# The Preparation of 2,6-Diaminopyrazine, 2,6-Diazidopyrazine and Some of Their Derivatives

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A much improved synthesis of the heretofore difficultly obtainable 2,6-diaminopyrazine (**4**) was afforded by the low-pressure catalytic hydrogenation (palladium on carbon) of 2,6-diazidopyrazine (**2**); reaction of 2,6-dichloropyrazine (**1**) and sodium azide gave **2** in 84% yield. The outcome of the reduction was found to be solvent dependent: 1,2-dimethoxyethane containing aqueous ammonia gave **4** in 83% yield; 1,2-dimethoxyethane alone gave 5-aminotetrazolo[1,5-*a*]-pyrazine (**3**) in 26% yield. Additional alternative syntheses of **3** and **4** are described. A number of acyl and azo derivatives of **4** were prepared. Reactions of **2** with dimethyl acetylenedicarboxylate and ethyl acetate (base catalyzed) leading to *vic*-triazole derivatives are also described.

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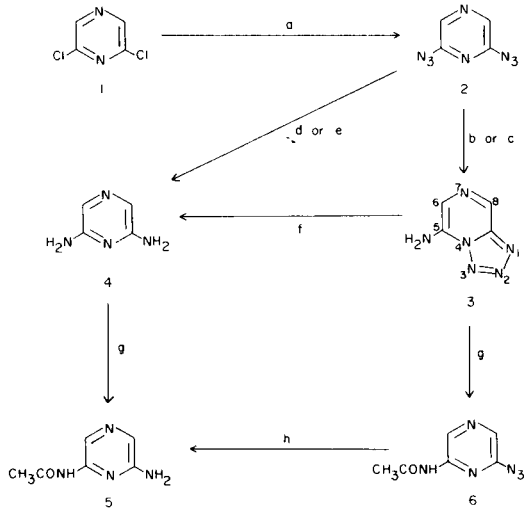
Preparation of 1,3,5,7,9b-pentaazaphenalene and 1,3,4,6,8,9b-hexaazaphenalene, ring systems described in a previous publication (2) both require 2,6-diaminopyrazine (**4**) as starting material. Existing methods for the preparation of **4** leave much to be desired both as to yield (3) and ease of preparation (4). We have found that **4** of excellent quality may be prepared in good yield (83%) by low-pressure catalytic (palladium on carbon) hydrogenation of 2,6-diazidopyrazine (**2**) in 1,2-dimethoxyethane (glyme) (peroxide free) containing aqueous ammonia. Use of glyme containing peroxides resulted in a lower yield (60%) of poorer quality **4**.

Without ammonia, the reduction takes a different course, yielding 5-aminotetrazolo[1,5-*a*]pyrazine (**3**) in 26% yield. The ability of ammonia to alter the course of catalytic reduction of tetrazolo[1,5-*a*]pyridine was observed by Boyer and co-workers (5). Although compound **3** is capable of isomerizing to the azide form, 2-amino-6-azidopyrazine, the ir data from the solid state and the pmr data from perdeuteriodimethylsulfoxide (DMSO-$d_6$) solution indicated the presence of **3** only (6). Thus a Nujol mull of **3** showed the absence of azide absorption in the 4.60 to 4.72 $\mu$m region and the presence of ($NH_2$) by absorption at 3.00, 3.05 $\mu$m. The pmr spectrum disclosed the presence of two exchangeable ($NH_2$) protons at $\delta$ 7.89 (broad) and two singlets at $\delta$ 7.61 and 8.83 ($H_6$ and $H_8$ of 3). This apparent stabilization of the tetrazole form of an azidoazomethine-tetrazole equilibrium by electron donating groups, in this case ($NH_2$), has been noted elsewhere (7). Catalytic hydrogenation (palladium on carbon) of **3** using 2-methoxyethanol containing aqueous ammonia as solvent gave **4**. Conversion of the amino group in **3** to acetamido, using acetic anhydride caused tetrazole destabilization and gave 2-acetamido-6-azidopyrazine (**6**). Catalytic hydrogenation (palladium on carbon) of **6** using ethanol containing aqueous ammonia as solvent gave 2-acetamido-6-aminopyrazine (**5**), a compound that was also prepared from **4** by reaction with acetic anhydride.

Sodium borohydride (8) and lithium aluminum hydride (9) have also been cited as reagents for reducing azides to amines. Interestingly, use of sodium borohydride in ethanol with **2** gave a 90% yield of **3** whereas lithium aluminum hydride in glyme resulted in a much lower yield (21%) of **4**.

The preparation of **2** in 84% yield involved the reaction

Scheme I




a, $NaN_3$/DMSO
b, $H_2$, Pd/C, glyme
c, $NaBH_4$, EtOH
d, $H_2$, Pd/C, glyme, $NH_4OH$
e, $LiAlH_4$
f, $H_2$, Pd/C, $MeOCH_2CH_2OH$, $NH_4OH$
g, $(CH_3CO)_2O$
h, $H_2$, Pd/C, EtOH, $NH_4OH$

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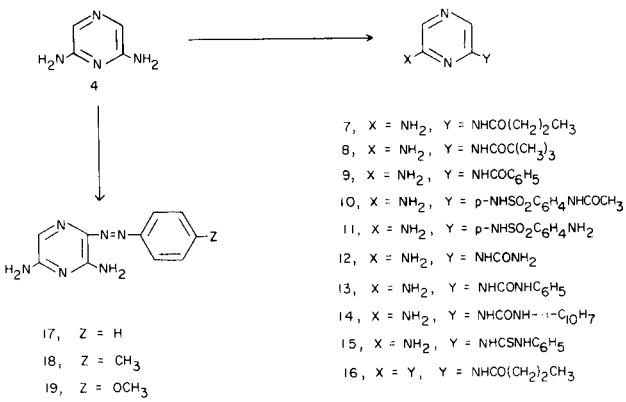
of 2,6-dichloropyrazine (**1**) with sodium azide in dimethyl sulfoxide. There appeared to be no 5-azidotetrazolo-[1,5-*a*]pyrazine present with 2 either in the solid state (ir, Nujol mull) or in deuteriochloroform solution (pmr) (6). An attempt to convert some of **2** to the tetrazole form by refluxing it in ethanol for 24 hours returned only **2** unchanged.

Since only a few derivatives of **4** are known (3,4), it seemed worthwhile to investigate the preparation of others, now that **4** is readily obtainable. In addition, a few reactions of **2** and **3** were undertaken.

Scheme 2 outlines the derivatives prepared from **4**. Acylated derivatives **7, 8, 9** and **16** were prepared by reacting **4** with the corresponding anhydrides. Reaction of **4** with *p*-acetaminobenzenesulfonyl chloride gave **10** which on subsequent alkaline hydrolysis yielded the sulfonanilamide derivative **11**. Reaction of **4** with nitrourea gave urea derivative **12**; the other urea derivatives, **13, 14, 15** were obtained by reaction of **4** with the respective isocyanate, or isothiocyanate. Azo derivatives **17, 18, 19** were obtained by coupling **4** with the corresponding diazotized aromatic amines.

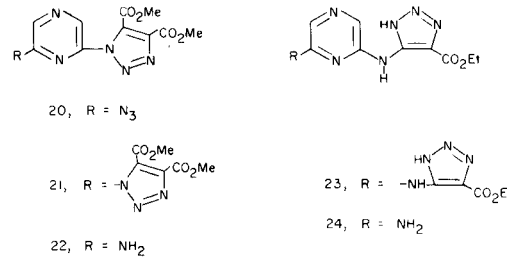
Scheme 2




Dimethyl acetylenedicarboxylate (DMAD), is known to react by cycloaddition with aryl azides (10) and with certain tetrazolopolyazines (11,12) to give 1-substituted-4,5-dicarbomethoxy-1,2,3-triazoles. Reaction of **2** with excess DMAD in refluxing glyme for 19 hours gave a mixture of 2-azido-6-(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**20**), (18%), and 2,6-bis(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**21**), (15%). There appeared to be none of the tetrazole form present with **20** either in the solid state (ir, Nujol mull) or in deuteriochloroform solution (pmr). Low-pressure catalytic reduction (palladium on carbon) of **20** in glyme containing aqueous ammonia gave 2-amino-6-(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**22**). Attempts to prepare **22** by reacting DMAD with **3** were unsuccessful.

Dimroth (13), and Lieber and co-workers (14) have shown that alkyl and aryl azides react with ethyl cyanoacetate under base catalysis at low temperatures to yield primarily 1-substituted-5-amino-1,2,3-triazoles. These compounds undergo irreversible isomerization to the more acidic 5-substituted amino-1,2,3-triazole isomer by refluxing them in pyridine. Even recrystallization from typical polar solvents causes partial isomerization. In an attempt to avoid this isomer problem, we investigated the reaction of **2** with ethyl cyanoacetate (2 moles) under strongly basic conditions (sodium hydride) in dimethyl sulfoxide at boiling-water bath temperature. A 30% yield of the desired *N,N'*-bis(4-carbethoxy-1,2,3-triazole-5-yl)-2,6-diaminopyrazine (**23**) was obtained. A reaction of **3** with ethyl cyanoacetate under reaction conditions similar to those used with **2** gave 2-amino-6-*N*(4-carbethoxy-1,2,3-triazole-5-yl)aminopyrazine (**24**) in 19% yield.

Figure 1




## EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting-point bath and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 735B spectrophotometer. Pmr spectra were determined on a Varian EM-360 spectrometer using TMS as an internal reference. Analyses were performed by Micro-Analysis Inc., Wilmington, Delaware. All evaporations were carried out on a rotary evaporator at reduced pressure.

The glyme, (1,2-dimethoxyethane) that was used as solvent in the catalytic reductions was freed of peroxides by distilling it from lithium aluminum hydride and was stored over calcium hydride under nitrogen. The following compounds were obtained from Aldrich Chemical Company and used without further purification: 2,6-dichloropyrazine, butyric anhydride, trimethylacetic anhydride, benzoic anhydride, *p*-acetaminobenzenesulfonyl chloride and dimethyl acetylenedicarboxylate. Woelm silica gel (70-230 mesh) for column chromatography was obtained from ICN Pharmaceutical Inc. Nitrourea was prepared using a method described in the literature (15).

2,6-Diaminopyrazine (**4**).

A. From Compound **2** and Hydrogen (Palladium on Carbon).

A solution of 9.72 g. (0.06 mole) of **2** in 135 ml. of peroxide-free glyme was added to a 500 ml. Parr low-pressure hydrogenation bottle containing 3.0 g. of 10% palladium on carbon catalyst.

After adding 8.0 ml. of concentrated aqueous ammonium hydroxide to the bottle and purging with hydrogen several times. the bottle was pressured with hydrogen to 50 psi. The mixture was shaken for 1 hour in a Parr hydrogenation apparatus; there was no pressure fall. The bottle was purged with hydrogen several times and repressured to 50 psi and shaken for one hour. This operation was repeated four more times, total shaking time, 7 hours. The contents of the bottle were removed with the aid of 20 ml. of glyme and the mixture was heated to boiling and filtered; the carbon catalyst was extracted with 50 ml. of boiling glyme and the combined filtrates were evaporated to dryness, 5.5 g. (83%) of an off-white solid, m.p. 136-137°. Recrystallization from acetonitrile/toluene, 75/25 gave white crystals, m.p. 137-138°, (Lit. m.p. 136° (4)); ir λ (Nujol): μm 2.95, 3.02 ($NH_2$); pmr (DMSO-$d_6$): δ 5.68 [s (broad) 4H, $2NH_2$, exchangeable with deuterium oxide], 6.99 (s, 2H, $H_3$, and $H_5$).

*Anal.* Calcd. for $C_4H_6N_4$: C, 43.63; H, 5.49; N, 50.88. Found: C, 43.78; H, 5.48; N, 51.06.

Use of ethanol or 2-methoxyethanol in place of glyme in the above reaction gave **4** in lower yields and of reduced purity.

B. From Compound **2** and Lithium Aluminum Hydride.

Under a nitrogen atmosphere a stirred mixture of 2.39 g. (0.036 mole) of lithium aluminum hydride (57.2% dispersion in oil) in 60 ml. of dry glyme, (initially at 25°) was treated dropwise with a solution of 4.86 g. (0.03 mole) of **2** in 70 ml. of dry glyme. The exothermic reaction was held below 50° by external cooling and then allowed to stir at ambient temperatures for 2 hours. Evaporation of the reaction mixture to dryness and extraction of the residue with 50 ml. of boiling acetonitrile gave 0.7 g. (21%) of crude **4**, m.p. 122-124°, after concentration of the extract to dryness. Recrystallization from acetonitrile/toluene, 75/25 and then toluene was required to give **4** identical in m.p. and spectral properties to **4** prepared as in method "A".

C. From Compound **3** and Hydrogen (Palladium on Carbon).

A solution of 0.75 g. (0.0055 mole) of **3** in 135 ml. of 2-methoxyethanol was added to a 500 ml. Parr hydrogenation bottle containing 0.70 g. of 5% palladium on carbon catalyst and 0.7 ml. of concentrated ammonium hydroxide. The bottle was purged with hydrogen several times and then pressured to 50 psi. The mixture was shaken for 4 hours and the contents of the bottle was then filtered at room temperature and the filtrate was evaporated. The oily residue was stirred with 15 ml. of ether and the precipitate which formed was collected by filtration, 0.35 g. (58%) of a beige solid, m.p. 136-138°, with spectral properties identical to **4** prepared using method "A".

The choice of 2-methoxyethanol as solvent for the reduction came by the fact that it was the only solvent that would dissolve more than minute amounts of **3** at room temperature and also be suitable for hydrogenation reactions.

5-Aminotetrazolo[1,5-*a*]pyrazine (**3**).

A. From Compound **2** and Hydrogen (Palladium on Carbon).

The reaction conditions and amounts of reagents used to prepare **4** from **2** using method "A" were followed exactly except that the concentrated ammonium hydroxide was omitted. The contents of the Parr hydrogenation bottle upon completion of reaction were a light grey, indicating something had precipitated during the reduction. The reaction mixture was heated to boiling, filtered and the filtrate was evaporated to dryness. The residue, a dark tacky solid, resisted purification.

The carbon-catalyst filter cake was extracted with 75 ml. of boiling 2-methoxyethanol and the extract was chilled and filtered to give 2.1 g. (26%) of a beige solid, m.p. 220° dec. (vigorous). Recrystallization from 2-methoxyethanol did not raise the decomposition point (the decomposition point varies slightly with the rate of heating, but is reproducible at a given rate); ir λ (Nujol): μm 3.00, 3.05 ($NH_2$) no significant absorption at 4-5 μm; pmr (DMSO-$d_6$): δ 7.61 (s, 1H, $H_6$), 7.89 [s, (broad), 2H, $NH_2$] 8.83 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.96; N, 61.74. Found: C, 35.08; H, 3.13; N, 61.46.

B. From Compound **2** and Sodium Borohydride.

A stirred solution of 7.29 g. (0.045 mole) of **2** in 210 ml. of ethanol was treated with 3.42 g. (0.09 mole) of pulverized sodium borohydride in one portion. During a 30 minute reaction period the temperature rose to ~55° and a tan precipitate formed. The reaction mixture was allowed to cool to room temperature, filtered and the filter cake was washed successively with water, ethanol and ether. The dried product weighed 5.5 g. (90%) and melted 220° dec. (vigorous) before and after recrystallization from 2-methoxyethanol. Its spectral properties were identical to those of **3** prepared by the catalytic hydrogenation of **2**.

2-Acetamido-6-azidopyrazine (**6**).

A mixture of 4 g. (0.028 mole) of **3** and 32.5 g. (0.318 mole) of acetic anhydride was refluxed for 15 minutes. From the ice-chilled reaction mixture 3.37 g. (68%) of a beige solid was collected (filtration) washed with ether and air dried, m.p. 172-173° dec. Recrystallization from ethanol gave a beige solid, m.p. 173-174° dec.; ir λ (Nujol): μm 3.18 (NH), 4.75 ($N_3$), 6.02 (C=O); pmr (DMSO-$d_6$): δ 2.22 (s, 3H, $CH_3$), 8.05 (s, 1H, $H_3$ or $H_5$), 9.17 (s, 1H, $H_3$ or $H_5$), 10.6 [s (broad) 1H, NH].

*Anal.* Calcd. for $C_6H_6N_6O$: C, 40.45; H, 3.40; N, 47.17. Found: C, 40.26; H, 3.81; N, 47.16.

2-Acetamido-6-aminopyrazine (**5**).

A. From Compound **6**.

A mixture of 0.89 g. (0.005 mole) of **6**, 0.25 g. of 10% palladium on carbon, 0.42 ml. of concentrated aqueous ammonium hydroxide and 100 ml. of ethanol in a 500 ml. Parr hydrogenation bottle was purged several times with hydrogen and then pressured with hydrogen to 50 psi. The mixture was shaken for 1 hour; there was no pressure fall. The bottle was purged with hydrogen, repressured to 50 psi and shaken for 1 additional hour. The contents of the bottle were removed with the aid of 20 ml. of ethanol, filtered, and the filtrate was evaporated to dryness, 0.59 g. (78%), m.p. 220-221°. Recrystallization from acetonitrile gave white needles, m.p. 225-226°; ir λ (Nujol): μm 2.96, 3.05 (NH), 6.02 (C=O); pmr (DMSO-$d_6$): δ 2.10 (s, 3H, $CH_3$), 6.28 [s, (broad), 2H, $NH_2$ (exchangeable with deuterium oxide)], 7.65 (s, 1H, $H_3$ or $H_5$), 8.50 (s, 1H, $H_3$ or $H_5$), 10.16 [s (broad), 1H, NHCO, (exchangeable with deuterium oxide].

*Anal.* Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.83. Found: C, 47.42; H, 5.46; N, 36.66.

B. From Compound **4**.

A solution of 2.2 g. (0.02 mole) of **4**, 1.84 g. (0.018 mole) of acetic anhydride in 60 ml. of dry glyme was refluxed for 1 hour. About 40 ml. of glyme was then slowly removed by distillation and the residue was refluxed for an additional half hour. The precipitate which had formed was collected by filtration after first cooling the reaction mixture to room temperature. The ether-washed and air-dried beige solid weighed 1.36 g. and melted 220-238°. Recrystallization from acetonitrile gave 0.42 g.

(15%) of white needles, m.p. 225-226°, identical to **5** prepared from compound **6**.

2,6-Diazidopyrazine (**2**).

**CAUTION!** 2,6-Diazidopyrazine was found to be both impact and heat sensitive: Thus hitting a small sample ~ 50 mg., with a hammer caused it to explode. Also heating a sample in a melting point capillary to 200° caused it to decompose violently with a sharp report; the glass capillary however was still intact.

A stirred solution of 12.0 g. (0.081 mole) of **1** in 160 ml. of dimethyl sulfoxide was treated with 5.2 g. (0.08 mole) of sodium azide in one portion. The mixture was stirred and heated to ~60° at which point a mild exotherm began, causing the temperature to rise a few degrees. After the exotherm was spent, an additional 5.2 g. (0.08 mole) of sodium azide was added in portions, the temperature being maintained at 60-65°. The reaction mixture was stirred and heated for an additional 2.5 hours at 60-65°, cooled to room temperature and poured into 150 ml. of ice water. The precipitate that formed was collected by filtration, washed well with water, and air dried, 10.85 g. (84%), m.p. 60-63°. Recrystallization from petroleum ether (30-60°) gave white needles, whose surface turned blue on standing in light, m.p. 61-63°; ir λ (Nujol): μm 4.60, 4.70 ($N_3$), no absorption at 7.75, 9.26 or 9.85 μm, bands assigned to the presence of a tetrazole ring (16,17); pmr (deuteriochloroform): δ 7.81 (s, $H_3$ and $H_5$).

*Anal.* Calcd. for $C_4H_2N_8$: C, 29.63; H, 1.24; N, 69.12. Found: C, 29.74; H, 1.32; N, 68.91.

The blue surface color, which colorless crystals of 2,6-diazidopyrazine develop on standing, was found to be due to a reaction with light, (daylight or fluorescent light). Thus a freshly recrystallized sample of **2** (recrystallized in a dimly lit room) was colorless. Upon exposure of this sample to sunlight, the surface of the crystals turned bright blue immediately. The material beneath the surface was still colorless. The blue color of the diazide does not seem to affect its reactivity, m.p. or ir. Long exposure (several weeks) to direct sunlight results in its decomposition. Therefore, samples of **2** were stored in a dark cupboard.

2-Amino-6-butyramidopyrazine (**7**).

A mixture of 1.1 g. (0.01 mole) of **4**, 1.42 g. (0.009 mole) of butyric anhydride and 10 ml. of dry glyme was refluxed for 2 hours. The reaction mixture was cooled to room temperature, filtered and the filtrate was evaporated to dryness. After stirring the residue with 15 ml. of ether, the beige crystals that formed were collected by filtration, washed with ether and air dried, 0.83 g. (46%), m.p. 135-142°. Recrystallization from toluene gave beige crystals, m.p. 158-159°; ir λ (Nujol): μm 2.89, 2.99 (NH) 5.92 (C=O); pmr (DMSO-$d_6$): δ 0.92 [t (J ~6 Hz), 3H, $CH_3$], 1.62 [sextet (J ~ 6 Hz) 2H, $CH_2$], 2.3 [t (J ~6 Hz), 2H, $CH_2$], 6.25 [s (broad), 2H, $NH_2$], 7.67 (s, 1H, $H_3$ or $H_5$), 8.52 (s, 1H, $H_3$ or $H_5$), 10.06 [s, (broad) 1H, NH].

*Anal.* Calcd. for $C_8H_{12}N_4O$: C, 53.31; H, 6.71; N, 31.09. Found: C, 53,46; H, 6.50; N, 31.29.

2-Amino-6-trimethylacetamidopyrazine (**8**).

A mixture of 2.2 g. (0.02 mole) of **4**, 3.35 g. (0.018 mole) of trimethylacetic anhydride and 15 ml. of dry glyme was stirred and refluxed for 5 hours. The reaction mixture was evaporated to a thick syrup which on standing overnight partially crystallized. Trituration with ether followed by filtration yielded 0.85 g. (24%) of a beige solid, m.p. 143-146°. Recrystallization from 2-propanol gave white crystals, m.p. 151-152°; ir λ (Nujol): μm 2.87, 3.0 (NH), 5.97 (C=O); pmr (deuteriochloroform): δ 1.32 (s, 9H, $(CH_3)_3C$), 4.75 [s(broad), 2H, $NH_2$ (exchangeable with deuterium oxide)], 7.75 [s (broad), 2H (one H exchangeable with deuterium oxide) (NH overlapping $H_3$ or $H_5$)], 8.88 (s, 1H, $H_3$ or $H_5$).

*Anal.* Calcd. for $C_9H_{14}N_4O$: C, 55.65; H, 7.26; N, 28.84. Found: C, 55.61; H, 7.01; N, 28.61.

Use of 0.06 mole trimethylacetic anhydride in the above reaction gave **8** in 42% yield but none of the diacylated product.

2-Amino-6-benzamidopyrazine (**9**).

A mixture of 1.1 g. (0.01 mole) of **4**, 2.1 g. (0.0092 mole) of benzoic anhydride, 0.79 g. (0.01 mole) of dry pyridine and 10 ml. of dry glyme was refluxed for 2 hours, and then evaporated to dryness. The residue was dissolved in 15 ml. of 1*N* sodium hydroxide and extracted with 3 x 15 ml. portions of ether. The combined extracts were dried (sodium sulfate) and evaporated to dryness, 0.25 g. (13%), m.p. 144-146°. Recrystallization from water (decolorizing carbon) gave beige crystals, m.p. 161-163°; ir λ (Nujol): μm 2.91, 3.03 (NH), 6.05 (C=O).

*Anal.* Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.59; H, 4.74; N, 26.33.

2,6-bis(Butyramido)pyrazine (**16**).

A mixture of 2.2 g. (0.02 mole) of **4**, 6.32 g. (0.04 mole) of butyric anhydride and 20 ml. of dry glyme was refluxed and stirred for 2 hours. Upon cooling to room temperature, 2.27 g. (45%) of **16** crystallized and was filtered, washed several times with ether and air dried, m.p. 276-282°. Recrystallization from 2-methoxyethanol gave silvery plates, m.p. 289-291°; ir λ (Nujol): μm 3.06 (NH), 6.00 (C=O).

*Anal.* Calcd. for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.61; H, 7.25; N, 22.50.

2-(*p*-Acetamidobenzenesulfonamido)-6-aminopyrazine (**10**).

A stirred cold (0°) solution of 4.4 g. (0.04 mole) of **4** in 60 ml. of dry pyridine was treated in portions with 4.7 g. (0.02 mole) of *p*-acetamidobenzenesulfonyl chloride over a 15 minute period, while maintaining the temperature at 0-3°. The orange thick slurry was allowed to warm to room temperature over one-half hour and then heated at 60-65° for 2 hours. The reaction mixture was then evaporated to a damp solid, diluted with 100 ml. of water, and the brown solids were collected by filtration after first adjusting the *p*H to ~6 with acetic acid. The crude product was stirred with 90 ml. of 5% sodium hydroxide (decolorizing carbon), filtered and the filtrate was adjusted to *p*H ~ 6 with acetic acid. Collection of the resulting precipitate by filtration followed by air drying gave 3.6 g. (59%) of a yellow-brown solid, m.p. 234-237°. Recrystallization from ethanol gave yellow crystals, m.p. 254-255°; ir λ (Nujol): μm 2.87, 2.96 (NH), 5.97 (C=O).

*Anal.* Calcd. for $C_{12}H_{13}N_5O_3S$: C, 46.89; H, 4.26; N, 22.79. Found: C, 46.57; H, 4.56; N, 22.59.

2-Amino-6-(*p*-aminobenzenesulfonamido)pyrazine (**11**).

A solution of 1.5 g. (0.0049 mole) of **10** in 10 ml. of 2*N* sodium hydroxide was stirred and refluxed for 2 hours. The reaction mixture was cooled to 10°, the *p*H adjusted to ~6 with acetic acid, and the resulting orange-brown precipitate was collected by filtration and air dried, 1.1 g. (85%) m.p. 242-243°. Recrystallization from ethanol/water: 50/50 gave yellow needles, m.p. 250-252°; ir λ (Nujol): μm 2.88, 2.95 (NH), no significant absorption 5.9-6.1 μm.

*Anal.* Calcd. for $C_{10}H_{11}N_5O_2S$: C, 45.27; H, 4.18; N, 26.40. Found: C, 45.48; H, 4.18; N, 26.18.

2-Amino-6-ureidopyrazine (**12**).

A suspension of 1.1 g. (0.01 mole) of **4**, 1.89 g. (0.18 mole) of nitrourea and 15 ml. of water was heated at a gentle boil for 30 minutes. During this time the solids gradually dissolved and gas evolution was in evidence. The reaction mixture upon chilling, yielded 0.15 g. (10%) of a brown solid, which was washed with water, air dried and recrystallized from water to yield beige crystals, m.p. indeterminate; ir λ (Nujol): μm 2.98, 3.18 (NH), 5.95 (C=O).

*Anal.* Calcd. for $C_5H_7N_5O$: C, 39.21; H, 4.61; N, 45.73. Found: C, 39.10; H, 4.57; N, 45.46.

*N*-(6-Amino-2-pyrazinyl)-*N'*-phenylurea (**13**).

A solution of 0.5 g. (0.0045 mole) of **4** and 0.43 g. (0.0036 mole) of phenyl isocyanate in 25 ml. of dry glyme was stirred at room temperature for 30 minutes; a precipitate formed after 5 minutes of stirring. The white crystals were collected by filtration, washed successively with ethanol and petroleum ether (30-60°), 0.51 g. (49%), m.p. 244-246°. Recrystallization from 2-methoxyethanol did not alter the melting point; ir λ (Nujol): μm 3.00, 3.10 (NH), 5.93 (C=O).

*Anal.* Calcd. for $C_{11}H_{11}N_5O$: C, 57.62; H, 4.48; N, 30.55. Found: C, 57.70; H, 5.05; N, 30.51.

*N*-(6-Amino-2-pyrazinyl)-*N'*-α-naphthylurea (**14**).

A solution of 1.0 g. (0.0091 mole) of **4**, 1.23 g. (0.0072 mole) of α-naphthyl isocyanate and 50 ml. of dry glyme was stirred for 1 hour at room temperature. The precipitate, which began forming after 5 minutes of stirring, was collected by filtration, washed successively with small amounts of ethanol and petroleum ether (30-60°) and air dried, 1.18 g. (59%) of an off-white solid, m.p. 240-242° dec. Recrystallization from 2-methoxyethanol gave cream-colored crystals, m.p. 245-246° dec.; ir λ (Nujol): μm 2.97, 3.08 (NH), 5.94 (C=O).

*Anal.* Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.08. Found: C, 64.39; H, 4.83; N, 24.89.

*N*-(6-Amino-2-pyrazinyl)-*N'*-phenylthiourea (**15**).

A solution of 1.1 g. (0.01 mole) of **4**, 1.08 g. (0.008 mole) of phenyl isothiocyanate and 10 ml. of dry acetonitrile was gently boiled and stirred for 10 minutes. Upon chilling the reaction mixture, 0.55 g. (28%) of **15** crystallized, and was filtered, washed with ether, dried and recrystallized from 2-methoxyethanol. White crystals of **15** melted at 224-225° dec.; ir λ (Nujol): μm 2.95, 3.15 (NH).

*Anal.* Calcd. for $C_{11}H_{11}N_5S$: C, 53.85; H, 4.52; N, 28.55. Found: C, 53.89; H, 4.62; N, 28.33.

2,6-Diamino-3-(*p*-methoxyphenylazo)pyrazine (**19**).

A cold (0°) solution of 2.46 g. (0.02 mole) of *p*-anisidine in 5 ml. of water and 5 ml. of concentrated hydrochloric acid (d. 1.19) was vigorously stirred while adding dropwise a solution of 1.46 g. (0.0212 mole) of sodium nitrite in 8 ml. of water. The temperature was maintained ~ 0° during the addition. The cold diazonium salt solution was allowed to stand for 5 minutes and was then stirred vigorously and treated in one portion with a solution of 2.27 g. (0.0206 mole) of **4** in 20.6 ml. of 1*N* hydrochloric acid. This was followed in a few moments by the addition of a solution of 7.34 g. (0.054 mole) of sodium acetate trihydrate in 8 ml. of water. The thick blue-black precipitate that formed was diluted with 100 ml. of water and stirred for 1 hour at ambient temperatures. The orange-brown granular solids that formed on adjusting the *p*H of the reaction mixture to ~ 10 with concentrated ammonium hydroxide were collected by filtration, washed with water, air then oven dried (60°), 4.7 g. (96%), m.p. 230-232° dec. Recrystallization from ethanol gave purple needles, which on crushing appeared brown, m.p. 232-233° dec.; ir λ (Nujol): μm 2.97, 3.16 ($NH_2$); pmr (DMSO-$d_6$): δ 3.87 (s, 3H, $OCH_3$), 7.03 [d (J = 8 Hz), 2H, benzene $H_3$ and $H_5$], 7.41 (s, 1H, pyrazine $H_5$), 7.77 [d (J = 8 Hz), 2H, $H_2$ and $H_6$], 8.10 [s (broad) 4H, (2 x $NH_2$)].

*Anal.* Calcd. for $C_{11}H_{12}N_6O$: C, 54.09; H, 4.95; N, 34.41. Found: C, 53.91; H, 5.20; N, 34.70.

2,6-Diamino-3-*p*-tolylazopyrazine (**18**).

The reaction conditions used to prepare **19** were followed exactly except that 2.14 g. (0.02 mole) of *p*-toluidine was used in place of *p*-anisidine. There was obtained 4.38 g. (96%) of crude **18**, m.p. 246-250° dec. Recrystallization from ethanol gave purple needles, which upon crushing appeared brown, m.p. 250-251° dec.; ir λ (Nujol): μm 2.98, 3.18 ($NH_2$); pmr (DMSO-$d_6$): δ 2.35 (s, 3H, $CH_3$), 7.21 [d (J = 8 Hz), 2H, benzene $H_3$ and $H_5$], 7.44 (s, 1H, pyrazine $H_5$), 7.65 [d (J = 8 Hz), 2H, benzene $H_2$ and $H_6$], 8.15 [s (broad), 4H, (2 x $NH_2$)].

*Anal.* Calcd. for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.67; H, 5.01; N, 36.73.

2,6-Diamino-3-phenylazopyrazine (**17**).

The reaction conditions used to prepare **19** were followed exactly except that 1.86 g. (0.02 mole) of aniline was used in place of *p*-anisidine. There was obtained 4.17 g. (97%) of crude **19**, m.p. 208-211° dec. Recrystallization from ethanol gave purple plates which upon crushing appeared brown, m.p. 210-212° dec.; ir λ (Nujol): μm 3.02, 3.20 ($NH_2$).

*Anal.* Calcd. for $C_{10}H_{10}N_6$: C, 56.06; H, 4.71; N, 39.23. Found: C, 56.20; H, 4.75; N, 39.51.

2-Azido-6-(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**20**) and 2,6-bis(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**21**).

A solution of 1.62 g. (0.01 mole) of **2** and 4.26 g. (0.03 mole) of dimethyl acetylenedicarboxylate in 12 ml. of dry glyme was stirred and refluxed for 19 hours. Upon chilling in an ice bath, 0.54 g., m.p. 149-151° dec., (18%) of **20** crystallized and was filtered and filtrate "A" was set aside for further work-up. Recrystallization of crude **20** from benzene gave beige crystals, m.p. 158-159° dec.; ir λ (Nujol): μm 4.7 ($N_3$), 5.75 (C=O); pmr (deuteriochloroform): δ 4.00 (s, 3H, $CH_3O_2C$), 4.08 (s, 3H, $CH_3O_2C$), 8.37 (s, 1H, pyrazine $H_3$ or $H_5$), 9.22 (s, 1H, pyrazine $H_3$ or $H_5$).

*Anal.* Calcd. for $C_{10}H_8N_8O_4$ (**20**): C, 39.48; H, 2.65; N, 36.84. Found: C, 39.62; H, 2.32; N, 36.73.

Filtrate "A" was concentrated to one-half volume, chilled and the slightly gummy precipitate was collected by filtration and was then stirred with 5 ml. of ether for 15 minutes. The insoluble material (1.2 g.) was filtered off and dissolved in 10 ml. of warm benzene and chromatographed on 40 g. of silica gel using benzene/ether as eluent. Analysis (tlc and ir) of the first few fractions coming off the column showed them to be a mixture of **20**, **21**, and several other unidentified compounds (0.10 g.). The remaining fractions yielded 0.65 g. (15%) of **21**, m.p. 155-158°. Recrystallization from benzene gave crystals which melted without decomposition at 156-158°; ir λ (Nujol): μm 5.73 (C=O) (no significant absorption at 4.5 to 5.0 μm); pmr (deuteriochloroform): δ 3.92 (s, 2 x 3H, $CH_3O_2C$), 4.02 (s, 2 x 3H, $CH_3O_2C$), 9.57 (s, 2H, pyrazine $H_3$ and $H_5$).

*Anal.* Calcd. for $C_{16}H_{14}N_8O_8$ (**21**): C, 43.05; H, 3.16; N, 25.11. Found: C, 42.78; H, 2.76; N, 25.40.

2-Amino-6-(4,5-dicarbomethoxy-1,2,3-triazole-1-yl)pyrazine (**22**).

A mixture of 1.0 g. (0.0033 mole) of **20**, 0.25 g. of 10% palladium on carbon, 0.42 ml. of concentrated aqueous am-

monium hydroxide and 100 ml. of peroxide-free glyme in a 500 ml. Parr hydrogenation bottle was purged with hydrogen and then pressured with hydrogen to 50 psi. The mixture was shaken for 1 hour in a Parr hydrogenation apparatus; there was no pressure fall. The bottle was purged with hydrogen, repressured to 50 psi and shaken for 1 additional hour. The contents of the bottle was removed with aid of ~ 20 ml. of glyme and the mixture was heated to boiling, filtered and the filtrate was evaporated to dryness: 0.8 g. (87%) of a white solid, m.p. 188-190° dec. Recrystallization from acetonitrile gave white crystals, m.p. 195-197° dec.; ir λ (Nujol): μm 2.92, 3.02 ($NH_2$), 5.77 (C=O); pmr (DMSO-$d_6$): δ 3.93 (s, 3H, $CH_3O_2C$), 4.03 (s, 3H, $CH_3O_2C$), 7.11 [s (broad), 2H, $NH_2$], 8.10 (s, 1H, pyrazine $H_3$ $H_5$), 8.41 (s, 1H, pyrazine $H_3$ or $H_5$).

*Anal.* Calcd. for $C_{10}H_{10}N_6O_4$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.20; H, 3.71; N, 30.08.

*N,N'*-bis-(4-Carbethoxy-1,2,3-triazole-5-yl)-2,6-diaminopyrazine (**23**).

A stirred solution of 2.49 g. (0.022 mole) of ethyl cyanoacetate in 15 ml. of dry DMSO was maintained at 15-20° by external cooling while 1.06 g. (0.022 mole) of sodium hydride (50% dispersion in oil) was added in portions. The mixture was stirred for an additional half-hour following completion of addition of the sodium hydride (temperature ~ 25°). Then, 1.62 g. (0.01 mole) of **2** was added in portions (external cooling held the temperature ~ 20° throughout the addition). After an additional stirring period of 20 minutes at ~ 20°, the black reaction mixture was heated for 1 hour on a boiling water bath, cooled to room temperature and poured into 160 ml. of ice water. The gelatinous precipitate which formed on adjusting the *p*H to ~ 6 with acetic acid was collected by filtration and the waxy filter cake was recrystallized from 2-methoxyethanol, 1.15 g. (30%) m.p. 256-257° dec. One further recrystallization from the same solvent gave peach-colored plates, m.p. 260-261° dec.; ir λ (Nujol): μm 3.04 (NH), 5.95 (C=O); pmr (DMSO-$d_6$): δ 1.30 [t (J ~ 6 Hz), 6H (2 x $CH_3$)], 3.40 [s (broad), 2H, (2 x NH)], 4.41 [q, (J ~ 6 Hz), 4H, 2 x $CH_2$)], 8.32 (s, 2H, pyrazine $H_3$ and $H_5$), 9.58 [s (broad), 2H, (2 x triazole NH)].

*Anal.* Calcd. for $C_{14}H_{16}N_{10}O_4$: C, 43.30; H, 4.15; N, 36.07. Found: C, 43.55; H, 4.08; N, 36.41.

2-Amino-6-*N*-(4-Carbethoxy-1,2,3-triazole-5-yl)aminopyrazine (**24**).

An amount of 0.96 g. (0.02 mole) of sodium hydride (50% dispersion in oil) was added in portions to a stirred solution of 2.72 g. (0.02 mole) of **3** in 20 ml. of dry dimethyl sulfoxide. The temperature rose from 25° to 40° and the mixture was stirred for an additional 20 minutes following completion of addition of the sodium hydride; during this time a gas was evolved. The addition of 2.26 g. (0.02 mole) of ethyl cyanoacetate caused the temperature to rise to ~ 57° and after being stirred for several minutes at this temperature, the reaction mixture was heated on a boiling water bath for 1 hour. The cooled reaction mixture was poured into 200 ml. of ice/water, acidified to *p*H ~ 6 with acetic acid, and the gummy precipitate was recrystallized from ethanol, 0.97 g. (19%) of a light-tan solid, m.p. 225-226° dec. A second recrystallization from ethanol gave the analytical sample, m.p. 228-229° dec.; ir λ (Nujol): μm 2.95, 3.03 (NH), 5.95 (C=O); pmr (DMSO-$d_6$): δ 1.42 [t (J = 6 Hz), 3H, $CH_3$], 3.57 [s (broad) 1H, NH], 4.42 [q (J = 6 Hz), 2H, $CH_2$], 6.61 [s (broad) 2H, $NH_2$], 7.56 (s, 1H, pyrazine $H_3$ or $H_5$), 7.97 (s, 1H, pyrazine $H_3$ or $H_5$), 9.20 [s, (broad) 1H, triazole NH].

*Anal.* Calcd. for $C_9H_{11}N_7O_2$: C, 43.37; H, 4.45; N, 39.34. Found: C, 43.19; H, 4.75; N, 39.41.

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