Pyrimidines. XVIII. 2,4-Diamino-5-nitro-6-arylaminopyrimidines. Nitration Study of 2,4-Diamino-6-chloropyrimidine and a Literature Correction[1]

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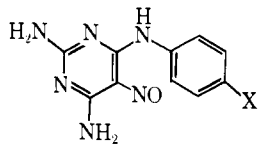
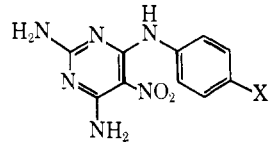
Nitration of 2,4-diamino-6-chloropyrimidine has been studied under a variety of reaction conditions. It was found that when equal volumes of concentrated H_2SO_4 and fuming HNO_3 were used, the product was 2-amino-4-nitramino-6-chloropyrimidine (IV) rather than 2,4-diamino-5-nitro-6-chloropyrimidine (IIIb), as previously reported. The desired 5-nitro derivative IIIb could be obtained in 61% yield when a large excess of concentrated H_2SO_4 (5:1 relative to the amount of HNO_3) was used. The optimum temperature for this reaction is 20–35°. Under these reaction conditions, 2,4-diaminopyrimidine (which was previously considered to be unnitratable) nitrated directly to give 2,4-diamino-5-nitropyrimidine in 22% yield. The authentic 2,4-diamino-5-nitro-6-(arylamino)pyrimidines were readily prepared from IIIb and substituted anilines. Preliminary antitumor screening indicated that 2,4-diamino-5-nitro-6-(*p*-bromoanilino)pyrimidine (IIa) possessed activity against the Walker 256 (WM) tumor system.

Direct nitration of pyrimidines is one of the most widely applicable methods for the preparation of 5-nitropyrimidines. This reaction usually requires the presence of at least two electron-donating groups substituted at the 2, 4, or 6 position of the pyrimidine ring.[2,3] Normally, the reactions are carried out at comparatively low temperatures with fuming nitric acid in the presence of concentrated sulfuric acid. 2,4,6-Triamino-5-nitropyrimidine, for example, was prepared recently by this method from the corresponding triaminopyrimidine in very good yield.[4]

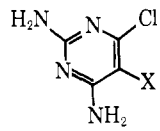
In view of the unexpected and interesting activity of several 2,4-diamino-5-nitroso-6-(arylamino)pyrimidines (I) against the Adenocarcinoma 755 tumor system,[5] study on the structural modifications of I was initiated in 1963.[6] Among these, preparation of the corresponding 5-nitropyrimidines (II) by the direct nitration of 2,4-diamino-6-chloropyrimidine[7] (IIIa) followed by the treatment of the resulting nitrated product with appropriate anilines, was reported.



Ia, X = Br
b, X = I

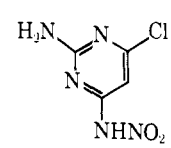


IIa, X = Br
b, X = I

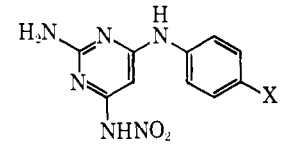


IIIa, X = H
b, X = NO_2
c, X = NH_2

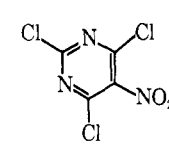
A continued study in our laboratories revealed that the initial nitration of IIIa under the previously described reaction conditions[6] yielded the isomeric 2-amino-4-nitramino-6-chloropyrimidine (IV),[8] rather than the reported 2,4-diamino-5-nitro-6-chloropyrimidine (IIIb), since reduction of the nitrated product yielded, instead of the expected 2,4,5-triamino-6-chloro derivative (IIIc), a product which was identified as IIIa. Consequently, the arylamino derivatives obtained from the nitrated products were actually 2-amino-4-nitramino-6-arylaminopyrimidines (V).



IV



V



VI

Efforts were then directed to the synthesis of the authentic 2,4-diamino-5-nitro-6-(arylamino)pyrimidines (II). One logical approach is to use 2,4,6-trichloro-5-nitropyrimidine[11] (VI) as a starting material. Robins, *et al.*,[11] reported that ethereal ammonia at 0° reacted with VI to give 2,4-dichloro-5-nitro-6-aminopyrimidine. When an ethereal solution of *p*-bromoaniline was allowed to react with VI under the same conditions, however, a bis(*p*-bromoanilino)-pyrimidine was isolated. This "bis" derivative was

(1) This investigation was supported by the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-65-94.

(2) G. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 290–294.

(3) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 138–142.

(4) J. A. Carbon, *J. Org. Chem.*, **26**, 455 (1961).

(5) D. E. O'Brien, F. Baiocchi, R. K. Robins, and C. C. Cheng, *J. Med. Pharm. Chem.*, **5**, 1085 (1962).

(6) D. E. O'Brien, F. Baiocchi, R. K. Robins, and C. C. Cheng, *ibid.*, **6**, 407 (1963).

(7) S. Gabriel, *Ber.*, **34**, 3362 (1901).

(8) The possibility of IV being the other isomeric 2-nitramino-4-amino-6-chloropyrimidine was ruled out as follows. Mild reduction of IV, according to the procedure of Gabriel and Colman,[9] gave 2-amino-4-hydrazino-6-chloropyrimidine, which was found to have the same spectroscopic and chromatographic properties as an authentic sample prepared from 2-amino-4,6-dichloropyrimidine with hydrazine hydrate by the method of Hirao, *et al.*[10]

(9) S. Gabriel and J. Colman, *Ber.*, **34**, 1234 (1901).

(10) I. Hirao, T. Fujimoto, Y. Kato, and H. Okazaki, *Kogyo Kagaku Zasshi*, **66**, 1682 (1963).

(11) R. K. Robins, K. L. Dille, and B. E. Christensen, *J. Org. Chem.*, **19**, 930 (1954).

obtained even when the reaction was carried out at −20°. This approach, therefore, is not feasible for the present study.

A facile synthesis of 5-nitropyrimidine was reported recently by Taylor and McKillop[12] involving the direct oxidation of 5-nitrosopyrimidines with 30% hydrogen peroxide in trifluoroacetic acid. When 2,4-diamino-5-nitroso-6-(*p*-bromoanilino)pyrimidine (Ia) was treated with peroxide under the same conditions, a product was obtained which was believed to be the N-oxide[13] of the desired 5-nitro (IIa) derivative. Although N-oxides were reported to be readily reduced by catalytic hydrogenation, the 5-nitro group of the resulting product would also be attacked. Hence, study of this approach was also discontinued.

Carbon[4] prepared several 5-nitropyrimidines in good yield by direct nitration of the corresponding pyrimidines. When the same conditions were used for the nitration of IIIa, a mixture of the nitraminopyrimidine IV and the desired 5-nitropyrimidine IIIb was obtained. Compounds IIIb and IV were readily separated by their interesting solubility difference in aqueous ammonia. The following deviations were noted between Carbon's[4] and our reported[6] nitration procedure. Carbon added the nitric acid to a solution of IIIa in sulfuric acid at 30–35°, with H_2SO_4/HNO_3 ratio at 3/1, whereas we added IIIa to the mixed acids (in the ratio of 1/1) at 20–25°.

In order to establish the factor(s) which are responsible for the preferential formation of IIIb over that of IV, a series of nitrations was carried out systematically which provided the following observations. The optimum temperature for this nitration is between 20–35°. When the nitration was run at 0–5°, the only solid isolated was the starting material IIIa; when the reaction temperature was elevated to 40–45°, nitration at position 5 occurred together with the hydrolysis of the 6-chloro group, resulting in the formation of 2,4-diamino-5-nitro-6-hydroxypyrimidine.[4] Our nitration studies also indicate that there is little difference in the sequence of addition.[19]

The importance of the H_2SO_4/HNO_3 ratio is readily demonstrated. When the ratio of 1/1 was used, the only isolated product was the nitraminopyrimidine IV; at a ratio of 2/1, both IV and IIIb were isolated in comparable yields; at a ratio of 3/1, the desired 5-nitro derivative IIIb became the major product, and the yield of IIIb was increased to 62% (with IV at 5%) when the ratio of acids was 5/1. These results suggest that the initial nitration of 2,4-diamino-6-chloropyrimidine (IIIa) probably occurs on the amino nitrogen resulting in the formation of IV, which then rearranges[20,21] in the presence of excessive sulfuric acid to give the desired 2,4-diamino-5-nitro-6-chloropyrimidine (IIIb). Additional support for this postulation is given by the fact that when IV was dissolved in concentrated H_2SO_4 at 30–35°, a similar rearrangement[20,21] did occur in a relatively short time to form IIIb.

Subsequent treatment of IIIb with substituted anilines readily yielded the desired 2,4-diamino-5-nitro-6-(arylamino)pyrimidines (II). The structure of II was confirmed by reduction of IIa with sodium hydrosulfite. The resulting 2,4,5-triamino-6-(*p*-bromoanilino)pyrimidine was found to be identical with the product obtained by the reduction of 2,4-diamino-5-nitroso-6-(*p*-bromoanilino)pyrimidine[5] (Ia).

The foregoing nitration information led us to investigate the direct nitration of 2,4-diaminopyrimidine,[22] which was previously believed to be unnitratable.[23] In a 5/1 mixture of H_2SO_4/HNO_3, a 22% yield of the desired 2,4-diamino-5-nitropyrimidine was obtained. The product was found to be identical with an authentic sample prepared from 2,4-dichloro-5-nitropyrimidine and ammonia.[24]

Preliminary antitumor evaluation of these 5-nitropyrimidines indicated that at a dose of 400 mg/kg, 2,4-diamino-5-nitro-6-(*p*-bromoanilino)pyrimidine (IIa) was active (T/C = 0.47) against Walker 256 (intramuscular).[25] At the same dose level 2,4-diamino-5-nitro-6-chloropyrimidine (IIIb) and 2,4-diamino-5-nitro-6-(*p*-iodoanilino)pyrimidine (IIb) were toxic when tested in albino rats.

Experimental Section[26]

Nitration of 2,4-Diamino-6-chloropyrimidine.—To an acid mixture containing 30 ml of fuming HNO_3 (sp gr 1.50) and 150 ml of concentrated H_2SO_4 was added, at 30–35° (with external cooling), 28.9 g (0.2 mole) of 2,4-diamino-6-chloropyrimidine.[7] After the addition was complete, the resulting solution was stirred at 30–35° for 30 min and then poured slowly over 1 kg of flaked ice with vigorous stirring. The acidic mixture was carefully adjusted to pH 8–9 by the dropwise addition of concentrated aqueous ammonia, keeping the temperature below 10°. The mixture was then filtered and the yellow solid product was washed with four 150-ml portions of water and dried *in vacuo* ($CaCl_2$). The dried product was recrystallized from absolute ethanol to give 23.5 g (62% yield) of 2,4-diamino-5-nitro-6-chloropyrimidine (IIIb) as yellow crystals: mp 220–222°; $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 7000), 338 (13,400); $\lambda_{max}^{pH\ 10}$ 235 mμ (ε 14,600), 267 (5100), and 340 (22,300).

Anal. Calcd for $C_4H_4ClN_5O_2$: C, 25.4; H, 2.12; N, 36.9. Found: C, 25.6; H, 2.41; N, 37.2.

(12) E. C. Taylor and A. McKillop, *J. Org. Chem.*, **30**, 3153 (1965).

(13) It is of interest to note that a characteristic ultraviolet absorption maximum at ~230 mμ (at pH 11) was observed with this compound. Similar absorption bands at this region were also noted with adenine 1-N-oxide,[14] hypoxanthine 1-N-oxide,[15] 2,6-diaminopurine N-oxide,[14] 2-chloroadenine 1-N-oxide,[16] isoguanine 1-N-oxide,[16] xanthine 3-N-oxide,[17] and 7-aminothiazolo[5,4-*d*]pyrimidine 6-N-oxide.[18] At ~pH 1 this particular band was not usually observed.

(14) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).

(15) E. C. Taylor, C. C. Cheng, and O. Vogl, *J. Org. Chem.*, **24**, 2019 (1959).

(16) R. M. Cresswell and G. B. Brown, *ibid.*, **28**, 2560 (1963).

(17) R. M. Cresswell, H. K. Maurer, P. Strauss, and G. B. Brown, *ibid.*, **30**, 408 (1965).

(18) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *J. Med. Chem.*, **8**, 190 (1965).

(19) In certain instances, the sequence of addition did produce different results; *cf.* ref 4 and ref 7 for the nitration of 2,4,6-triaminopyrimidine.

(20) For the "Fischer–Hepp Rearrangement" in pyrimidine derivatives, see (a) K. Shirakawa, *J. Pharm. Soc. Japan*, **73**, 635 (1953); (b) J. A. Barone, *J. Med. Chem.*, **6**, 39 (1963); (c) D. Söll and W. Pfleiderer, *Ber.*, **96**, 2977 (1963).

(21) For a detailed discussion of arylnitramine rearrangements (which were reported to be both inter- and intramolecular), see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 625–628.

(22) (a) E. Büttner, *Ber.*, **36**, 2227 (1903); (b) T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **34**, 175 (1905).

(23) Dr. D. J. Brown, The Australian National University, private communication (unpublished work of the late R. P. Royer). See ref 3, pp 10 and 140.

(24) (a) O. Isay, *Ber.*, **39**, 250 (1906); (b) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951); (c) E. C. Taylor and M. J. Thompson, *J. Org. Chem.*, **26**, 5224 (1961).

(25) The biological testing was performed by the Screening Contractors of CCNSC. For the procedure and criteria of animal screening, see *Cancer Chemotherapy Rept.*, **No. 25**, 1 (1962).

(26) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

The ammoniacal filtrate was carefully acidified to pH 1 by the addition of concentrated HCl at 20°. The precipitated off-white solid was filtered, washed with water, ethanol, and ether, and dried at 80° *in vacuo*, to give 1.9 g (5% yield) of 2-amino-4-nitramino-6-chloropyrimidine (IV), which decomposed violently at 228°; $\lambda_{max}^{pH\ 1}$ 298 mμ (ε 11,700), 364 (5500); $\lambda_{max}^{pH\ 11}$ 285 mμ (ε 8300), 311 (7400). This product was found to be identical with that reported previously.[6] [R_f values of IIIb = 0.68 (1:1, ethanol–water), 0.15 (4% sodium citrate); of IV, 0.76 (1:1, ethanol–water), 0.64 (4% sodium citrate), 25°, descending].

This nitration reaction has also been studied systematically under various conditions and the results are reported as follows. When the reaction was carried out at 0–5°, only starting material IIIa was isolated. At 20–25°, yields and relative ratio of the products isolated were similar to those obtained when the reaction temperature was at 30–35°. Slow addition of fuming nitric acid to a solution of IIIa in concentrated H_2SO_4 at 30° gave results similar (yields and relative ratio) to those obtained in the previously described sequence of addition.

When the ratio of cond H_2SO_4/fuming HNO_3 was 3/1 (150 ml of H_2SO_4/50 ml of HNO_3), at 20–35°, a yield of 40–50% of IIIb, along with 15–20% of IV, was obtained. When the ratio of H_2SO_4/HNO_3 was 2/1 (100 ml of H_2SO_4/50 ml of HNO_3), a yield of 35–37% of IIIb, in addition to 27–30% of IV, was obtained.

When the ratio of H_2SO_4/HNO_3 was reduced to 1/1 (50 ml of H_2SO_4/50 ml of HNO_3), only the nitraminopyrimidine IV was isolated. The yields were 30% at 20–25°, 35–40% at 30–35°, and 45% at 40–45°. When the ratio of H_2SO_4/HNO_3 was kept at 3/1 and the reaction temperature at 40–45°, the isolated white solid product was found to be 2,4-diamino-5-nitro-6-hydroxypyrimidine: mp >360°; $\lambda_{max}^{pH\ 1}$ 324 mμ (ε 15,900); $\lambda_{max}^{pH\ 11}$ 230 mμ (ε 13,400), 338 (19,100), identical with that prepared from 2,4-diamino-6-hydroxypyrimidine by the procedure of Carbon.[4]

Rearrangement of the Nitraminopyrimidine (IV) to 2,4-Diamino-5-nitro-6-chloropyrimidine (IIIb).—A solution of 3.5 g (0.0185 mole) of IV in 35 ml of concentrated H_2SO_4 was stirred at 30–35° for 1 hr. The acid solution was added to 250 g of flaked ice and the pH of the resulting mixture was adjusted to 8–9 by the dropwise addition of concentrated aqueous ammonia, keeping the temperature below 10°. The yellow solid was filtered, washed with water, dried, and recrystallized from 150 ml of absolute ethanol to give 1 g (29% yield) of analytically pure IIIb. This product was found to be identical in all respects with that obtained by the direct nitration of 2,4-diamino-6-chloropyrimidine.

Reduction of the Nitraminopyrimidine (IV). Method A.—Sodium hydrosulfite (7g) was added, in small portions, to a suspension of 3.5 g of IV in 70 ml of boiling water with stirring. After the addition was complete, the solution was boiled for 5 min, treated with decolorizing charcoal, and filtered. On cooling, the filtrate deposited off-white crystals, which were separated by filtration and dried at 80°. The product, mp 194–196°, weighed 0.5 g. The ultraviolet and infrared absorption spectra of this product are identical with those of an authentic sample of 2,4-diamino-6-chloropyrimidine (IIIa).

Method B.—To a solution of 1.5 g of IV in 50 ml of dimethylformamide was added Raney nickel, and the mixture hydrogenated at room temperature for 4 days. Several times during this period, the system was flushed with hydrogen to remove the ammonia that was produced during the reduction. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was treated with boiling acetone and the insoluble material was discarded. The acetone solution was evaporated until crystallization started to occur. On cooling, 0.7 g of white solid was collected. The product which melted at 195–197° was found to be identical with an authentic sample of 2,4-diamino-6-chloropyrimidine.

2,4-Diamino-5-nitro-6-(*p*-bromoanilino)pyrimidine (IIa).—To a solution of 5 g (0.0264 mole) of IIIa in 1000 ml of boiling absolute ethanol was added 5 g (0.029 mole) of *p*-bromoaniline. The resulting solution was refluxed for 2 hr with gentle stirring, during which time a yellow precipitate gradually separated. The precipitate, which was the hydrochloride salt of the desired product, was collected by filtration. It was then stirred at room temperature in 200 ml of concentrated aqueous ammonia and the resulting free base was recrystallized from a large volume of ethanol to give 5.3 g (59% yield) of analytically pure IIa: mp 248–249°; $\lambda_{max}^{pH\ 1}$ 238 mμ (ε 26,300), 327 (18,200), 257 sh (23,400); $\lambda_{max}^{pH\ 11}$ 255 mμ (ε 24,100), 342 (24,800).

Anal. Calcd for $C_{10}H_9BrN_6O_2$: C, 36.9; H, 2.79; N, 25.8. Found: C, 37.2; H, 2.90; N, 26.1.

2,4-Diamino-5-nitro-6-(*p*-iodoanilino)pyrimidine (IIb) was similarly prepared from 5 g (0.0264 mole) of IIIa and 6.4 g (0.029 mole) of *p*-iodoaniline to give 5.4 g (55% yield) of analytically pure IIb: mp 241–243°; $\lambda_{max}^{pH\ 1}$ 240 mμ (ε 29,000), 324 (17,500), 257 sh (26,400); $\lambda_{max}^{pH\ 11}$ 257 mμ (ε 26,400), 336 (20,500).

Anal. Calcd for $C_{10}H_9IN_6O_2$: C, 32.2; H, 2.39; N, 22.6. Found: C, 32.0; H, 2.60; N, 22.8.

Reduction of 2,4-Diamino-5-nitro-6-(*p*-bromoanilino)pyrimidine (IIa) with Sodium Hydrosulfite.—To a suspension of 3.25 g (0.01 mole) of IIa in 80 ml of boiling water was added portionwise, with stirring, 5.0 g (0.024 formula weight) of sodium hydrosulfite. After the addition was complete, the reaction mixture was boiled for 10 min, followed by careful addition of 10 ml of 18 *N* H_2SO_4. The resulting mixture was treated with decolorizing charcoal and filtered. On cooling, the filtrate deposited 1.3 g (32% yield) of 2,4,5-triamino-6-(*p*-bromoanilino)-pyrimidine sulfate as light yellow crystals, mp >360°. This product was found to be identical with that prepared previously by the reduction of 2,4-diamino-5-nitroso-6-(*p*-bromoanilino)-pyrimidine.[5]

Reaction of 2,4,6-Trichloro-5-nitropyrimidine (VI) with *p*-Bromoaniline and Ammonia.—To a solution of 7.5 g (0.033 mole) of VI in 250 ml of anhydrous ether cooled to −22° was added dropwise with vigorous stirring, a solution of 11.4 g (0.066 mole) of *p*-bromoaniline in 50 ml of anhydrous ether. The temperature during this addition was maintained between −22 and −20°. After the addition was complete, the mixture was stirred at −20° for 1 hr, after which time the solid that separated during the reaction was filtered, washed well with ether, ice water, and again with ether. This solid material (8 g) was placed in a sealed stainless steel container with 250 ml of ethanolic ammonia (saturated at 0°). The mixture was heated at 140 ± 5° for 12 hr. After cooling, the reaction mixture was evaporated to dryness and the residue was washed well with water. The resulting yellow solid was recrystallized from 1200 ml of absolute ethanol to give 5.1 g (32% yield) of 2(6)-amino-4,6(2)-bis(*p*-bromoanilino)-5-nitropyrimidine as analytically pure needles: mp 256–258°; $\lambda_{max}^{pH\ 1}$ 284 mμ (ε 22,000), 295 (22,000), 410 (16,700), 325 sh (13,900); $\lambda_{max}^{pH\ 11}$ 284 mμ (ε 24,100), 336 (13,900), 407 (17,200), 293 sh (22,400).

Anal. Calcd for $C_{16}H_{12}Br_2N_6O_2$: C, 40.0; H, 2.52; N, 17.5. Found: C, 39.7; H, 2.20; N, 17.5.

Oxidation of 2,4-Diamino-5-nitroso-6-(*p*-bromoanilino)-pyrimidine (Ia).—Aqueous H_2O_2 (30%, 6 ml) was added dropwise, over a period of 60 min, to a blood red solution of 3 g of Ia in 30 ml of trifluoroacetic acid. The temperature during this addition was kept at 30–35°. After the addition was complete, the color of the resulting solution was light red. The solution was allowed to stir at room temperature for 14 hr, during which time a yellow solid slowly separated. To the mixture was then added 75 ml of cold water, and the resulting suspension was stirred for 30 min. The yellow solid was collected by filtration, washed well with water, cold ethanol, and ether, then dried at 65°. The dried product was recrystallized from absolute ethanol to give 2.4 g (73% yield) of the N-oxide of 2,4-diamino-5-nitro-6-(*p*-bromoanilino)pyrimidine as yellow needles: mp 258–259°; $\lambda_{max}^{pH\ 1}$ 242 mμ (ε 25,200), 265 (23,900), 324 (17,000); $\lambda_{max}^{pH\ 11}$ 229 mμ (ε 25,500), 275 (25,400), 325 (16,000), 374 (8300).

Anal. Calcd for $C_{16}H_9BrN_6O_3$: C, 35.2; H, 2.66; N, 24.6. Found: C, 35.6; H, 2.70; N, 24.2.

Nitration of 2,4-Diaminopyrimidine.—To a solution of 5 g (0.024 mole) of 2,4-diaminopyrimidine sulfate in 25 ml of concentrated H_2SO_4 was added dropwise, with stirring, 5 ml of fuming nitric acid (sp gr 1.5). The temperature during the addition was kept between 30–35°. After the addition was complete, the solution was stirred at 30–35° for 30 min. The acid solution was added to 300 g of flaked ice with vigorous stirring. The pH of the resulting mixture was adjusted to 8–9 by the dropwise addition of concentrated aqueous ammonia, keeping the temperature below 15°. The light yellow precipitate was filtered and the yellow solid was washed with water and ethanol, and dried. The product, 0.8 g (22% yield), was found to be identical with an authentic sample of 2,4-diamino-5-nitropyrimidine.[24]

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