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Syntheses and Reactions of Nitrogen- and Sulfur-Analogs of 2-Piperazinone[1]

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2-Piperazinone oxime, 2-piperazinoneimine, and 2-piperazinethione were synthesized. The reaction mixture of ethylenediamine and glycolonitrile was treated with an excess amount of hydroxylamine in methanol to give 2-piperazinone oxime in a 53% yield. 2-Piperazinone oxime was easily reduced to 2-piperazinoneimine, which was then treated with hydrogen sulfide to yield 2-piperazinethione. Some reactions of these compounds are described.

Many methods of synthesizing 2-piperazinones have been developed since the derivatives were found to possess some pharmacological activities.[2] However, no variation in the exocyclic oxo-group has ever been reported.[3] It thus appeared of interest to obtain nitrogen- or sulfur-analogs of 2-piperazinone.

The present paper will describe the syntheses of 2-piperazinone oxime (VIIIa), 2-piperazinoneimine (IIIb), and 2-piperazinethione (XV), and their reactivities.

Strong *et al.* reported the synthesis of 2-piperazinone by the reaction of ethylenediamine (I) with formaldehyde and sodium cyanide in an aqueous solution.[2a] This reaction was postulated to involve, as an intermediate, *N*-(2-aminoethyl)glycinonitrile (IIIa) or cyclic amidine (IIIb), which would be hydrolyzed to afford 2-piperazinone. Thus, the isolation of the intermediate (III) might be possible, provided the reaction of I with glycolonitrile (II) was carried out in a non-aqueous medium. When I was treated with an equimolar amount of II in methanol at room temperature for 2 days, a yellow, oily material was obtained. The infrared absorption spectrum of the oil showed a medium absorption band at 1660 cm^{-1} characteristic of the carbon-nitrogen double bond, while a control measurement of infrared absorption spectrum showed that the initial mixture of I and II exhibited no band at 1660—1630 cm^{-1} in the region for the carbon-nitrogen double bond. The oil was treated with sulfuric acid in methanol to yield pale yellow crystals with a melting point of 205—208°C (decomp.). The elementary analysis of the product indicated the empirical formula, $C_4H_9N_3 \cdot H_2SO_4$, corresponding to the sulfate (IV) of III. A thin-layer chromatogram (TLC) of IV showed two spots. The R_f value (0.31) of one spot was found to be identical with that of an authentic 2-piperazinoneimine sulfate prepared by another route, described below. From these observations as well as the following reactivities, it seemed reasonable to assume that the above products (III) consisted of IIIb and another substance (IIIa).[4] When II was treated with an excess amount of I in methanol at 55—60°C, *N, N'*-bis-cyanomethylethylenediamine (V) was obtained as the sole isolated product. This was characterized by means of its infrared absorption spectrum and by conversion into a dibenzoyl derivative (VI) (Chart I).

In order to examine the reactivities of III, the reaction of III with hydroxylamine was attempted. When the reaction mixture of I and II (III) was treated with an excess amount of hydroxylamine in methanol, a slightly exothermic reaction occurred with an evolution of ammonia, and colorless crystals with a melting point of 171—173°C were obtained. The product gave an intense purple color with an aqueous solution of

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[1] Presented in part at 19th Annual Meeting of the Chemical Society of Japan, Yokohama, March, 1966.

[2] a) J. S. Strong, W. E. Craigant and V. T. Elkind (of Rohm and Hass Co.), U. S. Pat. 2649450 (Aug. 18, 1953). b) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940). c) R. L. Hodgson, I. R. C. Bick and D. J. Cram, *ibid.*, **76**, 1137 (1954). d) A. P. Phillips (to Burroughs Wellcome & Co. (U. S. A.), Inc.), U. S. Pat. 2958693 (Nov. 1, 1960). e) M. Masaki and M. Ohta, This Bulletin, **36**, 922 (1963). f) O. E. Fancker, S. Hayao and W. G. Strycker, *J. Med. Chem.*, **7**, 154 (1964). g) K. Masuzawa, M. Masaki and M. Ohta, *Chem. Pharm. Bull. Japan*, **14**, 194 (1966).

[3] Only one British Patent (Rohm & Hass Co.; 875135 (Aug. 16, 1961)) has referred to 4-substituted 2-piperazinethiones; unfortunately, neither the synthetic method nor their properties have been recorded.

[4] The other substance, with a R_f value of 0.58, might be IIIa, but it was not further investigated.

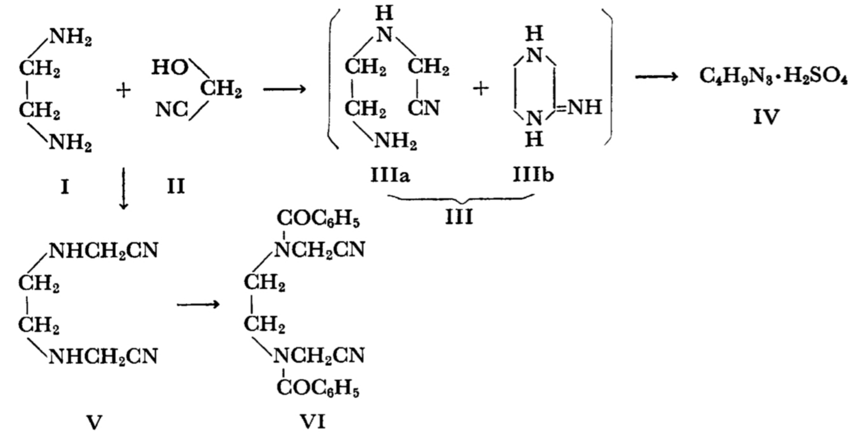

Chart I

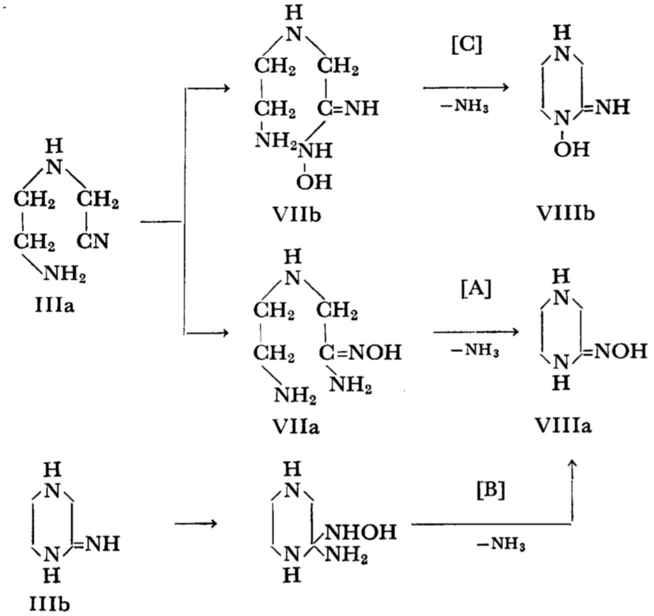

Chart II

ferric chloride and exhibited a strong infrared absorption band at 1660 cm^{-1}, which might be ascribed to the carbon–nitrogen double bond of amidoxime.[5] This observation and the elementary analysis indicate the structure of 2-piperazinone oxime (VIIIa) or 1-hydroxy-2-piperazinoneimine (VIIIb) for the product. Compound VIIIa would be formed from the reaction of either IIIa or IIIb with hydroxylamine (Course A or B), while VIIIb might be derived only from the reaction of IIIa and hydroxylamine (Course C) (Chart II).

However, only the structure VIIIa was supported by the following reactions. The product (VIIIa) was treated with 3N hydrochloric acid and methanol to afford methyl *N*-(2-aminoethyl)glycinate dihydrochloride (IX), which was isolated in a form combined with water. On the treatment of VIIIa with benzoyl chloride, a dibenzoyl derivative (X) was obtained, while treatment with tosyl chloride gave a tritosyl derivative (XI). The infrared absorption spectrum of the dibenzoyl derivative showed strong absorption bands in the ester region. The amidoximes have been known to react with nitrous acid or alkyl nitrite, yielding the corresponding amide.[6] The reaction of VIII with nitrous acid or amyl nitrite was next attempted, since it was expected to yield 4-nitroso-2-piperazinone (XII). All attempted reactions, however,

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[5] C. L. Bell, C. N. V. Nambury and L. Bauer, *J. Org. Chem.*, **29**, 2873 (1964).

[6] T. Wieland and D. Grimm, *Chem. Ber.*, **96**, 275 (1963).

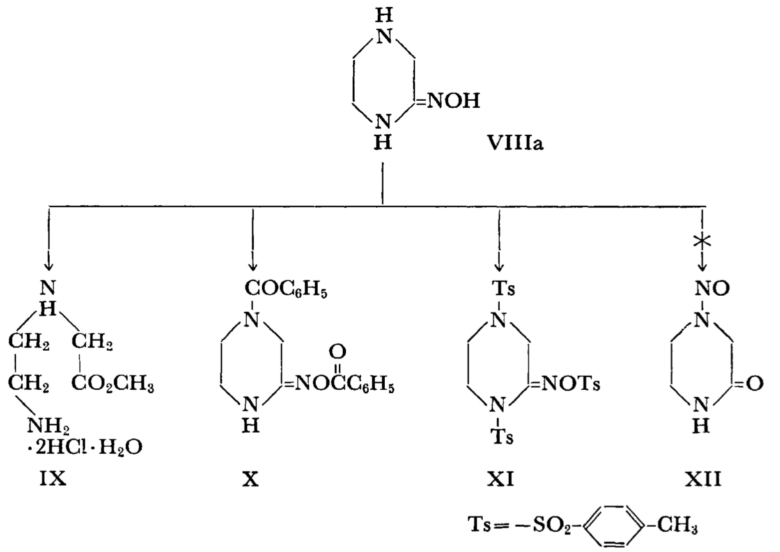

Chart III

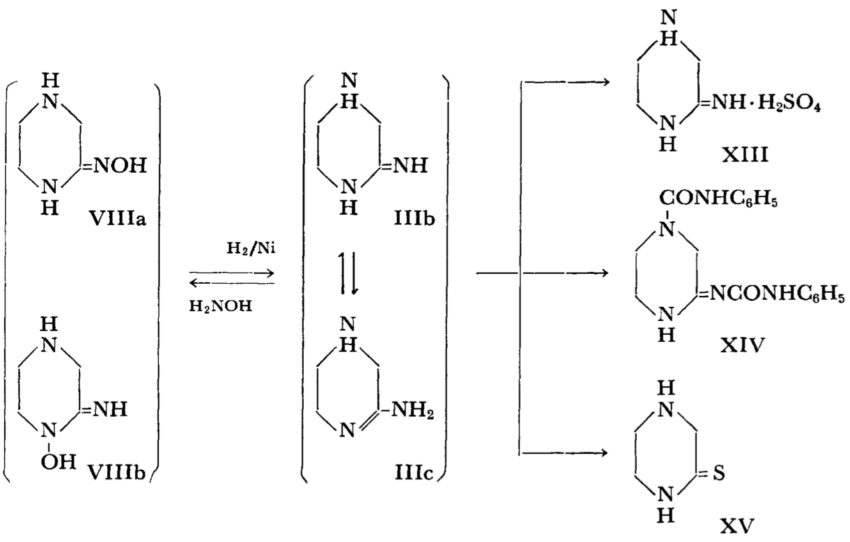

Chart IV

resulted only in the formation of a viscous oily substance, which gave a positive Lieberman test but which was unidentified, while the authentic XII was obtained in the form of crystals by the treatment of 2-piperazinone with amyl nitrite in *n*-butanol (Chart III).

Barber *et al.* have reported that the catalytic reduction of amidoxime gave the corresponding amidine.7) The amidoxime (VIIIa) was hydrogenated at room temperature in the presence of Raney-nickel to give, as expected, 2-piperazinone-imine (IIIb) which was characterized by means of its infrared absorption spectrum and by conversion into the crystalline sulfate (XIII) or the crystalline phenylureido derivative (XIV). Compound XIII had a melting point of 212°C (decomp.) and gave a spot (R_f 0.31) on thin-layer chromatogram. When the reduction product was again treated with hydroxylamine in methanol at room temperature, ammonia was evolved and the amidoxime (VIII) was obtained in a 46% yield.8) The amidoxime produced was identified by a comparison of its infrared absorption spectrum and by a mixed-melting-point determination with the original amidoxime (VIIIa). This fact excludes the alternative structure (VIIIb) for the amidoxime

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7) H. J. Barber and A. D. H. Self (of May & Baker, Ltd.), U. S. Pat. 2375611 (May 8, 1945).

8) The yield was calculated from the first material (VIIIa) used for reduction.

(VIIIa), because an easy transformation between the amidoxime (VIIIb) and the amidine (IIIb) would be impracticable under the above mild conditions.

When the cyclic amidine (IIIb) was treated with hydrogen sulfide, 2-piperazinethione (XV) was obtained in a 20% yield. The structure of XV was confirmed by its infrared absorption spectrum and by elementary analysis. In an attempt to prepare XV by another route, 2-piperazinone was directly treated with phosphorus pentasulfide in benzene or toluene, but no definite product could be obtained (Chart IV).

In a further investigation of the reactivities of III, the methanolic solution of III was treated with *N*-phenylhydroxylamine at 60°C; a small quantity of yellow needles (XVI) was thus obtained. The reaction of IIIb, prepared by the reduction of VIIIa, with *N*-phenylhydroxylamine also gave XVI. The elementary analysis of the product (XVI) showed the empirical formula $C_{10}H_9N_3$, which may suggest that XVI is 2-anilinopyrazine. Thus, 2-anilinopyrazine was synthesized by the reaction of 2-chloropyrazine with an excess amount of aniline.

However, the chemical properties of XVI apparently differed from those of 2-anilinopyrazine and the structure of XVI remains unidentified.

Experimental[9]

Ethylenediamine (I). Commerical anhydrous ethylenediamine was dried over metallic sodium. The dried ethylenediamine was then filtered and distilled; bp 116—117°C.

Glycolonitrile (II) was prepared by the published procedure[10] and had a bp of 97—99°C/15 mmHg (lit.[10] bp 99—100°C/17 mmHg).

Reaction of I with II. a) A solution of II (2.0 g) in methanol (3 m*l*) was added, drop by drop, to a solution of I (2.1 g) in methanol (3 m*l*), and the mixture was allowed to stand at room temperature for 2 days. After the solvent and the starting materials had been removed under reduced pressure from the reaction mixture, an oily product (III) was obtained. Its infrared spectrum showed an absorption band at 1660 cm^{-1} (m). The oily product (III) was converted to a crystalline solid by adding a solution of sulfuric acid in methanol. The solid was collected to give 6.8 g (98.5% yield) of brown crystals, which, after recrystallization from aqueous methanol, afforded a mixture of 2-piperazinoneimine sulfate (IIIb) and an unidentified compound as pale yellow crystals, mp 205—208°C (decomp.). TLC[11] $R_f=0.58$ and 0.31.

Found: C, 24.03; H, 5.82; N, 22.12%.

b) A mixture of I (12.0 g) and II (5.7 g) in methanol (30 m*l*) was warmed, with stirring, at 55—60°C for 5 hr. The mixture was then concentrated under reduced pressure to give a syrup which was distilled under reduced pressure to yield *N, N'*-bis-cyanomethylethylenediamine (V) as a viscous liquid (2.73 g, 27.3%), bp 133—135°C/1 mmHg. IR (liquid): 3300 (–NH–) and 2200 cm^{-1} (–CN).

N, N'- Bis-benzoyl - *N, N'*- bis - cyanomethylethylenediamine (VI), mp 142—144°C (from ethanol), was also prepared.

IR (KBr disk): 2240 (–CN) and 1665 cm^{-1} (–CONH–).

Found: C, 68.93; H, 5.37; N, 15.96%. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18%.

2-Piperazinone Oxime (VIIIa). A solution of hydroxylamine [from the hydrochloride (10.4 g) and sodium (3.4 g) in methanol (160 m*l*)] was stirred into a solution of III (corresponding to 0.1 mol) in methanol (20 m*l*) at room temperature. The mixture was then kept at room temperature for 2 days, by which time the evolution of ammonia had ceased. The solution was concentrated under reduced pressure to yield a brown syrup. The syrup solidified spontaneously upon standing. The product was recrystallized from isopropyl alcohol to give 6.1 g (53%) of colorless plates, mp 171—173°C. The crystals are very soluble in water and give an intense purple color with an aqueous ferric chloride solution. IR (KBr disk): 3380 and 3320 (–NH–), 3180—2800 (broad band) and 1660 cm^{-1} ($\rangle$C=N–).

The NMR spectrum exhibited a multiplet in the τ 6.7—7.1 region (4H) and a singlet at τ 6.6 (2H).[12]

Found: C, 41.97; H, 8.11; N, 36.74%. Calcd for $C_4H_9N_3O$: C, 41.72; H, 7.88; N, 36.50%.

Methyl *N*-(2-Aminoethyl)glycinate Dihydrochloride (IX). A solution of VIIIa (0.5 g) in 3 N hydrochloric acid (14.5 m*l*) was heated at 80°C for 3 hr, and the resultant solution was concentrated to dryness under reduced pressure. On adding methanol (4 m*l*) to the residue, 0.8 g (82.8%) of colorless needles was obtained. A portion of the product was recrystallized from methanol and analyzed; mp 188—190°C (decomp.).[13]

IR (KBr disk): 3480(OH), 3000—2500 (broad band) and 1720, 1250 cm^{-1} ($-COOCH_3$).

Found: C, 27.09; H, 7.37; N, 13.10%. Calcd for $C_5H_{12}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 26.92; H, 7.23; N, 12.55%.

Dibenzoyl Derivative (X) of VIIIa. This derivative (mp 190—191.5°C (from ethanol)) was obtained as colorless needles.

Found: C, 66.86: H, 5.30; N, 13.00%. Calcd for $C_{18}H_{17}N_3O_3$: C, 67.17; H, 5.42; N, 13.16%.

IR (KBr disk): 3320(–NH–), 1725 and 1250 ($OCOC_6H_5$), 1660—1620 cm^{-1} (=NCO– and –CN).

1, 4-*O*-Tritosyl-2-piperazinone Oxime (XI). A solution of tosyl chloride (3.8 g) in dioxane (30 m*l*) and a solution of sodium hydroxide (0.8 g) in water

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[9] All the melting points are uncorrected. The infrared spectra of the samples were measured on a Hitachi spectrophotometer, Model EPI S II.

[10] D. T. Mowry, *J. Am. Chem. Soc.*, **66**, 371 (1944).

[11] TLC: Solvent system: *n*-Butanol(4) - Acetic acid(2) - Water (1). Adsorbent: Silica gel (Wakogel 10). Sample: 2.5—5 μg (0.01 m*l* applied to plates). Detection: A solution of 1 g of *p*-dimethylaminobenzaldehyde in 100 m*l* of a mixture of 35% hydrochloric acid (50 m*l*) and ethanol (50 m*l*).

[12] The NMR spectrum was kindly determined by the Japan Electron Optics Lab. Co. on its Model G-60 at 60 Mc in a deuterium oxide solution, sodium dimethylsila pentasulfonate being used as the internal standard.

[13] T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, **1929**, 51.

(10 m*l*) were alternatively stirred into a solution of VIIIa (1.2 g) in water (12 m*l*). The temperature of the mixture was then raised from 15°C to 30°C. After the addition had been completed, the mixture was stirred for several more hours, and then the pale yellow solution was allowed to stand overnight, thus yielding 0.7 g of XI as amorphous crystals, mp 206—209°C. The analytical sample was recrystallized from ethanol to give colorless plates, mp 210—211°C. The infrared absorption spectrum of XI showed no absorption band in the regions for both the amino group and the hydroxyl group.

Found: C, 51.74; H, 4.53; N, 6.90%. Calcd for $C_{25}H_{27}N_3O_7S_3$: C, 51.97; H, 4.71; N, 7.27%.

4-Nitroso-2-piperazinone (XII). A mixture of 2-piperazinone (3 g) and amyl nitrite (4 g) in *n*-butanol (30 m*l*) was heated on a water bath for 2 hr, and the resultant solution was allowed to stand overnight at room temperature. The precipitate (XII) was then collected and recrystallized from ethanol to give yellow plates, mp 124—125°C. The yield was 2.7 g (70%).

Found: N, 32.77%. Calcd for $C_4H_7N_3O_2$: N, 32.55%.

2-Piperazinoneimine Sulfate (XIIII). A solution of VIIIa (1.5 g) in ethanol (70 m*l*) was shaken with Raney-nickel (1.0 g) at a pressure of 100 kg/cm^2 of hydrogen at room temperature for 1 hr. The catalyst was then removed by filtration, and sulfuric acid (1.0 g) in ethanol (20 ml) was added to the filtrate in order to precipitate a crystalline substance, which, after recrystallization from methanol-water, afforded the sulfate of IIIb as colorless needles, mp 212°C (decomp.). The yield was 1.9 g (76.0%).

IR (KBr disk): 3300—2500 (broad), 1660 (>C=N–) and 1120 cm^{-1} (sulfate).

Found: C, 24.08; H, 5.76; N, 21.00%. Calcd for $C_4H_9N_3 \cdot H_2SO_4$: C, 24.37; H, 5.63; N, 21.32%.

2-(*N*-Phenylcarbamoyl)imino-4-phenylcarbamoylpiperazine (XIV). The ethanolic solution obtained by the reduction of VIIIa (0.38 g) was evaporated to give IIIb (0.3 g) as an oil, which was used directly in the following reaction. The crude IIIb (0.3 g) and phenyl isocyanate (0.95 g) in chloroform (20 m*l*) were heated under refluxing for 4 hr. The resultant clear solution was passed through an activated alumina column. The column was then washed with ethanol (50 m*l*). The evaporation of the ethanolic eluate yielded a brown-yellow solid, which was recrystallized from *n*-butanol-ligroin to give 0.3 g (30%) of XIV as colorless needles, mp 172—173°C.

IR (KBr disk): 3370—3270 (–NH–, broad) and 1700, 1660—1640 cm^{-1} (–NHCO–).

Found: C, 64.18; H, 5.68; N, 21.23%. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76%.

Reaction of IIIb with Hydroxylamine. A solution of hydroxylamine [from the hydrochloride (0.42 g) and sodium (0.13 g) in methanol (8 m*l*)] was added to a solution of IIIb (0.4 g prepared from VIIIa) in ethanol (40 m*l*). The mixture was kept at 40°C for 5 hr, by which time the evolution of ammonia had ceased, and then warmed at 60°C for 1 hr. The solution was concentrated under reduced pressure to give a yellow solid. The product was recrystallized from isopropyl alcohol to yield 0.2 g of 2-piperazinone oxime (VIIIa) as colorless plates, mp 171—172°C, the melting point showed no depression in a mixing test with the VIIIa synthesized by the reaction of III (obtained by the reaction of I with II) with hydroxylamine.

2-Piperazinethione (XV). A solution of IIIb (1.95 g, prepared from VIIIa) in ethanol (125 m*l*) was saturated with hydrogen sulfide under cooling. The resultant yellow solution was allowed to stand at room temperature overnight, and then heated at 80°C for 4 hr. On cooling, the sulfur which separated from the solution was removed by filtration; the filtrate was concentrated under reduced pressure to give a viscous liquid. The oil solidified spontaneously upon standing. The product was recrystallized from isopropyl alcohol to give colorless prisms (0.45 g, 20%), mp 155—156°C (decomp.).

IR (KBr disk): 3200, 3150 and 3050(–NH) and 1585 cm^{-1} (–NHCS–).

Found: C, 41.64; H, 6.87; N, 24.32%. Calcd for $C_4H_8N_2S$: C, 41.37; H, 6.94; N, 24.13%.

Reaction of III (Obtained from I and II) with *N*-Phenylhydroxamine. A solution of *N*-phenylhydroxylamine[14] (1.8 g) in methanol (10 m*l*) was added, drop by drop, to a solution of III (corresponding to 0.0016 mol) in methanol (4 m*l*) at room temperature. When the mixture was warmed at 60°C with stirring, a yellow solid soon began to separate. After 5 hr, the mixture was concentrated under reduced pressure to yield an oily brown product. This oily product slowly solidified. The solid was collected, washed with isopropyl alcohol, and recrystallized from a small amount of benzene to yield yellow prisms (0.4 g; mp 265°C (decomp.)). The product (XVI) was soluble in dilute hydrochloric acid; it showed ultraviolet absorptions at $\lambda_{max}^{dioxane}$ 235 mμ (ε=13000) and 293 mμ (ε=10700).

IR (KBr disk): 3400, 1660, 1630, 1240 and 1250 cm^{-1}.

Found: C, 70.01; H, 5.24; N, 24.80%. Calcd for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55%.

Reaction of IIIb (Obtained from VIIIa) with *N*-Phenylhydroxylamine. A solution of *N*-phenylhydroxylamine (1.0 g) in ethanol (10 m*l*) was added to a solution of IIIb (0.92 g) in ethanol (60 m*l*), and the mixture was heated at 80°C for 5 hr, by which time the evolution of ammonia had ceased. Removal of the solvent yielded the product as a syrup, which was dissolved in hot isopropyl alcohol (4.5 m*l*); the solution was then filtered. The filtrate was allowed to stand in a refrigerator. After 2 days, the crystals were collected by filtration and washed with a small portion of benzene to give 0.62 g of XVI as yellow prisms, mp 265—266.5°C (unchanged by admixture with the XVI obtained by the reaction of III with *N*-phenylhydroxylamine).

2-Anilinopyrazine. A mixture of 2-chloropyrazine[15] (1.0 g) and aniline (4.0 g) was heated, with stirring, at 160°C for 7 hr. After the mixture had been kept overnight at room temperature, the aniline hydrochloride which had separated was filtrated off. Benzene (30 m*l*) was added to the filtrate. The benzene layer was washed twice with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in order to recover the original aniline and benzene.

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14) O. Kamm, "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 445 (1941).

15) G. W. H. Cheeseman, *J. Chem. Soc.*, **1960**, 242.

When carbon tetrachloride was added to the residue small needles slowly crystallized out. The product was collected (0.5 g, 33.4%) and recrystallized from ethanol-isopropyl ether to give yellowish plates, mp 132—133°C; the crystal showed ultraviolet absorptions at λ_{max}^{EtOH} 275 mμ (ε=23000) and 345 mμ (ε=6000).

IR (KBr disk): 3270 and 3200 (-NH-), 1630 and 1520 cm^{-1}.

Found: C, 69.85; H, 5.09; N, 24.38%. Calcd for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55%.