collected solid washed with water and dried; yield 0.8 g. (79.5%), m.p. 200–202°. Sublimation of this material at 190° (0.01 mm.) yielded bright yellow crystals, m.p. 203–205°, which were identical with an authentic sample of 2-amino-5,6-diphenylpyrazine-3-carboxamide.[32]

2-Methylaminopyrazine-3-carboxamide (37).—A mixture of 1.0 g. of 1-methyl-3-hydroxy-1-pyrazolo(b)pyrazine, 100 ml. of 95% ethanol and 5 g. of Raney nickel catalyst was heated under reflux for 2.5 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure to yield a light brown powder; yield 0.38 g. (37.5%), m.p. 196–197°. Sublimation of this material at 180° (0.1 mm.) yielded very light yellow rods, m.p. 200–201°. The reported melting point for this compound is 198–199°.[17]

Anal. Calcd. for $C_6H_8N_4O$: C, 47.4; H, 5.3; N, 36.8. Found: C, 47.5; H, 5.3; N, 36.6.

2-Anilinopyrazine-3-carboxamide (39).—A mixture of 6 g. of 1-phenyl-3-hydroxy-1-pyrazolo(b)pyrazine, 60 g. of Raney nickel catalyst and 600 ml. of ethanol was heated under reflux and stirred for 4 hours. The hot solution was filtered through Celite and the catalyst extracted with hot ethanol. The filtrate and extracts were combined and evaporated *in vacuo* to give a residue of brown needles; yield 3.2 g. (53%), m.p. 170–172°. The product could be obtained as large, greenish-yellow plates by slow crystallization from ethanol or in the form of needles by rapid cooling of concentrated ethanolic solutions. Both crystalline forms of the purified material melted at 175–176°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.7; H, 4.7; N, 26.2. Found: C, 61.9; H, 4.7; N, 26.7.

2-Aminopyrazine-3-carboxylic Acid Anilide (40).—A mixture of 5.0 g. of 2-phenyl-1-pyrazolo(b)pyrazine-3-one, 500 ml. of 95% ethanol and 50 g. of Raney nickel catalyst was heated under reflux for 3 hours. The solution was filtered from the catalyst. The catalyst was extracted several times with hot ethanol and the combined extracts and filtrate evaporated under reduced pressure to dryness. Sublimation of the solid residue at 160–170° (15 mm.) gave pale yellow needles in 52% yield, m.p. 104–106°. The product was obtained in the form of colorless needles after recrystallization from ethanol, m.p. 106–107°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.7; H, 4.7; N, 26.2. Found: C, 62.0; H, 4.8; N, 26.7.

A mixture of 2.0 g. of the above anilide and 50 ml. of 10% sodium hydroxide solution was heated under reflux for 2.5 hours. The resulting yellow solution was diluted with 50 ml. of water, cooled and extracted with two 30-ml. portions of ether. The aqueous layer was adjusted to *p*H 5 to give crystalline 2-aminopyrazine-3-carboxylic acid, m.p. 200–201°, identical with an authentic sample.[27,28] Evaporation of the ether extracts and treatment of the residual oil with acetic anhydride yielded 0.41 g. of acetanilide, m.p. 112–113°.

2-Benzylaminopyrazine-3-carboxamide (38).—A mixture of 3.75 g. of 1-benzyl-3-hydroxy-1-pyrazolo(b)pyrazine, 40 g. of Raney nickel catalyst and 400 ml. of ethanol was heated under reflux with stirring for 3 hours. The hot reaction mixture was filtered through Celite, the catalyst extracted several times with hot ethanol and the combined filtrate and washings evaporated to dryness *in vacuo* to give a residue of brown needles. Extraction of this residue with dilute ammonia and neutralization of the extract with acetic acid yielded 0.24 g. of unchanged starting material. Sublimation of the ammonia-insoluble solid at 130–140° (0.05 mm.) yielded 1.35 g. (38%) of a pale yellow solid, m.p. 123–124°. The product was obtained in the form of colorless needles, m.p. 125–126°, by recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.2; H, 5.3; N, 24.6. Found: C, 63.2; H, 5.3; N, 24.8.

2-Benzylaminopyrazine-3-carboxylic Acid (42).—A mixture of 1.0 g. of 2-benzylaminopyrazine-3-carboxamide and 10 ml. of 10% sodium hydroxide was heated under reflux for 2 hours and then adjusted to *p*H 4 with dilute hydrochloric acid. The solution was cooled and filtered to give 0.78 g. (78%) of a colorless solid, m.p. 160–163°. The product was obtained in the form of colorless plates, m.p. 166.5–168° upon recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.9; H, 4.8; N, 18.4. Found: C, 63.1; H, 4.7; N, 18.2.

2-Amino-5-methylpyrazine-3-carboxamide (36).—A mixture of 2 g. of 3-hydroxy-5-methyl-1-pyrazolo(b)pyrazine, 20 g. of Raney nickel catalyst and 200 ml. of ethanol was heated under reflux with stirring for 4 hours. The reaction mixture was worked up in the usual manner to give 0.93 g. (46%) of crude product, m.p. 194–196°. Recrystallization of this material from methanol gave small colorless plates, m.p. 203–204° alone and when admixed with an authentic sample of 2-amino-5-methylpyrazine-3-carboxamide.[27]

2-Amino-6-methylpyrazine-3-carboxamide (35).—Application of the above procedure to 3-hydroxy-6-methyl-1-pyrazolo(b)pyrazine yielded a crude orange-brown product which was purified by sublimation at 160–170° (18 mm.) to give a pale yellow crystalline solid, m.p. 235–236°, in 51.5% yield.

Anal. Calcd. for $C_6H_8N_4O$: C, 47.4; H, 5.3; N, 36.8. Found: C, 47.5; H, 5.2; N, 36.7.

2-Amino-6-methylpyrazine-3-carboxylic Acid (43).—A mixture of 1.0 g. of 2-amino-6-methylpyrazine-3-carboxamide and 10 ml. of 10% sodium hydroxide was heated under reflux for 2 hours and then adjusted to *p*H 4 with dilute hydrochloric acid. Chilling at 0° caused the separation of a colorless solid which was collected by filtration and recrystallized from aqueous ethanol; yield 0.72 g. (72%), m.p. 211–212° dec. This material is reported to melt at 210° dec.[16] and at 211–212° dec.[28]

PRINCETON, NEW JERSEY

(32) E. C. Taylor, THIS JOURNAL, **74**, 1651 (1952).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Dimerization of 2-Aminonicotinonitrile

BY E. C. TAYLOR,[1] ALDO J. CROVETTI[2] AND ROBERT J. KNOPF[3]

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2-Aminonicotinonitrile dimerizes under a variety of conditions to yield 2-[3-(2-aminopyridyl)]-4-aminopyrido[2,3-d]-pyrimidine (A) (III). The structure of III has been established by several hydrolytic and degradative experiments and the probable course of the reaction has been discussed. Several other heterocyclic *o*-aminonitriles have been shown to undergo a similar dimerization when heated with sodium ethoxide or ammonia.

A recent paper dealing with the synthesis of nicotinic acid derivatives from simple pyridine-N-oxide intermediates describes the preparation of 2-chloronicotinonitrile (I) and its conversion to 2-aminonicotinonitrile (II) by the action of alcoholic ammonia at 150°.[4] It was observed during this work that a small amount of a high melting, yellow solid always was formed concomitantly with 2-

(1) Frick Chemical Laboratory, Princeton University.
(2) Parke, Davis and Co. Fellow, 1953–1955.
(3) Parke, Davis and Co. Fellow, 1955–1957.
(4) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

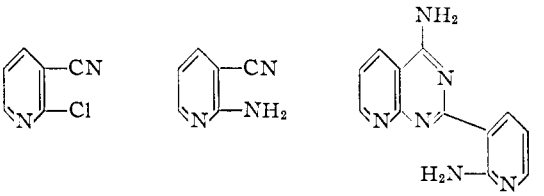
aminonicotinonitrile in the amination reaction. The present communication describes the proof of structure, mode of formation and chemical properties of this yellow material.

Subsequent investigation showed that this high melting, yellow "by-product" (henceforth designated A) was formed in yields as high as 86% when 2-chloronicotinonitrile (I) was heated with anhydrous ammonia at 190°. 2-Aminonicotinonitrile (II) was evidently an intermediate in the formation of A, since at low temperatures for short periods of time, II was the main product, while at higher temperatures for longer periods of time, A was the main product. Furthermore, II could be converted to A under similar conditions. Compound A also was formed from II upon heating the latter alone in a sealed tube at 190–200°, by treatment with one mole of sodium ethoxide in ethanol under reflux for several hours or by pyrolysis of its *p*-toluenesulfonic acid salt.

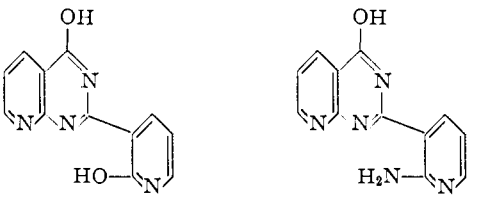
This yellow material (A) melted with decomposition at 338° and was soluble in acid but insoluble in base and in ordinary organic solvents. Analysis showed that the compound was isomeric with II, but a molecular weight determination established the empirical formula as $C_{12}H_{10}N_6$; *i.e.*, A was a dimer of II. The ultraviolet absorption spectrum in 0.1 *N* hydrochloric acid showed maxima at 253 mμ (log ε 4.10) and 360 mμ (log ε 4.19), with a shoulder at 275–283 mμ (log ε 3.75), indicating the presence of a bicyclic ring system in A. Examination of the infrared spectrum revealed the absence of absorption characteristic of a nitrile group and the presence of broad bands at 3132, 3260, 3320 and 3440 cm.$^{-1}$ (associated N–H) and at 1670 and 1615 cm.$^{-1}$ (C=N).

Hydrolysis of A with concentrated hydrochloric acid under reflux for five hours gave a high melting, amphoteric, yellow product (B), whose formula ($C_{12}H_9N_5O$) indicated the replacement of one amino group by a hydroxyl group. Treatment of either A or B with sodium nitrite in 30% sulfuric acid and then refluxing for several hours yielded another high melting, amphoteric, yellow compound (C), whose formula ($C_{12}H_8N_4O_2$) indicated the replacement of two amino groups in A by hydroxyl groups. The difference in reactivity of the two amino groups in A is striking. Thus, hydrolysis of only one amino group occurred when A was heated under reflux with: (1) concentrated hydrochloric acid for 12 hours, (2) concentrated hydrochloric acid and ethylene glycol for 36 hours, (3) 2.5 *N* sodium hydroxide for 24 hours, and (4) 85–95% sulfuric acid for 30 minutes. The monohydroxy monoamino compound (B) could be degraded by hydrolytic means, but only under strenuous conditions. Thus, treatment of B with 14% sodium hydroxide in a sealed steel bomb at 170–175° for seven hours gave, in addition to a 40–50% recovery of unchanged B, 2-aminonicotinic acid, which was identified by comparison with an authentic sample. Treatment of B with 95% sulfuric acid at 285–300° for 1.5 hours gave 2-aminopyridine, which was also identified by comparison with an authentic sample.

From the above evidence, it would appear that A is 2-[3-(2-aminopyridyl)]-4-aminopyrido[2,3-d]-pyrimidine (III). Since an amino group in the 4-position of a pyrido[2,3-d]pyrimidine is known to be hydrolyzed[5,6] readily and 2-aminopyridines are known to be resistant to vigorous hydrolysis conditions,[4,7] the monohydroxy compound B formed on hydrolysis of A is undoubtedly 2-[3-(2-aminopyridyl)]-4-hydroxypyrido[2,3-d]pyrimidine (IV). The replacement of the remaining amino group of B by hydroxyl upon vigorous diazotization is consistent with the known lability of 2-aminopyridines under these conditions,[7–9] and C can thus be formulated as 2-[3-(2-hydroxypyridyl)]-4-hydroxypyrido[2,3-d]pyrimidine (V).



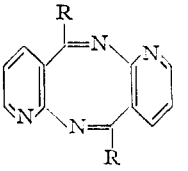
I II III (A)



V (C) IV (B)

Also, the stability of B (IV) toward dilute acid and alkali at reflux and the strenuous conditions necessary to degrade the molecule to 2-aminopyridine with concentrated sulfuric acid, and to 2-aminonicotinic acid with alkali, are consistent with known properties of other pyrido[2,3-d]pyrimidines. For example, 2,4-dihydroxypyrido[2,3-d]-pyrimidine is cleaved to 2-aminonicotinic acid when treated with 14% sodium hydroxide for four hours at 170° in a sealed tube. The same compound is degraded to 2-aminopyridine upon treatment with 100% sulfuric acid at 250–280° for 25 minutes.[10]

The only possible alternative structure for A, which could be considered to be consistent with any of the foregoing evidence, is the eight-membered ring structure VI, 5,11-diaminodipyrido-[2,3-b,3′,2′-f](1,5)diazocine. Immediate rejection of this formulation is possible on the basis of



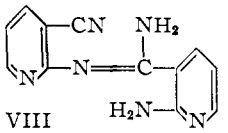
VI, R = $-NH_2$
VII, R = $-OH$

the unequivocal evidence outlined above for the

(5) R. K. Robins and G. H. Hitchings, THIS JOURNAL, **77**, 2256 (1955).
(6) E. C. Taylor and A. J. Crovetti, unpublished observations.
(7) H. S. Mosher in "Heterocyclic Compounds," Vol. 1, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 397.
(8) A. Philips, *Ann.*, **288**, 253 (1895).
(9) F. G. Mann and J. A. Reid, *J. Chem. Soc.*, 2057 (1952).
(10) A. C. McLean and F. S. Spring, *ibid.*, 2582 (1949).

non-equivalence of the two amino groups in A. Moreover, the dihydroxy derivative C, which, by the above formulation would be 5,11-dihydroxydipyrido[2,3-b,3',2'-f](1,5)diazocine (VII), has been previously reported[11,12] under the designation "2-aminonicotinic acid anhydride" and has been described as a colorless solid, m.p. (dec.) 390°, which is readily hydrolyzed to 2-aminonicotinic acid when heated under reflux with 30% potassium hydroxide for five hours. These facts are clearly inconsistent with the properties actually observed for the dihydroxy compound C.

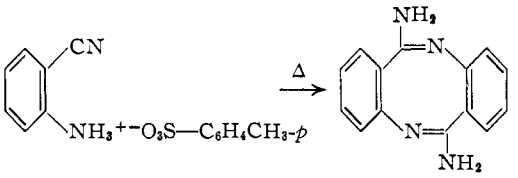
The formation of III (A) through the thermal or base-catalyzed self-condensation of 2-aminonicotinonitrile (II) probably occurs *via* the intermediate formation of an amidine VIII, arising by



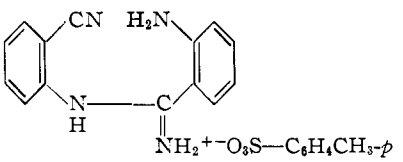
VIII

addition of an amino group of one molecule of 2-aminonicotinonitrile across the nitrile group of a second molecule, followed by a second, but intramolecular, condensation of the more basic amidine grouping of VIII across the remaining nitrile group to give the observed product. Analogous base-catalyzed additions of amino groups to nitriles (a modification of the familiar Thorpe condensation) are well known in pyrimidine chemistry.[13-15]

The only previously recorded example of an analogous dimerization of an *o*-aminonitrile is the formation of 6,12-diaminophenhomazine (IX) in 20% yield by the thermal cyclization of *o*-cyanoanilinium *p*-toluenesulfonate[16] (see, however, ref. 18). It would appear reasonable to postulate that the intermediate formed in this instance is the amidine X. Since this dimerization is acid catalyzed, protonation of the more basic amidine function leaves only the aromatic amino group free for the ring-closure addition, thus leading to an eight-



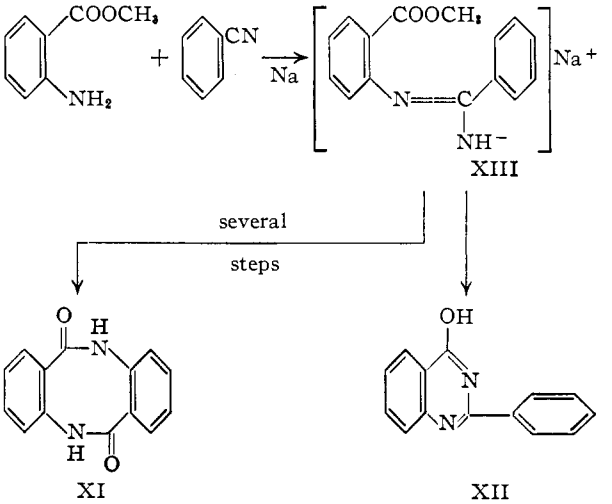
IX



X

rather than a six-membered ring. The observation that the *p*-toluenesulfonate salt of 2-aminonicotinonitrile yields A on pyrolysis rather than VI (see Experimental) is probably the result of dissociation of the salt under the reaction conditions, followed by thermal dimerization of the free base. It is significant that anthranilonitrile itself fails to react either with liquid ammonia at high temperatures or with sodium ethoxide in refluxing ethanol.[17]

The reaction of methyl anthranilate with benzonitrile in the presence of powdered sodium in benzene, or sodium ethoxide in ethanol, yields 6,12-dihydroxyphenhomazine (dianthranilide) (XI) as a main product and 4-hydroxy-2-phenylquinazoline (XII) as a by-product.[16] The formation of the latter, presumably as a result of cyclization of the intermediate amidine XIII, provides a somewhat closer parallel to the self-condensation of 2-aminonicotinonitrile to A reported here.



XIII

XI XII

A few preliminary experiments have shown that the base-catalyzed dimerization of heterocyclic *o*-aminonitriles may have synthetic applications in other systems. For example, treatment of 4-amino-5-cyanopyrimidine (XIV) with sodium ethoxide in refluxing ethanol afforded in good yield a high-melting, extremely insoluble product which proved to be isomeric with the starting material. Its infrared spectrum revealed the absence of a nitrile group, and we have thus, by analogy, assigned to it the structure 2-[5-(4-aminopyrimidyl)]-4-aminopyrimido[4,5-d]pyrimidine (XV). Similarly, 2-methyl-4-amino-5-cyanopyrimidine (XVI) yielded under the same conditions an isomeric product which did not contain a nitrile group, and to which we now have assigned the structure of 2-[5-(4-amino-2-methylpyrimidyl)]-4-amino-7-methylpyrimido[4,5-d]pyrimidine (XVII). However, 4-amino-5-cyano-6-methylpyrimidine, 3-amino-4-cyanopyrazole and 4-amino-5-cyano-1-methylimidazole were recovered unchanged after prolonged refluxing with sodium ethoxide in ethanol. It already has been reported that 2-amino-3-cyanoquinoline dimerizes upon heating with liquid

(11) L. Klisiecki and E. Sucharda, *Roczniki Chem.*, **3**, 251 (1923).

(12) O. Seide, *Ber.*, **57**, 1806 (1924).

(13) R. H. Wiley in "Organic Chemistry, An Advanced Treatise," Vol. 1V, ed. by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 723.

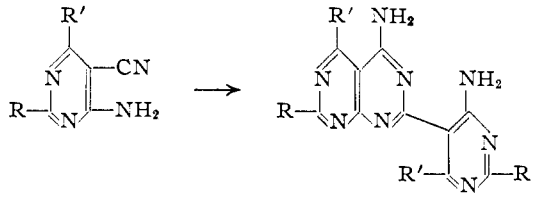
(14) A. Bendich in "The Nucleic Acids," Vol. 1, ed. by E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 81.

(15) G. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 234.

(16) F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 3429 (1954).

(17) The use of appropriately substituted anthranilonitriles, however, can lead under basic conditions to dimers containing 6- rather than 8-membered rings, *i.e.*, quinazolines. This phase of the investigation will be reported in a separate communication.

ammonia at 190° to 2-[3-(2-aminoquinolinyl)]-4-aminopyrimido[4,5-b]quinoline.[18]



XIV, R = R′ = -H XV, R = R′ = -H
XVI, R = $-CH_3$, R′ = -H XVII, R = $-CH_3$, R′ = -H

Experimental[19]

2-[3-(2-Aminopyridyl)]-4-aminopyrido(2,3-d)pyrimidine (A) (III). Method A.—A mixture of 15.0 g. of 2-chloronicotinonitrile and 80 ml. of liquid anhydrous ammonia contained in a glass liner was inserted in a steel pressure bomb and heated at 185–190° for 20 hours. The vessel was cooled, the ammonia vented carefully and the residue dissolved in dilute hydrochloric acid. The acid solution was filtered through a 0.5 inch layer of charcoal and the light yellow filtrate made alkaline by the addition of sodium hydroxide and adjusted to 700–800 ml. by addition of water. Cooling caused the separation of a light yellow solid which was collected by filtration, washed well with water, then with acetone and dried at 120° to yield 11.1 g. (86%), m.p. 328–332° dec. Sublimation at 270° (0.05 mm.) raised the melting point to 338° dec. and readily afforded an analytical sample; $\lambda_{max}^{0.1\ N\ HCl}$ 253, 275–283 (shoulder), 360 mμ; log ε 4.10, 3.75, 4.19.

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.5; H, 4.2; N, 35.3; mol. wt., 238. Found: C, 60.7; H, 4.0; N, 35.2; mol. wt., 218.

Method B.—The same product could be obtained in 50–60% yield by heating a mixture of 2-aminonicotinonitrile and liquid anhydrous ammonia at 185–190° for 5–7 hours. Under these conditions, unreacted starting material could usually be recovered in 35–40% yield.

Method C.—A mixture of 2.0 g. of 2-aminonicotinonitrile and 25 ml. of ethanol containing 0.386 g. of sodium was heated under reflux for 5 hours. The mixture rapidly turned yellow and a yellow solid separated after 2 hours. The reaction mixture was diluted with 25 ml. of water, allowed to stand at 50–60° for several hours and then chilled to 0°. The yellow solid which separated was collected by filtration, washed with ethanol, dried and then sublimed at 270° (0.05 mm.) to yield 1.2 g. (60%), m.p. 337°.

Method D.—The same product was obtained in low yield by heating 2-aminonicotinonitrile in a sealed tube at 190° for 19 hours, extracting unreacted starting material with ether and subliming the residue *in vacuo*.

Method E.—A mixture of 2.0 g. of 2-aminonicotinonitrile and 3.7 g. of *p*-toluenesulfonic acid in 20 ml. of water was warmed until a clear solution was obtained and then evaporated to dryness under reduced pressure. The residue was heated *in vacuo* at 170° for 3 hours, during which time a considerable amount of the *p*-toluenesulfonic acid salt of 2-aminonicotinonitrile sublimed from the mixture. The residue was dissolved in water, adjusted to *p*H 8 with dilute sodium hydroxide and the solution chilled. The solid which separated was collected by filtration, dried thoroughly and sublimed at 270° (0.05 mm.) to yield a small amount of light yellow crystals, m.p. 337° dec.

The products obtained by methods A, B, C, D and E were all identical as judged by mixed melting point determinations and by comparison of infrared and ultraviolet absorption spectra.

2-[3-(2-Aminopyridyl)]-4-hydroxypyrido(2,3-d)pyrimidine (B) (IV).—A mixture of 5.0 g. of 2-[3-(2-aminopyridyl)]-4-aminopyrido(2,3-d)pyrimidine and 50 ml. of concentrated hydrochloric acid was heated under reflux for 5 hours. Solution occurred during the first 30 minutes followed by a gradual separation of solid. The cooled reaction mixture was filtered, and the filtrate adjusted to *p*H 5–6, cooled and filtered. The combined solids were dissolved in dilute hydrochloric acid and reprecipitated by the addition of sodium hydroxide to *p*H 5–6. The light yellow solid which separated was collected by filtration, washed well with water followed by acetone and dried at 120° to give 4.25 g. (85%), m.p. 381° dec. The same product was obtained by heating 2-[3-(2-aminopyridyl)]-4-aminopyrido-(2,3-d)pyrimidine with a mixture of concentrated hydrochloric acid and ethylene glycol for 36 hours or with 2.5 *N* sodium hydroxide for 24 hours or with 85–95% sulfuric acid for 30 minutes. A sample was prepared for microanalysis by sublimation at 270° (0.05 mm.); $\lambda_{max}^{0.1\ N\ HCl}$ 271, 327–333 (shoulder), 353 mμ; log ε 3.88, 4.09, 4.17.

Anal. Calcd. for $C_{12}H_9N_5O$: C, 60.2; H, 3.8; N, 29.3. Found: C, 60.4; H, 3.5; N, 29.0.

Cleavage of IV to 2-Aminonicotinic Acid.—A mixture of 1.0 g. of 2-[3-(2-aminopyridyl)]-4-hydroxypyrido(2,3-d)-pyrimidine and 12 ml. of 14% sodium hydroxide was heated in a stainless-steel pressure bomb at 170–175° for 7 hours. The reaction mixture was diluted to 45 ml. with water, filtered through a layer of charcoal and the filtrate concentrated to 20 ml. and adjusted to *p*H 5 with hydrochloric acid. A yellow solid (0.54 g.) separated which was collected by filtration; concentration of the filtrate yielded 0.1 g. of a white solid. Sublimation of the yellow material at 160° (0.05 mm.) yielded a white solid and a residue consisting of unreacted starting material. The combined white solids were crystallized from water to yield pure 2-aminonicotinic acid, m.p. 310° dec. The reported[4] melting point for 2-aminonicotinic acid is 306–307° (cor.).

Cleavage of IV to 2-Aminopyridine.—A mixture of 2.0 g. of 2-[3-(2-aminopyridyl)]-4-hydroxypyrido(2,3-d)pyrimidine and 25 ml. of 95% sulfuric acid was heated under reflux (internal temperature 285–300°) for 1.5 hours. The cooled reaction mixture was poured onto ice and the resulting solution filtered through a layer of charcoal. The almost colorless filtrate was made strongly alkaline with sodium hydroxide and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness to give 0.11 g. of white crystals, m.p. 50–54°. A mixed melting point with an authentic sample of 2-aminopyridine (m.p. 55–57°) was 53–55°. Picrates of both samples were prepared by adding an ethanol solution of the solid to a solution of the theoretical amount of picric acid in ethanol. Both picrates melted at 224–225°, and no depression in melting point on mixing was observed. 2-Aminopyridine picrate is reported[10] to melt at 216–217°.

2-[3-(2-Hydroxypyridyl)]-4-hydroxypyrido(2,3-d)pyrimidine (C) (V).—A solution of 1.0 g. of 2-[3-(2-aminopyridyl)]-4-aminopyrido(2,3-d)pyrimidine in 16 ml. of sulfuric acid was cooled to 0–5° and a solution of 3.0 g. of sodium nitrite in 7.0 ml. of water added dropwise with shaking over a period of 15–20 minutes. The reaction mixture was removed from the ice-bath and heated on a steam-bath to 40–50° where solid started to separate. The mixture was then heated under reflux for one hour, diluted to 75 ml. with water, made alkaline to *p*H 9 by the addition of concentrated sodium hydroxide and filtered through a layer of charcoal. The filtrate was acidified with hydrochloric acid to *p*H 2–3 and chilled. The solid which separated was collected by filtration, washed well with water, then with acetone and dried at 120° to give 0.78 g. (77%) of a pale yellow solid, m.p. 370–378° dec. The analytical sample was prepared by sublimation at 295° (0.1 mm.), m.p. 378° dec.; $\lambda_{max}^{0.1\ N\ NaOH}$ 227–230 (shoulder), 315 mμ; log ε 4.30, 4.07.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.0; H, 3.4; N, 23.3. Found: C, 60.4; H, 3.4; N, 23.3.

2-[5-(4-Aminopyrimidyl)]-4-aminopyrimido(4,5-d)pyrimidine (XV).—To a solution of 0.46 g. of sodium in 30 ml. of absolute methanol was added 2.24 g. of 4-amino-5-cyanopyrimidine, and the mixture was heated under reflux for 15 hours. During this time the starting material slowly dissolved, and a light, finely-divided solid separated from the hot solution. The reaction mixture was chilled for several hours at 0° and then filtered. The filter cake was washed thoroughly with water and dried at 100° to give 2.10 g. (94%) of a powdery white solid which did not melt below 360°. The crude product was purified by dissolution in hot dilute mineral acid and then by precipitation with am-

(18) E. C. Taylor and N. W. Kalenda, THIS JOURNAL, **78**, 5108 (1956).

(19) All melting points are uncorrected. We are indebted for the microanalyses to Mr. Josef Nemeth, Mrs. Esther Fett and Mrs. Lucy Chang of the University of Illinois, and to Dr. Joseph F. Alicino of Metuchen, N. J.

monium hydroxide. The analytical sample was prepared by sublimation at 300° (0.05 mm.); $\lambda_{max}^{0.1\ N\ HCl}$ 250, 300 mμ; log ε 4.33, 3.94.

Anal. Calcd. for $C_{10}H_8N_8$: C, 50.0; H, 3.3. Found: C, 50.3; H, 3.4.

2-[5-(4-Amino-2-methylpyrimidyl)]-4-amino-7-methylpyrimido(4,5)pyrimidine (XVII) was prepared in 80% yield from 2-methyl-4-amino-5-cyanopyrimidine as described above and was purified analogously by reprecipitation from dilute acid solution and by vacuum sublimation; m.p. >360°; $\lambda_{max}^{0.1\ N\ HCl}$ 247, 297 mμ; log ε 4.32, 3.93.

Anal. Calcd. for $C_{12}H_{12}N_8$: C, 53.7; H, 4.5. Found: C, 53.7; H, 4.7.

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A Comparison of the Reactions of Some Amines with Nitrosoguanidine, Cyanamide and S-Methylisothiourea Hydrochlorides[1a,1b]

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A comparison of the reaction of p-$RC_6H_4NH_2 \cdot HCl$ (R = H, CH_3 and $(CH_3)_2N$) and phenylhydrazine with nitrosoguanidine supports the hypothesis of a prior dearrangement of nitrosoguanidine to cyanamide as advanced by Davis and his students.[3a,b] However, the results of a similar comparison with the series piperidine, 3-methylpiperidine, 2-methylpiperidine and *cis*-2,6-dimethylpiperidine at room temperature strongly favor an addition–elimination mechanism. A similar path is advanced for the behavior of S-methylisothiourea hydrochloride toward the same series of piperidines. Finally, it is demonstrated that the reaction of the corresponding piperidine hydrochlorides with both nitrosoguanidine and S-methylisothiourea proceeds *via* a cyanamide intermediate at reflux temperatures.

Davis and his students have suggested that the formation of guanidine derivatives from the interaction of alkylamines and nitrosoguanidine (eq. 2) is explicable in terms of a prior dearrangement of the substrate to cyanamide.[3a,b]

The isolation of small amounts of urea from the reaction of ammonia with nitrosoguanidine was construed as evidence for an alternate mode of dearrangement (eq. 1b) in which nitrosocyanamide is postulated as the reactive species.[3b]

$$NH_2C(NH)NHNO \begin{cases} \longrightarrow NH_2CN + (NH_2NO) \longrightarrow N_2 + H_2O & (1a) \\ \longrightarrow NH_3 + NONHCN & (1b) \end{cases}$$

$$RNH_2 + NH_2CN \longrightarrow RNHC(=NH)NH_2 \qquad (2)$$

Thiele had earlier considered a similar mechanism (eq. 1a) to explain the formation of aminoguanidine from the action of hydrazine on nitrosoguanidine.[4] However, the fact that the temperature required to cleave nitrosoguanidine is considerably higher than that necessary to initiate this reaction caused Thiele to abandon this hypothesis.

Recently McKay[5] advanced an attractive addition–elimination mechanism[6] to explain the reactions of amines with both nitro- and nitrosonitroguanidine. Furthermore, it appeared to us that the findings of Davis and Rosenquist[3b] could be explained on a similar basis. However, there is at present no direct evidence to vitiate the dearrangement hypothesis.

A preliminary study showed that the course of reaction between phenylhydrazine and nitrosoguanidine is markedly affected by pH. Refluxing an aqueous solution of phenylhydrazine hydrochloride and nitrosoguanidine, which is weakly acid, gave a mixture of anilinoguanidine (I) and 1-phenyl-1-aminoguanidine (II) in a ratio of *ca.* 2:1, but when free phenylhydrazine was used in place of its hydrochloride, only dicyandiamide could be isolated. A similar observation on the reaction of free aniline with nitrosoguanidine has been reported by Davis and Rosenquist.[3b]

$$C_6H_5NHNH_3^+ \cdot \xrightarrow[\text{or } NH_2CN]{NONH-C(=NH)-NH_2} C_6H_5NHNH-C(=NH)-NH_3^+ \ (\text{I}) \ + \ C_6H_5N(^+NH_3)-C(=NH)-NH_2 \ (\text{II})$$

A second series of reactions was carried out under identical conditions with cyanamide. It is evident from Table I that the reactions of phenylhydrazine with nitrosoguanidine and cyanamide in neutral and weakly acidic solution afford identical products in essentially the same yields.

It is pertinent to the succeeding discussion that the data regarding the effect of pH on aqueous solutions of cyanamide be summarized.[7] In strongly basic solution (pH 12) cyanamide is quantitatively hydrolyzed to urea at a rate which is proportional to the concentration of $(NHCN)^-$. In less basic solutions (pH 8–12) cyanamide dimerizes to dicyandiamide at a rate which is proportional to the

(1) (a) Abstracted in part from a dissertation submitted by C. Clinton Rila to the Graduate School of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This work was supported by U. S. NOTS, Inyokern, China Lake, Calif., Research Contract N 123S-61527, Task Order No. 3.

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(3) (a) T. L. Davis and A. J. Abrams, *Proc. Am. Acad. Arts Sci.*, **61**, 437 (1926); (b) T. L. Davis and E. N. Rosenquist, THIS JOURNAL, **59**, 2112 (1937).

(4) J. Thiele, *Ann.*, **273**, 133 (1893).

(5) A. F. McKay, *Chem. Revs.*, **51**, 312 (1952).

(6) An intermediate may be formed or the addition–elimination reactions occur simultaneously.

(7) For a complete discussion of the effect of pH on cyanamide see T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, London, England, 1937, p. 329.