.038 mol) in 2% aqueous HCl (250 ml). The reaction mixture was heated at 70–80° on a water bath for 3 hr, cooled, treated with charcoal, and filtered. The solvent was concentrated and the resulting solid was collected. The latter was treated with 30% aqueous potassium hydroxide to liberate the free base, which after recrystallization from benzene afforded

(7) Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Mass spectra were determined with a Model MS-902 mass spectrometer with a direct insertion probe and an ionizing current of 70 eV. Nmr spectra were determined in deuteriochloroform with a Varian A-60D spectrometer using tetramethylsilane as an internal standard. The ir scans were obtained with a Perkin-Elmer Model 225 spectrometer. No attempt was made to isolate or characterize the minor components in the reactions described.

5.3 g (60%) of the product, mp 202–203° (reported for *trans*-2,3-diphenyl-2,3-dihydropyrazine, mp 202–203° [1]).

**Registry No.**—1, 16635-95-3; 4, 951-87-1; 8, 31819-61-1; 9, 31819-62-2; glyoxal, 107-22-2.

**Acknowledgments.**—The authors wish to express their appreciation to Miss S. Swiatkowski for technical assistance and Dr. K. Doebel and Mr. R. Grulich for helpful discussions.

## Pyridazines. XLII. Tetrazolo–Azido Isomerizations of Isomeric Pyridotetrazolo[1,5-*b*]pyridazines

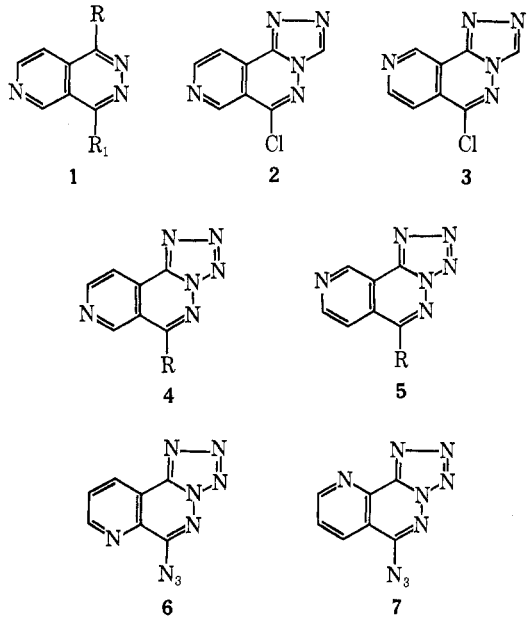
B. STANOVNIK, M. TIŠLER,* AND B. STEFANOV

*Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia*

*Received May 24, 1971*

Our previous investigations on tetrazolo–azido isomerizations of several heterocyclic systems[1-8] prompted an investigation of this phenomenon on 6-azidopyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**4**, R = $N_3$) and 6-azidopyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine (**5**, R = $N_3$). The synthesis of both isomers was accomplished from the corresponding 1-chloro-4-hydrazinopyrido[3,4-*d*]pyridazine (**1**, R = Cl; $R_1$ = $NHNH_2$)[9] or its isomer (**1**, R = $NHNH_2$; $R_1$ = Cl) as starting compounds. These were converted either to the isomeric pyrido-*s*-triazolo[4,3-*b*]pyridazines (**2** and **3**) or into tetrazolo analogs **4** and **5** (R = Cl). Upon hydrazinolysis and subsequent nitrosation the isomeric azido compounds **4** and **5** (R = $N_3$) were obtained. Moreover, the isomer **4** (R = $N_3$) is obtainable in a direct synthetic approach from 1,4-dichloropyrido[3,4-*d*]pyridazine and sodium azide. The structures of both isomers were established by the nmr spectra. The singlet for $H_{10}$ of compound **5** (R = $N_3$) appears at lower field than that for $H_7$ of compound **4** (R = $N_3$), as observed with similar polycyclic systems.[10,11] It was also observed that isomer **5** (R = $N_3$), when crystallized from ethanol, is transformed into the thermodynamically more stable isomer **4** (R = $N_3$).

In dimethyl sulfoxide-$d_6$ an equilibrium is established at 70°, consisting of about 33% of **5** (R = $N_3$) and 67% of **4** (R = $N_3$), whereas for the isomeric pair of 6-azidopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (**6**) and 6-azidopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (**7**)[1] the equilibrium mixture consisted of 42% of **6** and 58% of **7**. The determined enthalpy changes, $\Delta H$, for these isomerizations, which follow first-order kinetics, were calculated as −2.2 kcal/mol for **5** → **4** (R = $N_3$) and −1.3 kcal/mol for **6** → **7**, respectively. The Arrhenius activation energies, $E_a$, calculated from the rate constants, are 25.2 kcal/mol (**5** → **4**, R = $N_3$) and 27.8 kcal/mol (**6** → **7**), respectively. As anticipated, they are somewhat higher than those observed with the corresponding azidotetrazolo[1,5-*b*]pyridazines,[1] whereas the enthalpy changes are lower. The calculated $\Delta S^*$ values were −2 eu for **5** → **4** (R = $N_3$) and +7 eu for **6** → **7**.




### Experimental Section

Melting points were determined on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, and nmr spectra were taken on a JEOL JNM-C-60HL spectrometer using tetramethylsilane as internal standard.

1-Chloro-4-hydrazinopyrido[3,4-*d*]pyridazine and 4-chloro-1-hydrazinopyrido[3,4-*d*]pyridazine were prepared according to Matsuura and Okui.[9] They formed the corresponding benzylidene derivatives: **1** (R = Cl; $R_1$ = NHN=CHPh), mp 283–284° (from EtOH and DMF, 3:1).

*Anal.* Calcd for $C_{14}H_{10}ClN_5$: C, 59.26; H, 3.55; N, 24.69. Found: C, 59.20; H, 3.46; N, 24.83.

The benzylidene derivative of the other isomer (**1**, R = NHN=CHPh; $R_1$ = Cl) had mp 252° (from EtOH and DMF, 3:1).

*Anal.* Calcd for $C_{14}H_{10}ClN_5$: C, 59.26; H, 3.55; N, 24.69. Found: C, 59.00; H, 3.41; N, 24.74.

**6-Chloropyrido[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine (3).**—Compound **1** (R = Cl; $R_1$ = $NHNH_2$) (0.3 g) and diethoxymethyl acetate (1 ml) were gently heated until solution occurred and then boiled for 3 min. Upon cooling the separated product (0.26 g) was recrystallized from DMF and EtOH (1:3): mp 254° (it sublimes above 200°); nmr (DMSO-$d_6$) $\delta$ 9.52 (s, $H_3$), 8.28 (d, $H_7$), 9.25 (d, $H_8$), 9.88 (s, $H_{10}$), $J_{7,8}$ = 5.6 Hz.

*Anal.* Calcd for $C_8H_4ClN_5$: C, 46.73; H, 1.96; N, 34.07. Found: C, 46.45; H, 2.08; N, 34.33.

**6-Chloropyrido[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (2).**—The compound was prepared in the same way from compound **1** (R = $NHNH_2$; $R_1$ = Cl) (0.2 g) (yield 0.17 g): mp 260° (from EtOH and DMF, 1:3); nmr (DMSO-$d_6$) $\delta$ 9.50 (s, $H_3$), 9.40 (s, $H_7$), 9.25 (d, $H_8$), 8.45 (d, $H_{10}$), $J_{9,10}$ = 5.6 Hz.

*Anal.* Calcd for $C_8H_4ClN_5$: C, 46.73; H, 1.96; N, 34.07. Found: C, 47.10; H, 2.22; N, 34.26.

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(11) B. Stanovnik, M. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968).